

**Lars Ernster Commemorative Issue****Guest Editors: Enrique Cadenas and Kelvin J. A. Davies****POTENTIAL HEALTH IMPACTS OF EXCESSIVE FLAVONOID INTAKE**

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Abstract—Plant flavonoids are common dietary components that have many potent biological properties. Early studies of these compounds investigated their mutagenic and genotoxic activity in a number of in vitro assays. Recently, a renewed interest in flavonoids has been fueled by the antioxidant and estrogenic effects ascribed to them. This has led to their proposed use as anticarcinogens and cardioprotective agents, prompting a dramatic increase in their consumption as dietary supplements. Unfortunately, the potentially toxic effects of excessive flavonoid intake are largely ignored. At higher doses, flavonoids may act as mutagens, pro-oxidants that generate free radicals, and as inhibitors of key enzymes involved in hormone metabolism. Thus, in high doses, the adverse effects of flavonoids may outweigh their beneficial ones, and caution should be exercised in ingesting them at levels above that which would be obtained from a typical vegetarian diet. The unborn fetus may be especially at risk, since flavonoids readily cross the placenta. More research on the toxicological properties of flavonoids is warranted given their increasing levels of consumption. © 2000 Elsevier Science Inc.

Keywords—Flavonoids, Toxicity, Mutagenicity, Genotoxicity, Quercetin, Free radicals

INTRODUCTION

Plant flavonoids are diphenylpropane derivatives that exert a wide range of biochemical and pharmacological effects. Their antioxidant properties [1,2], cytostatic effects in tumorigenesis [3], and ability to inhibit a broad spectrum of enzymes, such as protein kinase C [4], tyrosine protein kinase [5], and topoisomerase II [6,7], have led researchers to regard these compounds as potential anticarcinogens and cardioprotective agents. These findings have contributed to the dramatic increase in the consumption and use of dietary supplements containing high concentrations of plant flavonoids by some health-conscious individuals. Marketing strategies by manufacturers of flavonoid concentrates and herbal remedies advertise and often exaggerate their nontoxic therapeutic effects, most of which are not substantiated by regulated clinical trials. Furthermore, manufacturers' recommended doses of these products might far exceed

the flavonoid dose one could attain from a typical vegetarian diet. This, coupled with the common misconception that if a little of something is good then more is better, may result in individuals ingesting extremely high levels of these compounds.

Despite the apparently beneficial health effects of flavonoids, several studies indicate their mutagenicity and genotoxicity in both bacterial and mammalian experimental systems [8–10] (Table 1). This may be due to their activity as pro-oxidants [11,12] in generating free radicals that damage DNA or their inhibition of DNA-associated enzymes such as topoisomerase. Unrepaired or misrepaired oxidative DNA damage can result in DNA strand breaks and mutations [13,14] that may lead to irreversible preneoplastic lesions. Furthermore, high intakes of these compounds may potentiate other deleterious effects due to their diverse pharmacological properties, which may alter drug and amino acid metabolism, modulate the activity of environmental genotoxicants, and alter the activity of other key metabolizing enzymes. While there is ample evidence that a flavonoid-rich diet may promote good health and provide protection from age-related diseases, there remains uncertainty regarding the conditions and the levels of flavonoid intake neces-

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Table 1. Mutagenicity and Genotoxicity Studies on Flavonoids

Mutagenic in the Ames assay	[78] [77] [79]
Induction of recombinational mutations	[8]
Induction of chromosomal aberrations and sister chromatid exchanges	[80] [9]
Generation of micronuclei in human lymphocytes	[82] [81]
Formation of hydrogen peroxide, super-oxide, and hydroxyl radicals	[83]
Strand scission in DNA	[89]
Pro-oxidant activity resulting in DNA degradation and lipid peroxidation	[90] [12]
Pro-oxidant activity and inhibition of glutathione-S transferase	[91]

sary to pose a potential health hazard. Therefore, this review will seek to evaluate the potential toxicity of some of these compounds, particularly at levels higher than those generally found in a normal diet, but which may be attained through supplementation of plant extracts.

