MELLIFERA REVIEW ARTICLE

Flavones (Apigenin, Luteolin, Chrysin) and Their Importance for Health

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Received: 14th March, 2020; accepted: 4th May, 2020; published: 29th June, 2020

A B S T R A C T

It has been shown in recent years that foods called functional foods may protect against certain types of cancer, cardiovascular diseases and cognitive dysfunctions. In the studies performed, the flavonoids (apigenin, chrysin, luteolin) which are subclass of flavonoids have been shown to have antioxidant, antiinflammatory, antiallergic, neuroprotective and cardioprotective effects and it is presented as the current treatment method in the treatment of some diseases. The structure function, nutritional resources and potential therapeutic properties of the flavones, which are also used as supplement in the compost, have been studied. The purpose of this review is to evaluate the therapeutic effects of flavones in certain diseases. The positive effect of flavones on health can be proven in many experimental studies and can be proven in the long run.

Keywords: Functional nutrients, flavones, apigenin, luteolin, chrysin

Introduction

Polyphenolic flavonoids are among the wide variety of phytochemicals found in the human diet. Current studies reveal that dietary flavonoids are inversely related to many cancers and age-related diseases [1]. Average flavonoid intake in the diet of humans varies between 20 and 1,000 mg / day [2]. Theories and randomized clinical studies on the cancer prevention mechanisms of flavonoids are still ongoing. The levels of total flavonoids in foods are affected by factors such as plant species, environment, genetics, light, maturity, harvest [3]. Flavones, a subset of flavonoids, form glycosylation and contain a hydroxylated β-ring. In preclinical models, especially Apigenin, Luteolin and Crisis have neuroprotective, anti-inflammatory, antioxidant effects [4]. It is estimated that the majority of metabolic diseases are caused by oxidative stress, so it is important that studies have shown the

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positive effect of flavones on oxidative stress related diseases. It is necessary to examine the current approaches about flavones in order to create evidence for their use in the treatment of flavones.

Sources of Flavones, Bioavailability and Functions

Regular intake of flavones with nutrients is associated with a reduced risk of a number of chronic diseases, including cancer formation, cardiovascular diseases (CVD) and neurodegenerative disorders. Extensively consumed fruits, vegetables and beverages contain various amounts of flavone.

Fruit peels, celery, parsley, paprika, chamomile, mint, ginkgo biloba, red wine, buckwheat, tomato peel, paprika are rich sources of flavone. The accumulation of flavonoids in plants is positively associated with the amount of sunlight received. Flavones are synthesized from the anthocyanidine / proanthocyanidin pathway from flavanones as direct biosynthetic precursors [5,6]. Flavones are present in their natural form, both as O and C-glycosides. Flavones cannot be absorbed from the intestines at plasma concentrations of <1 μmol / L [7]. Flavones have antioxidant, anti-inflammatory, neuroprotective, cardioprotective and antiallergic effects. Flavones reduce the reactive species (hydroxyl, superoxide and nitric oxide) of intracellular free radicals, also the effect of preventing damage to biomolecules such as lipids, proteins and DNA.

Flavones can also inhibit the activity of free radical producing enzymes such as xanthine oxidase, nicotinamide adenine dinucleotide phosphate oxidase, or inducible nitric oxide synthase, and can modulate intracellular levels of the pro-oxidant [8].

Apigenin and Effects of Apigenin on Health

Apigenin is a flavonoid found in some plants, fruits, and vegetables (parsley, chamomile, celery, vine spinach, artichoke, and thyme). The genus *Apium* (celery, carrot or parsley family) is also known as Umbelliferae [9]. Apigenin was first described in 1900 and was synthesized in 1939. The naturally occurring glycoside conjugates in Apigenin are more water-soluble. In in vivo conditions, glycoside conjugates are digested and hydrolyzed by bacteria in the gut to form molecules of free apigenin [10]. There is only one review on the antimicrobial effect of apigenin in the

