Health promotion by flavonoids, tocopherols, tocotrienols, and other phenols: direct or indirect effects? Antioxidant or not?[1–4]

Barry Halliwell, Joseph Rafter, and Andrew Jenner

ABSTRACT

Foods and beverages rich in phenolic compounds, especially flavonoids, have often been associated with decreased risk of developing several diseases. However, it remains unclear whether this protective effect is attributable to the phenols or to other agents in the diet. Alleged health-promoting effects of flavonoids are usually attributed to their powerful antioxidant activities, but evidence for in vivo antioxidant effects of flavonoids is confusing and equivocal. This may be because maximal plasma concentrations, even after extensive flavonoid intake, may be low (insufficient to exert significant systemic antioxidant effects) and because flavonoid metabolites tend to have decreased antioxidant activity. Reports of substantial increases in plasma total antioxidant activity after flavonoid intake must be interpreted with caution; findings may be attributable to changes in urate concentrations. However, phenols might exert direct effects within the gastrointestinal tract, because of the high concentrations present. These effects could include binding of prooxidant iron, scavenging of reactive nitrogen, chlorine, and oxygen species, and perhaps inhibition of cyclooxygenases and lipoxygenases. Our measurements of flavonoids and other phenols in human fecal water are consistent with this concept. We argue that tocopherols and tocotrienols may also exert direct beneficial effects in the gastrointestinal tract and that their return to the gastrointestinal tract by the liver through the bile may be physiologically advantageous. *Am J Clin Nutr* 2005;81(suppl):268S–76S.

KEY WORDS Flavonoid, polyphenol, antioxidant, gastrointestinal tract, tocopherols, free radicals, iron, cancer

INTRODUCTION

Foods and beverages rich in flavonoids have been associated with decreased risk of age-related diseases in several epidemiologic studies (1–9), and the concept that flavonoids and other phenolic compounds are responsible is supported by some animal and in vitro studies (10–12). Flavonoids have powerful antioxidant activities in vitro, being able to scavenge a wide range of reactive oxygen, nitrogen, and chlorine species, such as superoxide, hydroxyl radical, peroxyl radicals, hypochlorous acid, and peroxynitrous acid. They can also chelate metal ions, often decreasing metal ion prooxidant activity (13–19). Because considerable evidence indicates that increased oxidative damage is associated with and may contribute to the development of all major age-related diseases (20–26), it has been logical to attribute the alleged protective effects of flavonoids to their antioxidant ability.

There are several caveats, however. First, protective effects of foods and beverages rich in flavonoids do not necessarily equate to protective effects of flavonoids (27, 28). As an analogy, some studies showed that consumption of foods rich in vitamin C decreased levels of oxidative DNA damage in vivo, whereas vitamin C consumption alone did not (reviewed in references 24, 27, and 29). Second, flavonoids and other phenols are complex molecules and are likely to have multiple potential biological activities, such as inhibiting telomerase (30), affecting signal transduction pathways (31–33), inhibiting cyclooxygenases and lipoxygenases (34–36), decreasing xanthine oxidase (37), matrix metalloproteinase (38), angiotensin-converting enzyme (39), and sulfotransferase (40) activities, and interacting with sirtuins (41). Flavonoids may also interact with cellular drug transport systems (42), compete with glucose for transmembrane transport (43), interfere with cyclin-dependent regulation of the cell cycle (44), and affect platelet function (45).

Third, although flavonoids can be absorbed through the gastrointestinal (GI) tract, maximal plasma concentrations achieved are low, usually not more than 1 μmol/L, in part because of rapid metabolism by human tissues and colonic bacteria (46–65). Many of the products of metabolism, such as methylated and glucuronidated forms, must have decreased antioxidant activity because of the blocking of radical-scavenging phenolic hydroxyl groups (60). Therefore, whether plasma concentrations of flavonoids in vivo can be sufficient to exert systemic antioxidant actions (or any of the other effects suggested above) is difficult to predict and must be tested with in vivo experimentation.

