Flavonoids: Prospective Drug Candidates

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Abstract: The purpose of this review is to discuss the recent developments related to the chemistry and medicinal properties of flavonoids. Major flavonoids that show well categorized structures and well defined structure function-relationships are: flavans, flavanones, flavones, flavanonols, flavonols, catechins, anthocyanidins and isoflavone. The biological properties of flavonoids include antioxidant, anti-inflamatory, antitumoral, antiviral and antibacterial, as well as a direct cytoprotective effect on coronary and vascular systems, the pancreas and the liver. These characteristics place them among the most attractive natural substances available to enrich the current therapy options.

Key Words: Flavonoids, medicinal properties, absorption, disease.

CHEMISTRY, CLASSIFICATION AND OCCURRENCE

The flavonoids belong to a large group of low-molecular-weight polyphenolic compounds biosynthesized from both the shikimic acid and acetic acid pathways. Flavonoids are the product of the condensation of the three malonyl-CoA units (C-2) and a *P*-coumaric acid unit (C-9) to give a basic nucleus (C6-C3-C6) composed of two benzene rings connected by a three-carbon unit such as an oxygen-containing pyrene ring. Their structural features comprise a fundamental skeleton of the 2-phenyl chromone with a variety of substitution patterns in the A-ring (characteristically a phloroglucinol or resorcinol hydroxylation pattern) and B-ring (usually catechol, pyrogallol or 4′-hydroxylated) [1, 2]. The oxidation level of the three-carbon unit (C-ring) gives rise to different classes of flavonoids including flavans, flavanones, flavones, flavanonols, flavonols, catechins, anthocyanidins, and isoflavone, among others (Fig. (**1**)).

Flavonoids are mainly present in nature as glycosides although free aglycones can be found as major constituents in several plants. The glycosilation of a phenolic alcoholic hydroxyl group of a flavonoid aglycone can occur through the hemiacetal bound (O-glycosides) or straight attachment to the C-1 of the sugar unit *via* a carbon-carbon bond (C-glycosides). A few monosaccharides, such as D-glucose and L-rhamnose, which are the most common, and other less frequent glucorhamnose, galactose, xylose and arabinose, or combinations of these (di- or trisaccharides), can bind to hydroxyl groups or directly to a carbon atom at different positions on the flavonoid aglycone [1, 3-5]. The O-glycosilation of the flavonoid molecule occurs most frequently at the C-3 and/or C-7 positions and for C-glycoside flavonoids the preferential glycosilation sites are at positions C-6 and C-8. The large number of flavonoids found in nature is due to the innumerable combinations between flavonoid aglycones and sugars units.

The flavonoids are very widespread in nature and are the largest group of natural products known. They are present in plants in many different glycosidic forms, for example, quercetin-3-rutinoside (rutin), quercetin-4′-glucoside and quercetin-3,4′-glucoside, which are the most common. Besides their roles in plants, flavonoids are important components in the human diet and are found in fruits, vegetables, seeds, nuts, grains, spices and beverages (wine, tea and beer). Quercetin is considered one of the most common flavonol aglycones in the human diet due its high concentration in several foods including onions, kale, french beans, broccoli, lettuce, tomatoes, apples and beverages [1, 6]. Other flavonols in the diet include kaempferol (broccoli), myricetin (berries), and isorhamnetin (onion) [1, 5, 6]. The glycoside flavanones mainly occur in citrus fruits and are represented by hesperetin-7-rutinoside and naringenin-7-rutinoside, which are the major flavonoids of oranges and mandarins. The glycosides naringenin-7-neohesperoside and narirutin are typically found in grapefruit. Pears, grapes, peaches, vegetables, tea and red wine are sources of catechins that occur as aglycones or esterified with gallic acid [7-9]. The main flavones in the diet are apigenin and luteolin and most important sources are red pepper, celery, cereal grains and aromatic herbs [9, 10]. Edible fruits, such as plums, apples, eggplant, and many berries have important contents of anthocyanidins and their glycosides, which are the compounds responsible for the red, blue or violet color. The most common anthocyanidins are pelargonidin, cyanidin, delphinidin, and malvidin [1, 11]. The predominant isoflavonoids are the genistein and daidzein

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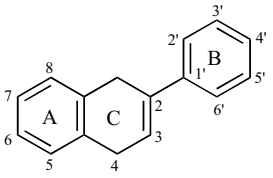
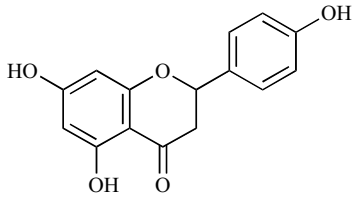
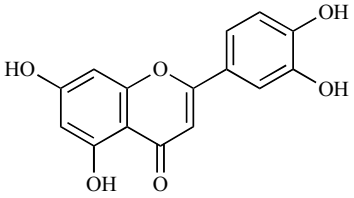


