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Review

Flavonoids in Our Foods: A Short Review

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Abstract

The aerobic metabolism in biological systems, produces reactive oxygen species (ROS) known as prooxidants even in basal conditions. If the formation of prooxidants increases, it leads to oxidative stress/damage. Various diseases in humans (cancer, chronic diseases, cardiovascular problems etc.) accompanies with prooxidant damage. Endogenous and exogenous antioxidants protect biomolecules against the damage of prooxidants.

Flavonoids are potent antioxidant molecules, which scavenge free radicals *in vitro*. They are found in fruits, vegetables, bark, roots, flowers and certain beverages. It has been reported that these natural products produce a wide variety of biological effects, like antiviral, anti-allergic, anti-inflammatory, anti-carcinogenic, antidiabetic effects. Flavonoids are important for human diet and have beneficial effects on health like chelating trace elements involved in free radical production, scavenging ROS and upregulating or protecting antioxidant defenses. In addition, they have known to modulate different cytochrome P450 enzymes such as CYP1A1/1A2, CYP1B1, CYP2C9, and CYP3A4/3A5. Flavonoids and their metabolites in organism may cause flavonoid-drug interaction, and it may lead to toxicity of drug or inefficient therapeutic effects of drug. However, knowledge on the mechanisms of action of flavonoids is still not fully understood. The information about correlation of structure-biological effect is limited.

There are six major subclasses of flavonoids are flavanols, flavanones, flavonols, flavones, anthocyanidins, and isoflavones. This review summarizes the types of flavonoids, possible mechanisms of action and pharmacokinetic specialties, bioavailability, properties and drug interactions of these flavonoids.

Keywords: Flavonoids, pharmacokinetic, biological activity, cytochrome P450, drug interactions

INTRODUCTION

The aerobic metabolism in biological systems produces reactive oxygen species (ROS) even in basal conditions, which are known as prooxidants. Biomolecules like nucleic acids, lipids and proteins could be damaged because of prooxidants. Endogenous and exogenous antioxidants provide protection to biomolecules against the damage of prooxidants. If the formation of prooxidants increases, it will lead to oxidative stress/damage. Various diseases in humans (cancer, chronic diseases, cardiovascular problems etc.) accompanies with prooxidant damage (1).

Polyphenolic substances are plentiful micronutrients in human diet and having protective effects against degenerative diseases. Their effects of health depend on the quantity consumed and their bioavailability. Polyphenolic substances have antioxidant properties, which takes attention for oxidative stress in certain diseases. Active substances of polyphenols found in medicinal plants modulate the activity of a large class of enzymes and receptors (2). Polyphenols are not absorbed with uniform efficacy. The intestinal/hepatic enzymes and the gut microflora extensively metabolize them. Polyphenolic substances are classified respectively as flavonoids, lignans, stilbenes and phenolic acids (benzoic/cinnamic acid and derivatives).

Flavonoids are a significant class of natural compounds, which have a polyphenolic structure, extensively found in fruits, vegetables and certain their beverages. They have various favorable biochemical and biological effects associated with various diseases (3). Flavonoids are potent antioxidant molecules,

which scavenge free radicals *in vitro*. The name of flavonoids are derived from Latin "*flavus*" which means yellow (4). Beyond from the physiologic roles in plants; they are secondary plant metabolites, which are noteworthy components of human diet, although they are considered as non-nutritious. Flavonoid levels in plants increase in different environmental conditions, such as drought, strong/weak light, heavy metals, ultraviolet radiation (UV), ozone, low/high temperature, etc (5).

CHEMISTRY AND METABOLISM OF FLAVONOIDS

Flavonoids are polyphenolic substances which are found everywhere of plants and having a structure of benzo-γ-pyrone (6). Flavonoids are synthesized in plants from phenylalanine, tyrosine and malonate by phenylpropanoid pathway (6, 7). The basic flavonoid structure is flavan nucleus which is composed of 15 carbon atoms arranged in three rings which are named A, B and C. Substitution and different oxidation level of the rings (A, B, C) forms various flavonoid subclasses (Figure 1). Flavonoids are found as aglycones, glycosides and methylated derivatives in the nature (7). The condensed structure is either α-pyrone or its dihydro derivative. The position of benzenoid substituent at the 3-position is called isoflavonoids. Flavonoids also found methyl and acetyl esters in nature. The glycosidic linkage located in positions 3 or 7 and L-rhamnose, D-glucose, glucorhamnose, galactose and arabinose could be the carbohydrate residue (6, 7).

Absorption of dietary flavonoids depends on its physicochemical properties like molecular size, configuration, lipophilicity, solubility and pKa. (pK_a is the negative base-10 logarithm of the acid dissociation constant (K_a) of a solution). Based on the structure (glycoside or aglycone) flavonoids can be absorbed from small intestine or colon. Aglycones are absorbed easily from the small intestine, but flavonoid glycosides have to be converted into aglycone form for absorption. The hydrophilic flavonoid glycosides are transported across the small intestine through the intestinal Na+-dependent glucose cotransporter (SGLT1) (6). Flavonoids absorption are also suppressed from efflux of multidrug resistance-associated protein 2 (MRP-2). But, positively charged anthocyanidins which is one of the subgroup of flavonoids, may not effected by MRP-2 efflux (8).

Flavonoid glycosides hydrolyzed to aglycone forms by a broad-specific β-glucosidase enzyme (BSβG) in enterocytes. Also, β-glycosidase that is placed in the brush border of small intestine, called lactase phloridzin hydrolase (LPH) hydrolyzes some flavonoid glycosides (8). After the hydrolysis, aglycone form can be absorbed from small intestine (6). LPH can hydrolyze a broad range of glycosides (glucosides, galactosides, arabinosides, xylosides and rhamnosides) of flavonoids (6). The glycosides, which are not substrates for LPH, are transported toward the colon. The bacteria in the colon can hydrolyze flavonoid glycosides. The absorption capacity of colon is much less than the small intestine (Figure 2 and 3).