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literature. Although there are insufficient studies, it has been shown that apigenin or its glycosides are divided into metabolites by certain gut bacteria and affect the health of gut [11]. There are many studies in the literature investigating the cancer prevention mechanisms of apigenin. Studies argue that apigenin can be used in the cell to prevent cancer types such as breast cancer, uterine cancer, colon cancer, lung cancer, ovarian-prostate cancer, skin cancer, liver cancer and stomach cancer [12]. Breast cancer can be prevented by inhibition of telomerase activity. Cisplatin, a chemotherapeutic drug, causes DNA damage. In a study, it was observed that the use of apigenin and cisplatin together in the treatment of breast cancer had a synergistic effect in reducing telomerase activity [13]. The mechanism underlying apoptosis-inducing effect of apigen in colon cancer treatment is thought to inhibit the transcription activator (STAT3) phosphorylation of the apigen and anti-apoptotic proteins (Bcl-xL and Mcl-1). Apigenin stimulates the proliferation of cancer cell lines, reproducing by division and apoptosis formation in a dose-dependent manner [14]. Treatment of apigenin significantly improves weakened heart functions. In one study, male rats were fed a high-fat diet for three months. Then, in order to create a Type 2 Diabetes model in these mice, 100 mg / kg STZ treatment was applied, and cardiac measurements were performed by administering 100 mg / kg apigenin daily for 4 months in diabetic mice. In this study, apigenin, Kaspaz3 and NF-κB / P65 ', influenced the signal path, regulated GSH-Px, MDA and SOD levels and was determined to be effective in regulating oxidative stress [15]. Apigenin prevents dopamine-related oxidative stress in melanocytes. In the treatment of vitiligo, an immune system disease, antioxidant apigenin can be used with its effects on Nrf2 expression and genes [16]. Another study investigating the roles of apigenin in diabetic cardiomyopathy has been reported to decrease in diabetes and cardiomyopathy markers with apigenin treatment in mice treated with streptozosine (50 mg / kg) for 5 days [17]. It has been suggested that apigenin can provide a clinically beneficial effect for these neurodegenerative disorders by targeting neuroinflammatory processes, such as cytokine suppressive anti-inflammatory drugs (CSAIDs). In a study investigating the therapeutic effect of apigen on glial fibril acidic protein-interleukin 6 (GFAP-IL6), it was found that the number of active microglia in the

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cerebellum and hippocampus decreased by 25-30% [18]. In a study investigating the effect and possible mechanism of the combination of apigenin and ischemic conditioning on renal ischemia-reperfusion injury in rats, the combination has been shown to inhibit the TLR4 / NF-sinyalB signaling pathway in renal ischemia / reperfusion injury and provide great protection against renal ischemia / reperfusion injury in rats [19]. Apigenin shows a strong power in the treatment of paclitaxel resistant hypoxic tumors [20]. Another study investigating the potential anticancer properties of Apigenin on human breast cancer; while apigene does not act in normal cells, it has been found to be genotoxic in selected cancer cells, cells that have the potential to oxidize lipids. Combined with the low cytogenotoxic and pro-cell death activities of Apigenin and its low toxicity to normal cells, it is argued that this natural flavone may be used as an anticancer agent in the future [21]. In a study conducted to examine the growth inhibitory effects of apigenin, different doses of apigenin were given to HCT116 cells. Apigenin low concentrations (6.25 μM) didn't affect cell viability, whereas high concentrations of Apigenin (25 and 50 μM) were found to significantly reduce cell viability of HCT116 cells. Morphological and qualitative changes were also observed in the cells given apigenin [22]. In a study examining the effect of apigen on muscle atrophy due to sciatic nerve denervation, mice with impaired sciatic nerves were fed a diet containing 0.1% apigenin for 2 weeks. Muscle atrophy resulting from denervation was found less in apigenin given mice and it was observed that apigenin inhibits muscle atrophy caused by denervation due to its inhibitory effect on inflammatory processes in the muscles [23].