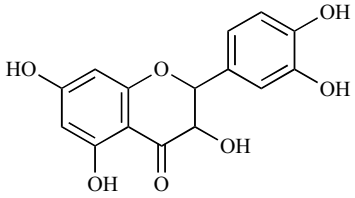
FLAVAN NUCLEUS



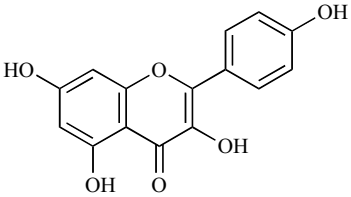
(FLAVANONE)
2,3-dihydro-5,7-dihydroxy-2-(4-dihydroxyphenyl)-
4H-1-Benzopyran-4-one (naringenin)



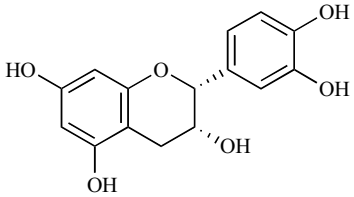
(FLAVONE)
5,7-dihydroxy-2-(3,4-hydroxyphenyl)-
4H-1-benzopyran-4-one (luteolin)



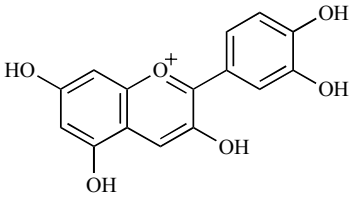
(FLAVANONOL)
2,3-dihydro-3,5,7-trihydroxy-2-(3,4-dihydroxyphenyl)-
4H-1-benzopyran-4-one (taxifolin)



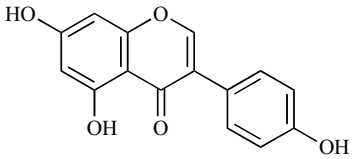
(FLAVONOL)
3,5,7-trihydroxy-2-(4-hydroxyphenyl)-
4H-1-benzopyran-4-one (kaempferol)



(FLAVANOL)
(2R,3R)-3,4-dihydro-3,5,7-trihydroxy-2-(3,4-dihydroxyphenyl)-
4H-1-benzopyran((-)-epicatechin)



ANTHOCYANIDIN NUCLEUS
3,5,7-trihydroxy-2-(3,4-dihydroxyphenyl)-
1-benzopirilium cyanidin



ISOFLAVONE NUCLEUS
5,7-dihydroxy-3-(4-hydroxyphenyl)-
4H-1-benzopyran-4-one (genistein)

Fig. (1). Representative structure of main classes of flavonoids.

found in high concentrations in soybean and soy products [12, 13].

ABSORPTION AND METABOLISM

An important factor in the absorption efficiency of flavonoid glycosides in the intestine is the sugar moiety, as demonstrated for quercetin glucosides, aglycone and rutin supplements [14]. Flavonoid aglycones are hydrophobic in nature and can be transported across membranes by passive diffusion. The glycoside moiety increases the hydrophilicity of the flavonoid molecule which reduces the possibility of passive transport. This leads to the theory that flavonoids are absorbed by active transport [1]. Evidence is accumulating that epithelial brush border membrane transporters play a role in the absorption of dietary (iso)flavonoids. Indirect evidence indicates that some flavonoid glycosides can be absorbed intact in the small intestine through the sodium-dependent glucose transporter 1 (SGLT-1), as reported for

quercetin-3-glucoside and quercetin-4′-glucoside [14-16] (Fig. (**2A**)).

On the other hand, the flavonoids can return to the intestinal lumen through efficient efflux transport, most likely due to the apical multi-drug resistance protein- 2 (MRP-2), a characteristic intestinal efflux pump, as in the efflux of quercetin-4′-β-glucoside, (-)-epicatechin and (-)-epigallocatechin-3-gallate [17, 18]. It has been described that before absorption flavonoids are cleaved by specific enzymes either in the lumen or inside the cells of the gut. Lactase-phlorizin hydrolase (LPH) is anchored in the brush-border membrane in the small intestine and catalyzes extracellular hydrolysis of some glucosides [19, 20]. Another enzyme, located intracellularly and with broad specificity, is the cytosolic β-glucosidase (CBG). It is found in abundance in the small intestine, liver and kidney of mammals and requires active transport of hydrophilic glucosides into the cells [20]. Concerning LPH activity, it has been shown that the enzyme cleaves some flavonols and isoflavone glycosides such as: quercetin- 4′-glucoside, quercetin-3-glucoside, quercetin-3, 4′-glucoside, 3′-methylquercetin-3-glucoside, genistein-7-glucoside, and daidzein-7-glucoside. However, quercetin-3-rhamnoglucoside (rutin) and naringenin-7-rhamnoglucoside (naringin) are not substrates for this enzyme [19, 21]. In addition, β-glucosidase (BCG) activity is reported to act on flavonoid and isoflavone glycosides according to the position and the structure of the sugar moiety attached to the flavonoid aglycone [22] (Fig. (**2A**)).

