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FLAVONOIDS - FOOD SOURCES AND HEALTH BENEFITS

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ABSTRACT

Flavonoids are a group of bioactive compounds that are extensively found in foodstuffs of plant origin. Their regular consumption is associated with reduced risk of a number of chronic diseases, including cancer, cardiovascular disease (CVD) and neurodegenerative disorders. Flavonoids are classified into subgroups based on their chemical structure: flavanones, flavones, flavonols, flavan-3-ols, anthocyanins and isoflavones. Their actions at the molecular level include antioxidant effects, as well the ability to modulate several key enzymatic pathways. The growing body of scientific evidence indicates that flavonoids play a beneficial role in disease prevention, however further clinical and epidemiological trials are greatly needed. Among dietary sources of flavonoids there are fruits, vegetables, nuts, seeds and spices. Consumption of these substances with diet appears to be safe. It seems that a diet rich in flavonoids is beneficial and its promotion is thus justifiable.

Key words: *flavonoids, cancer, cardiovascular diseases, neurodegenerative disorders*

STRESZCZENIE

Flawonoidy to grupa związków bioaktywnych występujących powszechnie w żywności pochodzenia roślinnego. Aktualne dane literaturowe wskazują, że substancje te, spożywane wraz z dietą człowieka, wykazują działanie ochronne przed wieloma chorobami przewlekłymi, w tym przed niektórymi nowotworami oraz schorzeniami układu sercowo-naczyniowego, a ponadto pozytywnie wpływają na układ nerwowy. W zależności od struktury chemicznej wyróżnia się takie podklasy flawonoidów jak: flawony, flawanony, flawonole, flawanole, antocyjany i izoflawony. Przypuszcza się, że mechanizm działania tych substancji opiera się na ich silnych właściwościach antyoksydacyjnych oraz innych mechanizmach, takich jak zdolność do modulowania licznych szlaków enzymatycznych. W wielu badaniach wykazano ich korzystne działanie w prewencji chorób przewlekłych. Jednakże poznanie dokładnego metabolizmu tych substancji wymaga prowadzenia dalszych badań. Źródłami flawonoidów w diecie człowieka są warzywa, owoce, orzechy i nasiona, a także niektóre przyprawy. Spożywanie tych substancji wraz z dietą człowieka wydaje się być bezpieczne. Uzasadnionym zatem wydaje się promowanie diety bogatej we flawonoidy.

Słowa kluczowe: *flawonoidy, nowotwory, choroby sercowo-naczyniowe, choroby neurodegeneracyjne*

INTRODUCTION

Flavonoids are a diverse group of plant metabolites with over 10,000 compounds that have been identified until now. However, only very few of them have been investigated in detail [25]. They have several important functions in plants, such as providing protection against harmful UV radiation or plant pigmentation. In addition, they have antioxidant, antiviral and antibacterial properties. They also regulate gene expression and modulate enzymatic action [25]. All naturally occurring flavonoids possess three hydroxyl groups, two of which are on the ring A at positions five and seven, and one is located on the ring B, position three. Biochemical actions of flavonoids depend on the presence and position of various substituent groups, that affect metabolism of each compound. They can be found in free or bound forms: aglycones or β-glycosides [17]. The flavonoid subclasses, based on types of chemical structure, include: flavonols, flavones, flavanones, flavanols, anthocyanins and isoflavones [17, 20]. Table 1 shows some common examples according to this classification.

Antioxidant properties of foodstuffs depend not only on polyphenol content, but also on their type. For instance, quercetin and catechin demonstrate the greatest antioxidant properties *in vitro* [6, 11, 36]. However, their

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Table 1. Subclasses of flavonoids; authors' selection based on [17]

Subclass	Examples of compounds
Flavonols	Quercetin, kaempferol, myricetin
Flavones	Luteolin, apigenin, tangeretin
Flavanones	Naringenin, hesperetin
Flavanols,	Catechin, epicatechin, epigallocatechin, glausan-3-epicatechin, proanthocyanidins
Anthocyanins	Cyanidin, delphinidin, pelargonidin, malvidin
Isoflavones	Genistein, daidzein

human metabolism is incompletely understood. Current studies on biological effects of flavonoids focuse on their absorption mechanisms, metabolism and bioavailability. Thus, in order to elucidate their physiological role, molecular studies are required. The results would enable to evaluate their effectiveness in the treatment and prevention of certain diseases, together with eventual risks arising from their use [18, 33].

