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Review Article

Natural flavonoids: classification, potential role, and application of flavonoid analogues

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ABSTRACT

Nowadays, it is assumed that natural flavonoids occurring in fruits and plant derived-foods are relevant, not only for organoleptic properties or technological reasons, but also because of their potential health-promoting effects, as suggested by the available experimental and epidemiological studies. This large group of phenolic plant constituents can be divided into several classes: flavanols, flavanones, flavonols, isoflavones, flavones and anthocyanins depending on the differences in their structures.The beneficial biological effects are also attributed to flavonoid analogues and their metal complexes. These compounds are characterized by antioxidant, pharmacological, anti-inflammatory, anti-allergic, antiviral, anticarcinogenic, as well as therapeutic and cytotoxic properties. Furthermore, they possess a wide range of applications including various fields of industry.

Keywords: Flavonoids; Flavonoid analogues; Application; Properties; Medicine.

1. INTRODUCTION

For many years, increasing attention is paid to the presence of bioactive compounds in the diet favorably affecting the human body [1]. Biologically active substances contained in the food considerably reduce the risk of lifestyle diseases (diabetes, arteriosclerosis, cataracts, Alzheimer's disease, Parkinson's disease) [2]. These substances include polyphenolic compounds, which are characterized by high antioxidant activity, and hence antiviral, anti-inflammatory and anticancer [3]. Polyphenols are substances commonly found in plants and belong to the basic elements of the diet. One of the most famous groups of polyphenols are flavonoids [4, 5]. These compounds are mainly accumulated in the edible parts of plants, particularly in fruits and vegetables. Flavonoids are responsible for red and dark blue color of berries, as well as orange and yellow coloring citrus fruits. In the human body they play a similar role as vitamins [6, 7].

Flavonoids with biological activity are often called bioflavonoids. They possess the ability to capture superoxide, hydroxyl and lipid radicals [8]. Flavonoids have a long history of medicinal use, mainly for support of healthy capillary and blood vessel function. They are marketed as anti-inflammatory and anti-spasmodic remedies [9]. What is more, flavonoid analogues and their metal complexes play a significant role in agriculture, industrial and pharmaceutical chemistry [10].

Flavonoids are divided to several subgroups, and it is important and should be mentioned that the biological and chemical properties of flavonoids

belonging to different subgroups can be quite different [11].

This review will present the most important and valuable properties of natural flavonoids and its analogues, namely: antioxidant, pharmacological, anti-inflammatory, anti-allergic, antiviral, anti-carcinogenic, as well as therapeutic and cytotoxic properties. What is more, the most noteworthy applications of flavonoids will be also included. These applications will contain various branches of industry, including agriculture, skin protection, potential clinical applications, as well as prospects for the metabolic engineering of bioactive flavonoids.

2. FLAVONOIDS AND ITS POTENTIAL ROLE

2.1. Classification and structure

Flavonoids belong to a large group of phenolic plant constituents [11]. They are presented as derivatives of 2-phenyl-benzo-γ-pyrone. The carbon atoms in flavonoid molecules are assembled in two benzene rings, commonly denoted as A and B, which are connected by an oxygen containing pyrene ring (C). A common part in the chemical structure of all flavonoids is carbon skeleton based on flavan system (C_6-C_3-C_6) (Fig. 1) [12]. Condensation of A and B ring leads to the formation of chalcone, which undergoes cyclization involving isomerase and formed flavanone - initial compound for the synthesis of flavonoids other groups.

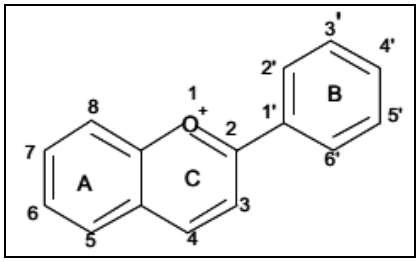


Figure 1. The structure of flavylium cation.

Due to the differences in the structure of flavonoid compounds, flavonoids are classified as flavanols, flavanones, flavonols, isoflavones, flavones and anthocyanins (Fig. 2). Among other flavonoid compounds can be also included compounds such as biflavonoids (e.g. ginkgetin), prenylflavonoids, flavonolignans (e.g. silybin), glycosidic ester flavonoids,chalcones and proanthocyanins [13].

2.2. Flavanols

Flavanols constitute a greatly complex group of polyphenols in the range from the monomeric flavan-3-ols (e.g. catechin, epicatechin, gallocatechin) to polymeric procyanidins known as condensed tannins [14]. Flavanols mainly occur in fruits and derived products, for example fruit juices or jams. This group also appears in tea, red wine, cocoa, apples, kiwi and cereals. However, they almost do not exist in vegetables and legumes except lentils and broad beans. Flavanols can be found in peels or seeds of fruits and vegetables as well, which are often removed during eating or processing, therefore their intake is also limited [15].

It is confirmed that flavanols can stimulate the levels of nitric oxide in the blood of smokers and reverse some of their smoking-related impairment in blood vessel function. Researchers from Germany have shown significant increases in circulating nitric oxide and flow-mediated dilation after ingestion of drinks containing 176-185 milligrams of flavanols (dose potentially exerting maximal effects). These changes are correlated with growth in flavanol metabolites. Dr. Heissfrom American College of Cardiology strongly believed that chronic consumption of flavanol-rich foods leads to sustained increases in endothelial function or the prevention of future cardiovascular ailments [16].
Catechin is the most important representative of the group of flavanols. Catechins are known as the major building blocks of tannins. These compounds may be found in the seeds and skins of fruits which are not fully ripened. Several types of catechins can be distinguished: catechin, gallocatechin, catechin 3-gallate, gallocatechin 3-gallate, epicatechin, epigallocatechin, epicatechin 3-gallate, epigallocatechin 3-gallate (Fig. 3). The main sources of catechin are green and black tea, red wine, chocolate, apricot, apples, peach, red raspberry, and blackberry [17].