Once absorbed, flavonoids are subject to 3 main types of conjugation: methylation, sulfation and glucuronidation [23]. The metabolic steps in polyphenol metabolism are catalyzed by enzymes. The levels and sites of enzyme expression in human tissues determine the metabolic fate and the pharmacokinetics of ingested polyphenols and their glycosides [24]. The most important enzymes involved in flavonoids metabolism are: catechol-*O*-methyltransferase (COMT; EC 2.1.1.6), which methylates polyphenols and has the highest activity in the liver and kidneys [25]. Phenol sulfotransferases (P-PST, SULT; EC 2.8.2.1) are cytosolic enzymes that transfer sulfate moieties to hydroxyl groups from substrates such as iodothyronines, phenols and hydroxyarylamines mainly in the liver [23, 24, 26]. UDP glucuronosyl transferase (UDPGT, UGT; EC 2.4.1.17) catalyzes the conjugation of polyphenols to glucuronic acid in endoplasmic reticulum in the intestine, liver and kidney. In humans, the liver has the greatest capacity for glucuronidation while in rats, the highest level of glucuronyl transferase activity was observed in the intestine [26-28].

Conjugation reactions with glucuronic acid and/or sulfate seem to be the most common type of metabolic pathways for the flavonoids [1]. This conjugation first occurs in the gut barrier and these conjugates then reach the liver, where they are further metabolized [26]. For example, catechin is extensively methylated in the liver [29] and increased plasma total (+)-catechin levels were observed after hydrolysis of its glucuronide and sulphate derivatives from volunteers that ingested red wine [30]. Otake *et al.* [31] using human liver microsomes demonstrated that hepatic UDP-glucuronosyl transferase isoforms were the main factor responsible for galangin metabolism into two major glucuronides conjugated at the 7- and 3- positions. Also, Vaidyanathan and Walle [32] demonstrated no glucuronidation of (-)-epicatechin by human liver and small intestinal microsomes. However, in rats, (-)-epicatechin was efficiently metabolized by liver microsomes with formation of two glucuronides. In the same study, the authors concluded that sulfation also occurred in both the liver and intestine in human and rats.

On the other hand, glycoside flavonoids that are not absorbed in the small intestine along with the conjugated metabolites that are excreted in bile can be metabolized by microflora when they reach the colon (Fig. (**2B**)). Glycoside flavonoid-hydrolyzing enzymes have been identified in fecal flora cultures. Bokkenheuser *et al.* [33], recovered three enzyme-producing strains that, using β-glucosidases, α-rhamnosidases, and/or β-galactosidases, were capable of converting rutin to quercetin. Also, it was shown that at least some of the bacterial glycosidases are able to cleave glycosidic bonds and flavonoid-saccharide bonds in the gut [19]. The profile of metabolites has been demonstrated in studies with quercetin, rutin and naringin. The flavonoid metabolism produces aromatic acids such as phenylvaleric, phenylpropionic, phenylacetic and benzoic acids with easy absorption through the colonic barrier [34-36].

Metabolites of flavonoids in general (and also microflora metabolites), aglycones, glycosides and conjugated metabolites which are not absorbed, may follow two pathways of excretion: *via* the biliary or the urinary route. Large conjugated metabolites are more likely to be eliminated in the bile whereas small conjugates such as monosulfates are preferentially excreted in urine [27]. When excreted in bile, the flavonoids are passed to the duodenum and metabolized by intestinal bacteria, which results in the production of fragmentation products and/or the hydrolysis of glucurono- or sulfoconjugates [37]. The resulting metabolites which are released may be reabsorbed and enter an enterohepatic cycle or being excreted in feces [38, 39] (Fig. (**2B**)). For each flavonoid, the beneficial effect will be dependent upon their absorption and availability in the body. Thus, these factors should be considered in any interpretation of the potential health effects of flavonoids.

MEDICINAL PROPERTIES

1. Antioxidant Activity

The major mechanisms of action of antioxidant agents are suppression of reactive oxygen species formation, either by inhibition of enzymes or chelating trace elements involved in free radical production; scavenging of reactive oxygen species (ROS); and upregulation or protection of antioxidant defenses [40].