Flavonoids may undergo at least three different intracellular metabolism pathways: oxidative metabolism, cytochrome P450-related metabolism and conjugation with glucuronic acid, sulfate and glutathione (4, 6, 8). In addition, colonic microflora takes part in the flavonoid metabolism. In colonic microflora, the hydrolysis of flavonoid glycosides, flavonoid glucuronides and flavonoid sulfates occur (8). Flavonoids can be degraded different phenolic acids, carboxylic acid and carbon dioxide in the colon

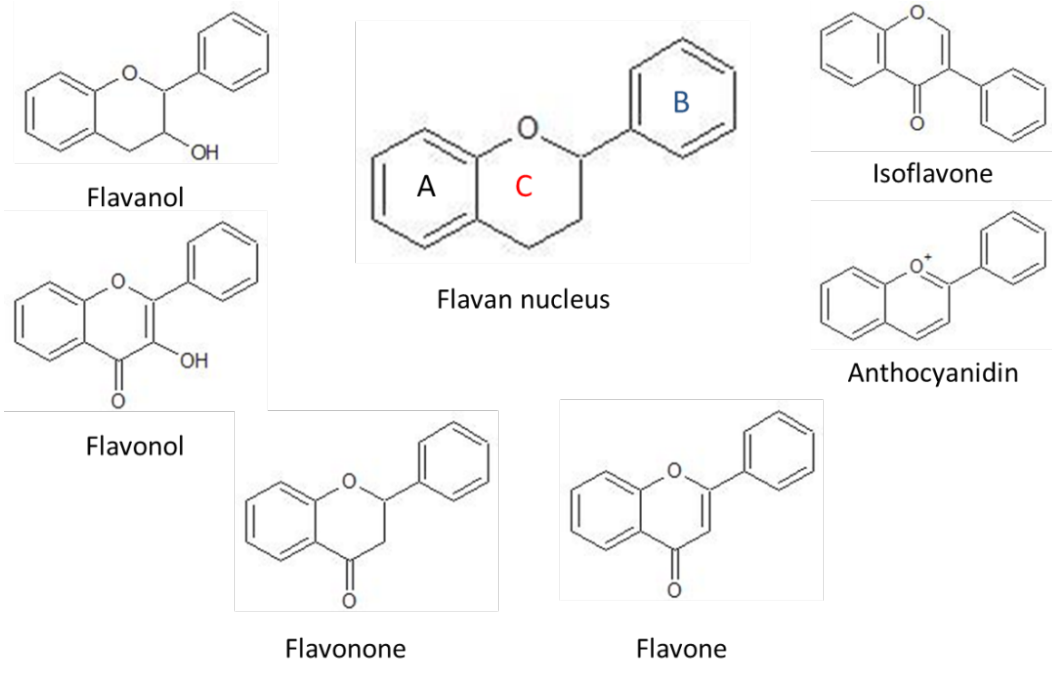

Figure 1. Basic flavan structure and chemical structures of flavonoid subgroups.

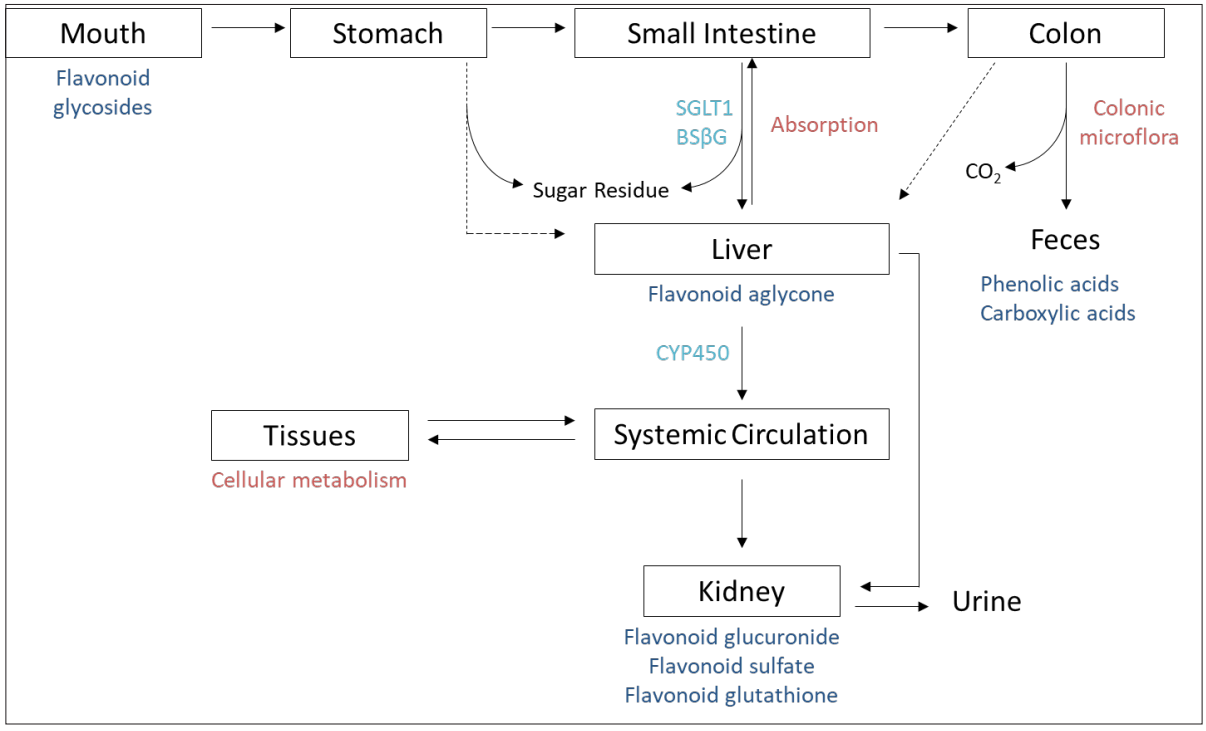

Figure 2. Biotransformation of flavonoids

by gut microflora (8). Catechol-like structures can be a substrate of catechol-O-methyltransferase. As a result of conjugation reactions, flavonoid aglycones cannot found free in plasma and urine, except for catechins (6). Depending on the food source, bioavailability of particular flavonoids differs significantly (6)