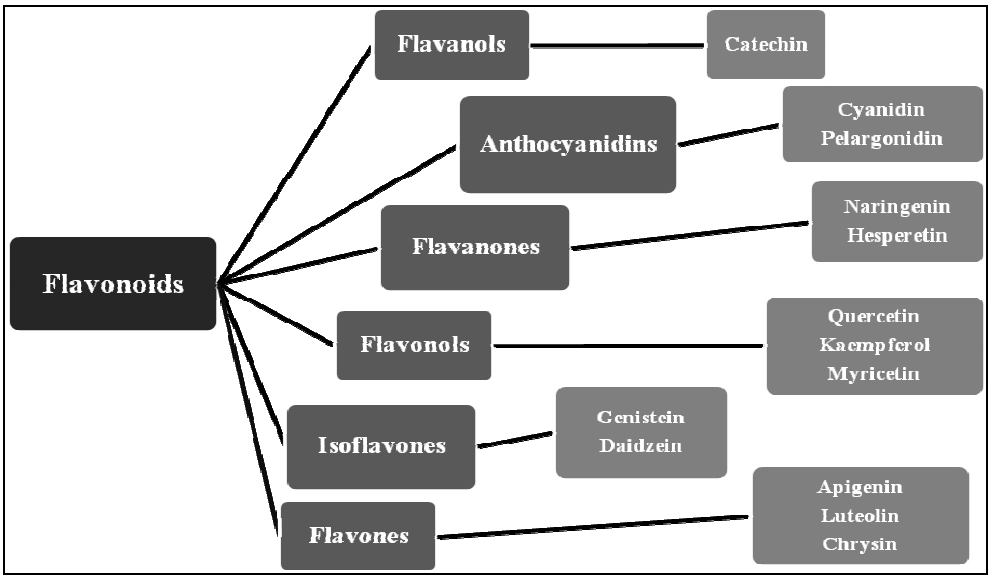


Figure 2. Distribution of flavonoids commonly occurring in plants.

Catechin prevents protein oxidation by its free radical scavenging capacity. Furthermore, it possesses ability to reduce covalent modification of protein induced by ROS or by-products of oxidative stress [18].

Additionally, catechin exhibits anti-atherosclerotic properties. It has been shown the inhibition of the oxidation of low-density lipoprotein (LDL), endothelin reduction and block the platelet aggregation [19, 20]. Catechins have also revealed anti-carcinogenic activity. Epigallocatechin 3-gallate may inhibit urokinase which is u-plasminogen activator. This enzyme is often expressed in human cancer cells. Catechins can restrain cell proliferation and induce apoptosis, as well as modulate and inhibit the NFKB activity [17].

Likewise, catechin polyphenol seems to be an effective promoter of thermogenesis [21]. Furthermore, catechin and epicatechincan act as enzymes. They also play a crucial role in defense against pathogens of tea. [22]. In turn, green tea catechins have been presented to possess antibiotic effects because of their function in disrupt during the bacterial DNA replication process [23]. Black tea catechins have antidiabetic properties. It is well-known that black tea have the highest α-amylase and α-glucosidase inhibitory activity [24]. It has been also suggested that catechin causes the increase of insulin activity, but there is no evidence enough to confirm this state [25].

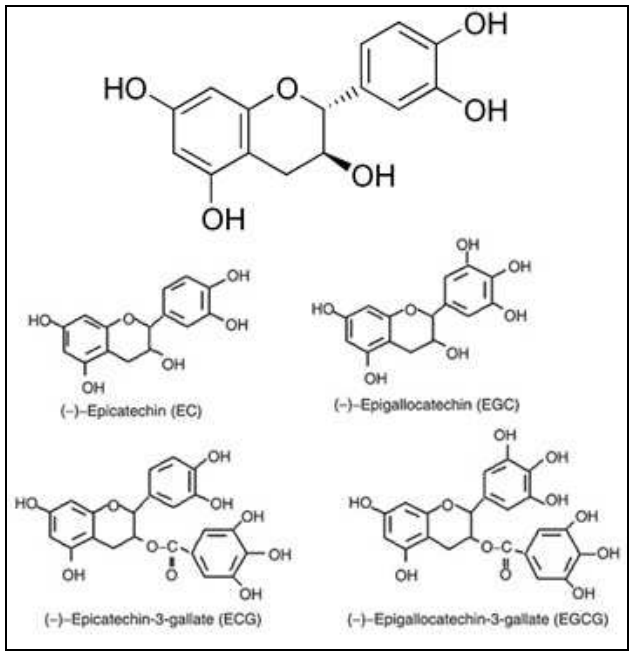


Figure 3. Chemical structure of green tea catechin.

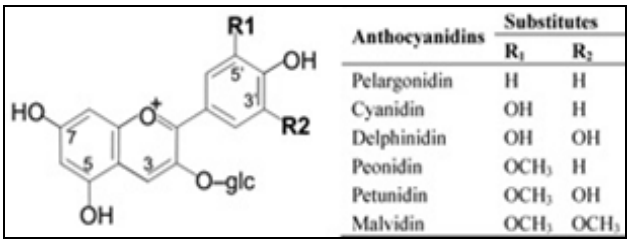
2.3. Anthocyanidins

Anthocyanidins are a group of phyto-chemicals, as natural pigments are responsible for blue, red, purple and orange colors present in many fruits and vegetables, as well as in many fruit- and vegetable-based food products. Over and above 500 different anthocyanidins are known and have been described in literature [14, 26]. This flavonoid group dominates in teas, honey, fruits, vegetables, nuts, olive oil, cocoa and cereals. They can be also found in berries (e.g. black currant, blueberries,

strawberries, elderberries), their juices, as well as red wine [27].

