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Health-Promoting Properties of Apigenin and Kaempferol

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Abstract

The relationship between diet and health has long been known. An important group of biologically active compounds in foods are polyphenols that occur in plants and are not produced in humans or animals. Bioflavonoids, also known as flavonoids, are water-soluble, plant-based pigments that exhibit antioxidative, anti-inflammatory, antiallergic, antiviral, and anticarcinogenic properties. Human body does not synthesize flavonoids and the only way to benefit from their therapeutic potential is through supplementation.

Keywords: Bioflavonoids, Apigenin, kaempferol, IL-10, TNF-α

Bioactive Compounds in Food

Food provides both essential nutrients and extranutritional constituents, the latter known as bioactive compounds. Numerous studies imply that these bioactive substances exhibit some health-promoting properties, especially in terms of preventing cardiovascular and neoplastic diseases [1,2].

Bioactive compounds form a widely distributed and structurally diverse group found in both plant and animal products. Examples of plant bioactive substances are flavonoids, a large class of compounds that includes catechins, isoflavones, anthocyanins and phenolic acids. Many flavonoids have been shown to possess a wide range of biological functions, including antioxidative, anti-inflammatory and antineoplastic properties. The most significant examples are lycopene, the predominant carotenoid in tomatoes, organosulfur compounds in onions and garlic, as wells as monoterpenes found in citrus fruits, cherries and herbs. Other note worthy examples of bioactive compounds include saponins in legumes, terpenoids synthetized by citrus fruits, lignans found in flax seed, barley and soy, and tannins present in blackberries, tea, coffee, chocolate and red wine [3].

Although a large number of bioactive compounds have been catalogued, there are still a lot of substances present in food that require identification and whose potential therapeutic potential needs to be studied.

Properties of Bioflavonoids

Bioflavonoids, also known as flavonoids, are water-soluble, plant-based pigments that exhibit antioxidative, anti-inflammatory, antiallergic, antiviral, and anticarcinogenic properties. Human body does not synthesize flavonoids and the only way to benefit from their therapeutic potential is through supplementation [4].

Every day human body is exposed to millions of free radicals, whose activity frequently contributes to the development of numerous diseases. Bioflavonoids, similarly to vitamins A, C and E, have been shown to act as antioxidants, eliminating free radicals and toxic metabolites from the body. Moreover, they help protect vitamin C from oxidation, exhibit antibacterial properties, improve digestion by stimulating bile production, lower cholesterol levels, and prevent the formation of cataract. As antioxidants, bioflavonoids protect LDL from oxidation and stimulate immune response [5]. They are responsible for maintaining the right level of collagen that keeps cells, fibrous tissues and cartilage in good condition. They also improve blood flow in vessels and strengthens capillary walls [5]. Thanks to their anti-inflammatory and analgesic properties, they are used to alleviate pain in osteoarthritis.

The recommended dose of bioflavonoid intake is 500 mg a day, which can be increased to 1500 mg in postmenopausal women. The richest sources of bioflavonoids are both flesh and peel of citrus fruits, as well as other foods and products such as wine, green tea, onion grape peel, and apples. They are also present in numerous plants used for medicinal purposes [4,5]. Although bioflavonoids are generally safe for humans, overdosage can cause nausea and diarrhea. Excessive intake should particularly be avoided by pregnant women.

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Structurally, bioflavonoids are based on the so-called flavonoid backbone, which is composed of three rings. Modifications within the third ring allow for the differentiation of various flavonoid compounds, whose structure can be subject to further modifications of hydroxyl, methoxy, or isoprenyl groups. Flavonoids can form dimeric structures, as well as O- and C-glycosides. In plants they occur predominantly in the aglycone and O-glycoside forms [4].

The sugar group in glycoside structure typically consists of glucose, but also of galactose, xylose, rhamnose, and arabinose. Sugars are bonded to a hydroxyl group at C-7 position of the C-ring in flavones and isoflavones, at positions C-3 or C-7 in flavonoles flawonoli, and at positions C-3 or C-5 in anthocyanins. Differences in occurrence and structural composition of flavonoids underlie their classification into specific subgroups.