The antioxidant activity of flavonoids and the mechanisms involved in their action are extensively revised by Pietta [41] and Amic *et al.* [42]. The configuration and total number of hydroxyl groups are determinant factors in the mechanisms of antioxidant activity of flavonoids. Particularly, the B-ring hydroxyl configuration is significant as a scavenger of ROS and reactive nitrogen species (RNS) [43, 44]. Furthermore, a 3′,4′-catechol structure in the B-ring and the presence of 6-hydroxyl group potentiates lipid peroxidation inhibition as well as the free radical scavenger effect

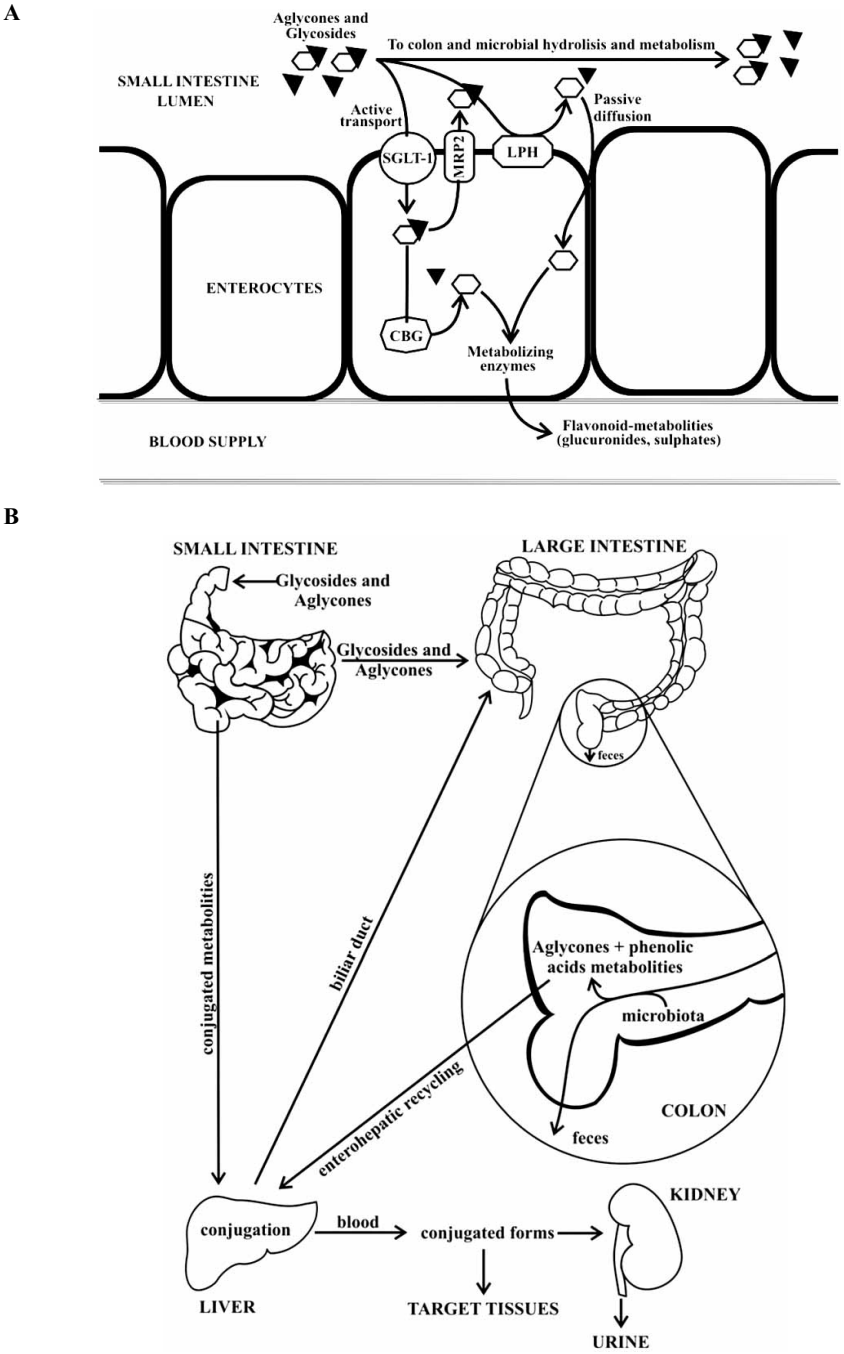


Fig. (2). Schematic representation of intestinal absorption (**A**) and metabolism of flavonoids (**B**). SGLT-1 = sodium-dependent glucose transporter-1; MRP-2 = multidrug-resistance associated protein-2; LPH = lactase phloridzin hydrolase; CBG = cytosolic β-glucosidase. Fig. (**A**) was adapted from Nemeth *et al*., (2003) [20].

[45, 46]. Different classes of compounds are able to scavenge reactive species including: catechin, luteolin, kaempferol, 3-O-methyl-quercetin, naringenin, kaempferol 3-O-D-glycoside, kaempferol-3-O-(2′′,6′′-di-O-*p*-trans-coumaroyl) glucoside, 6-hydroxyluteolin glycosides, hesperidin and quercetin [46-49].