Anthocyanidins have appeared as aglycone form which is structurally based on the flavylium or 2-phenylbenzopyrilium cation possessing hydroxyl and methoxyl groups present at different positions of the basic structure [28].

The most common anthocyanidins occurring in fruits and vegetables are: cyanidin, pelargonidin, delphinidin, malvidin, petunidin and peonidin. These compounds depend on the number and position of the hydroxyl and methoxyl groups as substituents (Fig. 4) [29].



Anthocyanidins	Substitutes	
	R_1	R_2
Pelargonidin	H	H
Cyanidin	OH	H
Delphinidin	OH	OH
Peonidin	OCH_3	H
Petunidin	OCH_3	OH
Malvidin	OCH_3	OCH_3

Figure 4. Structures of the most well-known anthocyanidins in plant-derived foods.

Anthocyanidins have been revealed to play an essential role in cardiovascular disease, cholesterol decomposition, visual acuity, as well as antioxidant efficacy, and cytotoxicity [30].

Anthocyanidins are able to act on different cells participating in the development of atherosclerosis. These compounds have been demonstrated to have protective effect against TNF-α induced MCP-1 (chemokine monocyte chemotactic protein 1) excretion in primary human endothelial cells. MCP-1 is one of the direct reasons of atherogenesis [31]. Anthocyanidins, mainly delphinidin and cyanidin have been proved to prevent expression of vascular endothelial growth factor (VEGF), which is stimulated by platelet derived growth factor in vascular smooth muscle cells by preventing activation of p38 mitogen-activated protein kinases (p38 MAPK) and c-Jun N-terminal kinase (JNK) [32].

Edible berries are supposed to have anti-angiogenic properties. Angiogenesis is a term used to describe formation of new blood vessels. It is especially undesirable in situations including tumor formation or varicose veins due to the fact that it provides food for tumor growth and cancer metastases [33].

It should be mentioned that anthocyanidins possess influence on cholesterol distribution through protection of endothelial cells from CD40-induced proinflammatory signalling [34].

Many studies strongly suggested a significant relationship between improved visual acuity with anthocyanin consumption. Particular attention should be paid to enhancement of rhodopsin regeneration by which anthocyanidins enhance visual acuity. The greatest effects are assigned to compounds from black currant [35].

Furthermore, it has been demonstrated that addition of bilberry anthocyanidins is able to dissolve the toxic intermediates and fibrils, and, thus the toxicity of the intermediates was hence neutralized [36].

Principal therapeutic benefits attributable to anthocyanidins include antioxidant protection. Free radicals damage lipids and proteins and menace DNA integrity. Antioxidants are intense scavengers of free radicals and correspond to inhibition of neoplastic processes. Anthocyanidins protect DNA integrity and bolster tissue antioxidant levels [30].

2.4. Flavanones

Flavanones are extensively disseminated in around 42 larger plant families, especially in *Compositae*, *Leguminosae* and *Rutaceae*. Depending on the type of plants, flavanones can be discovered in all parts of plants - above and below ground, from vegetative part to generative organs: branches, bark, stem, leaves, roots, flowers, fruits, seeds, rhizomes, peels etc. Due to the high spread of flavanones in foods, naringenin and hesperetin-aglycones (Fig. 5) seem to be of particular interest [37]. Hesperetin (4'-methoxy-5,7,3'-trihydroxy-flavanone) is distinctive flavanone of lemon, orange, lime and tangelo [38]. Naringenin (5,7,4'-trihydroxyflavanone) can be found in grapefruit and sour orange. Tomatoes and their products are also rich in this flavonoid. Naringenin can be described both as aglycone or glycosides [39].

Flavanones belong to the flavonoid compounds frequently found in the plant world, constituting the daily human diet, as well as medicinal plant materials [41]. The main directions

of the pharmacological activity of flavanones are: radical scavenging, anti-inflammatory, anticancer, cardiovascular, and antiviral effects [37].

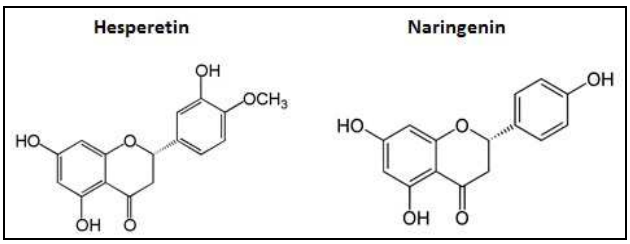


Figure 5. Structure of flavanones in the aglycone forms.

The antioxidant activity of flavanones depends on the number and spatial location of phenolic OH groups. Flavanones show a higher antioxidant activity in a hydrophilic environment. This environment causes the reduction of antioxidant potential by some flavanones (hesperetin, neohesperidin) while others (narirutin, naringin, naringenin) become pro-oxidant. Generally, widespread dietary flavanones which do not possess catechol nucleus are classified as weak antioxidants and their metabolites are supposed to be even less strong. Thereby, the most meaningful mechanisms involved in their health effects must be unrelated to their antioxidant activity [42].

Naringenin flavanones are very efficient in inhibition of pro-inflammatory cytokines induced by lipopolysaccharide in macrophages and reduced production of nitrate and nitrite which are indicators of inflammatory process to control the formation of intestinal edema [43, 44].

