

Which Sources of Flavonoids: Complex Diets or Dietary Supplements?¹

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ABSTRACT

There is increasing interest in the potential health benefits of dietary flavonoids. Fruits and vegetables, tea, and cocoa are rich natural sources of flavonoids. Epidemiological studies have indicated that consumption of these foods is likely to be associated with a reduced risk of cardiovascular disease, but the etiology of this benefit is not yet clearly defined. Furthermore, in some acute interventions, a positive effect of tea and cocoa on vascular function has been reported. An alternative source of flavonoids is dietary supplements, which have become increasingly popular in the recent past. In this context, it needs to be critically evaluated whether vascular health-promoting and other positive properties of flavonoid-rich diets can be replaced by purified flavonoids as dietary supplements. Plant sources of flavonoids contain a complex mixture of secondary plant metabolites and not only flavonoids per se. This complex mixture of secondary plant metabolites cannot be simply exchanged by single purified compounds as dietary supplements. If flavonoids are given as dietary supplements, toxicity issues as well as nutrient drug interactions need to be taken into account. Purified flavonoids given in high doses as dietary supplements may affect trace element, folate, and vitamin C status. Furthermore, they may exhibit antithyroid and goitrogenic activities. In this review article, the available literature on the safety issues surrounding high dose supplemental flavonoid consumption has been summarized. *Adv. Nutr.* 2: 8–14, 2011.

Introduction

There is increasing evidence that a diet rich in fruit and vegetables may be associated with a reduced risk of cardiovascular diseases (CVD),⁴ with CVD representing the leading cause of death in Western societies (1). A meta-analysis of 9 cohort studies (comprising >220,000 men and women) showed that fruit and vegetable consumption was inversely associated with the risk of CVD. Importantly, the risk of CVD was dose dependent and decreased by 4% for each additional portion per day of fruit and vegetables and by 7% for fruit consumption (2). In the European Prospective Investigation into Cancer and Nutrition study (3), the intake of vegetables, legumes, and fruit was significantly associated with reduced risks of CVD mortality and mortality due to non-CVD/noncancer causes [RR = 0.88 (95% CI = 0.81–0.95) and 0.90 (0.82–0.99), respectively] in a diabetic population comprising >10,000 individuals. In a meta-analysis including >250,000 individuals, He et al. (4) quantitatively reported on the relation between fruit and vegetable intake and the incidence of stroke. Compared with individuals who consumed <3 servings/d of fruit and vegetables, the pooled RR of stroke was 0.89 (95% CI = 0.83–0.97) for those

consuming 3–5 servings/d and 0.74 (0.69–0.79) for those consuming >5 servings/d. Overall, there seems to be strong epidemiological support for the recommendations to consume at least 5 servings/d of fruit and vegetables.

In addition to a number of potentially bioactive components such as fiber, folate, antioxidant vitamins, and potassium, fruits and vegetables are important sources of dietary flavonoids (5,6). Furthermore, flavonoid-rich tea (*Camellia sinensis*) and cocoa represent relatively concentrated sources and their impact on vascular function is becoming apparent (7,8). Due to their widespread occurrence, flavonoids are regularly ingested by humans. The individual intake of flavonoids, however, varies considerably depending on the type of diet consumed. A number of epidemiological studies have examined the impact of total or individual flavonoid intake. For example, Huxley and Neil (9) assessed the relation between dietary flavonol intake and coronary heart disease mortality in a meta-analysis comprising 7 prospective cohort studies. The authors concluded that high dietary intake of flavonols from fruits and vegetables as well as from tea and red wine may be associated with a decrease in CVD mortality in free-living populations (9). To the best of our knowledge, there is currently no meta-analysis reporting the effect of dietary flavonoid supplements on CVD risk. Nevertheless, the use of dietary flavonoid supplements is becoming increasingly popular (10).

Cell culture studies using endothelial cells, monocytes, smooth muscle cells, and platelets have helped us to identify the potential

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⁴ Abbreviations used: ABC-transporter, ATP-binding cassette transporter; CVD, cardiovascular disease; CYP, cytochrome P450 monooxygenase; EGCG, epigallocatechin gallate; GTC, green tea catechin; GST, glutathione-S-transferase; SULT, sulfotransferase; SV, simvastatin; SVA, simvastatin acid; UGT, UDP-glucuronosyltransferase.