Polyphenols were subdivided according to their basic skeletal structure into phenolic acids (derivatives of benzoic and cinnamic acids) and flavonoids. The latter comprise a number of subclasses: flavones, flavanones, flavonols, flavanols, isoflavones, and anthocyanins [4].

Flavonoids form a well-knows group of plant pigments. Anthocyanins and proanthocyanidins may appear red, purple, or blue. Most frequently occurring in nature are the glycosides of cyanidin, delphinidin, malvidin, and petunidin, found in such foods as red and black grapes, blueberries, and red wine. Flavones, such as apigenin, hesperetin, quercetin, and kaempferol, provide yellow pigment to plants and can be found in green tea, grape peels, ginkgo biloba leaves, and apples [3,5]. Other examples of flavones are myricetin and rutin, of which the latter is commonly used in pharmacotherapy for blood vessel protection.

Flavanols are catechins and epicatechins whose substantial quantities can be found in green tea and grape seeds. Another subclass, flavanons, comprises such compounds as hesperidin and naringenin present in citrus peels. Hesperidin improves the elasticity of capillaries and strengthens the inner lining of a blood vessel, whereas naringenin affects the level of lipids in the blood. The latter can be found in Citrosept drops, a dietary supplement used to lower cholesterol levels and boost immunity [4,5]. Among isoflavones, the most noteworthy example is genistein, which exhibits strong anticarcinogenic properties and can be found in substantial quantities in soy. It has been noticed that genistein intake correlates negatively with mortality rates from breast and prostate cancer [6,7].

Examples of phenolic acids are gallic, ellagic, salicylic, hydroxybenzoic, and chlorogenic acids. They exhibit antibacterial, antifungal, and diaphoretic properties. Other examples of phenolic compounds are tannins, whose astringent properties are used to stop diarrhea, and capsaicin, commonly found in plasters and ointments used to treat neuralgia [7].

Metabolism of Polyphenolic Compounds

Flavonoids occur mainly as aglycones and glycosides. The former are hydrophobic in character, which allows for their passive diffusion through cell membranes, whereas the latter are strictly hydrophilic, which negatively affects transportation via passive diffusion.

The epithelium of the small intestine contains beta-glucosidase, which catalyzes the hydrolysis of the beta-glycosidic bonds and thus enable the absorption of free aglycones [7,8].

Flavonoids are metabolized via phase 1 and phase 2 enzymatic reactions, the former being hydroxylation and demethylation, whereas the latter consisting of O-methylation and conjugation with sulfuric or glucuronic acids. Phase 1 takes place in the liver, followed by partial intestinal metabolism.

Flavonoid compounds are eliminated with bile and urine. Additionally, they are subject to enterohepatic circulation, which significantly affects elimination time and prolongs their activity [7].

Functions of polyphenolic compounds

The most prevalent form of polyphenolic compounds in our everyday diet is glycosides, whose average intake ranges from a few milligrams to 1 gram. The overall average content of flavonoids in the Mediterranean diet is anything between 100-1000mg, as compared to flavonoid deficient diets, where the intake is limited to 23-28 mg.

Polyphenols have long been used to treat a variety of diseases. So far, they have been shown to prevent cardiovascular diseases, inhibit neoplastic cell proliferation, influence the central and peripheral nervous systems, relieve menopausal symptoms, strengthen the walls of blood vessels, decrease allergic response and increase diuretics.

Rutoside, diosmin and hesperidin are used to treat peripheral circulation disorders. Silymarin is a potent agent in the prevention and treatment of liver diseases, while soy-derived isoflavones, which exhibit a range of estrogen-like effects, are recommended for the prevention and treatment of menopausal symptoms [7,8].

The influence of flavonoids on the smooth muscle tissue found within the walls of blood vessels has been known for a long time. Luteolin, apigenin and genistein glucosides are known for their ability to prevent hypertension [6].

Flavonoids significantly reduce the risk of death from cardiovascular diseases. They also regulate cholesterol levels, boosting the amount of HDL and decreasing LDL concentrations. This phenomenon was first observed in France and called „the French paradox".

