PL - 8

Flavonols, Flavones, Flavanones and Human Health: Epidemiological Evidence

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ABSTRACT

Polyphenolic flavonoids are among a wide variety of phytochemicals present in the human diet. Basic research, animal model, and human studies suggest flavonoid intake may reduce the risk of several age-related chronic diseases. The vast number of flavonoids and mixtures of their subclasses, including flavonols, flavones and flavanones, and the variety of agricultural practices that affect their concentration in foods have presented a challenge to the development of adequate food composition databases for these compounds. Nonetheless, dietary assessments have been applied to cohort and case-control epidemiological studies and several reveal an inverse association with risk of some forms of cancer, cardiovascular disease, and other chronic conditions. Those observational studies that have examined these relationships with regard to flavonols, flavones, and flavanones are reviewed. The requirement for caution in interpreting these studies is discussed with regard to the limited information available on the bioavailability and biotransformation of these flavonoids. As the totality of the available evidence on these flavonoids suggests a role in the prevention of cancer and cardiovascular disease, further research is warranted, particularly in controlled clinical trials.

Key words: flavonoids, flavonols, flavones, flavanones, epidemiological evidence, cancer, coronary heart disease

Abbreviations: CHD, coronary heart disease; CVD, coronary vascular disease; MI, myocardial infarction

INTRODUCTION

Observational studies consistently report inverse relationships between fruit and vegetable consumption and many degenerative diseases, such as cancer and heart disease.[1-5] However, epidemiological methods do not readily reveal which compounds in these food groups are responsible for these health benefits; indeed, compounds potentially responsible for significant contributions to such outcomes include several vitamins and minerals, soluble and insoluble fibers, and phytochemicals such as the carotenoids and indoles. Increasing attention has recently been focused on polyphenolic compounds, particularly the flavonoids.

Flavonoids are synthesised by all vascular plants and are present throughout our diet in fruits, vegetables, nuts, seeds, herbs, spices, and whole grains. Within the plant, flavonoids are involved in electron transport during photosynthesis,[6] serve as antioxidants against the pro-oxidant effects of ultraviolet light,[7] and act against bacterial, fungal and viral pathogens as well as some insect predators.[8] Human consumption of flavonoids is significant not only via plant foods[9,10] but also via intake of plant extracts such as tea, coffee and red wine.[11] Average flavonoid intakes in selected countries are shown in Table 1.

Table 1. Estimated dietary intake of flavonoids in different countries

Country	Population	Flav-onols	Flav-ones	Flav-anones	Cate-chins	Antho-cyanidins	Iso-flavones	Sum	Refer-ence
Scotland	n = 81 (4 day weighed intake)	19	0.1	1	59			79.1	51
Wales	n = 1,900 men, aged 45~59 y (FFQ; weighed dietary intake)	26.3						26.3	25
Finland	n = 10,054, 39±16 y (diet history)	4	<1	20				24	21
Holland	n = 4,807, 67.4±7.8 y (FFQ)	26.6						26.6	18
Holland	n = 806 men, 65~84 y (dietary history)				72			72	16
USA	n = 34,789 men, 40~75 y (FFQ)	19.9	0.2					20.1	24
USA	n = 38,445 women, ≥45 y (FFQ)	23.9	0.7					24.6	22
USA (Iowa)	n = 34,492, 55~69 y (FFQ)	13.84	0.06					13.9	23
Japan	n = 115 women, 29~78 y (diet history)	16	<1				47	63	52
Germany (Bavaria)	n = 119, 19~49 y (7 d diet protocols)	12		13.2	8.3	2.7		54	53

Estimates are based on incomplete tables of flavonoid aglycones in foods in mg/d. No study provides values for all subclasses of flavonoids, hence listed values are likely underestimated.

Flavonoids are most commonly divided into six subclasses based on the connection position of the B and C rings as well as the degree of saturation, oxidation, and hydroxylation of the C ring as: flavonols, flavones, flavanones, flavan-3-ols (or catechins), isoflavones, and anthocyanidins (Fig. 1 and Fig. 2). Examples of some structures of individual flavonoids of each group are presented in Table 2. The content of individual flavonoids and flavonoid subclasses in foods can vary markedly, even between similar foods.[12,9] As a result, diverse dietary patterns can provide considerably different intakes of these nutrients. Examples of the principal flavonoids present in some common foods are provided in Table 3.