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underlying cellular and molecular mechanisms by which dietary flavonoids may affect vascular health. These *in vitro* studies in cultured cells indicate that purified flavonoids may positively affect critical steps in atherogenesis, including LDL oxidation (11,12), inflammation (13), chemotaxis (14), cell adhesion (15), foam cell formation (16), smooth muscle cell proliferation (17), and platelet aggregation (18). Furthermore, there is evidence that purified flavonoids activate endothelial NO synthetase (8,19) and inhibit arginase (20), thereby increasing the concentration of vasodilatory NO.

Based on cell culture studies, further *in vivo* studies in laboratory rodents, including mice (21) and rats (22), as well studies in (cholesterol-fed) rabbits (23) indicate potential positive effects of dietary flavonoids on vascular health. There are also several studies in humans that suggest a role of flavonoids as dietary supplements in CVD prevention (for review, see 24,25). Overall, all subclasses of flavonoids (Fig. 1), including anthocyanidins (26), flavonols (27), flavones (28), flavanones (28), flavanols (8), and isoflavones (29), have been investigated *in vitro* and *in vivo* in terms of their potential to prevent CVD.

There is currently an extensive range of flavonoid supplements on the market (30). Suppliers of such supplements recommend daily flavonoid intakes in amounts that are many times higher than those doses which can normally be achieved from a flavonoid-rich diet. For instance, the flavonol quercetin has been marketed as a dietary supplement with recommended daily doses of up to 1 g and more (31), whereas the daily quercetin intake from foods has been estimated to be 10–100 mg (32,33). Another example are isoflavone-based nutraceuticals (e.g. pills, tablets, extracts), which are one of the most widely tested and used flavonoid supplements so far (30). The declared content of isoflavones is variable (e.g. 50, 135,

and 500 mg) and different daily doses are recommended. However, at present, no specific dosage of isoflavones has been established to exert a beneficial effect (30). Isoflavones are scarce in Western diets compared with Asian diets, because the main isoflavone sources are soy-derived products.

The question arises whether supplements containing such supra-physiological flavonoid levels may exhibit adverse effects (Table 1). In addition, it is likely that a large proportion of individuals taking dietary flavonoid supplements are also taking conventional drugs (34). The concomitant intake of “supra-nutritional” flavonoid doses together with conventional drugs may lead to flavonoid-drug interactions (34). This additionally raises concerns about the safe use of dietary flavonoids.

Current status of knowledge

Flavonoid-trace element interactions

Purified flavonoids (35) as well as flavonoid-rich extracts (36) have been reported to chelate iron *in vitro*. Ren et al. (37) studied the complexation mechanisms of several flavonoids (quercetin, luteolin, galangin, kaempferol, and chrysin) with iron. The most important chelation site was the 3-hydroxyl-4-carbonyl group followed by the 4-carbonyl-5-hydroxyl group. Quercetin and iron form orthogonal Fe-O bonds. Three quercetin molecules are required to saturate the bonds of a single Fe ion *in vitro*.

As far as green catechins are concerned, the galloyl group seems to be mainly responsible for iron binding, with the green tea catechin (GTC) epigallocatechin gallate (EGCG) containing 2 galloyl groups. In this context, in a randomized, double-blind, placebo-controlled trial, Ullmann et al. (38) studied nonheme iron absorption in response to pure crystalline EGCG. Nonheme iron absorption

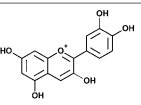
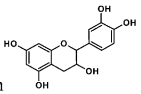
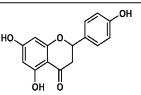
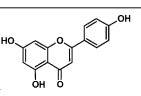
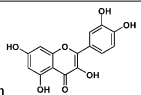
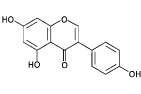
Flavonoid group	Examples	Food sources	Chemical structure
Anthocyanins	Cyanidin, Pelargonidin, Peonidin	Aubergine, blackberry, black currant, blueberry	 Cyanidin
Flavan-3-ols, Procyanidins	Catechin, Epicatechin, Epigallocatechin	Chocolate, green tea, beans, cherry	 Epicatechin
Flavanones	Hesperidin, Naringenin, Eriodictyol	Orange juice, grapefruit juice, lemon juice	 Naringenin
Flavones	Apigenin, Luteolin	Parsley, celery, capsicum pepper	 Apigenin
Flavonols	Quercetin, Kaempferol, Myricetin	Onions, apples, curly kale, leek	 Quercetin
Isoflavones	Genistein, Daidzein, Glycitein	Soy flour, soybeans, soymilk	 Genistein

FIGURE 1 Examples, chemical structure, and main dietary sources of major classes of flavonoids.