Flavanones have not been extensively studied for their anticancer properties. However, the major citrus flavanones may have potential in working against carcinogenesis by minimizing DNA damage, tumor proliferation and development [45]. Flavanones, mainly naringenin, show antimutagenic activity manifested in the protection against DNA damage by their capacity to absorb UV light. The moderate antioxidant capacity of flavanones is found helpful in protecting against mutation by free radicals generated nearly DNA. It is confirmed that naringenin participates in presenting antimutagenic changes by stimulating DNA repair, following oxidative damage in human prostate cancer cells [46]. The pharmacological importance of flavanones may also be estimated by their effect against tumor development. It is confirmed the influence of hesperetin and naringenin on the development of breast cancer induced by 7,12-dimethylbenz-anthracene in female rats [47]. Furthermore, flavanones present an important antiproliferative activity against prostate, breast, colon, lung and melanoma cancerous cell lines [48].

Flavanones are believed to have anti-atherosclerosis potential. The studies demonstrated the reduction of atherosclerosis in mice fed with high fat-high cholesterol diet using naringenin supplementation at nutritionally relevant level. This result could be exerted to improve dyslipidemia and biomarkers of endothelial dysfunction, as well as changes in gene expression. Thus, flavanones may prevent from cardiovascular disease [49].

2.5. Flavonols

Flavonols (3-hydroxyflavones) are one the most analyzed subgroup of flavonoids due to the importance referring to their antioxidant properties and other biological activities. This class of polyphenolic phytochemicals occurs in commonly consumed vegetables, fruits and plant based beverages. Major sources of these compounds are part of grape berries, apple, tomato, onion, broccoli and red lettuce. In addition to fruits and vegetables, beverages such as green tea, black tea and red wine constitute also a significant source of flavonols [50]. Among major flavonols can be distinguished quercetin, kaempferol or myricetin. The structures of the most common flavonol aglycones are presented below (Fig. 6) [51].

Flavonols ensure plentiful health benefits. For instance, the intake of flavonols in increased quantities is related to reduced risk of cardiovascular diseases. This can imputed to their antioxidant properties which have been of interest for considerable time [51].

The efficacy of flavonols as antioxidant agents mostly depends on their chemical structure. There are three structural attributes constituting the most significant determinants: the catechol structure in the B ring, which is a radical target site; the 2,3-double bond in conjugation with a 4-keto function, which are responsible for electron delocalization from the B ring and the additional presence

of both 3- and 5-hydroxyl groups for maximal radical-scavenging potential and strongest radical absorption [50].

Antioxidant activity of flavonols may protect against oxidative damage to cells, lipids or DNA. Furthermore, these properties are the result of the presence of aromatic rings of the flavonoid molecule, which permit the donation and acceptance of electrons from free radical species. This aids in suppressing free radicals. Moreover, the consumption of flavonols is connected with reduced risk of stroke and cancer. Additionally, some of these compounds are believed to prevent osteoporosis and possess anti-inflammatory or neuroprotective properties [51].

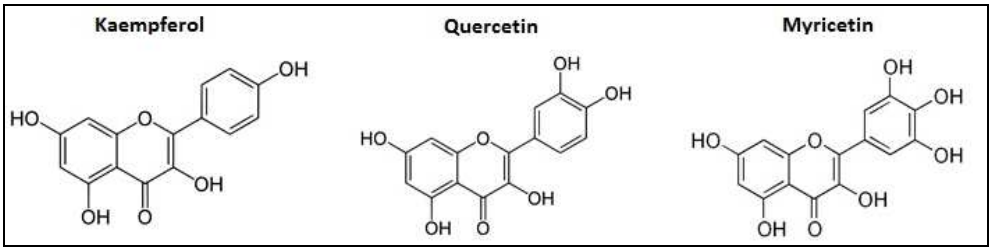


Figure 6. Structures of the major flavonol aglycones.

Quercetin is the major representative of the flavonol subclass which as powerful antioxidant prevents from oxidation of low density lipoproteins in vitro. It is a water-soluble plant pigment commonly found in green tea, red wine, apples, onions, leafy vegetables. Quercetin protects cellular structures and blood vessels from the damaging effects of free radicals (antioxidant and anti-inflammatory activity). What is more, this flavonol improves blood vessel strength and stems the activity of catechol-O-methyltransferase that suppress the neurotransmitter norepinephrine. This action may lead to elevated levels of norepinephrine, thermogenesis, and fat oxidation. Furthermore, quercetin acts as antihistamine agent preventing from allergies or asthma. Antioxidant properties of quercetin have evinced in LDL cholesterol reduction and heart disease protection. It can also block an enzyme resulting in sorbitol accumulation which has been associated with nerve, kidney or eye damage in diabetics. Quercetin may protect against cataract formation. It could be also examined as phytoestrogen [11].

Kaempferol is a flavonol antioxidant occurring in fruits and vegetables, mainly in broccoli. Many studies have presented the advantageous effects of dietary kaempferol in decreasing the risk of chronic diseases, particularly cancer. Furthermore, it can strengthen the antioxidant defense against free radicals, which support the cancer development. Kaempferol has been investigated to modulate a number of key elements in cellular signal transduction pathways related to angiogenesis, apoptosis, metastasis, and inflammation. It is confirmed that kaempferol meaningfully inhibits cancer cell growth and angiogenesis, as well as generates cancer cell apoptosis. However, this flavonol seems to maintain normal cell viability, usually exerting a protective effect [52].

Myricetin is succeeding natural flavonol, commonly consumed through human diets such as vegetables, fruits tea, red wine, and berries. Significantly, myricetin may ameliorate insulin resistance. In addition, this flavonol performs activity including antioxidative stress, anti-non-enzymatic glycation, anti-hyperlipidemia, anti-inflammation, anti-aldose reductase [53]. Myricetin appears to be an effective agent to quit smoking [54].