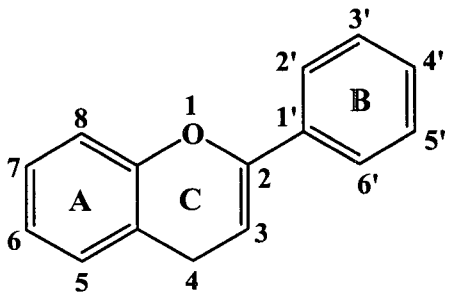

Fig. 1. Basic structure and numbering system of flavonoids.
Flavonoids contain two aromatic rings (A and B) that are linked via an oxygenated heterocycle (ring C).

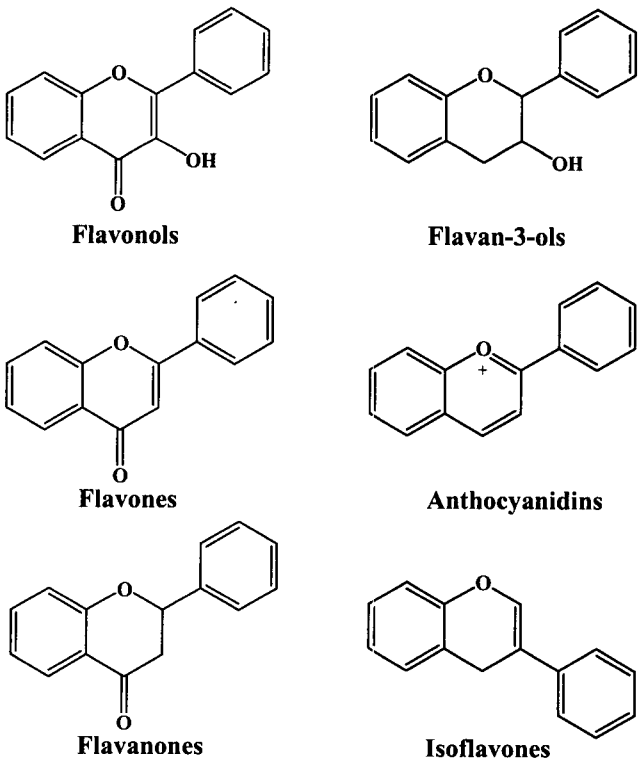

Fig. 2. Subclasses of flavonoids.
Individual flavonoids are structurally distinct due to different patterns of hydroxylation, methylation and conjugation with various mono- and disaccharides.

Table 2. Structures of individual flavonoids

Flavonoid subclass	Flavonoid	Substituents					
		3	5	7	3'	4'	5'
Flavonols	quercetin	OH	OH	OH	OH	OH	H
	kaempferol	OH	OH	OH	H	OH	H
	myricetin	OH	OH	OH	OH	OH	OH
Flavones	apigenin	H	OH	OH	H	OH	H
	luteolin	H	OH	OH	OH	OH	H
Flavan-3-ols	catechin	OH	OH	OH	OH	OH	H
	epigallocatechin	OH	OH	OH	OH	OH	OH
	epigallocatechin gallate	G	OH	OH	OH	OH	OH
Flavanones	hesperetin	H	OH	OH	OH	OCH_3	H
	naringenin	H	OH	OH	H	OH	H
	eriodictyol	H	OH	OH	OH	OH	H
Anthocyanidins	cyanidin	OH	OH	OH	OH	OH	H
	malvidin	OH	OH	OH	OCH_3	OH	OCH_3
	petunidin	OH	OH	OH	OCH_3	OH	OH
Isoflavones	genistein	H*	OH	OH	H	OH	H
	daidzein	H*	H	OH	H	OH	H

Individual molecular structures of flavonoids are determined by the addition of hydroxyl, methyl, and methoxy groups, most commonly at positions, 3, 5, 7, 3', 4' or 5' on the flavonoid nucleus. The number and positioning of hydroxyl groups together with the degree of saturation of the C ring determines the antioxidant capacity of individual flavonoids. G=gallate, H*=in the case of isoflavones, H it attached to position 2, due to the connection of C and B ring at position 3.