CHARACTERISTICS AND CONTENT OF FLAVONOIDS IN COMMON FOODS

Flavonoids are widespread in nature, occurring in all plant families, and are found in considerable quantities in fruits, vegetables, grains, cola, tea, coffee, cocoa, beer, and red wine [15–17]. In the U.S., the daily dietary intake of mixed flavonoids is estimated to be in the range of 500 to 1000 mg [18], but can be as high as several grams in those supplementing their diets with flavonoids or flavonoid-containing herbal preparations such as ginkgo biloba, Pycnogenol 227 (Horphag Research, Ltd., Guernsey, UK), or grape seed extract. Assuming that absorption from the gastrointestinal tract is effective, such intakes could provide pharmacologically active concentrations in body fluids and tissues.

Among the major groups of flavonoids in the human

diet are the flavonols, proanthocyanidins (which include the catechins), isoflavonoids, flavones, and flavanones [19,20] (Fig. 1). The closely related lignans (resorcylic acid lactones) have similar properties to flavonoids, and are therefore included here for completeness. Quercetin, a flavonol, is the most predominant flavonoid in the human diet and estimates of human consumption are in the range of 4 to 68 mg per day based on epidemiological studies in the U.S., Europe, and Asia [21–24]. Among these studies, the Japanese population had the highest levels of flavonol intake, which was mainly attributed to their green tea consumption.

Biological activities ascribed to quercetin include its antiviral [25,26], anti-inflammatory [27], antiproliferative [28,29], and antimicrobial properties [30]. Quercetin is found in high concentrations in commonly consumed foods such as onions, apples, kale, [15], red wine, and green and black teas [17] (Table 2). Due to absorption differences in conjugated forms, the bioavailability of quercetin varies greatly in foods. Hollman and coworkers found that the absorption of quercetin- β -glucosides was far greater than the absorption of quercetin without its sugar moiety [31]. Additionally, the quercetin glucosides in onions are more readily absorbed than those found in tea [32] and the rutinoides found in apples [33].

Red wine and tea also contain high levels of catechins that are condensed tannins, which contribute to the astringency of these beverages. Catechins comprise approximately 30% of unprocessed tea leaves, the bulk of which is epigallocatechin-3-gallate (EGCG), the most biologically active component found in green tea [34]. EGCG is known as a potent antiproliferative and cytostatic agent of human cancer cell lines [35,36], and has been recognized as a potent antioxidant and chemoprotective agent [37,38].

Isoflavones, coumestans, and lignans, commonly called “phytoestrogens,” are nonsteroidal compounds with weak estrogenic activity. These compounds may compete with endogenous hormones, as well as inhibit a

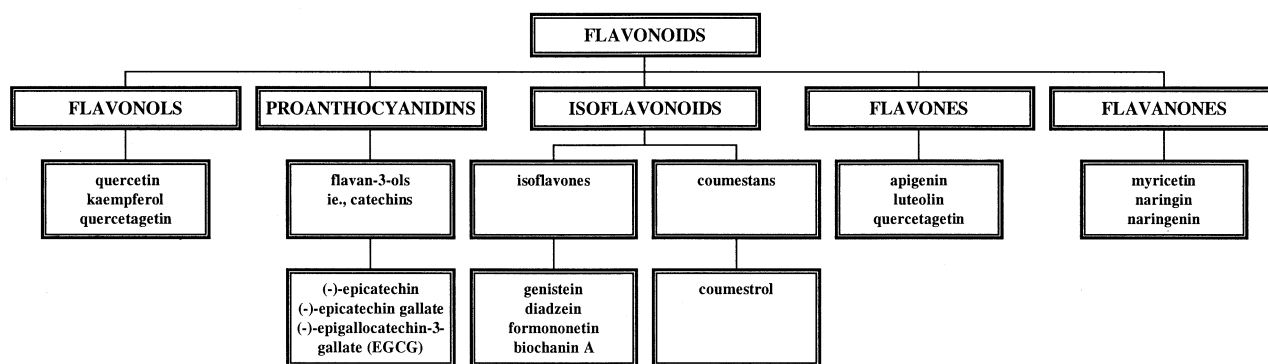


Fig. 1. Family of major dietary flavonoid groups.