The flavonoid heterocycle contributes to antioxidant activity by permitting conjugation between the aromatic rings and particularly through the presence of a free 3-OH which can be potentiated by the presence of a 3′,4′-catechol explaining the potent antioxidant activity of flavan-3-ols and flavon-3-ols which possess the latter feature [50, 51]. Also, the carbonyl group at C-4 and a double bond between C-2 and C-3 are important features in relation to the high antioxidant activity of flavonoids [51, 52]. Furthermore, the number of polyhydroxy or polymethoxy substituents determines the difference in the antioxidant activities of flavonoids probably due to the hydrophobicity and molecular pla-

narity induced by the substitution models [45, 50]. Another important feature of antioxidant agents is the presence, number and position of glycosides in the flavonoid structure. In general, aglycones are more potent antioxidants than the corresponding glycosides, as demonstrated by daidzein, genistein and their 7-glycosides, kaempferitrin and the flavonol glycosides in green tea [52-56].

One of the most well known antioxidant activities of flavonoids is the inhibition of the enzymes responsible for superoxide anion production, such as xanthine oxidase [57]. Also, flavonoids inhibit the enzymes of the cyclooxygenase and lipoxygenase pathway [58] and microsomal monooxygenase, glutathione *S*-transferase, mitochondrial succinoxidase, and NADH oxidase, all involved in ROS generation [59]. Another possible contributory mechanism to the antioxidant activity of flavonoids is the ability to efficiently chelate trace metals through interaction with the catechol moiety in the B-ring, 3-hydroxyl, 4-oxo groups in the heterocyclic ring, and 4-oxo, 5-hydroxyl groups between the heterocyclic and the A-rings, decreasing the availability of these metals to participate in the generation of free radicals [60, 61].

2. Anti-Inflammatory Activity

Several cellular action mechanisms have been proposed to explain the *in vivo* and *in vitro* anti-inflammatory activity of flavonoids. They can modulate the functions and activities of inflammatory and immune cells through, for instance, inhibition of histamine release from mast cells, immunosuppressive effects on T-cell proliferation and IL-2 synthesis, and regulation of secretion of IgG, IgM and IgA isotypes [58, 62]. There are also reports concerning flavonoid actions over a range of cellular types such as platelets, eosinophils, neutrophils, mast cells, basophils, macrophages and monocytes [to review see 62, 63].

In addition, one of the direct actions of flavonoids is modulating the activity of arachidonic acid (AA) metabolizing enzymes [58]. The formation of AA is the rate limiting step in the synthesis of prostaglandis, leukotrienes and the platelet activating factor. This pathway is triggered by phospholipase A_2 (PLA_2). AA undergoes metabolism to several active products (eicosanoids) by two major routes: the cyclooxygenase and lipoxygenase pathways. The immediate products of the cyclooxygenase pathway are endoperoxides (PGG_2 and PGH_2), which are converted to prostaglandins ($PGE_{2\alpha}$, PGF_2Q and PGD_2) by prostaglandins synthetase enzymes, as well as thromboxanes (TXA_2 and TXB_2) and prostacyclins (PGI_2) by the corresponding synthetases. The lipoxygenase pathway converts AA to hydroxyl fatty acids, including hydroperoxyeicosatetraenoic acids (HPETEs), which are then metabolized to hydroxyeicosatetraenoic acids (HETEs). The HETEs and their leukotriene metabolites are important mediators of inflammatory responses [64].

The first flavonoid inhibitor of PLA_2 activity discovered was quercetin, which inhibits the activity of PLA_2 from human neutrophils and several other sources. Also, other flavonoids have been reported to inhibit PLA_2 activity, for example, hesperetin, naringenin, kaempferol, myricetin and biflavonoids [64, 65].

The cyclooxygenase (COX) enzyme exists basically in two different isoforms: COX-1 and COX-2 [66, 67]. Some flavonoids such as luteolin, 3′,4′-dihydroxyflavone, galangin, and morin inhibit COX activity [68]. Inhibition was also observed for baicalin, (+)-catechin, rutin, chrysin and its derivatives, kaempferol and quercetin in different animal tissues and cells [58, 69]. Studies on flavonoid inhibition of COX-2 have been rarely reported. An inhibitory activity against COX-2 or COX-1/COX-2 are reported for some flavan-3-ols such as catechin and 4′-Me-gallocatechin and for two dihydrochalcones [70-72]. Lipooxygenase (LOXs) enzyme isoforms also act in inflammatory processes and are responsible for generating hydroxy acids and leukotrienes (LTs) from AA. Flavonols, including kaempferol, quercetin, morin and myricetin, have been found to be stronger LOX inhibitors than flavones [69, 73].

Nitric oxide (NO) is one of the cellular mediators of physiological and pathological processes involved in inflammatory events and it is biochemically synthesized from L-arginine by nitric oxide synthase (NOS) isoforms [74, 75]. Quercetin, apigenin, luteolin, genistein, kaempferol, chrysin and its derivatives were found to inhibit NO production to act against NOS isoforms both by inhibition of induced NOS (iNOS) activity or down-regulation of iNOS expression from different cell types [76, 77]. Furthermore, evidence supports the idea that certain flavonoids act as modulators of proinflammatory gene expression.