FLAVONOIDS CONSUMPTION AND SAFETY

At present, consumption of dietary flavonoids is regarded as safe. Nevertheless, it is worth noting that the use of pharmaceutical products that contain high doses of bioactive substances is increasing. Such supplements provide an alternative source of flavonoids to those obtained from the diet. It is of concern that the toxicity of concentrated sources of flavonoids is unknown, together with their interactions with other dietary components or taken medications [12]. Administration of large doses of a single flavonoid may decrease bioavailability of trace elements, vitamins or folic acid. Besides, it may exert an adverse effect on the thyroid function [12]. There is a special concern about possible side effects of taking several flavonoid-containing products at the same time as flavonoid-flavonoid interactions are little known so far [12]. A consumer may be misled that flavonoids are entirely safe because they are so-called 'natural' products. Uncontrolled use of pharmaceutical preparations containing flavonoids may come out disadvantageous for health. Furthermore, the packaging labels for some dietary supplements have scant information about safety, adverse reactions, interactions, contraindications, and efficacy [7, 12].

It is clear that the molecular mechanisms of action of flavonoids need to be thoroughly understood and intensive research on this problem should be performed. However, it should be emphasised that in the light of recent findings the best and safest source of these substances is a properly balanced diet.

DIETARY CONSUMPTION AND SOURCES OF FLAVONOIDS

It is estimated that inhabitants of the Western Europe consume on average 100 – 1000 mg flavonoids/day/person [17, 36]. This was confirmed by the European Prospective Investigation into Cancer and Nutrition (EPIC) study, which showed the median daily intake of flavonoids in Greek and Spaniard subjects equal to 93 mg ($n \geq 28,000$) and 126.1 mg ($n = 40,683$) per

Table 2. Content of flavonoids, according to their sub-classes, in chosen foodstuffs (mg/100g foodstuff); authors' selection based on [2]

Flavanones		Flavones	
Artichokes	12.51	Kohlrabi	1.3
Grapefruit juice	18.98	Red grapes	1.3
Orange juice	18.99	Lemons	1.9
Oranges	42.57	Chicory	2.85
Limes	46.40	Celeriac	3.90
Lemons	49.81	Green pepper	4.71
Grapefruit	54.50	Artichokes	9.69
Dried oregano	412.13	Fresh parsley	216.15
		Dried oregano	1046.46
		Dried parsley	4523.25
Flavonols		**Anthocyanins**	
Apples	Mean 3.40	Hazel nuts	6.71
Cooked brussel sprouts	5.24	Morello cherries	7.45
Fresh figs	5.47	Pears	12.18
Dried & sweetened cranberries	6.91	Black grapes	21.63
Buckwheat	7.09	Red table wine	23.18
Chicory	8.94	Pecan nuts	25.02
Morello cherries	9.41	Strawberries	27.76
American bilberries	10.59	Red bilberries	40.15
Blackcurrants	11.53	Raspberries	40.63
Cooked asparagus	15.16	Red cabbage	63.50
Fresh cranberries	21.59	Red currants	75.02
Goji berries	31.20	Blackberries	90.64
Red onions	38.34	American bilberries	141.03
Rocket lettuce	69.27	Black currants	154.77
Radish	78.09	Chickpeas	262.49
Sorrel	102.20	Bilberries	285.21
Elderberry juice concentrate	108.16	Aronia	349.79
Dried parsley	331.24	Elderberry juice concentrate	411.4
Fresh capers	493.03		
Flavanols			
Apple juice	5.96	Cooked broad beans	20.63
Apricots	8.41	Blackberries	42.5
Peaches	8.6	Cocoa, dry powder	52.73
Apples	9.17	Dark chocolate	108.60
Red table wine	11.05	Black tea, brewed	115.57
Pecan nuts	15.99	Green tea, brewed	116.15

person respectively [9, 39]. The Greek survey was performed in 1992 – 1996 and thus the results may be underestimated as the database concerning flavonoid levels in foodstuffs was incomplete that time. On the other hand, it is assumed that inhabitants of countries in the Far East, such as Japan, because of high intake of legumes, soy and tea, may consume up to 2 g of flavonoids daily [36]. In contrast, the Polish National Multi-centre Health Survey (WOBASZ) demonstrated that the mean flavonoid intake in the Polish population was 1 g/person/day [41].