Table 2. Flavonoid Sources and Levels in Commonly Consumed Foods

Flavonoid	Common Sources	Levels (mg/kg) ^a	Per 6 oz. serving (mg) ^a	References
Quercetin	Onion	284–486	48–83	[15]
	Apple	21–72	3.6–12	[15]
	Kale	110	19	[15]
	Red wine	4–16 mg/l	0.7–2.7	[17]
	Green/black teas	10–25 mg/l	1.7–4.2	[17]
Genistein/diadzein	Tofu	159–306 (genistein)	27–52	[16]
		57–117 (diadzein)	9.7–20	
	Soy milk	21 (genistein)	4.9	[16]
		6.8–7.2 (diadzein)	1.2	
	Soy milk formula	19–23 (genistein)	3.2–3.9	[101]
		15–19 (diadzein)	2.5–3.2	
Coumestrol	Alfalfa sprouts	47	8	[44]
	Clover sprouts	281	48	[44]
Secoisolariciresinol	Flaxseed	817	139	[55]
	Flaxmeal	2260	384	[55]
Apigenin/luteolin	Millet (fonio)	150 (apigenin)	25.5	[63]
		350 (luteolin)	59.5	
Naringin	Grapefruit juice	100–800 mg/l	17–136	[93]

^a mg in wet weight.

number of enzymes involved in estrogen metabolism [39–42]. Genistein and diadzein are the primary isoflavones with estrogenic properties. They are found in legumes such as lentils, chickpeas, soybeans, and other soy-based products such as tofu, miso, soy milk, and tempeh [16,43,44] (Table 1). Daily dietary intake of soy protein in heavy soy consumers such as in Asian populations is estimated to be 20 to 80 g, whereas the average Western dietary intake is approximately 1 to 3 g [45]. Assuming a total isoflavone concentration of soy-based products to be in the range of 1 to 3 mg/g, expected daily isoflavone intakes would range from 20 to 240 mg for Asians, and 1 to 9 mg in other populations.

Genistein has been considered the primary anticancer constituent in soy, based on putative *in vitro* activities that include its ability to inhibit topoisomerase I and II activity [46], inhibit protein tyrosine phosphorylation [47], induce differentiation of cancer cell lines [48,49], and act as an estrogen antagonist [50]. Other studies show the suppressive effects of genistein on breast carcinoma cells through angiogenesis inhibition, G₂-M arrest, induction of p21^{WAF/CIP1} expression, and apoptosis [51,52]. Coumestans, such as coumestrol, are found in high concentrations in alfalfa and clover [44] and have been recognized, along with formononetin, as the cause of infertility in grazing herbivores [53]. While coumestrol acts as an estrogen mimic directly, formononetin has to be metabolized to the estrogenically active compounds diadzein, equol, or O-demethylangolensein.

Lignans are present in many fruits, vegetables, tea beverages, and cereal grains such as flaxseed. Flaxseed is one of the richest sources of phytoestrogens [54]. It contains very high concentrations of the lignan 2,3-bis(3-methoxy-4-hydroxybenzyl)butane-1,4-diol (secoisolar-

iciresinol) [55] (Table 1), which is a precursor to the primary mammalian lignans, enterolactone and enterodiol [56]. Lignans are known for their antioxidant activity, and have recently been associated with a reduction in hypercholesterolemic atherosclerosis in animal feeding studies [57]. Schottner et al. have demonstrated their weak estrogenic activity and high affinity for human sex hormone-binding globulin, which may enhance estrogen clearance and contribute to a decreased risk of hormone-dependent cancers [58]. These findings have led to an increased consumption of flaxseed as an anticarcinogen and cardioprotective agent. However, the long-term effects of prolonged supplementation with a highly bioactive estrogenic substance such as flaxseed have not been studied. It may be that excessive intake could contribute to the growth of some estrogen-dependent tumors and feminization in men.

Unlike the phytoestrogens mentioned above, flavones do not possess estrogenic activity. However, the flavones, apigenin and luteolin, act as potent inhibitors of aromatase and 17 β -hydroxysteroid oxidoreductase, enzymes involved in estrogen metabolism [59,60]. Studies have also demonstrated these flavones and several glycosylflavones are potent goitrogens [61–63] particularly in association with millet consumption (Table 2).