Various thermal effects such as drying, microwaving, heating, boiling and pasteurization affect the bioavailability of flavonoids in foods. For example, it has been reported that the content of quercetin of filtered fruit juices can decrease at 56°C in 4 days, but no effect at 90°C in 60 seconds. The flavonol content of the fresh cut potatoes can increase 100% with storage 4°C under light or long-term storage in darkness (4°C, 6 months). The onion processing conditions, which are baking for 176°C, 15 minutes and sautéing for 5 minutes causes increase of quercetin conjugates. The brown onion processing conditions, which are boiling for 20 minutes causes and frying 5–15 minutes causes 14.3% and 23–29% loss of quercetin conjugates respectively. The red onion processing conditions, which are boiling for 20 minutes causes and frying 5–15 minutes causes 21.9% and 23–29% loss of quercetin conjugates respectively (9).

CLASSES OF FLAVONOIDS

Flavonoids can be divided into different subclasses depending on the carbon substituent on C ring, which the B ring is attached to, and the degree of unsaturation and oxidation of the C ring. The flavonoids in which the B ring is linked in the 3-position are called isoflavones. The main subgroups of flavonoids are flavanols, flavanones, flavonols, flavones, anthocyanidins and isoflavones (Figure 1) (3, 10).

Flavanols

Flavanols found in fruits and fruit derivatives predominantly like juices or jams, tea, red wine, kiwi, cocoa and cereals. The peels and seeds of fruits and vegetables contain significant amount of flavanols. Flavanol intake by the diet is limited, because of their removed peels and seeds during eating or processing (11).

Flavanols induces the release of nitric oxide (NO) to the blood. In smokers, flavanols can improve some damage in blood vessels, which cause by tobacco. It was showed that increase in NO, after the ingestion of drinks containing flavanols have been related with flavanol metabolites. The long-term consumption of flavanol-rich foods result permanent improvement in endothelial function, and prevent oncoming cardiovascular diseases. Results of various researches show that, flavanols isolated from green, black and red tea leaves have strong antioxidant properties (12).

Catechins are the most prominent subgroup of flavanols, found in the seeds and the peel of fruits, which are the building blocks of tannins. Catechin, gallocatechin, catechin 3-gallate, gallocatechin 3-gallate, epicatechin, epigallocatechin, epicatechin 3-gallate, epigallocatechin 3-gallate are found in the subclass of catechins.

Catechin (5, 7, 3′, 4′-tetrahydroxyflavan-3-ol) and epicatechin (3, 3′, 4′, 5, 7-flavanpentol) are noteworthy compounds in catechins. Catechins are found in green and black tea, chocolate, red wine, apricot, peach, apples, blackberry and red raspberry (13). Catechins prevent protein oxidation by scavenging free radicals. It can reduce the covalent modification in proteins, which caused