TABLE 1 Potential beneficial and adverse effect of flavonoid supplements¹

Beneficial effects	Adverse effects
Inhibition of LDL oxidation and induction of paraoxonase	Decrease in trace element bioavailability
Activation of endothelial NO synthetase and inhibition of arginase	Antithyroid and goitrogenic activity
Inhibition of chronic inflammatory processes	Impairment of folate uptake
Inhibition of chemotactic proteins (e.g. MCP1) and cell adhesion molecules (e.g. ICAM1, VCAM1, E-selectin) expression	Inhibition of vitamin C transport
Inhibition of smooth muscle cell proliferation	Nutrient–drug interactions
Inhibition of platelet aggregation	Estrogenicity

¹ MCP1, Monocyte chemotactic protein-1; E-selectin, endothelial-selectin; ICAM1, intracellular adhesion molecule-1; VCAM1, vascular cell adhesion molecule-1.

was dose-dependently decreased by 14 and 27% due to 150 and 300 mg/d EGCG relative to the placebo group. Furthermore, Sandstroem et al. (39) studied the effect of green tea or rosemary extract added to foods on nonheme iron absorption in humans. Iron absorption decreased from (mean \pm SD) 12.1 \pm 4.5% to 8.9 \pm 5.2% ($P < 0.01$) in the presence of green tea extract (37 mg catechins) and from 7.5 \pm 4.0% to 6.4 \pm 4.7% ($P < 0.05$) in the presence of rosemary extract (32 mg of phenolic substances).

Ma et al. (40) have recently shown that polyphenols also inhibit heme iron absorption mainly by reducing basolateral iron exit rather than decreasing apical heme iron uptake in intestinal cells.

It should be considered that iron element bioavailability seems to be not only impaired by purified flavonoids or flavonoid extracts but also by flavonoid-rich food items such as green and black tea, coffee, cocoa, red wine, and legumes (41–44).

The flavonoid concentration of dietary supplements is likely to be many times higher than those consumed as part of a normal diet. Thus, for individuals at risk of iron deficiency, dietary flavonoid supplements may be problematic. In addition, interactions between flavonoids and copper (45) as well as manganese (46) have been reported.

Interactions between flavonoids and folate as well as vitamin C and vitamin E

GTC have been shown to inhibit the activities of enzymes involved in folate uptake. Using an in vitro enzyme activity assay, we observed a time- and dose-dependent inhibition of dihydrofolate reductase activity by EGCG and a green tea extract (47). A recent cell culture study showed that certain gallated derivatives of green tea polyphenols, namely EGCG, the predominant catechin in green tea, and epicatechin gallate, inhibited folic acid uptake in Caco-2 cells (48). In our studies in rats, green tea extract significantly decreased serum 5-methyl-tetrahydrofolate concentrations (47). In agreement with the cell culture studies, a study in humans suggests a potential risk of diminished folic acid bioavailability by both green and black tea extracts (49). However, in our human pilot study, no differences in plasma folate concentrations in response to dietary GTC supplementation were observed (47).

Song et al. (50) demonstrated that flavonoids, such as quercetin, inhibit sodium dependent vitamin C transporter 1 in cultured cells. Furthermore, quercetin significantly inhibited ascorbate absorption in rats (50). To the best of our knowledge, interactions between flavonoids and vitamin C in humans have not yet been reported.