Given the wide and varied distribution of flavonoids in the human diet, their potential bioactivity may be underestimated particularly in their use as food supplements. Consequently, this raises questions regarding their possible health risks and benefits, meriting a closer examination of the bioavailability and absorption of these compounds.

METABOLISM AND PHARMACOKINETICS OF FLAVONOIDS

Although the metabolism of flavonoids has not been well characterized, studies have shown that there is great variability in the preferential pathways among individuals [64,65], which may be due to differences in gut microflora populations. Early studies considered flavonoids nonabsorbable due to their general occurrence as conjugates of sugars called glycosides [18]. Only free flavonoids called aglycones were thought to penetrate the intestinal wall. Complete degradation of flavonoids was assumed to occur through pyrone ring cleavage by resident intestinal microorganisms producing phenylacetic and phenylpropionic acids and other inert byproducts [66]. However, while pyrone ring cleavage does occur, glycosidases release aglycones from their parent sugars allowing their absorption through the intestinal wall. Rapid HPLC techniques used to analyze flavonoids and their degradation products in human urine and feces have provided evidence of methylation, hydroxylation, O-methylation, sulfation, and glucuronidation, which occur as products primarily of liver and intestinal microbial transformation [67,68]. Metabolic animal studies have shown that quercetin may be rapidly converted to the nonmutagenic 3'-O-methylquercetin metabolite [69,70]. Additionally, kinetic analyses have shown that this reaction is catalyzed by catechol-O-methyltransferase (COMT) and is inhibited by homocysteine in a concentration-dependent manner [70]. Thus, an ongoing folate deficiency that results in reduced plasma folate levels, and an increase in the homocysteine to methionine ratio, may inhibit the COMT-mediated metabolism of potentially mutagenic flavonoids.

A number of *in vitro* studies have demonstrated the antioxidant activity of tea flavonoids, and have attributed this activity to quercetin and the major tea catechin, EGCG. To determine metabolism and distribution of catechins in humans, plasma catechin levels in volunteers were measured following ingestion of green or black tea [71]. Plateau levels of total catechins in plasma of these individuals reached approximately 1.0 and 0.3 μM for green and black teas, respectively, following consumption of five cups of tea. Since EGCG accounts for the majority of green tea catechins, this would reflect a biologically significant steady state plasma level. Studies by Sazuka et al. have also shown that EGCG has a high affinity for blood proteins [72], and therefore a long half-life. Similarly, the existence of intermolecular bonds between albumin and quercetin conjugates is supported by *in vitro* absorbance and fluorescence and animal studies [73]. Quercetin is eliminated slowly from the body being circulated as a quercetin-albumin complex. It may be that this longer elimination time could allow these

compounds to dissociate from blood proteins and interact with cellular proteins and DNA.

Studies by van der Elst and coworkers demonstrated that iodine-labeled synthetic flavonoids administered to pregnant rats traverse the fetal blood-brain barrier and accumulate in higher levels in the fetal brain than in the mother herself [74]. Twenty-four hours after dosing, the mother eliminated 60 to 70% of the flavonoid, whereas 17% of the initial dose was still present in the fetal compartment. These results were confirmed in studies by Adlercreutz et al. that showed the free transfer of phytoestrogens from the mother to the neonate based on measurements in maternal and cord plasma [75]. These results suggest that the fetus may be exposed to high circulating levels of flavonoids, which may elicit toxic responses that may otherwise be innocuous to the mother.

MUTAGENICITY AND GENOTOXICITY OF FLAVONOIDS

Exposure to mutagenic or premutagenic agents in the diet is considered an important factor in the etiology of human cancers [76]. Early studies of flavonoids first documented the mutagenicity of quercetin [77–79] in its capacity to cause base-pair substitutions and frame-shift mutations in the Ames test, induce chromosomal aberrations and sister chromatid exchanges in CHO cells [80], and generate micronuclei in human lymphocytes in the absence and presence of activation [81,82] (Table 1). Early structure-activity studies by Hodnick et al. [83] of the inhibition of mitochondrial succinoxidase by flavonoids showed that at a biological pH, quercetin, myricetin, and quercetagenin caused mitochondrial respiratory bursts and underwent autooxidation resulting in hydrogen peroxide, superoxide, and hydroxyl radical formation. While the redox potentials of most flavonoid radicals are lower than those of the superoxide and alkyl peroxy radicals [84], their effectiveness in generating lipid peroxidation, DNA adducts, and mutations may be biologically significant. Inhibition of mitochondrial enzymes by flavonoids through generation of active oxygen species at pH 7.5 may contribute to their antineoplastic and cytotoxic potential, similar in action to the antineoplastic agents adriamycin [85,86] and 2,3-dichloro-1,4-naphthoquinone [87,88].