Fourth, flavonoids are essentially xenobiotics, as indicated by their patterns of metabolism, and cytotoxic effects have been observed in vitro and in vivo (66–70). Again, the physiologic relevance of such effects is unclear. Many cell culture studies might have been confounded by the rapid oxidation of polyphenolic compounds in cell culture media, generating H_2O_2 and quinones/semiquinones, which could account for the cellular effects observed (71–73). It is unlikely, however, that all of the cellular effects of flavonoids observed in cell culture studies are

[1] From the Department of Biochemistry, Faculty of Medicine, Singapore (BH, AJ), and the Department of Medical Nutrition, Karolinska Institute, Huddinge, Sweden (JR).

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[3] Supported by the Singapore Biomedical Research Council.

[4] Address reprint requests and correspondence to B Halliwell, Department of Biochemistry, Faculty of Medicine, MD 7, 8 Medical Drive, Singapore 117597, Singapore. E-mail: bchbh@nus.edu.sg.

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artifacts (71, 74). The purpose of this article is to review our recent studies relating to the aforementioned issues, to compare our data with those of others, and to reinforce our concept (75) that flavonoids may exert direct protective effects within the GI tract.

DO FLAVONOIDS EXERT ANTIOXIDANT EFFECTS IN VIVO?

O'Reilly et al (46) examined this issue among healthy young volunteers who were switched from a flavonoid-rich diet to a flavonoid-poor diet. They measured F_2-isoprostane concentrations in plasma, as an index of lipid peroxidation and oxidative DNA damage in white blood cells, with gas chromatography-mass spectrometry (46, 76). The experiment was a randomized crossover study with two 14-d treatments with a flavonoid-poor diet or a flavonoid-rich diet, with a 14-d washout period between treatments. During the flavonoid-rich dietary treatment period, subjects were asked to consume one 150-g onion cake (containing 89.7 mg quercetin) and one 300-mL cup of black tea daily. During the flavonoid-poor dietary treatment period, subjects were asked to avoid the consumption of specified flavonoid-rich foods and of tea and to consume 6 g/d high-oleic acid sunflower oil (containing 76% 18:1 and 14% 18:2n−6), as contained in the 150-g onion cake. Subjects were advised to make no changes to their diets or lifestyle other than those necessary for compliance with the study. During the last 7 days of each dietary treatment phase, subjects were asked to maintain a 7-d food diary. At the end of each treatment phase, venous blood samples were collected from subjects after an overnight fast, and height and weight were recorded. With the flavonoid-rich diet, plasma quercetin concentrations increased from undetectable concentrations to 221.6 ± 37.4 nmol/L ($n = 32$).

F_2-isoprostane measurement is currently regarded as the best method to measure lipid peroxidation in vivo (77, 78). Concentrations remained unchanged whether the subjects were on the flavonoid-rich diet or the flavonoid-poor diet. There was also no effect on the plasma concentrations of oxidized LDL, measured as malondialdehyde-LDL antibody titers (46). There is controversy regarding how best to measure oxidative DNA damage; therefore, it is best not to accept conclusions regarding the effects of dietary interventions on this parameter unless they are supported by several studies using different methods (24). Nevertheless, our studies provided no evidence for an antioxidant effect of quercetin in vivo, among the healthy subjects examined, against either lipid oxidation or oxidative DNA damage (46, 76).