It has been observed that in countries where flavonoid-rich diets prevail, the incidence and mortality from cardiovascular diseases is significantly lower, despite relatively high intake of saturated fats. A scientific insight into the French paradox has brought researchers' attention to resveratrol, which has been shown to prevent the aggregation of platelets and stimulate vasculogenesis by activating the Vascular Endothelial Growth Factor (VEGF). It also stimulates the synthesis of nitric oxide, which results in vasodilation and increased blood flow [5,6,7].

The anticarcinogenic activity of flavonoids is connected with their ability to inactivate carcinogens by interfering with phase 1 and 2 of their biotransformation.

Polyphenols can also affect the activity of central nervous system. There is some scientific data suggesting their affinity and ability to activate GABA benzodiazepine receptors.

Polyphenolic compounds are also known for their antiallergic properties. Quercetin combined with calcium salts and rutin together with ascorbic acid are commonly used in pharmacotherapy to treat symptoms of various allergies.

The last reported property of flavonoids is their ability to increase diuretics, as observed through the use of flavonoid-rich goldenrod

and birch leaf [5,6].

The present paper attempts to evaluate the anti-inflammatory properties of apigenin and kaempferol.

Characteristics of Apigenin

Apigenin is one of the most precious citrus bioflavonoids, belonging to the flavone class and found in many fruits and vegetables, as well as in leaves and stems of vascular plants.

Apigenin is used in both traditional and alternative medicine. Its richest dietary sources are apples, endive, beans, broccoli, grapes, onions, tomatoes, and tea. The richest herbal source is wild chamomile (Matricaria chamomilla), but considerable amounts of apigenin can also be found in parsley, thyme, peppermint, and primula [9].

As medicinal plant material, apigenin is used to treat gastrointestinal inflammation and spasticity, as well as bacterial infections. When applied topically, both apigenin and apigenin 7-O-β-glucoside are absorbed into deeper tissues. The compound exhibits antioxidative, anti-inflammatory, and anticarcinogenic properties. Recent studies on rats suggest that apigenin can inhibit histamine secretion and thus limit allergic responses [9].

The anti-inflammatory effects of apigenin are connected primarily with its ability to inhibit the activity of 5-lipoxygenase and cyclooxygenase. These enzymes are crucial for the synthesis of prostaglandins and leukotrienes, which act as inflammatory mediators. It is particularly important that apigenin can be used to block cyclooxygenase-2 (COX-2), expressed in cells during inflammation, which results in the inhibition of leukocyte migration into the affected tissues, regulation of vascular tone, and decreasing of inflammation [10].

The ability to inhibit COX-2 via a NO-dependent pathway was noticed in the development of inflammatory diseases, including disorders of the central nervous system. Research results suggest that apigenin is one of the most active inhibitors of COX-2 and iNOS expression in LPS-stimulated macrophages. Apigenin inhibits the immune response by inactivating the NF-B transcription factor [10].

In inflamed endometrial cells, with the increased expression of COX-2, apigenin inhibited the expression of COX-2, without affecting the expression of the PTGS1 gene that encodes COX-1. This might mean that apigenin affects only inflamed cells, without exerting influence on healthy cells [9,10,11].

COX-2 inhibitors can be found among the anti-inflammatory drugs available on the Polish pharmaceutical market. Unfortunately, they tend to trigger numerous side effects, so their use is limited to strictly justified medical cases. The ability of apigenin to inhibit COX-2 creates major opportunities for the development of pharmaceutical technology [11].

The anti-inflammatory activity of apigenin is also connected with its ability to inhibit IL-1β.

TNF-α expression in macrophages and human monocytes stimulated with LPS [9].

An increase in IL-1β expression has been observed in the course of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease or multiple sclerosis. IL-1β activation stimulates the transcription of other pro-inflammatory cytokines, such as TNF-α and IL-6, through the activation of NF-B transcription factor [9].

It has also been revealed that apigenin exhibits antiallergic properties. Liang et al. (1999), have reported that it blocks the secretion of the IL-8 pro-inflammatory cytokine in LPS-stimulated cells [10].