We recently studied the effect of dietary quercetin, catechin, and genistein on tissue vitamin E levels in rats. The concentrations of α - and γ -tocopherol in the plasma, liver, lung, and cortex of

flavonoid-fed rats were not significantly different from the concentrations measured in control rats receiving the flavonoid-free basal diet (51). Furthermore, dietary supplementation of growing pigs with green tea polyphenols did not affect tissue vitamin E levels and plasma antioxidant capacity in pigs (52). Similarly, in humans, urinary excretion of the α -/ γ -tocopherol metabolites was not significantly affected by dietary intervention with an aqueous green tea supplement (53). Daily dietary quercetin supplementation did not affect concentrations of plasma α - and γ -tocopherols or plasma antioxidative capacity in humans (54). Based on our studies in mice, rats, and humans, it is therefore unlikely that the flavonoids investigated may impair plasma vitamin E status in vivo.

Antithyroid and goitrogenic activity of flavonoids

Flavonoids may exhibit antithyroid and goitrogenic activity. Ferreira et al. (55) studied the in vitro effects of various flavonoids on thyroid type 1 iodothyronine deiodinase activity in a murine thyroid microsome fraction and found type 1 iodothyronine deiodinase activity significantly inhibited by isoflavones, quercetin, and catechins.

In a rat study by Chandra and De (56), a decreased activity of thyroid peroxidase and 5'-deiodinase was reported in response to dietary green tea extracts. Serum thyroid hormone tri-iodothyronine and thyroxine levels were found to be significantly reduced and associated with a significant elevation of serum thyroid-stimulating hormone. The authors concluded that green tea extracts at high doses could adversely alter thyroid function (56).

Furthermore, isoflavones have been reported to inhibit thyroid hormone biosynthesis and may exert at high concentrations goitrogenic effects in humans. Milerova et al. (57) found a significant correlation between circulating isoflavone concentrations in blood and thyroid function. However, a recent long-term human study in almost 400 osteopenic, postmenopausal women suggested that genistein aglycone intake does not significantly increase the risk of clinical or subclinical hypothyroidism at the dose of 54 mg/d (58). There are also other safety issues associated with high-dose isoflavone intakes, mainly related to their estrogenicity (59). Due to the possible adverse effects of isoflavones and the lack of consensus regarding the health benefits derived from isoflavones consumption, the AHA does not recommend the use of isoflavone supplements (60).

Flavonoid-drug interactions

Flavonoids are subject to the same metabolic pathways as “classical” xenobiotics. Thus, flavonoids may interfere with the absorption, tissue distribution, metabolism, and excretion of drugs, altering their pharmacokinetics profiles (34). Indeed, many in vitro studies

have shown effects of flavonoids on various cytochrome P450 monooxygenase (CYP) isoforms, Phase II conjugation enzymes, and drug transporters [reviewed in (34,61,62)]. In addition, flavonoids were able to alter the pharmacokinetics of concurrently administered drugs in some animal models (34).

Interactions of flavonoids with CYP. A number of studies have shown inhibition of various CYP by flavonoids [reviewed in (34,61)]. Among the various CYP isoforms (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, and 3A5), isoforms belonging to the CYP3A subfamily like CYP3A4 and 3A5 play a prominent role. They are the major CYP isoforms in the liver and intestinal tract and are responsible for the metabolism of ~50% of all prescribed drugs (63,64). The flavonols quercetin and kaempferol were shown to inhibit the metabolism of the calcium channel blockers nifedipine and felodipine by CYP3A4 in human liver microsomes at concentrations > 10 $\mu\text{mol/L}$, with the flavanone naringenin being less potent (65). Similar results were obtained in other studies using 17 β -estradiol, felodipine, or nifedipine as substrates for CYP3A4 (65,66). In addition to the 2 mentioned flavonols, the flavonol myricetin, the flavone apigenin, and the biflavone I3,II8-biapigenin were also reported to inhibit CYP3A4 activity at low micromolar concentrations in human liver microsomes (67).