Luteolin and Effects of Luteolin on Health

Luteolin (LUT) is a common flavonoid that is abundant in many herbal products, including broccoli, peppers, thyme, peanuts, and celery. In vitro and in vivo studies have shown that LUT has neuroprotective effects [24]. LUT sensitizes cancer cells to cytotoxicity by suppressing cell survival pathways such as phosphatidylinositol 3-kinase (PI3K), nuclear factor kappa B (NF-κB), X-linked apoptosis inhibitor (XIAP) and stimulation of apoptosis pathways. The anticancer property of LUT has been associated with induction of apoptosis and inhibition of cell proliferation, metastasis and angiogenesis

[25]. Due to its bacteriostatic properties and potent antioxidant potential, LUT is valuable in the treatment of a variety of diseases, including peptic ulcers. With this antioxidant effect, LUT reduces kidney anemia by reducing oxidative stress in the kidney. In a study on wound healing in diabetic rats, different LUT concentrations were applied in MTT analysis on 3T3 fibroblast cells. Annexin V and cell cycle analyzes were performed. Significant improvement was observed in the groups treated with LUT compared to control. LUT increased the live population of 3T3 cells and the cell population in the G2M phase compared to the control group [26,27]. Another study shows that LUT treatment is able to reduce fat accumulation by acting on serotonin-related receptors ser-6 and mod-1 [28]. In a study examining the effects of LUT on colon cancer in obese mice; different groups were formed as normal diet (ND), high-fat diet (YYD), high-fat diet with 0.0025% LUT, high-fat diet with 0.005% LUT. As a result, it was observed that body weight, colon weight / height and tumor rate increased significantly in the YYD group compared to the ND group [29]. In YYD, LUT supplementation significantly reduced colon weight / length and the rate of colon tumors but did not change body weight. It has been reported that plasma tumor necrosis factor (TNF-a) levels and inducible nitric oxide synthase and cyclooxygenase-2 protein increase colonic expression in response to YYD, and these effects are suppressed by LUT supplementation [30].

In a study testing the effects of LUT on sunburn, LUT in human keratinocytes exposed to physiological doses of UVB has been shown to weaken cell death caused by UVB by inhibition of apoptotic signaling. LUT has inhibitory effects on UVB-induced release of inflammatory mediators, IL-1 and prostaglandin-E2. LUT increases the survival rate of normal keratinocytes [31].

Inhibition of osteoclast differentiation and bone resorption is considered an effective therapeutic approach in the treatment of postmenopausal bone loss. In one study, oral administration of LUT (5 and 20 mg / kg per day) to the ovarian-removed mice prevented the reduction of bone resistance while increasing the bone mineral density and bone mineral content in the femur. These data strongly demonstrate that LUT has the potential to prevent bone loss in postmenopausal osteoporosis by reducing

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osteoclast differentiation and function [32]. In patients with heart transplantation, the hypothermic protection of the heart takes 4-6 hours and over time, calcium accumulation causes cell death. LUT protects the heart and vessels by reducing oxidative stress-induced damage in cells. Because of this feature, it is used in Chinese medicine to protect the donor hearts for a longer time. In a study investigating the protective role of LUT in modulating the cardiomyocyte calcium cycle, 7.5, 15 or 30 μmol / l LUT-supported solutions were used to protect cardiomyocytes. The results showed that three doses of LUT supplementation reduced calcium overload by providing a cardioprotective effect over a 6-hour protection period [33]. LUT increases the effect of cisplatin used in breast cancer treatment by decreasing Bcl-2 expression. Studies show that a combination of cisplatin and LUT supplements may be a potential treatment in ovarian cancer [34].

There are cytokine-neuropeptide interactions in the pathogenesis of diseases in the brain. Especially myalgic encephalomyelitis syndrome and autism spectrum disorder are negatively affected by the release of corticotropin hormone and neurotensin. Natural flavonoid LUT and tetrametoxyluteolin inhibit these processes and provide neuroprotective effect. Tetrametoxyluteolin is metabolically more stable and absorbed more [35]. In one study, mice fed a high-fat diet were given LUT supplement or celery fiber containing high amounts of luteolin. These supplements have been reported to reduce weight by reducing the activity of gastric inhibitory polypeptide and hepatic glucogenic enzymes, reducing insulin sensitivity, inflammation (IL1-6) and dyslipidemia [36].