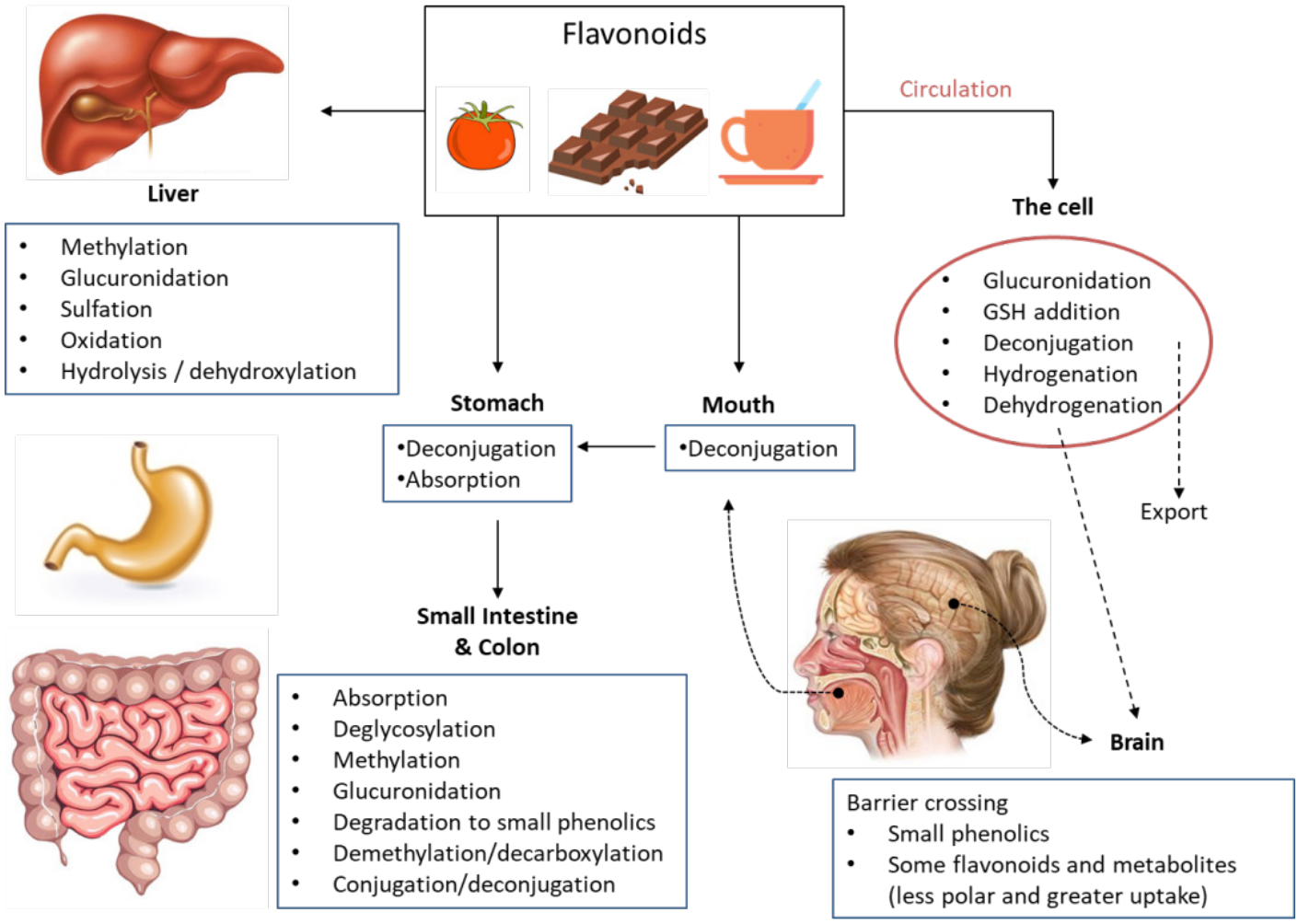

Figure 3. Metabolism and distribution of flavonoids in human (10).

by oxidative stress (14). Catechins show anti-atherosclerotic properties, which prevent low-density lipoprotein (LDL) oxidation (13). In addition, catechins have anti-carcinogenic and anti-mutagenic activity by inhibition of mutagens and carcinogens, invasion and metastasis. Catechins hinder cell proliferation, induce apoptosis, and modulate/inhibit nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activity (13). Catechins play a significant role in defense against pathogens of the tea which effects like an antimicrobial agent (13). Catechins and caffeine show synergistic activity, which may stimulate thermogenesis. Catechins can also inhibit multiple enzymes, which take a part in allergy and inflammation (13). In addition, catechins are suggested as antidiabetic substances (15).

Flavanones

In different plant species, flavanones can be found in branches, stem, leaves, roots, flowers, fruits. Particularly naringenin and hesperetin are the most important and common aglycones in the foods. Flavanones are crucial in nutrition and important plants in medicine. Substantial pharmacological properties of flavanones comprise radical scavenging, anti-inflammatory, anticancer, cardioprotective and antiviral effects (16). Mostly, dietary flavanones are called as weak antioxidants, which do not have a catechol structure.

Flavanones' antioxidant activity effects from the number and spatial position of hydroxyl substituent bound in phenol ring. Flavanones show high antioxidant activity in a hydrophilic environment. According to the environment, flavanones may be act as antioxidant or oxidant.

Naringenin (5, 7, 4′-trihydroxyflavanone) presents predominantly in grapefruit, sour orange and tomatoes which can be present both aglycone and glycoside form. In sweet orange, tangelo, lemon and lime represent low amounts of naringin. Narirutin is rich in grapefruit, although less than naringin. Naringenin-7-neohesperoside has a bitter taste due to glucose moiety. Naringenin content of these fruits may remarkably effect from food-processing procedures (16).

Hesperetin (4′-methoxy-5.7.3′-trihydroxyflavanone) is the prominent flavanone and its glycosides which can be found in citrus fruits. Aglycone form is less found in nature than glycosides. Hesperidin (hesperetin-7-rutinoside) exist high amounts in lemon, sweet orange, limes, tangerine. The rate of hesperetin/naringenin is almost fixed in citrus fruits. Also, significant amounts