2.6. Isoflavones

Isoflavones are distinctive and very important subclass of flavonoid compounds. Their structures constitute the 3-phenylchromen skeleton which is chemically derived from the 2-phenylchromen skeleton by an aryl-migration mechanism. Isoflavones are mostly found in legumes, especially in soy. However, their presence has been also

reported in green split peas, split peas, chickpeas, black beans, lima beans, clover sprouts, and sunflower seeds. Furthermore, these compounds are included in the composition of several foods, vegetarian formulations, soy products in infant foods etc. [55]. The major isoflavones in human diet are genistein and daidzein (Fig. 7), which exist in four related chemical structures, namely aglycones, the 7-O-glucosides, the 6'-O-acetylglucosides and the 6'-O-malonylglucosides [56].

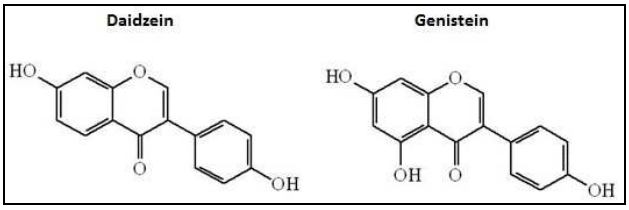


Figure 7. Chemical structures of major isoflavones.

Isoflavone compounds appear to possess effects on cardiovascular and menopausal health, and even are able to prevent cancer. They are considered as natural products that may be salutary to postmenopausal women in cardiovascular health. Furthermore, isoflavones are supposed to be responsible for the lipid lowering effects. They can also simply bind estrogen receptors - beta which are essential receptors in the central nervous, as well as cardiovascular systems. Isoflavones may also have antioxidant effects on blood vessels [57].

Soy isoflavones are promising dietary supplements for prevention of breast cancer. Isoflavones connect estrogen receptors (ER) and can variably work as either estrogen agonists or antagonists which depends on estrogen environment. It has been reported that the highest isoflavone dose brought to significantly lower breast proliferation and uterine size in the high-estrogen environment. Moreover, demographic and epidemiologic studies demonstrate that high dietary intake of soy isoflavones can reduce breast cancer risk [58].

Isoflavones, often determined as dietary phytoestrogens are used as food additives to preclude menopause-related disorders [56]. It is confirmed that diet containing soy protein rich in isoflavones has influence on the hormonal status and regulation of the menstrual cycle [59].

One of the major isoflavone - daidzein inhibits the class I isoenzymes of human alcohol dehydrogenase (ADH) and the human mitochondrial aldehyde dehydrogenase (ALDH-2), which may extinguish alcohol consumption in humans. Furthermore, daidzein shows antioxidant effect [60]. Another well-known isoflavone, genistein is a potential chemopreventive (therapeutic) agent in the treatment or prevention of various kinds of cancer. Genistein is supposed to possess an anabolic effect on bone by acting directly on osteoblasts, and prevent bone loss [61, 62]. Furthermore, genistein intake has been connected with decreased BMI, waist circumference, weight, and total body fat mass in postmenopausal women [63].

2.7. Flavones

Flavones are very similar structurally to flavonol compounds, having an extra hydroxyl substitution at the carbon 3-position. The major flavones are included apigenin and luteolin (Fig. 8). Luteolin occurs in vegetables and fruits such as broccoli, celery, carrots, parsley, onion leaves, cabbages, peppers, chrysanthemum flowers, and apple skins [64]. While apigenin can be found in onions, parsley, wheat sprouts, tea, oranges, chamomile, and in some seasonings [65].

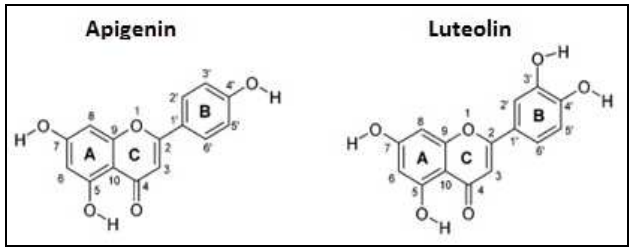


Figure 8. The major structures of flavones.

Apigenin is a principal component of chamomile, which is responsible for antibacterial, antiphlogistic, and antispasmodic effects. Recently, apigenin has captured the interest as beneficial and health promoting agent because of its low internal toxicity and differential results in normal against cancer cells relative to other structurally related flavonoids. It has been reported that apigenin possesses prominent anti-inflammatory, anti-carcinogenic and antioxidant properties. Apigenin

has been demonstrated to inhibit benzo[a]pyrene and 2-aminoanthracene-induced bacterial mutagenesis [65]. Furthermore, the studies have proved that apigenin supports metal chelation, scavenges free radicals and stimulates phase II detoxification enzymes in cell culture and in *in vivo* tumor models. Apigenin may act as severe inhibitor of ornithine decarboxylase, an enzyme playing an essential role in tumor promotion. The anti-carcinogenic effects of this flavone is indicated in a skin carcinogenesis model [67].