Table 3. Flavonoid content of selected foods

Flavonoid subclass	Compound	Food source	Content (mg/100 g)
Flavonols	quercetin	onion, raw	15.36
	kaempferol	broccoli, raw	9.37
	myricetin	apples	4.42
		black grapes	2.99
Flavones	apigenin	celery, raw	5.92
	luteolin	parsley, raw	303.24
		thyme, fresh	56.00
Flavan-3-ols	catechin	apples	9.09
	epigallocatechin	red wine	11.90
	epigallocatechin gallate	green tea	132.12
		black tea	34.26
Flavanones	hesperetin	oranges	43.88
	naringenin	lemons	49.81
	eriodictyol	grapefruit	54.50
Anthocyanidins	cyanidin	blueberries	112.55
	malvidin	raspberries	47.60
	petunidin	red wine	9.19
		red onion	13.14
Isoflavones	genistein	soymilk	9.65
	daidzein	tofu	28.15

Content of selected flavonoids in the edible portion of foods are taken from the USDA Database for the Flavonoid Content of Selected Foods (http://www.nal.usda.gov/fnic/foodcomp/Data/Flav/flav.html, March, 2003), except for isoflavone values, which are derived from the Iowa State University Database on the Isoflavone Content of Foods (http://www.nal.usda.gov/fnic/foodcomp/Data/isoflav.html, April, 2004).

This review focuses on epidemiological studies investigating health effects of flavonols, flavones and flavanones. In considering this literature, it is important to keep in mind the very limited information available in nutrient databases about these compounds, e.g., among the flavonols, results are limited almost exclusively to quercetin, kaempferol, and myricetin. As reviews on the potential health benefits of the isoflavones[13,14] and catechins[15-17] have been published recently, these flavonoid classes are not covered in this report. Absent useful databases of the anthocyanidin content of common foods, little epidemiological information is available about this class of flavonoids.

Cardiovascular Disease

Seven high quality epidemiological studies have reported on the effects of dietary flavonol, flavone, and flavanone intake and cardiovascular disease (CVD) (Table 4). Two Dutch studies, the Rotterdam Study[18] and the Zutphen Elderly Study[19,20] observed inverse correlations between the intake of these flavonoids and CVD incidence. After a 5.6-year follow-up,[18] found a 65% reduction in the relative risk for nonfatal myocardial infarction (MI) in a cohort of 4807 subjects aged >55 years, but only a non-significant 7% reduction in the risk for fatal MI. In examining the Zutphen Elderly Study, a 10-year follow-up of 805 men aged 65~84 years,[19,20] found a significant reduction in the relative risk of CVD mortality in the highest quartile of daily intake (>30 mg) of flavonols and flavones; while this level of intake also predicted a 38% lower incidence of first MI, this association was not

Table 4. Effect of dietary flavonoids on CHD incidence-epidemiological studies

Country	Study population	Flavonoid intake/d	Compared with	Incident	Relative risk (95% CI)	Reference
Holland	Rotterdam Study n=4807, ≥55 y (mean 67.4±7.8 y) 5.6 y follow-up	>33 mg flavonols[2]	<23 mg	MI Fatal MI Nonfatal MI	0.76 (0.49, 1.18) ○ 0.93 (0.57, 1.52) ○ 0.35 (0.13, 0.98) ●	18
Holland	Zutphen Elderly Study, n=805 men, 65~84 y 10 y follow-up	>30 mg flavonols and flavones[3]	<19 mg	CHD mortality First MI	0.47 (0.27, 0.82) ● 0.62 (0.24, 1.05) ○	19,20
Wales	Caerphilly Study n=1900 men, 45~59 y 14 y follow-up	>34 mg flavonols[2]	<19 mg	Ischemic heart disease	1.6 (0.9, 2.9) ○	25
Finland	Finnish Mobile Clinic Health Examination Survey n=10,054, >15 y 28 y follow-up	>33 mg total[1] flavonols (4) flavones (2) flavanones (3)	<6 mg	Ischemic heart disease mortality	0.93 (0.74, 1.17) ○	21
		>4.3 mg quercetin	<1.7 mg	Ischemic heart disease mortality	0.79 (0.63, 0.99) ●	
		>0.9 mg kaempferol	<0.2 mg	Ischemic heart disease mortality	0.82 (0.66, 1.02) ○	
		>0.2 mg myricetin	<0 mg	Ischemic heart disease mortality	1.14 (0.92, 1.40) ○	
		>21 mg hesperetin	<2 mg	Ischemic heart disease mortality	0.95 (0.76, 1.19) ○	
		>6 mg naringenin	<0.5 mg	Ischemic heart disease mortality	0.98 (0.78, 1.22) ○	
USA	Woman's Health Study n=38,445, ≥45 y 6.9 y follow-up	47 mg flavonols and flavones[3] (median)	9 mg (median)	CVD	0.88 (0.68, 1.14) ○	22
		>33 mg quercetin (median)	<7 mg (median)	CVD	0.96 (0.74, 1.25) ○	
USA (Iowa)	n=34,492 women, 55~69 y 10 y follow-up	>29 mg (median) flavonols and flavones[3]	<4 mg (median)	Fatal CVD	0.62 (0.44, 0.87) ○	23
		>19 mg quercetin (median)	<3 mg (median)	Fatal CVD	0.74 (0.52, 1.06) ○	
USA	Health Professionals Follow-up n=34,789 men, 40~75 y 5 y follow-up	>40 mg flavonols and flavones[3]	<7 mg	Non fatal MI Non-fatal MI with history of CHD	1.08 (0.81, 1.43) ○ 0.63 (0.33~1.20) ○	24