Another important drug metabolized by CYP3A4 is the statin simvastatin (SV), a 3-hydroxy-3-methylglutaryl CoA reductase inhibitor primarily used for the treatment of hyperlipidemia. The lactone SV, which is an inactive prodrug like its analogue lovastatin, is transformed into the active form SV acid (SVA) in the plasma, liver, and probably intestinal mucosa by esterases with lactonase activity (68,69). The major enzyme responsible for metabolism of the parent prodrug SV and its active form SVA is CYP3A4 (70). Oxidative products of CYP-dependent metabolism (e.g. 3'-hydroxy, 6'-hydroxy, 3',5'-dihydrodiol metabolites) show no or only minimal inhibitory activity toward 3-hydroxy-3-methylglutaryl CoA reductase. CYP-dependent hydroxylation in turn increases the rate of subsequent conjugation and excretion; thus, potent CYP3A4 inhibitors are able to increase the plasma concentration and area under the plasma concentration-time curve of SV and SVA severalfold (71,72). Because quercetin was shown to inhibit CYP3A4 activity in vitro (see above), it was speculated by Cermak et al. (73) that high doses of quercetin might be able to increase the bioavailability of SV and SVA. However, quercetin (10 mg/kg) coadministered with SV (0.25 mg/kg) in pigs decreased plasma concentrations of SV during the first 5 h after intake. Thus, the authors excluded an inhibitory effect of quercetin on CYP3A4-mediated metabolism of SV, although quercetin did inhibit CYP3A4 in human liver microsomes (see above). One explanation for the lack of CYP3A inhibition by the flavonol in vivo could be the fact that hepatic quercetin concentrations did not reach a level that was shown to be bioactive in in vitro experiments (73).

Flavonoids have also been shown to influence the activity and/or expression of other CYP isoforms. For example, some flavonoids are potent inhibitors of CYP1A2. This isoform is mainly expressed in the liver and metabolizes several important drugs such as caffeine, theophylline, warfarin (see below), or propranolol (64). The pentamethoxyflavone tangeretin, which occurs in the peel of oranges and tangerines, inhibited the activity of CYP1A2 in human liver microsomes in a competitive manner (74). The grapefruit flavanone naringenin inhibited CYP1A2-dependent 3-demethylation of caffeine in human liver microsomes (75). The activity of this CYP isoform was also inhibited at low micromolar concentrations by the flavonols galangin and quercetin as well as by the biflavone I3,II8-biapigenin (76–78).

Cranberry juice has been implicated in interacting with warfarin. Warfarin is used for anticoagulation to a target international normalized ratio of 2.0–3.0 for most indications or 2.5–3.5 for high-risk indications; however, many drugs and dietary supplements induce fluctuations in the international normalized ratio (79). Such fluctuations may lead to therapeutic failure or bleeding complications (79). Flavonoids in cranberry juice are suspected to inhibit CYP2C9, the enzyme responsible for metabolism of S-warfarin, which would increase warfarin levels (80,81). S-warfarin is the more active enantiomer, whereas R-warfarin is mainly metabolized by CYP3A4 and CYP1A2. Alternatively, cranberry juice flavonoids might displace warfarin from albumin binding sites and transiently potentiate an anticoagulant response (82). Recent review and analysis of the literature revealed that ingestion of large volumes of cranberry juice (>600 mL/d) may destabilize warfarin therapy (79,83). However, small to moderate amounts of juice are not expected to cause such an interaction (79,83). It is not known how cranberry concentrates or supplements might interact with warfarin (83).

Interactions of flavonoids with phase II enzymes. The conjugation of drugs to increase their hydrophilicity is a major pathway in drug metabolism. It is performed by phase II enzymes. UDP-glucuronosyltransferases (UGT) use UDP-glucuronic acid as a cosubstrate and transfer glucuronic acid to available substrates. Generally, glucuronidation is a detoxification process that converts xenobiotics into less or nontoxic and more water-soluble metabolites, thereby facilitating their excretion in the urine or bile (84). Another group of phase II enzymes are sulfotransferases (SULT) that catalyze the transfer of a sulfonate group to an appropriate substrate (85). Other phase II reactions are the conjugation of drugs with glutathione by glutathione-S-transferases (GST) or acetylation of xenobiotics by N-acetyltransferases (86). It has been shown that all these phase II enzymes are affected by flavonoids in cell and animal models. For example, the flavone chrysin (25 $\mu\text{mol/L}$) induced an increase in mRNA levels, protein expression, and enzyme activity of the UGT isoform 1A1 in human Hep G2 cells and human colon carcinoma cells (87,88). At the same concentration, other flavones (e.g. apigenin, baicalein, and diosmetin) as well as the flavonols quercetin and kaempferol increased either the transcription or enzymatic activity of UGT1A1 in Hep G2 cells (89,90). Feeding rats a diet containing 1% (wt:wt) quercetin for 2 wk increased UGT activity in the small intestine and liver (91). In the same study, flavone increased UGT activity in the large intestine and liver at a dietary concentration of 0.5% (wt:wt) (91). In vivo perfusion of human jejunum with an onion and broccoli extract containing 60 $\mu\text{mol/L}$ quercetin significantly increased UGT1A1 mRNA in shed enterocytes. This was confirmed in Caco-2 cells with pure quercetin (92).