How do our data compare with those of others? The findings are mixed but, overall, the results are consistent with our conclusions. We confine our comments to recent studies with humans, and we avoid discussing studies carried out with unreliable biomarkers, such as plasma thiobarbituric acid-reactive substances. Boyle et al (79) found that rutin supplementation did not affect urinary concentrations of 8-hydroxy-2'-deoxyguanosine (8OHdG) (a putative biomarker of whole-body oxidative DNA damage) (80), F_2-isoprostanes, or malondialdehyde in human volunteers, but there was an effect on pyrimidine oxidation products, as measured with the comet assay (although not on endogenous DNA strand breaks) (79). Fruit juice consumption decreased oxidative DNA damage in lymphocytes in one study (81) and plasma F_2-isoprostane concentrations in others (82, 83), but fruits and vegetables failed to decrease any marker of oxidative damage, including concentrations of F_2-isoprostanes and DNA damage markers, in other studies (84, 85). Grape skin extract (86) and parsley (87) were reported not to decrease concentrations of end products of oxidative protein damage, measured as plasma protein 2-aminoadipic semialdehyde residues, in healthy volunteers. Caccetta et al (88) found that plasma F_2-isoprostane concentrations decreased significantly among human smokers after consumption of alcohol-free red wine, but either red or white wine alone had no effect, which perhaps suggests a prooxidant action of other wine constituents, such as alcohol. Kiwi fruit consumption decreased DNA base oxidation, as measured with the comet assay, among human volunteers, possibly by accelerating DNA repair (89), and Thompson et al (90) reported decreased lipid peroxidation (urinary isoprostanes and malondialdehyde) and lymphocyte 8OHdG concentrations among subjects who consumed more fruits and vegetables, which contradicts other studies (84, 85). Similarly, green tea extract failed to decrease urinary isoprostane concentrations among healthy female subjects (91), as did either green or black tea in a study with mainly male subjects (92), but there was a decrease in plasma concentrations of phosphatidylcholine hydroperoxide, an acceptable biomarker of lipid peroxidation, in a study with male subjects in Japan (93). In other studies, green tea was observed to decrease urinary 8OHdG concentrations and lipid peroxidation (measured as malondialdehyde concentrations in the urine) among both smokers and nonsmokers (94, 95). However, black tea had no effect in one of those studies (95). It should be noted that concentrations of malondialdehyde in the urine, unlike those of isoprostanes, can be affected by changes in diet (96–99); therefore, use of urinary malondialdehyde concentrations as a measure of lipid peroxidation must be undertaken with caution if the diet is changed. Young et al (100), in a well-designed, crossover, intervention study with subjects on a low-flavonoid diet, found no effect of green tea extract on urinary 8OHdG excretion. Interestingly, they also found that the low-flavonoid diet itself (excluding tea, wine, fruits, and vegetables) decreased plasma protein oxidation (2-aminoadipic semialdehyde and γ-glutamyl semialdehyde) and urinary 8OHdG excretion, in apparent contradiction to other studies (as reviewed above; also see reference 101). In another study (102), those authors noted increased plasma protein oxidation after fruit juice intake. Much more work must be devoted to the establishment of generally acceptable biomarkers of oxidative protein damage; even F_2-isoprostanes and 8OHdG do not fulfill all of the criteria for ideal biomarkers (25, 103). Finally, diets enriched in soy were found to decrease plasma F_2-isoprostane concentrations among human volunteers (104). It is clear that the data are confusing and self-contradictory.

INTERPRETATION OF CHANGES IN LDL OXIDIZABILITY AND PLASMA TOTAL ANTIOXIDANT CAPACITY

Several other biomarkers are frequently used to assess in vivo antioxidant effects of phenols. For example, many studies have examined the effects of flavonoids on the resistance of LDL to ex vivo oxidation. However, such studies are difficult to interpret, because flavonoids and their metabolites that might partition between lipoproteins and plasma in the circulation could conceivably wash out from LDL during the lipoprotein isolation procedures, which are usually prolonged. Measurement of

changes in the lag time to LDL oxidation ex vivo must be performed with great care, to avoid misinterpretation (eg, attributable to seasonal effects among humans) (105, 106). Therefore, we place little weight on such studies. Similarly, several reports claimed changes in plasma total antioxidant capacity after consumption of phenolic compounds (107); this is worth some thought. Plasma total antioxidant capacity, as measured with a range of assays, is $> 10^3$ μmol/L (22). Detection of a statistically significant increase in most assays would thus require a minimum of 20–50 μmol/L extra antioxidant to be present. However, concentrations of unconjugated flavonoids found in vivo, even with high dietary intakes, are far below this, usually ≤ 1 μmol/L (see above). Some metabolites might exert significant antioxidant activity but this seems unlikely, because modifications of hydroxyl groups decrease antioxidant ability and concentrations of metabolites are quite low. It is more likely that the interventions cause increases in the concentrations of the major plasma antioxidants, such as ascorbate and urate, and increases in urate concentrations are not necessarily beneficial (108). Finally, it must be emphasized that any effect on any measurable parameter observed with fruit juices, beverages, soy products, or vegetables is not necessarily an effect of the flavonoids or other phenolic compounds that the products contain.