IL-8 induces chemotaxis in neutrophils, causing them to migrate toward the site of infection. It is also responsible for angiogenesis and the release of lysosomal enzymes, which in consequence leads to pathogen destruction. Alongside neutrophils, IL-8 cooperates with T lymphocytes, NK cells, and basophils. Since it is associated with the occurrence of allergic diseases, the fact that it can be inhibited by apigenin can give an insight into the antiallergic properties of the flavonoid [13].

In the course of allergic diseases, a substantial increase in the secretion of immunoglobulin E (Ig-E) can be observed. An increased level of Ig-E is often related to the occurrence of infection or autoimmune disease. In a study carried out by Yano et al. (2006) on C57BL/6N mice, it has been observed that an apigenin-rich diet lowered the level of Ig-E in a considerable way. Usually, high levels of Ig-E are also connected with high levels of IL-4 and IL-13 secretion, but this time no influence of apigenin on these cytokines has been observed. The secretion of IL-2, IL-4, IL-6, IL-10 and IL-12 at the level of mRNA has not been affected either [16].

Yano et al. (2006) have observed the influence of apigenin on TNFR1 levels. The soluble receptor of TNFR1 is found in numerous bodily fluids and represents the extracellular domain for TNFR1. High levels of soluble TNFR1 have been observed in human blood, plasma and urine in the course of infections and autoimmune diseases [16].

The tumor necrosis factor alpha (TNF-α) induces the expression of numerous proteins, such as I-B, JNK1/2, p38MAPK and ERK1/2. The use of apigenin decreased the expression of I-B exclusively, which was the result of its inhibiting effect on the kinase that phosphorylates TNF-α. Additionally, apigenin inhibits the TNFα dependent translocation of p65 protein to the nucleus, thus inhibiting the expression of genes responsible for inflammatory response [15].

In the course of inflammatory diseases and during chronic inflammation, vascular bed expansion and increased expression of Cell Adhesion Molecules (CAMs) can be observed. By impairing monocytes' ability to adhere to endothelial cells, apigenin inhibits the expression of ICAM and VCAM [15].

Numerous research implies that apigenin could also be used in cancer treatment protocols. In studies involving the MDA-MB-453 cell line, characterised by ErbB2 over expression and 5-fluorouracil resistance, the use of apigenin at doses of 20μM and 30μM increased the sensitivity of cancer cells to chemotherapy. Apigenin doses of 5, 10, 50 and100 μM resulted in caspase 3 activation and finally in apoptosis when combined with 5-fluorouracil. The use of doses higher 10 μM together with 5-fluorouracil also led to apoptosis, but this time it was through the inhibition of Akt expression [17].

However, high doses of apigenin triggered some adverse changes in cells. Some researchers suggest that the use of apigenin at doses of 100 μM results in DNA intercalation and cell death, but lowers doses, for instance administered together with mitomycin C, can protect healthy cells from the cytotoxic effects of chemotherapeutic drugs. In conclusion, low doses of apigenin can increase the sensitivity of cancer cells to cytostatic drugs and at the same time protect healthy cells from their toxicity [17].

To treat autoimmune diseases and prevent transplant rejection, it is common to use cyclosporine a [18].

Despite its therapeutic properties, apigenin has an adverse effect on renal function. Chakravarthy S, et al. (2010) have reported that combining apigenin with cyclosporine A reduced kidney damage through the inhibiting effect on c-myc expression [19].

Some research has also been conducted into the influence of apigenin on noradrenaline, dopamine and serotonin transmission in mice, and revealed that the compound has antidepressant properties [20].

Characteristics of Kaempferol

Kaempferol is a flavonoid and phytoestrogen, widely distributed in the plant world. It can be found in apples, onions, citrus fruits, grapes, red wine, gingko biloba, tea leaves, blackthorn flowers, and larkspur flowers, among numerous other sources [21].