Important dietary sources of flavonoids are vegetables, fruits, seeds, some cereals, together with wine, tea and certain spices. Table 2 demonstrates flavonoid content in chosen foodstuffs. It should be noted that the presence of particular flavonoids in vegetables and fruits depends on the crop variety, location and type of cultivation, as well as the specific plant morphological part [13]. Differences in flavonoid contents between varieties of species are usually small, although in a few cases very high amounts have been observed, e.g. in certain berries and tea prepared from leaves of the Quingmao tree [2].

EFFECTS OF FLAVONOIDS ON THE CARDIOVASCULAR SYSTEM

The well recognised anti-oxidant properties of flavonoids resulted in the interest about their potential role in prevention of cardiovascular diseases [18]. For example, a recent study clearly showed health benefits of dietary flavonoids as there was a positive association between their intake and reduction of the risk of cardiovascular death in adult Americans [22]. The study demonstrated that both male and female subjects who consume large amounts of flavonoids (the top quintile) had the 18% lower mortality risk of cardiovascular diseases (CVD) compared to those whose intake was in the lowest quintile. Another study [3] demonstrated that high flavonoid consumption (flavones and flavanols) protected against hypertension. Subjects whose intake of these substances was in the top quintile, in comparison with those of the lowest consumption, exhibited the 8% risk reduction of development of this condition [3].

Atherosclerosis is a multifactorial disease. High blood concentration of oxidatively modified low density lipoproteins (ox-LDL) accelerates its development. Other causative factors include blood vessel inflammation and disorders of coagulation [18, 31]. Because of their antioxidant and chelating properties, flavonoids inactivate reactive oxygen species (ROS) and this way counteract plasma LDL oxidation and ameliorate inflammation of the blood vessel endothelium. Furthermore, flavonoids decrease activity of xanthine oxidase, NADPH oxidase, and lipoxygenase ie. the enzymes that increase ROS production. Anti-arteriosclerotic action of flavonoids is related also to the reduction of inflammation in the blood vessel wall through inhibition of the influx of leucocytes. Flavonoids also decrease activity of such enzymes as 15-lipoxygenase (15-LOX) and cyclooxygenase (COX, particularly COX-2). These enzymes participate in formation of, prostaglandins and leukotrienes, substances that mediate inflammation, from arachidonic acid. Decline in their secretion results in reduction of synthesis of prostaglandin PGE2, leukotriene B4 and thromboxane A2, what in turn leads to decrease in inflammation and platelet aggregation. Inhibition of these enzymes results also in protection of LDL against oxidation and regulates capillary pressure back to normal [18].

Beyond of protection of blood vessels against ox-LDL, antiatheromatous action of flavonoids results also from suppression of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA) activity. This enzyme plays a key role in the synthesis of cholesterol in the human body, and thereby influences its plasma levels. Inhibition of its activity lowers intracellular cholesterol concentrations and results in the following increase in expression of LDL receptors. This in turn raises the cellular lipoprotein uptake and removal of cholesterol from the circulation. Hesperetin is a good example of a flavonoid, found in lemons and oranges, which reduces blood cholesterol level in the aforementioned way [18]. Furthermore, a randomised, double-blind study, that included cell culture, demonstrated in subjects with metabolic syndrome that oral administration of 500 mg of hesperetin daily over 3 weeks stimulated endothelial nitric oxide (NO) formation, what was probably related to the decreased activity of proinflammatory cytokines. This study showed that a three week hesperetin supplementation improves endothelial function, reduces inflammation and beneficially affects lipid profile in patients with metabolic syndrome [27].

It was shown that such flavonoids as rutin and its derivatives, along with hesperetin, help seal and reinforce blood vessel walls [18, 23]. These substances, similarly to vitamin C, enhance collagen synthesis and thus make the connective tissue in blood vessels more elastic. Rutin and its derivatives are used as a medication aimed at regulation of capillary permeability and improvement of peripheral circulation [23]. Flavonoids, such as quercetin or rutin, have anti-aggregating properties, and thereby reduce the risk of clot formation near the damaged endothelium [18]. By interaction with platelet integrins, these substances prevent platelets from sticking. They also stimulate NO formation in the vascular endothelium what facilitates vasodilation, and thus plays a key role in regulation of blood pressure [18].

Obesity is an important and independent risk factor for CVD and is strongly associated with dyslipidaemia, insulin resistance and type 2 diabetes [29]. Research on the effects of long-term flavonoid dietary supplementation in obese or normal body mass mice, in comparison with diet without addition of these substances, showed improved lipid profile, decreased insulin resistance and reduced visceral adipose tissue mass. The non-obese mice that consumed flavonoids demonstrated reduced levels of atherogenic cholesterol fractions (non-HDL cholesterol) [29]. These findings confirm the protective effects of flavonoids on the cardiovascular system.