We conclude that the available literature provides no consistent support for systemic antioxidant effects of dietary phenolic compounds. In addition, alterations in the concentrations of even generally accepted biomarkers could be attributable to accelerated removal (eg, DNA repair or metabolism of F_2-isoprostanes), rather than decreased formation, and decreases in such concentrations should not automatically be assumed to represent antioxidant effects (103). It is also not clear whether the effects of flavonoids on cyclooxygenase/lipoxygenase observed in vitro and in isolated cells can occur in vivo. Freese et al (91) found no effect of green tea extract consumption on thromboxane production among female subjects, and chocolate phenolic compounds did not decrease in vivo prostaglandin production for either gender (109).

DO FLAVONOIDS ACT IN THE GI TRACT?

We proposed that antioxidant and other protective effects of flavonoids and other phenolic compounds could occur before absorption, within the GI tract itself (75). This could account for the ability of flavonoid-rich foods to protect against gastric, and possibly colonic, cancer, although it must not be assumed that any protective effect of flavonoid-rich foods is attributable to antioxidant actions of the flavonoids (110) or to flavonoids at all, rather than to other components in the foods. For example, ingestion of green tea was reported to rapidly decrease prostaglandin E_2 concentrations in human rectal mucosa (111), consistent with inhibition of cyclooxygenase activity (34).

The logic behind our hypothesis (75) is that phenolic compounds present in plasma at < 1 μmol/L concentrations are present in the stomach and intestinal lumen at much higher concentrations after consumption of foods and beverages rich in such compounds (112–115). Because absorption of phenolic compounds is incomplete, they enter the colon, where they and their products of bacterial fermentation can exert beneficial effects. Indeed, high-flavonoid diets probably influence the microbial composition of gut flora (113, 114). This concept led us to perform studies measuring the phenolic content of human fecal material, as described below.

The GI tract is constantly exposed to reactive oxygen, chlorine, and nitrogen species, many from the diet and others from activation of phagocytes in the gut. The stomach is especially affected; indeed, Kanner and Lapidot (116) referred to the stomach as a "bioreactor." Sources of reactive species include the following: 1) mixtures of ascorbate and Fe^{2+} in the stomach during iron uptake, which represent a powerful prooxidant combination (22); 2) heme proteins in the diet, which are also potential powerful prooxidants (22); 3) lipid peroxides, cytotoxic aldehydes, and isoprostanes in the diet (96, 98, 116–118) [gastric juice may promote lipid peroxidation (116)]; 4) nitrite in saliva and in foods converted to HNO_2 by gastric acid, forming nitrosating and DNA-deaminating species (75, 119); 5) high concentrations of H_2O_2 in certain beverages (75, 103, 120, 121); 6) the presence in the GI tract of highly oxidizable, prooxidant, phenolic compounds such as hydroxyhydroquinone (103, 122); and 7) activation of immune cells naturally present in the GI tract by diet-derived bacteria and toxins (123).

Flavonoids and other phenolic compounds might exert direct protective effects in the GI tract, by scavenging reactive oxygen and chlorine species. They could inhibit heme protein-induced peroxidation in the stomach. They are able to inhibit DNA base deamination by HNO_2-derived reactive nitrogen species (119). Phenols might up-regulate toxin-metabolizing or antioxidant defense enzymes in the GI tract (124, 125). They might chelate redox-active transition metal ions and decrease their prooxidant potential (17, 22). Dietary iron is usually not completely absorbed, especially among subjects on Western diets. Unabsorbed dietary iron enters the feces, where it could represent a prooxidant challenge to the colon and rectum (126–130). Indeed, diets rich in fat and low in fiber may aggravate this prooxidant effect (123). Phenolic compounds, by chelating iron, may help to alleviate prooxidant actions of colonic iron (**Figure 1**). Effects of ascorbate and vitamin E in decreasing fecal mutagenicity have been reported (131).