Kaempferol exhibits spasmolytic, anti-inflammatory, antiallergic and antifungal properties. Additionally, it stabilizes the structure of connective tissue proper and strengthens the walls of blood vessels. It has also been found that kaempferol reduces the level of glucose in blood and inhibits the activity of aldolase reductase, thereby preventing neuropathy and retinopathy, which are the most typical diabetes complication.

Kaempferol also acts as an antioxidant, protecting cells from oxidative damage. By exerting beneficial influence on the metabolism of lipids, it significantly reduces the risk of atherosclerosis.

Kaempferol has an inhibiting effect on the secretion of such proinflammatory cytokines as a IL-6 and IL-8, as well as the Monocyte Chemotactic Protein (MCP-1) [21].

Just like apigenin, kaempferol can activate sirtuins, which are NAD-dependent histone deacetylases induced as a result of calorie restriction. An association between sirtuin activation and insulin secretion has been suggested. Numerous studies confirm that kaempferol produces a 30% increase in ATP production. Additionally, it has been found to influence the secretion of thyroid hormones through activation of the Dio2 gene, which is responsible for bioactive 3,3',5-triiodothyronine (T3) production and consequently boosts metabolism [22].

Some research results show that kaempferol administered at doses of 5,10,20 inhibits μM the TNF-induced production of IL-6 in mouse osteoblasts [23].

In macrophages stimulated with LPS or cytokines, kaempferol reduced the activity of iNOS and COX-2 by inhibiting the activity of STAT-1, as well as NF-B and AP-1 transcription factors. As for endothelium cells, kaempferol, like apigenin, reduced the expression levels of such adhesion proteins as VCAM, ICAM-1 and E-selection [24].

Numerous research results indicate yet another way of inhibiting the immune response by means of kaempferol. The flavonoid has been found to intensify the expression of Heme Oxygenase 1 (HO-1) in RAW 264.7 cells stimulated with LPS [25].

In the course of inflammatory diseases, such as Crohn syndrome, changes in the expression of the gene that encodes for heme oxygenase-1 have been observed. By stimulating the expression of heme oxygenase-1, symptoms of the disease can be alleviated [25].

Heme Oxygenase 1 is an enzyme that catalyzes the degradation of heme. This produces ferrous iron, carbon monoxide, and biliverdin, which reduces to free bilirubin.

Bilirubin is an antioxidant, found in extracellular fluid, which might reduce the risk of cardiovascular diseases and decrease lipid oxidation. The products of heme oxygenase 1 activity - bilirubin and CO – reduce the secretion of proinflammatory proteins. The ability of flavonoids to increase bilirubin levels might suggest that their protective properties are also connected with heme degradation [25].

It has also been shown that kaempferol inhibits the growth of neoplastic cells. Studies into the influence of kaempferol and quercetin reveal that the two can work synergistically. Additionally, kaempferol might reduce cellular resistance to vinblastine and paclitaxel in cases of chemoresistance, the flavonoid sensitized cells to therapy [26].

Some tumors are characterized by high levels of P-glycoprotein (Pgp) expression, which is connected with resistance to chemotherapy. In a study involving the KB-V1 cell line, characterized by high Pgp expression, kaempferol significantly increased the sensitivity of cells to chemotherapeutic agents [27,28].

Kaempferol has the ability to increase ROS levels in cells, as well as limit the activity of SOD-1 and TRX-1. By enhancing intracellular oxidative stress, kaempferol induces apoptosis in glioma cells, which is connected with the activation of caspase 3 expression and a decrease in the expression of Bcl2 protein [29].

Conclusion

Bioflavonoids are a large class of compounds typically found in plants, including fruits, vegetables, herbs and spices, which contain most significant amounts of the molecules. As such, bioflavonoids may be categorized into flavanones, flavanols, flavones, isoflavones, flavonols, and anthocyanes, which have been shown to have a wide range of biological functions, including antioxidative, anti-inflammatory, vasodilative, anticoagulative and proapoptotic properties. Various health benefits of a flavonoid-rich diet have been recorded over time. Therefore, numerous in vivo and in vitro research has been conducted to demonstrate their protective and therapeutic role in a wide spectrum of diseases.

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