The tumor necrosis factor-α (TNF-α) and IL-1β are prominent contributors to chronic inflammatory disorders [78]. Genistein and other flavonoids are reported to inhibit IL-1β, IL-6, and TNF-α production in several kinds of cells [79, 80]. Activation of NF-κB is inhibited by genistein, apigenin, kaempferol, oroxylin A [77, 81], epigallocatechin 3-gallate and amentoflavone [82, 83] while quercetin, rutin and luteolin inhibits the expression and production of TNF-α and intercellular adhesion molecule 1 (ICAM-1) in mice [84, 85]. Another flavonoid, myricitrin, has also been described as an inhibitor of the nociceptive responses in models of acute pain by inhibiting of phosphatidylinositol 3-kinase (PI3K) and protein kinase C (PKC) activities, NO production, iNOS over expression and NF-kB activation [86, 87].

3. Protective Effects on Coronary Disease and Vascular Activity

Atherosclerosis is a chronic inflammatory response in the walls of arteries, in large part due to the deposition of lipoproteins (plasma proteins that carry cholesterol and triglycerides). There is much evidence that oxidized low density lipoprotein (LDL) is responsible for cholesterol loading of macrophages, foam cell formation and atherogenesis [88, 89]. LDL is oxidized by free radicals generated by endothelial cells, macrophages and smooth muscle cells. Therefore, it has been hypothesized that oxidized LDL is the responsible for the initiation and promotion of atherogenesis [90, 91].

In this regard, several aglycone and polyhydroxylated flavonoids, such as quercetin, morin, hypoleatin, setin, gossypetin and galangin, are potent inhibitors of LDL oxidation *in vitro* by macrophages or copper ions. They may reduce the formation of free radicals (for instance, chelating divalent

metal involved in the Fenton reactions), and protect the α-tocopherol present in the LDL structure from oxidative damage or regenerate it [92, 93]. Along with all of the activity of flavonoids against atherogenesis, they may inhibit adhesion and platelet aggregation as well as promote vascular smooth muscle relaxation. The antiaggregatory effects of flavonoids seems to influence the platelet activation pathway, such as the inhibition of the enzymes involved in AA metabolism as well as the inhibition of platelet aggregation by antagonizing thromboxane formation and thromboxane receptor function [94, 95].

The antioxidant actions of flavonoids appear to participate in their antithrombotic action. The antithrombotic and vasoprotective actions of quercetin, rutin, and other flavonoids have been attributed to their ability to bind to platelet membranes and scavenge free radicals, restoring the biosynthesis and action of endothelial prostacyclin and endothelial-derived relaxing factor [96-98]. Flavonoids with anti-platelet activity include isobavachalcone and neobavaisoflavone, luteolin, genistein, quercetin, apigenin and kaempferol derivatives [99-101]. One of the flavonoid mechanisms of platelet aggregation inhibition is to increase cyclic AMP (cAMP) levels through adenylate cyclase activation and phosphodiesterase inhibition [102, 103]. Quercetin-4′-O-β-D-glycoside inhibited collagen-stimulated tyrosine phosphorylation of platelet and quercetin inhibits the intracellular Ca^{2+} mobilization suggesting that these flavonoids act as inhibitors of the trigger signal for thrombus formation [104, 105]. These results have been recently confirmed in humans by Hubbard *et al.* [106].

In addition to their antiaggregatory effects, flavonoids appear to increase vasodilation by inducing vascular smooth muscle relaxation which may be mediated by the inhibition of PKC, phosphodiesterase, or by decreased cellular Ca^{2+} uptake [102]. Luteolin, naringenin and eriodictyol have been shown to promote the relaxation of rat aorta contractions induced by Ca^{2+}, noradrenaline and K^{+} [107]. Quercetin, chrysin and (-)-epicatechin also have vasorelaxant effects [108-111].

4. Antitumoral Activity

Cancer is a disease caused by a combination of exogenous and endogenous factors which results in a cellular cyclo imbalance (mitosis/apoptosis) turning normal cells into cancer cells [2].

The flavonoids are one of the most promising anticancer natural products that have been studied [112-114]. They interfere with a large number of regulatory pathways such as: cellular growth, energy metabolism, apoptosis, cell division, transcription, gene repair, neuronal transmission, inflammation, and stress response which may be involved in tumorigenesis [2, 62]. Quercetin has been reported to inhibit many biochemical events associated with tumor promotion, such as alteration in PKC activity and interactions with calmodulin [115, 116]. Also, quercetin strongly inhibits the expression of the mutated p53 (tumor suppressor gene) protein preventing the accumulation of newly synthesized p53 protein without affecting the steady-state mRNA levels of p53 in cancer cell lines [117, 118]. This flavonoid also exhibited antiproliferative effects in: drug-resistant leukemia cells *in vitro* and *in vivo*, colon and hepatocellular cancers in rats and mice and exerted growth-inhibitory effects on several malignant tumor cell lines *in vitro* [119-123].