Results are adjusted for confounding factors but methods of adjustment varied in different studies. Hirvionen et al, 2001 and The Seven Country study (Hertog et al, 1995) is not included in the above table as data on the statistical significance was not shown or data collection and statistical analysis was different. [1]Sum of kaempferol, quercetin, myricetin, isorhamnetin (flavonols), apigenin, luteolin (flavones), hesperetin, naringenin and eriodictyol (flavanones). [2]Sum of quercetin, kaempferol and myricetin. [3]Sum of quercetin, kaempferol, myricetin, luteolin and apigenin. ●, significant result; ○, not significant result. Abbreviations: MI, myocardial infarction; CVD, cardiovascular disease.

statistically significant. In contrast, the Finnish Mobile Clinic Health Examination Survey,[21] a 28-year follow-up study with >10.000 subjects, found no significant correlation between flavonol, flavone, and flavanone intakes and CVD mortality. However, when these data were limited only to intake of the flavonol quercetin, CVD mortality was reduced by 21% in those with a daily intake >4 mg.

In contrast to the Dutch studies, three large cohort studies in the US, each with >34.000 participants, were unable to identify a significant correlation for dietary flavonoid intake and CVD incidence.[22-24] The discrepancy between these sets of studies may be explained, in part, on the younger ages, greater ratio of women:men, and/or other lower risk factors in the US cohorts. Results from the Caerphilly Study in 1900 Welsh men, aged 45～59 years, which found a non-significant 60% increase in CVD risk with flavonol intake, may be confounded by other variables, such as the strong association between tea drinking and smoking in this population; further, tea provided 82% of total flavonoid intake in this cohort where essentially all the tea was consumed with milk.[25] While milk has been suggested to impair the bioavailability of flavonoids, several small intervention trials have failed to confirm this effect.[26-29]

The analysis by Hertog et al. (1995)[30] of the Seven Country Study revealed that varying flavonoid intake might partially explain different rates of disease incidence and mortality in different countries. They reported that 8% of the between-country variation of CVD mortality was explained by a high intake of dietary flavonols while intake of saturated fat explained 73% and smoking 9% of the variation.

It is important to keep in mind that each of these epidemiological studies were based exclusively on dietary assessments, with all the limitations imposed by these methods, without validation of exposure by biomarkers, such as the concentration of flavonoids (and/or their active metabolites) in plasma or target tissues. Such investigations are warranted in future studies and may also provide needed information about the impact of nutrient-nutrient interactions and inter-individual differences affecting flavonoid bioavailability.

Cerebrovascular Disease

To date, four major epidemiological studies have investigated the effect of flavonol, flavone, and/or flavanone intake on cerebrovascular disease (Table 5). The results are equivocal as two studies support the hypothesis that these flavonoids reduce the risk of stroke while two others report no effect.[21,23,31,32] The potential importance of long-term flavonoid intake is underscored here as the two studies suggesting a protective action employed a follow-up of 15～28 years, whereas those with a null association examined this relationship for <10 years.