Other studies by Rahman et al. [89] have shown that flavonols such as quercetin cause strand scission in DNA through the transient reduction of Cu(II) to Cu(I) and generation of oxygen species due to interactions with functional groups that drive the redox cycling of this and other transition metals. Reactive oxygen species such as peroxy and hydroxyl radicals may also be responsible for the DNA degradation seen in isolated rat liver nuclei treated with myricetin [90], naringenin, and morin [12].

While the active oxygen scavengers, mannitol, superoxide dismutase, and catalase had no inhibitory effect on DNA degradation by naringenin and morin, mannitol partially inhibited peroxidation of nuclear membranes. Additionally, these compounds have the ability to impair functions in components of the nuclear antioxidant defense system, glutathione and glutathione-S transferase, resulting in oxidative DNA damage [91].

It has also been shown that flavonoids that contain phenol B rings, such as apigenin and naringin, can undergo glutathione-dependent pro-oxidation in the absence of transition metals [92,93]. These compounds were shown to catalyze superoxide formation during glutathione oxidation. Again, this behavior strongly suggests involvement of active oxygen species, and that pro-oxidant or antioxidant activity of flavonoids is dependent on the redox state of their biological environment.

FLAVONOIDS AS TOPOISOMERASE INHIBITORS

The cytotoxic potential of many flavonoids may be due to their activity as topoisomerase II inhibitors. Genistein, biochanin A, equol, myricetin, and quercetin have been identified as potent topoisomerase II inhibitors at low concentrations, similar in activity to the epipodophylotoxins widely used in cancer therapy [6,94,95]. Topoisomerase II inhibitors cause an accumulation of enzyme-DNA covalent intermediates called cleavable complexes, that may lead to double-strand DNA lesions at topoisomerase-binding sites, such as the one in a break-point cluster region of the *MLL* gene. The *MLL* gene, located on chromosome band 11q23, has been identified as one of the most common loci involved in chromosomal translocations in patients with secondary leukemias following chemotherapy with topoisomerase II inhibitors, such as etoposide and adriamycin [96]. It has also been observed that nearly 80% of all infants with de novo leukemia bear these same *MLL* translocations [97, 98]. These findings suggest that the 11q23 disruptions in the *MLL* gene may occur in utero and may be associated with maternal consumption of naturally occurring topoisomerase II inhibitors. Recent epidemiologic studies of childhood leukemia by Ross and coworkers support this hypothesis [99,100]. They found that increasing maternal consumption of topoisomerase inhibitors elevated acute myeloid leukemia risk in infants by nearly 10-fold. High levels of flavonoid intake by the mother may, therefore, be a risk factor for infant leukemia.

Differential pathways in flavonoid metabolism are major determinants of their potential DNA topoisomerase II-inhibitory activities. For example, while diadzein is not a topoisomerase II inhibitor, its metabolite, equol, inhibits both topoisomerase I and II activity. The hydro-

genation of genistein to dihydrogenistein has been shown to result in a loss of topoisomerase II-inhibiting capacity [94]. Genistein conjugates formed through sulfation and glucuronidation and the major quercetin metabolite, 3'-O-methylquercetin, may lose topoisomerase II-inhibitory potential based on structural-activity studies by Austin et al. [6]. These studies showed O-methylated flavonoids to exhibit little, if any, topoisomerase II-inhibitory activity.