WHAT PHENOLIC COMPOUNDS ARE PRESENT IN THE GI TRACT?

The phenolic compounds in the GI tract include unabsorbed compounds from the diet plus products of microbial metabolism by the gut flora; considerable evidence shows that this metabolism is extensive, and diets rich in phenols probably have effects on the composition of the colonic flora (113, 114, 132–138). We therefore examined the content of phenolic compounds in the human colon. In recent years, many studies have shown that components of the aqueous phase of human feces (fecal water) are more efficient in altering the growth characteristics of colonocytes than are components of the solid phase (139–142). Because fecal water interacts more with the colonic epithelium than does the solid fecal phase and thus may have more influence on the development of colon disease, we measured the concentrations of phenolic compounds in human fecal water. This aqueous fraction contributes an average of 70–75% of total fecal wet weight.

Fecal water was prepared as described previously (139). Briefly, stool samples were homogenized in a stomacher (2 min) and centrifuged at 30 000 $\times$ g for 2 h, and the upper water layer was filtered. Samples were acidified and loaded onto solid-phase

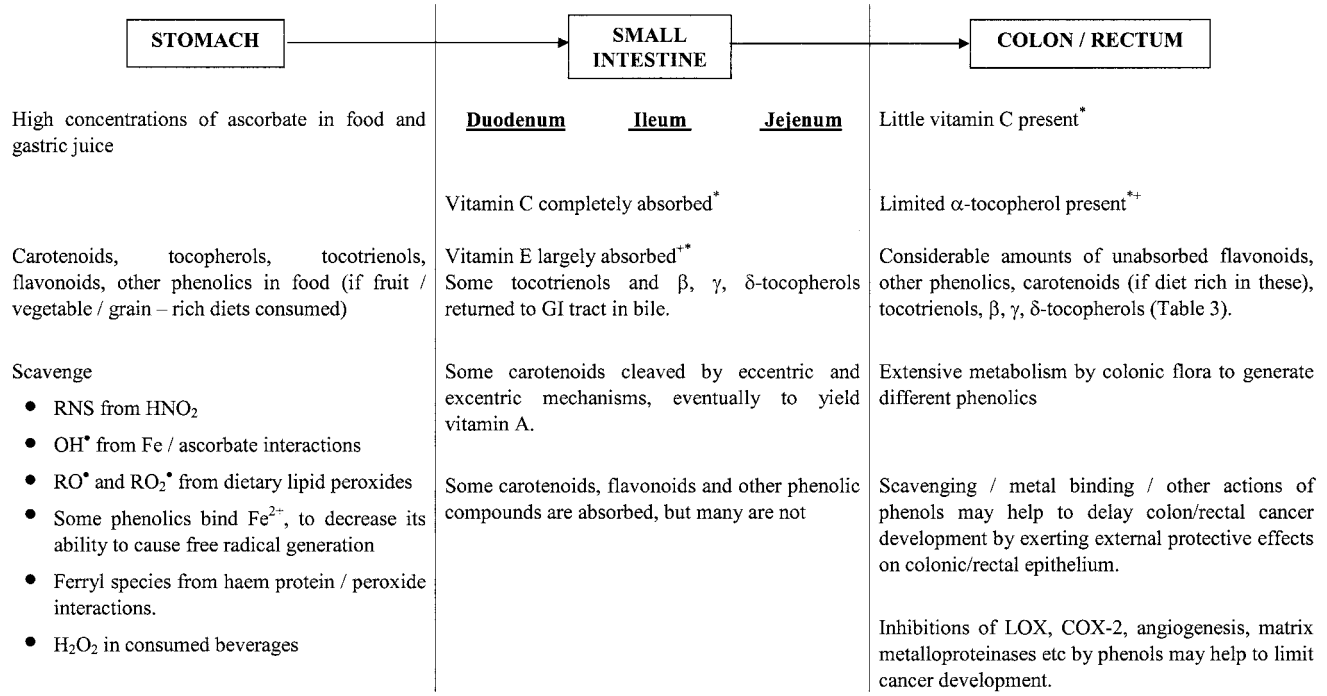

FIGURE 1. Dietary antioxidants and the GI tract. *, Except when supplements are taken. This diagram refers to normal dietary intake. +, There is considerable intersubject variability in the efficiency of GI uptake of vitamin E. RNS, reactive nitrogen species.

extraction columns containing diatomaceous earth (100 mg/100 μL fecal water sample). After 5 min, phenolic compounds were eluted with 1.8 mL ethyl acetate. The organic solvent was removed with nitrogen gas, and the dry sample was derivatized with 10 μl acetonitrile plus 50 μl *N,O*-bis(trimethylsilyl)trifluoroacetamide plus 1% trimethylchlorosilane for 4 h at 50 °C. Derivatized samples were analyzed with gas chromatography-mass spectrometry, with helium as the carrier gas and with a fused silica capillary column (12 m × 0.2 mm inside diameter) coated with cross-linked 5% phenylmethylsiloxane (film thickness: 0.33 μm; Agilent/J & W, Palo Alto, CA). Selected-ion monitoring was performed with the electron-ionization mode, at 70 eV.