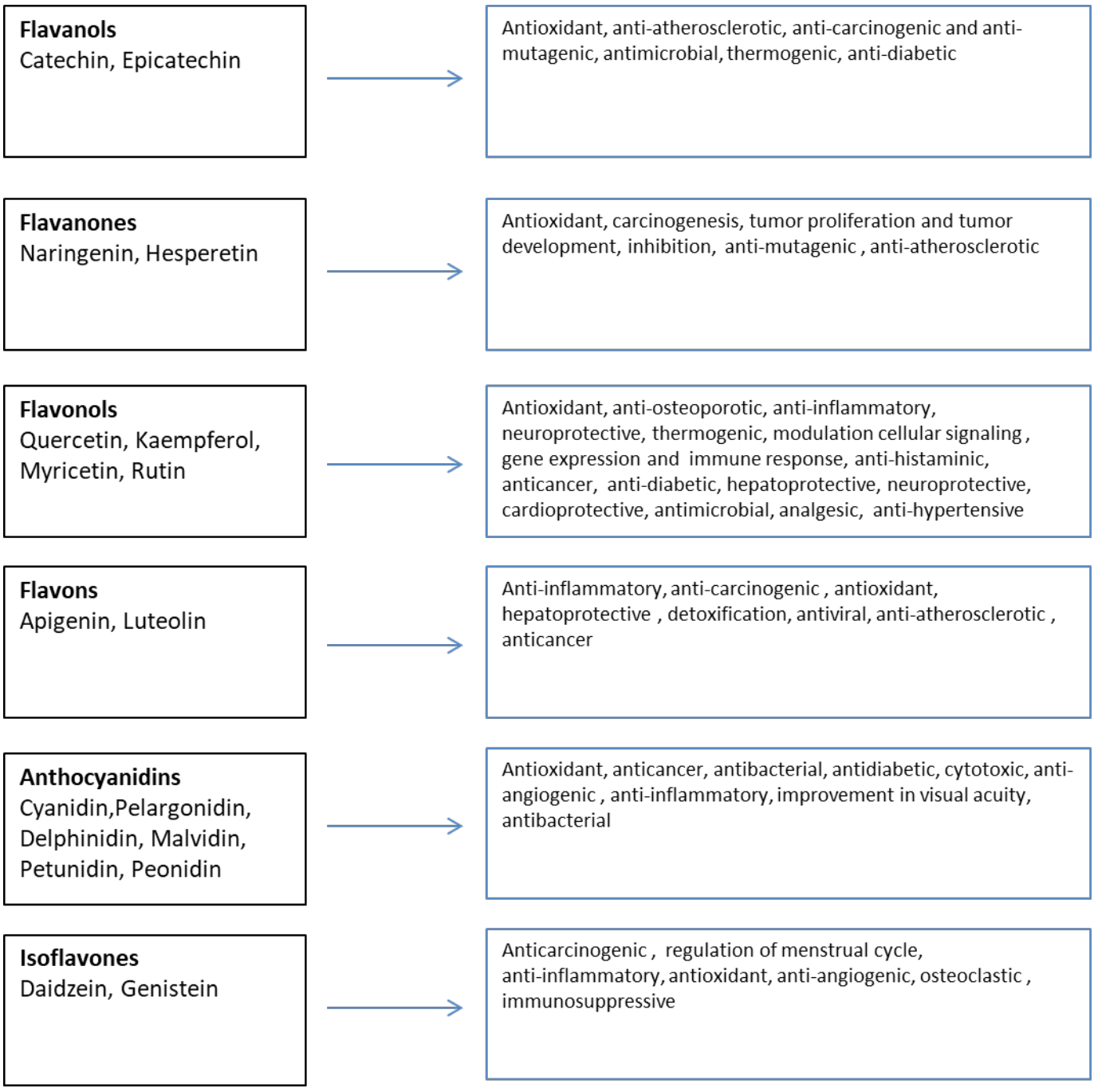

Figure 4. Flavonoids and their related biological activity

of hesperetin found in grapefruit, which tangelo and sour orange are particularly abundant in neohesperidin (16).

Naringenin flavanones are quite efficient for inhibiting pro-inflammatory cytokines and reduces intestinal edema which caused by production of nitrate and nitrite (17). Flavanones have not been broadly studied for anticancer properties. Some flavanones may have a potential for blocking carcinogenesis, tumor proliferation and tumor development. Naringenin stimulates DNA repair and shows anti-mutagenic property because of absorbing UV light. Flavanones may also effective against tumor development. The antitumor influence of naringenin and hesperetin is also has mentioned in breast cancer (18). Flavanones may have anti-atherosclerotic properties. Naringenin may be used for treating dyslipidemia and improving endothelial dysfunctions (19).

Flavonols

Flavonols (3-hydroxylflavones) are the one-subgroup flavonoids, which is the most analyzed for their important antioxidant properties and biological activities. It can be found in mostly in vegetables, fruits and their drinks. Important sources of them are berries, grapes, tomato, apple, onion, red lettuce and broccoli. Also, drinks like black tea, green tea and red wine contain prominent source of flavonols (20). Rutin, quercetin, kaempferol and myricetin are the most known

and important compounds of this subclass (21).

Flavonols may act as antioxidant and protect biomolecules from oxidative damage. Additionally, the presence of aromatic hydrocarbon rings of the flavonoid compound permits exchange electrons from free radicals and suppressing them. Flavonols may be prevent osteoporosis, and they have anti-inflammatory and neuroprotective properties (21).

Rutin (3, 3′, 4′, 5, 7-pentahydroxyflavone-3-rhamnoglucoside) is abundant in different types of plants. It has antibacterial, antiviral, antifungal, anti-allergic, antioxidant, antidiabetic, neuroprotective, anticancer, nephroprotective, anti-angiogenic, antihypertensive and anti-inflammatory activity. Rutin can modulate some signal transduction pathways and improve thyroid functions (22). Most of the biological activities of rutin are related to its aglycone form quercetin.

Quercetin (3, 3′, 4′, 5, 7-pentahydroxyflavone) is the most studied and important flavonol, which has powerful antioxidant properties, protects low-density lipoprotein from oxidation *in vitro* (23). Quercetin frequently found in green tea, apples, red wine, grapes, onions, leafy vegetables and it has poor water solubility. Quercetin is an aglycone, but ordinarily found in plants the form of rutin and rhamnose glycosides (23). Quercetin helps to protect cellular structures and blood vessels from oxidative stress caused by free radicals, which shows antioxidant and anti-inflammatory activity. It strengthens blood vessels and blocks catechol-O-methyltransferase (COMT) activity, which suppress norepinephrine. It may cause thermogenesis with the increased levels of norepinephrine and fat oxidation. Quercetin inhibits inducible nitric oxide synthase (iNOS), xanthine oxidase (XO), lipoxygenase (LOX) and cyclooxygenase (COX) enzymes, decreases leukocyte immobilization, modulate cellular signaling and gene expression (23). In addition, quercetin acts like antihistaminic agent counter allergies and asthma. Other important features are low-density lipoprotein (LDL) reduction and protection from cardiovascular disease, inhibit aldose reductase enzyme and decrease in sorbitol accumulation in nerves, kidneys and eyes in diabetes mellitus, and act like estrogen hormone, which the term called phytoestrogen (19).