Plants rich in luteolin have been used as Chinese traditional medicine for hypertension, inflammatory diseases, and cancer treatment. Luteolin possesses multiple biological effects such as anticancer, anti-allergy, and anti-inflammation [68]. Thus, luteolin behaves as either antioxidant or prooxidant biochemically [69]. These biological effects can be related to each other, for example the anti-inflammatory properties are associated with its anticancer activity. Its anticancer properties are related to the induction of apoptosis, including DNA damage, redox regulation and protein kinases, inhibition of cell metastasis, proliferation, and angiogenesis. Furthermore, luteolin may sensitize diversity of cancer cells to therapeutically induced cytotoxicity through damping cell survival pathways and stimulating apoptosis pathways. Luteolin is also called blood-brain barrier permeable. This statement makes it suitable to the therapy of central nerve system diseases, including brain cancer [68]. Additionally, luteolin is examined as antioxidant - it has been reported that luteolin is able to inhibit ROS-induced damage of lipids, protein and DNA. Luteolin may show its antioxidant properties through protecting or extending endogenous antioxidants such as: glutathione reductase, glutathione-S-transferase, superoxide dismutase [69]. Luteolin presents its anti-inflammatory effect by damping the production of these cytokines and their signal transduction pathways [64].

3. FLAVONOID ANALOGUES - ITS BIOLOGICAL ACTIVITY AND HEALTH EFFECTS

Many studies have reported that flavonoid analogues possess plentiful intrinsic properties for human being, supposing even more than flavonoids. The examples of the most important flavonoid derivatives are shown below.

The most extensively distributed glycosides of hesperetin are hesperidin and neohesperidin (Fig. 9). Hesperidin (hesperetin-7-rutinoside) occurs in higher contents in sweet oranges, lemons, limes, tangerine and tangor species of citrus fruits, while neohesperidin (hesperetin-7-neohesperidoside) is present in tangelo and sour orange. Hesperetin glycosides are more predominant in nature than the aglycone form [38].

The most abundant naringenin glycosides are naringin and narirutin (Fig. 10). Naringin (naringenin-7-neohesperidoside) gives bitter taste because of its glucose moiety. Naringin mostly occurs in grapefruits and sour oranges. Another greater naringenin glycoside is narirutin (naringenin-7-rutinoside) which is detected in higher levels in tangerine, tangor, tangelo and sweet orange [39].

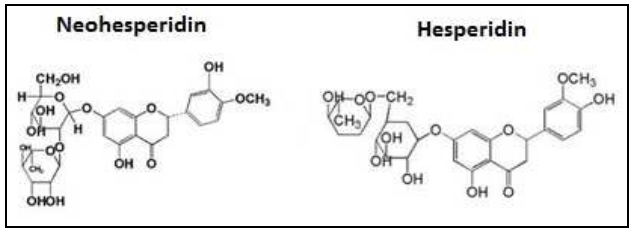


Figure 9. Structure of hesperetin derivatives - glucoside forms: neohesperidin (neohesperidoside) and hesperidin (rutinoside).

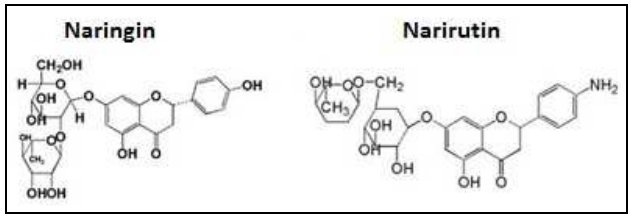


Figure 10. Structure of naringenin derivatives - glucoside forms: naringin (neohesperidoside) and narirutin (rutinoside).

Inflammation is the most obvious diagnostic of immune defense. The most common symptoms are: pain, swelling, and redness in the affected tissues [70]. Due to a dysfunctioning of the immune response many chronic diseases are noticed in human populations. It is believed that hesperidin is able to inhibit kinases and phosphodiesterases which

are responsible for cellular signal transduction and activation over an inflammation response. Hesperidin is considered as gently anti-inflammatory agent because of the reduction in the volume of exudates and the number of migrating leucocytes by 48% and 34%, respectively [71]. Furthermore, hesperidin is supposed to decrease yeast-induced hyperthermia in rats and inhibit lipopolysaccharide-induced overexpression of cyclooxygenase-2, inducible nitric oxide synthase, overproduction of prostaglandin E2, and nitric oxide [72, 73]. In addition, it has been also demonstrated the antiviral activity of hesperidin against parainfluenza, polio, herpes simples,and syncytial viral infections [74].

The main directions of pharmacological activity of naringenin derivatives include: estrogenic activity, cholesterol-lowering properties, anti-inflammatory, antiulcer, antispasmodic, and anticancerogenic activity. In contrast, the prenylated derivatives of naringenin (6-PIN and 8-PN), present in hops and beer, revealed antioxidant properties [41].

Anthocyanins are classified as anthocyanidin derivatives. Anthocyanins are glycosylated polyhydroxy and polymethoxy derivatives of flavilium salts and are members of the flavonoid family, possessing a characteristic C_3-C_6-C_3 carbon structure [28]. Anthocyanin pigments are supposed to be used in folk medicine all over the world. For instance, bilberry anthocyanins have been exploited in the treatment of microbial infections, diarrhea or vision disorders for many years. In recent years, studies have shown the particular properties of isolated anthocyanin pigments. Some reports indicate that anthocyanin activity is getting up when delivered in mixtures, in contrast to isolates [75]. Studies have presented that dietary supplementation with berries rich in anthocyanins were efficient in reducing oxidative stress [30]. It is confirmed that anthocyanin extracts from bilberry, chokeberry and elderberry have exhibited endothelium-dependent relaxation capacity in porcine coronary arteries [76]. Furthermore, chronic intake of anthocyanins increased cardiac glutathione concentrations in rats [77].