A number of studies have shown that flavonoids can be potent inhibitors of cytosolic SULT isoforms [reviewed in (34)]. In particular, quercetin exhibited a potent inhibitory impact on SULT activity in several in vitro investigations. Quercetin inhibited sulfation of 4-nitrophenol, a model substrate for SULT1A1, the major phenol SULT in human liver, and the sulfation of several drugs (e.g. salbutamol, minoxidil, paracetamol, and apomorphine) in human liver cytosol, with IC₅₀ concentrations in the nanomolar range (93–97).

We have previously shown that dietary quercetin significantly affected the activity of hepatic GST, whereas dietary catechin significantly changed NAD(P)H quinone oxidoreductase-1 activity (26%) in rats. Changes in GST and NAD(P)H quinone oxidoreductase-1 activity were partly reflected on mRNA levels. Our data indicate that dietary flavonoids modulate phase II enzymes in rat liver. This

in turn may affect the ability of the organism to detoxify endogenous and exogenous xenobiotics (98).

Interactions of flavonoids with drug transporters. A substantial number of studies demonstrate effects of flavonoids on transporters involved in drug metabolism (34,61,62). There are 2 main classes of transporters that are involved in the uptake and efflux of drugs and drug conjugates: 1) the ABC transporters, which belong to the ATP-binding cassette family; and 2) the transporters of the solute carrier family (34,61). Among the ABC transporters, interactions have been shown with P-glycoprotein, multi-drug resistance associated proteins (MRP1 and MRP2), and with breast cancer resistance protein (BCRP) (99). Most of the studies have demonstrated inhibitory effects of flavonoids on the substrate efflux in cells that either endogenously expressed these transporters or that were transfected with them [reviewed in (34,99)]. This flavonoid-ABC-transporter interaction could be beneficial for poorly absorbed drugs but could also result in severe drug intoxication, especially for drugs with a narrow therapeutic window. On the other hand, flavonoids are themselves substrates of ABC transporters. These proteins can affect the oral availability and tissue distribution of these compounds, modifying their beneficial effects (62,100). In contrast to the well-described interactions of flavonoids with ABC transporters, evidence for potential flavonoid effects on transporters of the solute carrier family is less clear.

Concluding remarks

Flavonoids that derive from fruits and vegetables are consumed in relatively low quantities. Furthermore, fruits and vegetables contain a complex mixture of secondary plant metabolites and not only flavonoids per se. This complex mixture of secondary plant metabolites cannot be simulated by single purified compounds as dietary supplements. Fruits and vegetables may contain other micronutrients (e.g. vitamin C, potassium, and folate) as well as dietary fiber; the latter is known to positively affect satiety, lower the dietary energy density, and decrease circulating LDL-cholesterol.

In this context, it has been stated by Ross and Kasum (101) that “the sum of parts (total fruit and vegetable intake) is more important in providing health benefits than only 1 plant constituent.” There is no such thing as a “magic bullet” (102) and we have to be critical in supplying flavonoids as a supplement, which may exceed the nutritive flavonoid intake manifold compared with vegetarian diets without supplements. People may also take more than 1 dietary flavonoid supplement at the same time and almost nothing is known about flavonoid-flavonoid interactions. It has been criticized that consumers may have too little information about product safety, contraindications, interactions, or effectiveness of supplements (30,103).

The consumer may have the misperception that dietary flavonoid supplements are devoid of toxicity and, therefore, they are safe to use because these compounds are “natural” (104). Also, when developing functional foods, the issue of the safety of flavonoids needs to be taken into account.

Acknowledgments

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