Kaempferol (3, 4′, 5, 7-tetrahydroxyflavone) is a flavonols antioxidant substance, which can be found in fruits and vegetables like leek, broccoli, green cabbage, kale, parsley, grapes, spinach, fennel, raspberry and blackberry (24). In several studies, kaempferol has beneficial effects in reducing the risk of chronic diseases. Both kaempferol and its glycosides act as antioxidant *in vitro* and *in vivo* studies (24). Antioxidant effects are related to inhibition of ROS generating enzymes like xanthine oxidase, scavenging hydroxyl radicals for preventing Fenton reaction, inducing antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT) and preventing lipid peroxidation (24). Kaempferol prevents LDL-oxidation, which causes protection against atherosclerosis. It acts as an anti-inflammatory compound by blocking the synthesis of pro-inflammatory chemokines and inhibiting COX, LOX and iNOS enzymes. Kaempferol has been known for modulating crucial elements in signal transduction pathways related to inflammation, metastasis, apoptosis and angiogenesis. It can induce apoptosis, inhibit cancer cell growth, angiogenesis and metastasis, which is confirmed *in vitro* (23). Also, it can inhibit cytochrome P450 enzymes, which prevents the activation of carcinogenic agents (24). Various papers have been reported that, kaempferol and its glycosides have antibacterial, antiviral, antifungal and antiprotozoal activities (24).

Myricetin (3, 3′, 4′, 5, 5′, 7-hexahydroxyflavone) is a natural flavonols, which commonly consumed with human diets like vegetables, fruit teas, red wine and berries. The most known effects are iron-chelating, antioxidant, anti-inflammatory and anticancer properties (25). Various studies have been showed that, myricetin has an activity against DNA polymerases, RNA polymerases, reverse transcriptases, telomerases, kinases and helicases. Myricetin is identified as a cytotoxic compound, which is effect in various cancer types. In addition, it can inhibit important enzymes, which are associated in the initiation and progression of cancer. Various studies have been shown that myricetin can modulate immune response and function by modulating the level of cytokines. Myricetin has been showed anti-inflammatory properties by inhibiting cyclooxygenase-2 (COX-2) and iNOS enzymes and production of pro-inflammatory cytokines (25). Myricetin has been reported as an anti-allergic compound, which may block IgE-mediated histamine release. In addition, myricetin have been shown anti-diabetic, hepatoprotective, neuroprotective, cardioprotective, antimicrobial, analgesic and anti-hypertensive activities *in vitro* or/and *in vivo* (25).

Flavones

Flavones are similar to flavonols structurally, have an extra hydroxyl group at the carbon 3-position. The most known and well-studied flavones are apigenin and luteolin. Flavones are found in vegetables and fruits like onions, parsley, wheat sprouts, tea, oranges, broccoli, celery, carrots, parsley, onion, cabbages, pepper, apple, chamomile, and some spices (26, 27).

Apigenin (4′, 5, 7-trihydroxyflavone) is a primary component of chamomile, which found in parsley, celery, onions, oranges, maize, rice, tea, and wheat sprouts (26). Apigenin has been shown potential strong therapeutic effects against various diseases. Apigenin has significant anti-inflammatory, anti-carcinogenic and antioxidant properties. Apigenin is suggested as a hepatoprotective agent in oxidative stress induced liver damage by regulating multiple genes at higher doses *in vivo* (26). Apigenin chelates metal ions, scavenges free radical and induces phase II enzymes, which takes a part in detoxification (26). Apigenin acts like an anti-carcinogenic agent by inducing apoptosis both *in vitro* and *in vivo*. Apigenin induces autophagy but at the same time, it induces the resistance against chemotherapy (26). Some of apigenin glycosides have been showed antiviral properties. Apigenin shows anti-atherosclerotic effect by preventing LDL oxidation. Apigenin has been showed anti-inflammatory properties by reducing the expression of COX-2, IL-8, and tumor necrosis factor alpha (TNF-α) *in vitro* (26). It also inhibits mitogen-activated protein kinase (MAPK) phosphorylation. Apigenin has been

found effective in rheumatoid arthritis, autoimmune diseases, hemostasis, neurological disorders, and ischemia reperfusion injury. Because of the low toxicity and beneficial effects, it is a popular subject in many diseases (26).

Luteolin (3′, 4′, 5, 7-tetrahydroxyflavone) is found in carrot, pepper, celery, peppermint, thyme, rosemary, oregano, lettuce, artichoke, pomegranate, chocolate, turnip and cucumber (27). Luteolin and luteolin glycosides have antioxidant properties, which scavenge free radicals caused by oxidative damage, chelate metal ions. Also, they inhibit prooxidant enzymes which causes free radical generation and induce antioxidant enzymes both *in vitro* and *in vivo*. Luteolin has anticancer properties. It inhibits cell proliferation, metastasis, angiogenesis, stimulates apoptosis pathways and sensitizes cancer cells (27). Luteolin also pass through blood-brain barrier, which is important for central nervous system diseases (28). It protects DNA, lipids and protein from oxidative damage and increase endogenous antioxidant enzymes, such as glutathione reductase (GR), glutathione-S-transferase (GST) and superoxide dismutase (SOD) (29). Its anti-inflammatory effects come from inhibiting the production of cytokines and their signal transduction pathways. Luteolin and luteolin glycosides have antibacterial, antiviral, and antifungal properties (27).

Anthocyanidins

Anthocyanidins are phytochemical pigments and a subclass of flavonoids, which are responsible for many different colors in plants. Anthocyanidins found in various fruits and vegetables. Anthocyanidins found predominantly in tea, honey, fruits, vegetables, nuts, olive oil, cocoa and cereals, berries and red wine (30). Common anthocyanidins found in fruits and vegetables are cyanidin, pelargonidin, delphinidin, malvidin, petunidin and peonidin, which are having a different number and position of the hydroxyl and methoxyl group substituents (31).