Another examples of natural flavonoid analogues are few 7-hydroxy-8-formylchromones (A) and their partially hydrogenated derivatives, lavinal (B), and 4,7-dihydroxy-6-methyl-5-methoxy-8-formylflavan (C) which have been discovered by large class of natural flavonoids (Fig. 11) [78]. These first two compounds protrude together in plants of the family Annonaceae, like *Desmoschinensis*, *Desmoscochinchinensis*, *Dasymaschalonrostratum*, and *Unonalawii*. The last one can be found in roots of *Desmoscochinchinensis*. The composition of these three flavonoids isolated from *D. cochinchinensis* showed antimalarial activity while lavinal itself was seen as virtual AIDS agent.Moreover, the analogs obtained through the synthesis of compounds similar to angular α-pyrono[2,3-*f*]chromones are very promising that they have activity against *S. aureus* and *E. coli* [78]. On the other hand, Lewis and Shaw in their study shows that either leucocyanidin as natural flavonoid or its hydroxyethylated and tetraallyl derivatives are able to protect the gastric mucosa against aspirin challenge. Furthermore, leucocyanidin and its synthetic analogues significantly increased mucus thickness [79]. Additionally, Verghese et al. presented that flavone-based analogues obtained from complex natural product simocyclinone D8 can inhibit DNA gyrase, and may act as topoisomerase poisons and DNA intercalators [80].

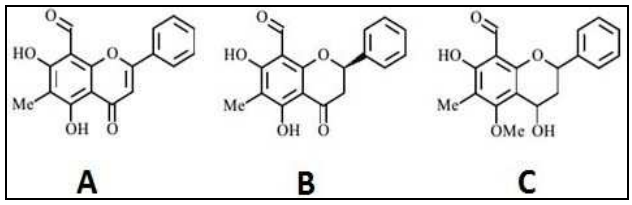


Figure 11. Analogues of natural flavonoids.

Silybin and its analogues have been reported as chemopreventive agents for certain cancers. They are also able to fast repair DNA bases from oxidative damage by pulse radiolysis method. Moreover, silybin and its analogues preserve DNA from radiation damage at micromolar concentrations [81].

Synthesized a novel series of N1-(flavon-7-yl)amidrazones incorporating N-piperazines and related congeners through the reaction of the hydrazonoyl chloride derived from 7-aminoflavone and 7-amino-2-methylchromen-4-one with the appropriate piperazine are supposed to be anticancer agents and possess antitumor activity against breast cancer [82].

4. APPLICATION OF FLAVONOIDS AND ITS ANALOGUES

4.1. Medicinal uses

Natural flavonoids and their derivatives have been a beneficial source of bioactive molecules in medicines much before the advancement of other modern therapeutics in the post-genomic period [83].

Flavonoids possess various applications in food industry. Some compounds seem to be widely used as sweetening agents or food colors, while many others play a significant role as flower pigments - thus they are found useful in horticulture and cut flower industry. These compounds have been reported to show antifungal, antibacterial or antiviral properties [84]. Plentiful flavonoids and its derivatives, both natural and synthetic, have been studied as potential medicinal agents which prevent human diseases including malaria and HIV. For example, the alleviation of toothache by chewing on a willow twig which is based on the presence of salicylic acid derivatives, thus it gives an opportunity to use acetyl salicylic acid and its many synthetic variants to alleviate minor pain. Naturally occurring, as well as synthetic flavonoid derivatives have demonstrated many medicinal uses. Seeds of the milk thistle *Silybum marianum*, which are rich in active flavanolignans have been used as a remedy for liver disease for long time. Well-known chalconediglucoside and the isomeric flavanonediglucoside are responsible for the antihepatotoxic activity of *Butea* extracts. Furthermore, it has been confirmed that flavonoids are active against HIV. Besides, 5,6,7-trihydroxyflavone 7-*O*-glucoside presented the ability of inhibition the human T-cell leukemia virus type 1 (HTLV-1). Another flavonoids: quercetin and fistein (5-deoxyquercetin) have shown activities similar to that of the drug Adriamycin. Moreover, phenolic compounds (e.g. proanthocyanidins and gallic or ellagic acid derivatives) have been suggested to inhibit specific ligands at 16 receptors sites [85].

Flavonoids and their derivatives may act as efficient agents against plants viruses, mainly potato virus X (PVX) and tobacco mosaic virus (TMV) [86]. As antibacterial agents may participate in the field of strains of pathogenic bacteria to routinely used antibiotics. Furthermore, there are many reports in the literature documenting antifungal activity of flavonoids. Thus, they may be used as potential biocides (e.g. phytoalexin analogues). Alkyl derivatives of flavonoids prevent from variety of wood-destroying fungi and Gram-positive, as well as Gram-negative bacteria. On the other hand, flavan-3-ols play an important role as antiscorbutic elements of foods [84].

4.2. Food uses

The characteristic flavor of *Citrus* species is related to flavonoids as sweetening agents. Moreover, the taste of common beverages, such as wine, beer or tea is also caused by flavonoid features. The structure of the diglycoside plays an essential role in determining taste properties. It has been reported that loss of rhamnose from naringin or neohesperidin, leaving only the 7-*O*-glucosides, did not cause the decline of bitterness. Otherwise, it is observed that the movement of rhamnose to position 3 or 4 of glucose gives compounds gently bitter taste while the movement of rhamnose substituent from position 2 on the glucose to position 6 results in loss of bitterness. Removal of both sugars caused a complete loss of taste, thus a sugar group at position 7 specifies structural requirements. On the other hand, the sweet taste is due to the presence of dihydrochalcones. For sweetness in tea is probably responsible the compound, called aspalathin. Surprisingly, the replacement of the rhamnose with glucose to provide the 2'-*O*-β-D-glucoside eliminates any element of sweetness from the compound. This glucoside - phloridzin possesses quite bitter taste. Moreover, rhizomes have been the subject of studies to determine the chemical nature of their sweet-bitter components [84, 87, 88].