Concentrations of phenolic compounds were highly variable among individuals and, for each individual, were affected by diet (data not shown). Quercetin, naringenin, isorhamnetin, formononetin, and hesperetin were the major flavonoid components. All other polyphenolic compounds were present at < 0.2 μmol/L (**Table 1**). In contrast, phenolic compounds of lower molecular mass, some but not all (143, 144) of which are likely to be products of microbial degradation, were present at much higher concentrations (**Table 2**) than were flavonoids. Major components were phenylacetic acid, 3-phenylpropionic acid, 3,4-dihydroxycinnamic acid (caffeic acid), 3-hydroxyphenylacetic acid, benzoic acid, 3-(4-hydroxy)phenylpropionic acid, 3,4-dihydroxyphenylacetic acid, 4–hydroxyphenylacetic acid, 4-hydroxy-3-methoxyphenylcinnamic acid (ferulic acid), and 3,4-dihydroxyphenylpropionic acid. Concentrations of other phenolic acids and phenolic compounds ranged from 0.04 to 8.5 μmol/L (mean concentrations). Although the relative contributions of different sources of phenolic acids in the colon, including diet, microbial metabolism, and excretion from colonic cells into the GI tract, has yet to be established, we are currently investigating the concentrations of phenolic compounds in the fecal bulk, to evaluate the bioavailability of fecal phenolic compounds in the colon.

TABLE 1
Concentrations of polyphenols in fecal water prepared from 15 human volunteers[1]

Polyphenol	Mean concentration	SD	Lowest concentration observed	Highest concentration observed
	μmol/L	*%*	*μmol/L*	*μmol/L*
Quercetin	0.74	95	0.00	2.31
Naringenin	0.61	176	0.00	4.04
Isorhamnetin	0.51	230	0.00	4.44
Formononetin	0.36	241	0.00	3.20
Hesperetin	0.23	219	0.00	1.65
Daidzin	0.10	166	0.00	0.61
Epicatechin	0.09	112	0.01	0.31
Apigenin	0.07	167	0.00	0.31
Catechin	0.06	138	0.00	0.31
Kaempferol	0.05	113	0.00	0.16
Biochanin A	0.04	162	0.00	0.28
Eriodictyol	0.04	172	0.00	0.27
Diosmetin	0.03	181	0.00	0.20
Phloretin	0.03	73	0.00	0.07
Resveratrol	0.02	170	0.00	0.12
Genistein	0.01	166	0.00	0.05
Diosmetin	ND			
Luteolin	ND			

[1] Derivatized samples were injected into an Agilent gas chromatography-mass spectrometry system and analyzed with selected-ion monitoring. Concentrations were calculated with a standard calibration curve obtained with pure phenolic standards analyzed under identical conditions. ND, not detected.