Anthocyanins are glycone form of anthocyanidins, when the addition of carbohydrate residue occurs. Anthocyanidins have showed up as aglycone form, which is structurally based on the flvylium cation having hydroxyl, or methoxyl groups present at different positions of the main structure (32).

Anthocyanidins have antioxidant, anticancer, antibacterial, antidiabetic, cytotoxic, and anti-angiogenic properties. They have therapeutic effects in cardiovascular diseases, certain types of cancer, visual health, diabetes mellitus, obesity, and neurological disorders (31).

Anthocyanidins have higher antioxidant capacity comparing to anthocyanins. Anthocyanins are very unstable and highly reactive which causes the decrease in antioxidant capacity (31). They have protective against TNF-α induced monocyte chemoattractant protein-1 (MCP-1) secretion in endothelial cells. Delphinidin and cyanidin have been found protective against expression of VEGF (vascular endothelial growth factor), which is stimulated by platelet derived growth factor by preventing activation of p38 mitogen-activated protein kinases (p38-MAPK) and c-Jun N-terminal kinase (JNK) in vascular smooth muscle cells (33). Anthocyanins have anticancer activity on esophagus, colon, breast, liver, hematological and prostate cancers. They inhibit cell proliferation, inflammation, angiogenesis and induce apoptosis so they have chemoprophylaxis potential (31). In a study, black rice anthocyanins prevent metastasis in breast cancer cells by targeting MAPK pathway. Antidiabetic properties of anthocyanin and anthocyanidins have been researched intensively. Bilberry anthocyanins have been reported for improving hyperglycemia, insulin sensitivity via activation of adenosine-monophosphate-activated kinase (AMPK) in liver and muscles in type II diabetes (31). Anthocyanidins and anthocyanins are important for maintaining good vision. In several studies suggested an important relationship between improved visual sharpness and anthocyanin consumption. Anthocyanidins enhances rhodopsin regeneration, which causes improvement in visual acuity. Anthocyanidins have antibacterial activity against Gram-negative bacteria but Gram-positive bacteria do not effect from anthocyanins. In addition, anthocyanins have anti-obesity properties, which suppress mRNA levels of the enzymes involved in fatty acid synthesis and triacylglycerol synthesis (31).

Isoflavones

Isoflavones are prominent subclass of flavonoids. Their structure consists of the 3-phenylchromen skeleton via an aryl-migration mechanism. Isoflavones are predominantly present in legumes particularly in soybean. In addition, in green split peas, chickpeas, black beans, lima beans, clover sprouts, and sunflower seeds contain isoflavones (34). The important dietary isoflavones are genistein and daidzein, which found in four chemical structures respectively aglycones, 7-O-glycosides, 6′-O-acetylglycosides, and 6′-O-malonylglycosides (35).

Isoflavones has been found as positive influence on cardiovascular system and menopausal health, even are thought to prevent cancer. They can bind to estrogen receptors, which called beta are essential receptors in the central nervous system (CNS) and as well as in cardiovascular system. Isoflavones bind to the estrogen receptors and can acts as either partial agonist or antagonist, which depends on the environment. It is suggested that a rich diet containing isoflavones has beneficial effects on the hormonal status and regulation of menstrual cycle (36).

Daidzein (7, 4′-dihydroxyisoflavone) inhibits the class I isoenzymes of human alcohol dehydrogenase (ADH) and the human mitochondrial aldehyde dehydrogenase (ALDH-2) which takes a part in alcohol metabolism in humans. It has anti-inflammatory properties, which inhibits iNOS enzyme by inhibiting the transcription factors of STAT1 (signal transducer and activator of transcription 1) and NF-κB (37).

Genistein (4′, 5, 7-trihydroxyisoflavone) is a potential therapeutic agent for treating or preventing various cancer. It may show anabolic effect on bone, directly to osteoblasts and prevent bone density loss (34). Genistein intake has been linked with decreased body mass index (BMI), weight, total body fat mass and body measurements (34). Genistein has anti-inflammatory properties as the same pathway in daidzein, by inhibiting STAT1 and NF-κB

Table 1. Some flavonoid content in foods (FW: fresh weight).

	Foods	Content (mg 100g-1 FW or mg 100mL-1)	References
FLAVANOLS			
Catechin Epicatechin	Chocolate Beans Apricot Cherry Grape Peach Blackberry Apple Kiwi Green tea Black tea Red wine Cider	23,0-30,5 17,5-22,5 5,0-12,5 2,5-11,0 1,5-8,7 2,5-14,0 13,0 1,0-6,0 0,4 5,0-40,0 3,0-25,0 8,0-30,0 2,0	(2), (39), (40)
FLAVANONES			
Naringenin	Grapefruit juice, fresh Lemon juice, fresh Orange juice, fresh Orange, raw Pomelo juice, fresh	5,0-32,5 1,4 2,1-15,0 15,3 25,3	(2), (41)
FLOVONOLS			
Quercetin	Red leaf lettuce Asparagus Romaine lettuce Onion Green pepper Asuparana Cherry tomato Podded pea Tomato Broccoli Cherry Green tea Black tea Apple peel Red wine Spinach, raw Cocoa powder, unsweetened	10,3-30,6 23,6 12,0 11,0-41,9 / 149,0 9,9-14,7 4,3 3,3 1,7 1.6 1.6-3.2 0,5-1,2 / 3,3 2,1 1,9-2,5 2,3-2,7 / 2,2 0,9 4,9 20,1	(2), (39), (40), (41) (42), (9)
FLAVONS			
Apigenin	Celery Chili peppers, raw Thyme, fresh Peppermint, fresh Parsley, fresh	1,0-7,0 / 19,1 5,0-10,0 / 1,4 2,5 5,4 215,5	(2), (41)
ANTHOCYANIDINS			
Cyanidin	Blackberries Blood orange juice Blueberries, raw Currants, black, raw Elderberries, raw Grapes, red Red Onions, raw Plums, raw Raspberries, raw Red cabbage, raw	100,0-400,0 5,5 8,5 / 25,0-500,0 62,5/130,0-400,0 485,5 1,2 3,2 5,6 / 1,0-7,5 45,8 209,8	(2), (41)
ISOFLAVONES			
Genistein	Natto Soybeans Soymilk	37,7 81,0 1,5-8,5	(2), (41)