EFFECTS OF FLAVONOIDS ON THE NERVOUS SYSTEM

Effectiveness of flavonoids in prevention of age--related neurodegenerative diseases has been much investigated in the recent years. It concerns particularly dementia, Parkinson's and Alzheimer's diseases. It seems that flavonoids can modulate neuronal function [21, 26, 34, 38]. Diets rich in these substances were shown to beneficially affect maintenance of human cognitive functions, probably through protection of neurons, enhancement of their function and regeneration [38]. Reactive oxygen and nitrogen species are involved in the development of many neurodegenerative diseases, whilst dietary flavonoids have been shown to counteract effectively oxidative neuronal damage.

It was demonstrated that use of the extract from the gingobiloba plant, that is rich in flavonoids, may beneficially influence treatment of the age-related dementia and Alzheimer's disease [1]. Tangeretin, a flavonoid that belongs to the flavone subclass, found mainly in citrus fruits, was shown to provide protection in Parkinson's disease. Animal models of this condition is based on striatal damage by the neurotoxic substance 6-hydroxydopamine, what in turn leads to damage of the nigrostriatal pathway that connects the substantia nigra with the striatum. The latter is responsible, amongst others, for planning of body movements. Damage of this area underlies Parkinson's disease. It was shown that tangeretin given to mice passes the blood-brain barrier (BBB) and protects the nigrostriatal pathway against adverse effects of 6-hydroxydopamine [8].

The PAQUID study (Personnes Age'es QUID), published in 2007, convincingly demonstrated that dietary flavonoids in the elderly support their cognitive functions [16]. The 10 years long observation was performed in 1640 subjects aged above 65 years, free from dementia at baseline. The data about flavonoid consumption were obtained by means of a food frequency questionnaire that listed foodstuffs containing these substances. At each visit (four times) every subject underwent cognitive tests including Mini-Mental State Examination, Benton's Visual Retention Test and the 'Isaacs' Set Test. Participants whose flavonoid intake was in the two highest quartiles (ie. above 13.6 mg/day) had better cognitive function after 10 years than those who consumed less of these compounds. Moreover, subjects who ingested the least amounts of flavonoids (below 10.38 mg/day), lost on average 2.1 points in the Mini-Mental State Examination scale, while those with the highest consumption (above 17.7 mg/day) lost only 1.2 points. These findings demonstrated that regular consumption of dietary flavonoids exerts beneficial effect on cognitive function maintenance during aging [16].

The multitude of effects resulting from consuming flavonoids, both with foodstuffs and concentrated sources, appears to be related to two parallel processes. The first is regulation of the neuronal signal cascade what results in the inhibition of cell apoptosis that is caused by the action of neurotoxic substances. This promotes neuronal survival and differentiation [34]. Secondly, flavonoids seem to exert beneficial effects on the peripheral and central nervous systems by generation of changes in the cerebral blood flow. This can induce angiogenesis and growth of new nerve cells in the hippocampus. These processes are important for maintenance of neuronal and cognitive brain functions [34].

It seems that regular consumption of foods rich in flavonoids reduces the risk of neurodegenerative diseases and counteracts or delays the onset of age-related cognitive disorders. However, mechanisms of flavonoid action are not entirely clear. The question then arises as to when to use these substances to ensure their optimal effectiveness and which of them produce the strongest protection of the nervous system. Further studies on this wide group of compounds are therefore necessary to provide satisfactory answers to these questions.

ANTICANCER ACTION OF FLAVONOIDS

Chemoprevention is defined as the use of natural or synthetic substances to inhibit or reverse carcinogenesis [24]. Much attention, in this respect, is focused on flavonoids [4, 5, 10, 14, 19, 28, 35]. Epidemiological and clinical studies suggest that these compounds can prevent cancer through their interaction with various genes and enzymes [4]. It seems that biologically active substances found in foodstuffs may affect such stages of carcinogenesis as initiation, promotion and progression [24]. Many mechanisms of flavonoid action have been discovered. In the initiation and promotion stages, they include: inactivation of the carcinogen, inhibition of cell proliferation, enhancement of DNA repair processes, and reduction of oxidative stress. In the progression phase flavonoids may induce apoptosis, inhibit angiogenesis, exhibit antioxidant activity, and also cytotoxic or cytostatic action against cancer cells [4, 19, 24, 40].