In *in vivo* studies quercetin, kaempferol, and myricetin have been found to be able to inhibit carcinogen-induced tumors in rats and mice [124]. Other flavonoids such as catechin, epicatechin, quercetin, and resveratrol, polyphenolic compounds in red wine have been shown to inhibit growth of human breast and prostate cancer cells [125, 126]. The exposure of human epidermoid carcinoma cells to silymarin resulted in a significant decrease in ligand-induced activation of the epidermal growth factor receptor (EGFR) with an associated decrease in EGFR intrinsic kinase activity. This was accompanied by inhibition of DNA synthesis and cell growth [127].

The anticancer effects of genistein and its derivatives, such as biochanin A, daidzein, genistin and daidzin, have also been reported. They potently inhibit the growth of human breast carcinoma cell lines [128, 129]. *In vitro* studies have shown that such chemopreventive and antineoplastic effects are associated with the antioxidant activity of genistein and inhibitor activities in cell proliferation and angiogenesis [130, 131] as demonstrated recently for genistin and daidzin in M14 cells [132]. Effects of green tea on the inhibition of carcinogenesis in experimental animal models, along with its constituents, for example, (-)- epigallocatechin gallate, in all levels of cancer progression, namely initiation, promotion and transformation, have been described [133, 134].

Recently, Cárdenas *et al.* [135] studied the effects of various natural flavonoids, cinnamic acid derivatives, and a series of synthetic flavones on cell proliferation *in vitro* in established human and murine tumor cell lines. The most potent antiproliferative agents were caffeic acid *n*-butyl ester > 2′-nitroflavone > caffeic acid ethyl ester ~ 2′, 6-dinitroflavone > apigenin > 3′-bromoflavone ~ 2′-fluoro-6-bromoflavone. Some compounds showed a moderate effect, the order of cytotoxic activities being chrysin > 2′-fluoro-6-chloroflavone ~ 2′-chlorochrysin > α-naphthoflavone > β-naphthoflavone ~ 6-chloroflavone ~ 6-bromoflavone ~ 4′-nitroflavone. None of the natural or synthetic compounds tested affected the proliferation of epithelial cells derived from normal mammary glands of mice or fibroblastic cells of the mouse embryo, suggesting a selective action against tumor cells. Besides the flavonoid actions described above, they can also influence adhesion molecules, metastasis and angiogenesis as well as apoptosis, gene expression and mutagenicity, which may contribute to its anticarcinogenic activity [see review 2, 62].

5. Antiviral Effects

Viruses are obligate intracellular parasites, which contain little more than bundles of gene strands of either RNA or DNA, and may be surrounded by a lipid-containing envelope [136]. Unlike bacterial cells, which are free-living entities, viruses utilize the host cell environment to propagate new viruses. They use the reproductive machinery and metabolic pathways of cells to provide energy and building blocks for new viral particles. In an alternative stage, the viral genes

may remain silent for a prolonged period inside the host cells [136].

A recent area of research that is of particular interest is the apparent inhibitory activity of some flavonoids against human immunodeficiency virus (HIV). The mechanisms of action of compounds such as baicalin, robustoflavone and hinokiflavone, robinetin, myricetin, quercetagetin, quercetin 3-*O*-(2´´-galloyl)-α-l-arabinopyranoside and chrysin seem to involve the inhibition of entry, infection, transcription and replication in cells as well as the inhibition of enzymes involved with these processes, for instance, reverse transcriptase, HIV-1 proteinase and integrase [137-141].

The effects of green tea constituents on the HIV-1 viral life cycle have being studied. It was found that (-)- epigallocatechin gallate caused the destruction of the viral particles and inhibited viral attachment to cells, post-adsorption entry into cells, reverse transcription and viral production from chronically-infected cells [142]. Epigallocatechin-3-gallate showed a dose-dependent effect on the inhibition of the replication HIV strains [143]. An inhibitory effect on HIV-1 replication was shown for tea flavin and catechin derivatives. These tea polyphenols are able to inhibit HIV-1 entry into target cells by blocking HIV-1 envelope glycoprotein-mediated membrane fusion [144].

The structural basis for the antiviral activity of naturally occurring flavonoids appears to be associated with non glycosidic compounds and hydroxylation at the 3´, 4´, 3, 5, and 7-position is apparently a prerequisite for antiviral activity [145]. A number of possible mechanisms whereby polyphenols may exert their antiviral action have been proposed. The action of flavonoids probably derives from their direct inactivation of the virus and/or from inhibition of the virus binding to the cells. They are also known to inhibit viral replication [146].