LUT has been found to have an effective antiviral activity against the Japanese encephalitis virüs [37]. Another study reported that administration of LUT in hepatitis B virus (HBV) mice reduced hepatocyte nuclear factor 4α (HNF4α) and DNA replication. This study suggests that LUT can be used for anti-HBV treatment [38]. Regular LUT treatment can create an antidepressant effect by reducing stress in the endoplasmic reticulum [39]. Mangiferin, another polyphenol in combination with LUT, has been found to increase long-term supplementation at high and low doses during sprint, exercise

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performance, muscle O_2 extraction and brain oxygenation [40].

Chrysin and Effects of Chrysin on Health

Chrysin, a natural flavone, is found in many plant extracts, including propolis and honey. It is one of the herbal medicines widely used in Asian countries. The chrysin has estrogenic, antiinflammatory, antibacterial, anti-diabetic, antitumor effects [41]. In humans, the acute dose of 400mg chrysin is not toxic. Daily doses of 0.5–3 g are recommended for the efficacy of the chrysin. Chrysin reduces toxicity in liver cells, inhibits novo DNA synthesis. The low toxicity and broad spectrum of antitumor activity underlines crystalline cancer treatment [42]. Doxorubicin (DOX) is one of the most effective chemotherapeutic drugs; however, the incidence of cardiotoxicity impairs its therapeutic index.

İn a study to investigate the protection of chrysin against DOX-induced acute cardiotoxicity, rats were given 25 and 50 mg / kg of chrysin for 12 days, and on the 12 th day, DOX (15 mg / kg) was given. It has been reported that doxorubicin triggers inflammatory responses by increasing levels of nuclear factor kappa-B (NF-κB), inducible nitric oxide synthase and cyclooxygenase-2, tumor necrosis factor-alpha, and the pre-doxorubicin chrysin significantly inhibits inflammatory responses [43].

Chrysin has beneficial effects on the brain due to antioxidant effect on neuronal activity disorder, memory impairment and neuronal cell death in rats [44]. Chronic cerebral hypoperfusion induced by occlusion of the bilateral carotid arteries is associated with neurological disorders and causes cognitive decline. In a study investigating the effects of chrysin on brain damage, it was seen that rats exposed to neuronal damage increased, Cell apoptosis was significantly reduced by treatment of chrysin (30 mg / kg) for a long time. Chrysin reduced lipid peroxidation, superoxide dismutase activation, and increased glutathione peroxidase activity. These effects have shown that chrysin may have therapeutic potential for the treatment of neurodegeneration and dementia caused by decreased cerebral blood flow [45].

Chrysin, an inhibitor of the aromatase enzyme that provides the balance of sex hormones, is found in high concentrations in honey and propolis. This flavonoid used

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by athletes as supplements is thought to have testosterone-enhancing effects. In a study investigating the relationship between urine testosterone and chrysin consumption for 21 days in volunteer male subjects, no change in testosterone levels was observed in volunteer male subjects [46].

Plasma PAI-1 increases under inflammatory conditions such as infection, obesity and atherosclerosis. In a study that examined the increase in PAI-1 caused by inflammation, it was observed that chrysin inhibits the production of PAI-1 [47].

Benign prostatic hyperplasia (BPH) is a health problem in men over sixty years old. In the study investigating the protective effects of chrysin in testosterone-induced BPH, rats were given 50 mg / kg of chrysin. Chrysin reduced testosterone-induced oxidative stress, caspase-3 level, Bax / Bcl-2 ratio and mRNA expression of p53 and p21 to normal levels. Chrysin reduced the nuclear factor kappa and inhibited mRNA expression of IGF-1R. These data show that chrysin plays a protective role against BPH [48].