TABLE 2
Concentrations of major phenolic compounds in fecal water prepared from 15 human volunteers[1]

Phenolic compound	Mean concentration	SD	Lowest concentration observed	Highest concentration observed
	μmol/L	*%*	*μmol/L*	*μmol/L*
Phenylacetic acid	409.55	87	8.43	1236.24
3-Phenylpropionic acid	287.05	82	8.71	657.37
3,4-DiOH-cinnamic acid (caffeic acid)	136.05	138	6.63	670.77
3-OH-phenylacetic acid	56.65	137	0.23	294.28
Benzoic acid	50.75	74	19.70	144.76
3-(4-OH-phenyl)propionic acid	44.32	159	0.59	209.55
3,4-DiOH-phenylacetic acid	25.82	272	0.47	277.34
4-OH-phenylacetic acid	21.84	81	3.05	73.44
4-OH,3-MeOH-cinnamic acid (ferulic acid)	18.33	159	0.64	108.11
3,4-DiOH-phenylpropionic acid	15.16	148	0.67	87.42
4-OH-benzoic acid	8.47	102	0.71	28.43
2,5-DiOH-benzoic acid	5.36	96	0.01	16.97
Catechol	4.97	94	0.31	14.08
3-OH,4-MeOH-cinnamic acid (isoferulic acid)	4.63	87	0.74	16.40
3-OH-benzoic acid	3.32	114	0.24	15.21
4-OH,3-MeOH-benzoic acid (vanillic acid)	2.80	188	0.11	17.76
3-*O*-Methylgallic acid	2.32	172	0.12	16.01
1,3,5-TriMeOH-benzene	2.24	99	0.29	7.50
1,2,3- or 1,2,4-TriOH-benzene	1.70	98	0.00	5.19
3,4-DiOH-benzoic acid	1.38	178	0.03	9.78
3,5-DiMeOH,4-OH-cinnamic acid	1.35	86	0.33	5.08
3,4,5-TriOH-benzoic acid (gallic acid)	1.26	86	0.17	3.91
4-OH,3,5-DiMeOH-benzoic acid	1.07	70	0.27	2.69
2,3-DiOH-benzoic acid	0.95	83	0.19	3.46
4-OH,3-MeOH-benzaldehyde (vanillin)	0.92	157	0.14	5.05
4-OH-cinnamic acid (*p*-coumaric acid)	0.84	47	0.30	1.50
2,6-DiMeOH-benzoic acid	0.80	78	0.12	2.62
3,4,5-TriMeOH-benzene	0.79	304	0.01	9.52
2-OH-benzoic acid	0.79	133	0.07	3.96
4-MeOH-phenylpropionic acid	0.76	159	0.01	4.72
3,4-DiOH-benzaldehyde	0.74	48	0.22	1.38
4-Ethylphenol	0.74	274	0.02	7.96
4-OH,3-MeOH-phenylacetic acid (homovanillic acid)	0.58	95	0.01	1.56
t-Cinnamic acid	0.55	121	0.02	2.49
4-*O*-Methyl-gallic acid	0.28	174	0.00	1.77
3,5-DiOH-benzoic acid	0.27	252	0.01	2.72
3-MeOH-phenylpropionic acid	0.26	50	0.07	0.47
4-MeOH-benzoic acid	0.22	86	0.02	0.60
4-Ethylbenzoic acid	0.20	54	0.06	0.39
3,4,5-TriMeOH-phenylpropionic acid	0.19	172	0.01	1.00
3-OH,4-MeOH-benzoic acid (isovanillic acid)	0.18	144	0.00	0.98
3,4,5-TriMeOH-cinnamic acid	0.17	51	0.03	0.31
2,3,4-TriOH-benzoic acid	0.15	139	0.00	0.63
3,4-DiMeOH-benzoic acid	0.12	177	0.00	0.81