The antiherpetic activity of several flavonoids against the herpes simplex virus type 1 and type 2 has being evaluated and morin, epicatechin, epicatechin gallate (flavanols), genistein (isoflavone), naringenin (flavanone), quercetin (flavonol), galangin, kaempferol, catechin, epigallocatechin, epigallocatechin gallate, chrysin, baicalin, fisetin, myricetin, and genistein showed significant effects [147, 148]. The antiherpetic activity and genotoxicity of catechin and some of its derivatives has also been confirmed by Savi *et al.* [149].

Homoisoflavonoids were identified as having low cytotoxicity and a good antiviral activity against Coxsackie viruses (CVB3, CVB4, CAV9) and Echovirus 30 (Echo30) which may be useful as an additional antiviral drug against these infections [150]. Furthermore, antiviral activity against the human cytomegalovirus (HCMV) has been shown for baicalein. The basic mechanism of action seems to be the blockage of HCMV infection through inhibiting it entry into the cells and its replication [151].

7. Antibacterial Activity

The use of flavonoids against bacterial, protozoan, and fungal infections has two purposes: (1) to kill the bacterial or fungal cells and (2) to counteract the spread and the effects of the bacterial toxins [152]. However, the mechanism by which this is accomplished is not known yet. Antibacterial mechanisms of action of flavonoids based on their structure-activity relationships [to review see 153] have been proposed, for example, inhibition of nucleic acid synthesis [154, 155], cytoplasmatic membrane function [156, 157] and energy metabolism [158].

Recently, the antibacterial activity of some flavonoids has been increasingly documented. Examples of such flavonoids are apigenin, galangin, chrysin, sophoraflavanone G and its derivatives, naringin and naringenin, epigallocatechin gallate and its derivatives, luteolin and luteolin 7- glucoside, quercetin, 3-*O*-methylquercetin and various quercetin glycosides, along with kaempferol and its derivatives [159-166]. Other flavones, isoflavones, flavanones, flavonols, flavonol glycosides and chalcones with antibacterial activity have also been identified [163, 167-170].

The activity of the flavonoids apigenin, baicalin and galangin against sensitive and antibiotic resistant strains of *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli* and *Pseudomonas aeruginosa* has been investigated and galangin and apigenin were shown to have an inhibitory activity [171]. Genistein presented inhibitory effects on the growth of staphylococcal strains, *Streptococcus pasteurianus, Bacillus cereus*, and *Helicobacter pylori,* whereas *Escherichia coli* growth was not suppressed. Daidzein, which is structurally similar to genistein, also inhibited the growth of *Staphylococcus aureus*, albeit with lower potency than genistein [172]. Although advances in understanding the role played by flavonoids in each particular pathology are still required, it is now clear that structure function-relationship of glycosylated flavonoids indicates a molecular mechanism which is crucial to the drug discovery process.

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ABBREVIATIONS

AA	=	Arachidonic acid
AMP	=	3'-5'- Adenosine monophosphate
cAMP	=	3'-5'-Cyclic adenosine monophosphate
CBG	=	Cytosolic β-glucosidase
COMT	=	Catechol-*O*-methyltransferase
COX	=	Cyclooxygenase
CVB	=	Coxsackie viruses
DNA	=	Deoxyribonucleic acid
EGFR	=	Epidermal growth factor receptor

HCMV	=	Human cytomegalovirus
HETE	=	Hydroxyeicosatetraenoic acid
HIV	=	Human immunodeficiency virus
HPETE	=	Hydroperoxyeicosatetraenoic acid
ICAM-1	=	Intercellular adhesion molecule 1
IgM, IgA, IgG	=	Immunoglobulines
IL-1β	=	Interleukin 1β
Il-6	=	Interleukin 6
LDL	=	Low density lipoprotein
LOXs	=	Lipooxygenase isoforms
LPH	=	Lactase-phlorizin hydrolase
LT	=	Leucotrienes
mRNA	=	Messenger ribonucleic acid
MRP-2	=	Apical multi-drug resistance protein- 2
NADH oxidase	=	Nicotinamide adenine dinucleotide oxidase
NF-κB	=	Nuclear factor-kappa B
NO	=	Nitric oxide
NOS	=	Nitric oxide synthase
$PGE_{2\alpha}$, PGF_2Q and PGD_2	=	Prostaglandins
PGI_2	=	Prostacyclin
PI3K	=	Phosphatidylinositol 3-kinase
PKC	=	Protein kinase C
PLA_2	=	Phospholipase A_2
P-PST, SULT	=	Phenol sulfotransferases
RNA	=	Ribonucleic acid
RNS	=	Reactive nitrogen species
ROS	=	Reactive oxygen species
SGLT-1	=	Sodium-dependent glucose transporter 1
TNF-α	=	Tumor necrosis factor-α
TXA_2 and TXB_2	=	Thromboxanes
UDPGT, UGT	=	UDP Glucuronosyl transferase

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