While there may be a relationship between maternal consumption of dietary topoisomerase II inhibitors and infant leukemia, the obvious question is whether populations that typically have high intakes of these compounds have higher rates of the disease. Due to reporting discrepancies and misdiagnoses, we may never have a definitive answer based on epidemiological data alone. Even less data is available on the possible health effects of feeding soy formulas, which contain substantial amounts of isoflavones [101], and other soy products to infants and small children. Studies by LaMartiniere et al. have shown that genistein administration to neonatal rats provides protection from chemically induced mammary tumors [102,103]. These findings have supported the idea that soy administration to infants may elicit lifelong protection against hormone-dependent cancers. While this is a worthwhile goal in an effort to prevent breast cancer, the potential for an increased risk of infant leukemias must be considered. Toxicological studies should be undertaken to determine if neonatal genistein administration could potentiate chromosomal translocations involving the *MLL* gene. Furthermore, the antithyroid properties of isoflavones may warrant additional studies into the indiscriminant use of these compounds in infant nutrition.

EFFECTS ON THYROID HORMONE PRODUCTION

Flavonoids decrease both iodide ion uptake and incorporation in animal studies [104,105]. These data are consistent with the endemic goiter described in populations where flavone-concentrated millet is their main dietary staple [61,63] and may explain thyroid disease described in soy-fed babies [106].

Studies by Divi et al. [107] showed that genistein, diadzein, quercetin, kaempferol, and naringenin inhibit thyroxine synthesis by acting as alternate substrates for tyrosine iodination, yielding mono-, di-, and tri-iodoisoflavones. These compounds were also shown to irreversibly inhibit thyroid peroxidase, essential to thyroid hormone synthesis. A clue to their mechanism of action may relate to the ability of phenolic compounds with a free resorcinol (metahydroxyphenol) moiety to inhibit thyroid peroxidase and lactoperoxidase [105]. Incubation of lactoperoxidase with ¹²C-labeled resorcinol resulted in

persistent, irreversible covalent binding. The proposed mechanism of action for enzyme inhibition involves the conversion of thyroid peroxidase to a free radical that reacts with a resorcinol moiety (which could be a flavonoid) and produces a flavonoid radical. The flavonoid radical could covalently bind to the catalytic amino acid residues on the enzyme, leading to enzyme inactivation. Therefore, flavonoids with a free resorcinol moiety may be potential thyroid goitrogens and carcinogens, particularly when consumed at high concentrations. Through their inhibitory activity in thyroid peroxidase synthesis, they can cause elevated thyroid-stimulating hormone levels, which promote thyroid gland growth and thyroid dysfunction.

SAFE FLAVONOID INTAKE

A number of epidemiological studies suggest that a decreased risk of heart disease and cancers of the breast [108], prostate [109], lung [110], colon [111], and stomach [112] is associated with increased consumption of fruits, vegetables, and soy products. Populations at lowest risk are Asians and vegetarians. Based on the average daily intake of flavonols (68 mg) and isoflavones (20–240 mg) in Asian populations, dietary exposures at these doses are not likely to cause adverse health effects. To date, no human data on the long-term effects of high-dose supplementation are available. The level of flavonoids required to induce mutations and cytotoxicity may not be physiologically achievable through dietary sources. However, the use of supplements, particularly antioxidant formulas and herbal mixtures that are commonly recommended in terms of gram rather than milligram doses, could result in exposure to potentially toxic levels. For example, typical manufacturers' recommended doses of quercetin supplements range between 500 and 1000 mg per day, which is 10 to 20 times what can be consumed in a typical vegetarian diet. This suggests that unregulated, commercially available flavonoid-containing supplements may have biologic activity that can adversely affect human health.

CONCLUSION

A significant number of studies provide evidence that the biologic activities of flavonoids may play a dual role in mutagenesis and carcinogenesis. They can act as antimutagens/promutagens and antioxidants/pro-oxidants, which is largely dependent upon the levels consumed as well as the physiological conditions in the body. Exposure to increased levels of flavonoids, whether through the diet or by supplementation, may potentially overwhelm the system, leading to the formation of reactive

oxygen species, and ultimately DNA damage. Furthermore, these effects may be enhanced in fetal development where there is rapid cell growth, which may increase sensitivity to phytochemical exposure. Indeed, little is actually known about the toxicology of excess flavonoid intake, while beneficial attributes are commonly overemphasized.

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