[1] Derivatized samples were injected into an Agilent gas chromatography-mass spectrometry system and analyzed with selected-ion monitoring. Concentrations were calculated with a standard calibration curve obtained with pure phenolic standards analyzed under identical conditions. OH, hydroxy; MeOH, methoxy. The following compounds were present at mean concentrations of < 0.1 μmol/L: 3,4-diMeOH-phenol, 3,5-diMeOH-phenol, 1,3,5-triOH-benzoic acid (phloroglucinol), 2-MeOH-benzoic acid, 3-MeOH-benzoic acid, 1,2-diOH,3-MeOH-benzene, 1,4-diOH,3-MeOH-benzene, 2,3-diMeOH-benzoic acid, 3,5-diMeOH-benzoic acid, 2,5-diMeOH-benzoic acid, 2,6-diOH-benzoic acid, 2,3,4-triMeOH-benzoic acid, 2,4,5-triMeOH-benzoic acid, 2-MeOH-phenylacetic acid, 3,4-diMeOH-phenylacetic acid, 3,4,5-triMeOH-phenylacetic acid, 2-MeOH-phenylpropionic acid, and 2-OH-cinnamic acid (*o*-coumaric acid).

TOCOPHEROLS AND THE GI TRACT: AN EXTENSION OF AN HYPOTHESIS

Vitamin E comprises multiple stereoisomers of 4 tocopherols (α, β, γ, and δ) and 4 tocotrienols (22, 145). All appear to be absorbed from the GI tract, but a tocopherol transfer protein in the liver selects α-tocopherol for incorporation into plasma lipoproteins, leading to ejection of some of the other tocopherols into the bile and thus back into the GI tract (145). γ-Tocopherol is also rapidly catabolized (146). High concentrations of these vitamin E constituents can be present in the fecal matter, relatively much higher than those in plasma (**Table 3**), especially for δ-tocopherol, γ-tocopherol, and the tocotrienols. It is possible that these agents, like the flavonoids, exert beneficial effects in the GI tract. Even α-tocopherol may not be completely absorbed (147), especially if

TABLE 3
Levels of tocopherols and tocotrienols in fecal matter[1]

Compound	Effective concentration mean	SD	Plasma mean concentration	SD	Fecal/plasma ratio
	mg/L	*mg/L*	*μmol/L*	*μmol/L*	
δ-Tocopherol	1.02	0.51	0.09	0.03	11.5
γ-Tocopherol	6.22	3.48	0.98	0.63	6.3
α-Tocopherol	32.62	10.81	16.99	5.63	1.9
δ-Tocotrienol	2.02	1.35	0.03	0.03	63.2
γ-Tocotrienol	7.52	5.13	0.03	0.03	289.4
α-Tocotrienol	2.55	3.29	0.08	0.09	31.9

[1] Concentrations were calculated by assuming that water is 75 ± 2% of the fecal mass and that there is uniform distribution of the compounds throughout this phase.

supplements are taken (147, 148). γ-Tocopherol can, for example, scavenge reactive oxygen and nitrogen species (149, 150) and inhibit cyclooxygenase (151). Additional work is needed to examine the role of tocopherols and tocotrienols in the GI tract.

CONCLUSIONS

Despite the enormous interest in flavonoids and other polyphenolic compounds as potential protective agents against the development of human disease, the real contributions of such compounds to health maintenance and the mechanisms through which they act are still unclear. The frequently proposed systemic antioxidant effects of flavonoids are not supported by strong consistent evidence in vivo. In our view, greater attention should be given to the biological effects of these compounds and their metabolites within the GI tract and to any possible effects on other tissues of flavonoid metabolites (eg, methylated, sulfated, and glucuronidated compounds) generated systemically, as well as products of colonic microbial metabolism that are absorbed.

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