Furthermore, flavonoids play a greatly important role in the production and pleasure of several well-known and commonly used beverages, especially tea, wine and beer. It is confirmed that flavonoids in grapes have a huge influence on the quality of wine. Two main groups of flavonoids are inherent in wine: anthocyanins which are responsible for the color of grapes and proanthocyanidins related to astringency. The anthocyanin chemistry of grapes constitutes a complex with five aglycones (cyanidin, petunidin, peonidin, malvidin

and delphinidin) occurring in various mixtures of 3-*O*-mono- and 3,5-di-*O*-monoglucosides some of which are acylated. The most general acid is *p*-coumaric. In addition, the acetaldehyde molecule plays a significant role in the aging of wine [84].

The most common problem of plagues brewers is the haze generation in their products. Hazes can be endless or they may occur during product's chilling. The principal collaborators of haze problem constitute polyphenolic compounds most of which are proanthocyanidins. In order to solve the problem is the removal of these compounds at source instead of having to resort to some physical methods of separation at a larger stage of production [89].

Honey is a natural product well-known due to its high alimentary and preventive-medicinal quality. From the chemical point of view, honey is extremely concentrated solution of a complex mixture of sugars. Aside from sugar groups, it possesses a wide range of smaller compounds, majority of which, containing polyphenols, are noted to have antioxidant properties. Because of beneficial effects of antioxidants on human health honey may be considered as a biomarker for environmental pollution and may cumulatively determine the level of water, air, plant and soil contamination over the forage area of the bees. Due to the importance of natural polyphenols, interest in their identification and quantification has significantly increased in recent years. Furthermore, the medical application of honeybee products, called apitheraphy has aroused an interest as popular and prophylactic medicine for diseases treatment as well as supporting overall health and well-being. Honey characteristics, such as sweetness, flavor and color, cause that honey is often used as a sugar substitute, a natural preservative or ingredient in plentiful of manufactured food products [90].

4.3. Leather tanning uses

One of the oldest processes involving polyphenolic compounds is the conversion of animal hides and skins into leather. The tanning process concerns handling hides with substances that protect the molecular form of the collagen fibers of which the hides are composed [84]. Vegetable tannins are supposed to be the earliest used agents in this transformation. Apart from the vegetable tannins, other reagents commonly used in tanning include salts of aluminium(III) and chromium(III), and the bifunctional organic reagent glutaraldehyde. Characterization of the nature of intermediates and the final product in any tanning process would clearly be of importance in mechanism-based attempts to enhance tanning efficiency or finished leather quality. Nowadays, the industry applies certain standards based on the physical characteristics of intermediate and final product, such as shrinkage and shrinkage temperature, and thermal properties, which do not give clear view to any underlying chemical and physicochemical transformations [91]. Vegetable tannins are important as retanning agent in the leather production and have been recognized as an important tanning agent in non-chrome tanning. Commercial vegetable tannins are not capable of radically changing the quality of the usual leather products, so that the appearance of a new vegetable tannin is of great importance. Tannins leave a distinctive spectroscopic signature in the tanned leather product by which the origin and type of the tannin used may be inferred. It is to be expected that processes using mixtures of tanning reagents will leave equally distinctive fingerprints in the leather product. The fingerprint reflects not only the process chemistry but also underlying molecular mechanisms whereby tanning converts unprocessed leather into a commercial product [92].

4.4. Natural pigments uses

Flavonoids constitute one of the largest groups of plant pigments, and some of them are often found in many kinds of plants. Nowadays, because of ingenious manipulations of genetic flavonoid material, it is possible to modify the flavonoid biosynthetic pathway in such way that plants may be prompted to produce novel compounds. There are some pros of this innovative method, namely it is likely to place the normal range of plant colors in the best practicable genetic background, that can possess such features as stature, cold hardiness, and disease resistance. Besides, it appears an opportunity to engineer novel flower colors. Flower color in majority plants requires the interaction of anthocyanins with flavone

or flavonol glycoside co-pigments. It has been reported that modification of flower color may be obtained by altering the genetic control of vacuolar pH [84].

Furthermore, natural plant dyes containing flavonoids are often used as mordant-dyes, except for catechins being considered as direct dyes. As mordants are considered substances combined with dyes (flavonoids) in order to define dyes on fibers. The example of mordant commonly used with flavonoids is a soluble aluminium salt, such as alum. The green color is usually created by the combination of the flavonoid-dye and indigo [93]. Many dyes present in plants are glycosides. The dye process is followed by the glycosidic bond breaking and formation of new bonds between the fiber and the dye. Thus, a water insoluble and washable coloration is produced. The major flavonoids occurring in yellow dyes are: quercetin O-galactoside (hyperoside), quercetin O-glucoside (isoquercetin), quercetin O-apioside, kaempferol O-galactoside, isorhamnetin O-glucoside or galacto-side and kaempferol O-glucoside (astragalin). On the other hand, tannins are commonly used in connection with other dyes, as a pretreatment to the fiber and produce mostly brown to black colors [94].

5. CONCLUSIONS

The biological properties of dietary flavonoids and their analogues have been indicated to be due to multiple mechanisms of actions including free radical scavenging, activation of survival genes and signaling pathways, transition metal ion chelation, regulation of mitochondrial function and bioenergetics, modulation of inflammation response, and even interactions with micro biota. Nevertheless, activity of flavonoids are not limited to their health promoting benefits but spread to a wide range of ecological interactions of plants, such as acting as a signal and defense molecule. Their applications in industry are beyond the limit of nutraceuticals and drug candidate molecules. The heterogeneous biological activities of flavonoid compounds and its derivatives depend on their structural diversity.

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