In another study, sperm motility, sperm concentration, and serum testosterone levels were significantly increased in mice given 50 mg / day of chrysin, while abnormal sperm rate was significantly reduced with chrysin therapy. It is thought that chrysin therapy can positively affect the reproductive system and can be used in the treatment of male infertility [49]. İn a study investigating the effect of chrysin on fertility, it was observed that blood testosterone level and sperm quality increased in roosters with increasing amount of chrysin supplements [50].

In a study with atopic dermatitis mice for use in chrysin skin allergies, serum IgE and IgG2a levels, mast cell infiltration, and serum histamine levels have been reported to decrease with treatment [51].

Chrysin has a similar effect to metformin, reducing blood glucose and triglyceride levels, reducing the secretion of pro-inflammatory cytokines and thus creating an antidiabetic and dyslipidemic effect [52]. Recently, animal models show that the dietary polyphenol chrysin is an effective inhibitor of fructose uptake by human intestinal epithelial cells. Reducing the effect of excessive amounts of fructose reduces metabolic syndrome parameter values [53].

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A study investigating the oxidative stress induced by tert-butyl hydroperoxide and the mechanism of action of this stress in rat hepatocytes, Depending on the dose of luteolin, apigenin and chrysin, it has been reported to increase the intracellular glutathione content and inhibit oxidative stress by increasing gene transcription through ERK2 / Nrf2 / ARE signaling pathways in rat primary hepatocytes. Among the studied flavones, chrysin had the best effect [54].

The ubiquitin-proteasome pathway plays an important role in regulating apoptosis and cell cycle. In recent years, some flavonoids have been reported to inhibit proteasome activity in tumor cells. It has been observed that the effect of flavones on the proteasome inhibitor is higher compared to other flavonoids. In studies, it has been observed that the inhibitory effect of tumor cells decreases in the order of luteolin, apigenin, and chrysin [55].

Conclusion

Flavones are polyphenolic components included in the daily diet. Nowadays, researchers are turning to the mechanism of action of functional components in foods and their relationship to health. In this review, the positive effects of flavones (Apigenin, Luteolin, Chrysin) on health are revealed. In vivo and in vitro studies show that flavones shorten the treatment time in inflammatory processes. Apigenin, luteolin and crisis have apoptosis effect in many cancer types. These flavones additionally play an important role in improving cardiovascular conditions, stimulating the immune system and improving renal dysfunction, protecting against muscle atrophies, exceeding fertility, diabetes and cholesterol control. Chrysin, which is found in propolis, has a preventive and reproductive protective effects, as well as a therapeutic potential in neurodegenerative diseases. A diet rich in flavones, integration of its modification into the diet can be a chemopreventive strategy for individuals with high cancer risk. To determine whether the therapeutic effects are beneficial for patients, more research and scientific evidence needs to be produced.

Flavonlar (Apigenin, Luteolin, Krisin) ve Sağlık İçin Önemi

Öz: Son yıllarda fonksiyonel gıdalar adı verilen gıdaların belirli kanser türlerine, kardiyovasküler hastalıklara ve bilişsel işlev bozukluklarına karşı koruyabileceği gösterilmiştir. Yapılan çalışmalarda, flavonoidlerin alt sınıfı olan flavonoidlerin (apigenin, krisin, luteolin) antioksidan, antienflamatuar, antialerjik, nöroprotektif

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ve kardiyoprotektif etkileri olduğu gösterilmiştir ve bazı hastalıkların tedavisinde mevcut tedavi yöntemi olarak sunulmuştur. Kompost takviyesi olarak da kullanılan flavonların, yapısal fonksiyonu, besin kaynakları, potansiyel tedavi edici özellikleri incenmektedir. Bu derlemenin amacı bazı hastalıklarda flavonların terapötik etkilerini değerlendirmektir. Flavonların sağlık üzerindeki olumlu etkisi birçok deneysel çalışma ile uzun vadede kanıtlanabilir.

Anahtar Kelimeler: Fonksiyonel besinler, flavonlar, apigenin, luteolin, krisin

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