Prevention of metabolic activation of procarcinogens is related to flavonoid interaction with phase I enzymes that are responsible for metabolism of various endogenous or exogenous substrates. This results from inhibition of the cytochrome P450 enzymes, such as CYP1A1 and CYP1A2. Flavonoids thus protect against cellular damage arising from the activation of carcinogenic factors. Another mechanism of their action is related to reinforcement of mutagen detoxification through induction of the phase II enzymes, such as glutathione S-transferase (GST) and UDP-glucuronyl transferase (UDP-GT), which detoxify and eliminate carcinogens from the body [4, 15].

The anticancer effects of flavonoids can also be explained by the cell cycle inhibition. There are two classes of regulatory molecules responsible for cell cycle progression: cyclins and cyclin-dependent kinases (CDKs), which are activated under the influence of mitogenic signals within the cell. The uncontrolled activation of CDKs plays a key role in the pathogenesis of cancer. Various types of cancer are linked to excessive CDKs activity through gene mutation. For this reason, much research is increasingly focused on substances that can inhibit or modulate CDKs. These actions may exhibited by such flavonoids as: genistein, quercetin, daidzein, luteolin, kaempferol, apigenin, and epigallocatechin.

Current evidence about the anticarcinogenic potential of flavonoids are however still equivocal. Some studies, that were performed in animals or various cell models, indicate that certain flavonoids may inhibit both cancer initiation and progression [10, 30, 37]. However, experiments on rats, conducted to determine the effect of tangeretin and quercetin on the risk of cancer occurrence arising from alphatoxin B1 induction (initiation and promotion of hepatic cancer) showed that whereas tangeretin administrated during tumour initiation reduced the number of precancerous lesions, quercetin did not exhibit such effect [30]. Another study showed that the development of lung cancer in mice exposed to tobacco smoke was arrested by consumption of both black and green teas. The results demonstrated that catechins contained in tea may protect against development of cancer [37]. A further research that tested influence of selected compounds on cultured human liver cells demonstrated that luteolin and apigenin also provided effective protection against cancer development. These flavonoids seem to inhibit CDKs. However, other studies indicate that flavonoids have weaker actions *in vivo* compared to that *in vitro* [11, 32]. An investigation on whether quercetin prevents lung cancer in mice showed that this substance, in spite of its strong biological activity, is not absorbed by these animals efficiently enough. The authors however suggest that further work should be focused on making the absorption mechanism of this substance more effective what would probably promote the expected anticancer action [32].

The studies quoted above were performed in animals, and so the conclusions should be extrapolated to humans with caution. Observational studies conducted on various human populations are also equivocal [10, 14, 35]. The Iowa Women's Health Study investigated the effect of dietary flavonoid consumption on the incidence of cancer of the lung, colon, breast and pancreas in 34,708 post-menopausal women who were observed in 1986 – 2004. Their dietary habits were determined by means of a food frequency questionnaire. Results showed that regular flavonoid consumption significantly reduced the risk of the lung cancer, particularly in the women who had stopped smoking. However, there was no evident effect of flavonoid consumption on the risk of other cancers [5]. Another study, performed in 34,408 women (aged above 45 years), demonstrated no significant link between intake of foods rich in flavonoids and the risk of cancer [35]. Despite of these findings, a meta-analysis of 12 studies showed a reduced risk of breast cancer in women, especially postmenopausal, who consumed large amounts of flavonoids, such as flavonols and flavones [14]. Further studies are therefore required to assess the promising influence of flavonoids on the human body.

SUMMARY

Flavonoids exhibit manifold effects in protection of the human body. However, the underlying mechanisms are still not fully understood. According to current knowledge, a diet that includes flavonoid containing products should be promoted. Among foods that provide large amounts of these substances there are: citrus fruits, blueberries, blackberries, onions, peppers, a variety of teas, and also oregano and parsley. However, it should be emphesized that toxicity of flavonoids consumed in large doses remains unknown. For this reason, use of their dietary supplements should be considered with caution. The question arises as to when to use these substances to enable their most effective action, and as to which flavonoids are the most beneficial to human health. It is presumed that flavonoids exert stronger effects *in vitro* than *in vivo,* and thus it is important to determine their mechanisms of action at the molecular level. Further studies in this area are therefore greatly needed.

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Conflict of interest

The authors declare no conflict of interest.

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