Cancer

Results from observational studies of flavonoid intake and cancer are mixed (Table 6). Examining the Caerphilly Study, Hertog et al. (1997)[25] found a non-significant 30% increase in all-cause cancer mortality associated with a daily flavonol intake of >34 mg. Hertog et al. (1994)[33] also reported a non-significant increase in cancer incidence in the Zutphen Elderly Study. In contrast, results from the much larger Netherlands Cohort Study on Diet and Cancer with 120,852 subjects followed for 4.3 years provided no correlation between flavonoid intake and cancer incidence.[34] However, with its 28-year follow-up, the Finnish Mobile Clinic Health Examination Survey obtained a significant inverse correlation between flavonol, flavone, and flavanone intake and the incidence of lung cancer.[21] When these data were focused solely on quercetin, intake of >4 mg daily was associated with a significant 23% reduction in cancer incidence.

Some case-control studies suggest that high intakes of quercetin may reduce the incidence of escphageal and

Table 5. Effect of dietary flavonoids on stroke incidence-epidemiological studies

Country	Study population	Flavonoid intake/d	Compared with	Incidence	Relative risk (95% CI)	Reference
Holland	Zutphen Study n=552 men, 50～69 y 15 y follow-up	>29 mg flavonols and flavones[3]	<18 mg	Stroke	0.27 (0.11, 0.70) ●	31
Finland	Finnish Mobile Clinic Health Examination Survey n=10,054, >15 y 28 y follow-up	>33 mg total[1] flavonols (4) flavones (2) flavanones (3)	<6 mg	Cerebrovascular disease	0.79 (0.64, 0.98) ●	21
		>4.3 mg quercetin	<1.7 mg	Cerebrovascular disease	0.86 (0.70, 1.05) ○	
		>0.9 mg kaempferol	<0.2 mg	Cerebrovascular disease	0.70 (0.56, 0.86) ●	
		>0.2 mg myricetin	<0 mg	Cerebrovascular disease	1.02 (0.84, 1.24) ○	
		>21 mg hesperetin	<2 mg	Cerebrovascular disease	0.80 (0.64, 0.99) ●	
		>6 mg naringenin	<0.5 mg	Cerebrovascular disease	0.79 (0.64, 0.98) ●	
Finland	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study n=26,593, male smokers, 50～69 y 6.1 y follow-up	>16 mg (median) flavonols and flavones[3]	<4 mg (median)	Cerebral infarction	0.98 (0.80～1.21) ○	54
USA (Iowa)	n=34,492 women, 55～69 y 10 y follow-up	>29 mg (median) flavonols and flavones[3]	<4 mg (median)	Stroke mortality	1.02 (0.59, 1.79) ○	23

Results are adjusted for confounding factors, but methods of adjustment varied in different studies. [1]Sum of kaempferol, quercetin, myricetin, isorhamnetin (flavonols), apigenin, luteolin (flavones), hesperetin, naringenin and eriodictyol (flavanones). [3]Sum of quercetin, kaempferol, myricetin, luteolin and apigenin.
●, significant result; ○, not significant result.

stomach cancers,[35,36] though a similar effect has not been observed for lung cancer.[37,38] Future studies that examine biomarkers of oxidative DNA injury and genetic susceptibility to cancer may better identify individuals and populations most responsive to a potential chemopreventive action of flavonoids.

Other Chronic Diseases

Employing data from the Finnish Mobile Clinic Health Examination Survey, Knekt et al. (2002)[21] examined the relationship between flavonoid intake and a variety of chronic diseases, including asthma, cataract, diabetes, and rheumatoid arthritis (Table 7). A diet rich in flavonols, flavones, and flavanones appeared generally to protect against asthma. Extrapolating these data for quercetin revealed an inverse correlation with both asthma and diabetes.