(37). In addition, genistein inhibits various enzymes like protein tyrosine kinase and topoisomerase II. It induces apoptosis and cellular differentiation, inhibits cell proliferation. It has antioxidant, anti-angiogenic, estrogenic, osteoclastic and immunosuppressive activity (38).

CONTENT OF FLAVONOIDS IN PLANTS

The main dietary sources of flavonoids are tea, citrus fruits and their juices, berries, wine, apples, vegetables and their juices and legumes (2). Intake of certain flavonoids may vary depending on the diet. Some flavonoid content in different foods is mentioned below (Table 1). These values have to be considered as estimated value, many factors may affect the flavonoid content of foods including agricultural practices, environmental conditions, ripening, storage and food processing (2).

FLAVONOID-DRUG INTERACTIONS

Flavonoids are known to modulate different cytochrome P450 enzymes such as CYP1A1/1A2, CYP1B1, CYP2C9, and CYP3A4/3A5 (43). The most studied flavonoid-drug interactions are the interactions with the CYP3A4. There are various studies about that, flavonoids can modulate drug metabolism; by changing the expression and/or activity of cytochrome P450 enzymes. There are various studies about that, flavonoids can modulate drug metabolism; by changing the expression and/or activity of cytochrome P450 enzymes which play a pivotal role in herb-drug pharmacokinetic interactions (44, 45).

Enormous or supplementary intakes of flavonoids may increase the toxicity of drugs, which are substrate of P-glycoprotein. Some antineoplastic and antifungal drugs, HIV protease inhibitors, immunosuppressive agents, H_2-receptor antagonists, antibiotics, anti-hypertensive agents and antiarrhythmic agents are substrate for P-glycoprotein (46). Some flavonoids inhibit breast cancer resistant protein (BCRP) mediated transport. Some antineoplastic drugs, antibiotics and β-blockers may cause inhibition of BCRP (46). Some other flavonoids are reported for inhibiting multidrug resistance protein (MRP) and they potentially affect MRP-mediated transport (47). Many antineoplastic drugs are associated with MRP-mediated transport (47). Flavonoids may increase the risk of bleeding when they co-administered anticoagulant, antiplatelet and non-steroid antiinflammatory drugs (NSAID) (48).

Quercetin, kaempferol and myricetin inhibit CYP3A4 *in vitro*. Prolonged exposure to quercetin lead to increase CYP3A4 mRNA expression in cell culture models (43). St. John's Wort extract, which is rich by the flavonol quercetin and non-phenolic hyperforin, induces CYP3A4 and CYP2C9. Kaempferol and quercetin may inhibit intestinal uridine 5′-diphospho-glucuronosyltransferase (UGT) *in vitro*. That action may cause to increase in the bioavailability of several drugs. Apigenin and luteolin have an inhibitory effect on CYP3A4 *in vitro*. They may cause increased level of drugs, which are transformed by CYP3A4. In various studies, the flavonols catechin and epigallocatechin mentioned about the inhibitory effect on CYP3A4 both *in vitro* and *in vivo*, but the mechanism hasn't been suggested (43). The flavanone glycoside naringin, which is abundant in grapefruit juice, has a well-known inhibitory effect on CYP3A4. The isoflavones genistein and daidzein may inhibit or induce CYP3A4. Conflicting data has been observed in some works *in vitro* and *in vivo*. Soy isoflavones administration cause the inhibition of CYP3A4, but administration of genistein causes modest induction of different CYP3A enzymes in healthy people (43). Isoflavones show both estrogenic/anti-estrogenic activities, which may cause the inhibition of CYP19 (aromatase) (49). Also, the isoflavone biochanin A was shown to reduce the bioavailability of tamoxifen-a substrate of P-glycoprotein and cytochrome 3A-and its metabolite 4-hydroxytamoxifen in experimental studies (50).

CONCLUSION

As a result, flavonoids have been found effective in different *in vitro* studies. They are extensively metabolized to their metabolites and eliminated in different ways from the organism. The complex pharmacological properties of distinct flavonoids, and their expected *in vivo* efficacy may be suspicious. Further research is necessary to understand the benefits of flavonoid intake as diet/supplement and enlighten the various health effects of flavonoids. In addition, it is important to note that the content of flavonoids in plants may vary according to the geography of the country, the components of the soil and the climate.

Flavonoids and their metabolites in the organism may cause flavonoid-drug interaction, and it may lead to drug toxicity or cause inefficiency in therapeutic effects of the drug. Enzyme induction may lead to loss of the therapeutic effect of the drug and failure of the treatment. Enzyme inhibition may cause the increase of side effects and may lead to drug toxicity. Therefore, the patients who have chronic diseases and are on a drug therapy should be careful about consuming herbal flavonoid products and/or flavonoid supplements to avoid flavonoid-drug interactions. At the same time, regarding the safety, ability, and various therapeutic effects of flavonoids: these are likely to have potential roles in prevention and therapy of chronic diseases. However, additional extensive clinical research on flavonoids is necessary.

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