Table 6. Effect of dietary flavonoids on cancer incidence-epidemiological studies

Country	Study population	Flavonoid intake/d	Compared with	Incidence	Relative risk (95% CI)	Reference
Finland	Finnish Mobile Clinic Health Examination Survey n=10,054, >15 y 28 y follow-up	>33 mg total[1] flavonols (4) flavones (2) flavanones (3)	<6 mg	all cancers	0.89 (0.74, 1.06) ○	
				lung cancer	0.64 (0.39, 1.04) ●	
				colorectal cancer	0.84 (0.43, 1.64) ○	
				breast cancer (in women)	1.23 (0.72, 2.10) ○	
		>4.3 mg quercetin	<1.7 mg	all cancers	0.77 (0.65, 0.92) ●	
				lung cancer	0.42 (0.25, 0.72) ●	
				colorectal cancer	0.62 (0.33, 1.17) ○	
				breast cancer (in women)	0.62 (0.37, 1.03) ○	
		>0.9 mg kaempferol	<0.2 mg	all cancers	0.94 (0.78, 1.12) ○	
				lung cancer	0.81 (0.51, 1.28) ○	
				colorectal cancer	1.13 (0.60, 2.12) ○	
				breast cancer (in women)	0.87 (0.53, 1.41) ○	
		>0.2 mg myricetin	<0 mg	all cancers	0.99 (0.83, 1.17) ○	
				lung cancer	1.20 (0.78, 1.83) ○	
				colorectal cancer	1.31 (0.71, 2.43) ○	
				breast cancer (in women)	0.95 (0.57, 1.60) ○	
		>21 mg hesperetin	<2 mg	all cancers	0.96 (0.80, 1.15) ○	
				lung cancer	0.74 (0.46, 1.18) ○	
				colorectal cancer	0.97 (0.50, 1.90) ○	
				breast cancer (in women)	1.08 (0.63, 1.86) ○	
		>6 mg naringenin	<0.5 mg	all cancers	0.96 (0.80, 1.15) ○	
				lung cancer	0.63 (0.40, 1.08) ●	
				colorectal cancer	0.93 (0.48, 1.82) ○	
				breast cancer (in women)	1.14 (0.67, 1.94) ○	
Wales	Caerphilly Study n = 1900 men, 45～59 y 14 y follow-up (FFQ; weighed dietary intake)	>34 mg flavonols[2]	<19 mg	all cancer mortality	1.3 (0.7, 2.3) ●	25
Holland	Netherlands Cohort Study on Diet and Cancer n=120,852, 55～69 y 4.3 y follow up (FFQ)	44 mg median flavonols and luteolin[4]	13 mg median	stomach cancer	0.86 (0.47, 1.57) ○	34
				colorectal cancer	0.97 (0.71, 1.32) ○	
				lung cancer	0.99 (0.69, 1.42) ○	
				breast cancer	1.02 (0.72, 1.44) ○	
		30 mg quercetin (median)	8 mg median quercetin	stomach cancer	1.08 (0.56, 2.05) ○	
				colorectal cancer	1.06 (0.77, 1.45) ○	
				lung cancer	0.81 (0.57, 1.17) ○	
				breast cancer	1.00 (0.70, 1.41) ○	
Holland	Zutphen Elderly Study n=738 men, 65～84 y 5 y follow-up (FFQ)	>30 mg flavonols and flavones[3]	<19 mg	all cause cancer incidence	1.21 (0.66, 2.21) ○	33
				lung cancer incidence	1.13 (0.38, 3.40) ○	
				all cause cancer death	1.43 (0.58, 3.54) ○	
Spain	n=354 cases, 354 controls	highest quartile of flavonol and luteolin[4] intake	lowest quartile	stomach cancer	0.44 (0.25, 0.78) ●	36
		highest quartile of quercetin intake	lowest quartile	stomach cancer	0.62 (0.35, 1.10) ●	
Spain	n=103 cases, 206 controls, mean age: 63 y	highest tertile of flavonol and luteolin[4] intake	lowest tercile	lung cancer	0.98 (0.44, 2.19) ○	37
		>7 mg quercetin	<2.5 mg quercetin	lung cancer	0.99 (0.44, 2.23) ○	
Hawaii	n=582 cases, 582 controls, mean age: 66.5 y	>69 mg flavonols (3) flavanones(2)[5]	<24 mg	lung cancer	0.80 (0.50, 1.40) ○	38
		>17 mg quercetin	<9 mg	lung cancer	0.70 (0.40, 1.10) ○	
Uruguay	n=111 cases, 444 controls	highest quartile of quercetin intake	lowest quartile	esophagus cancer	0.47 (0.23, 0.93) ●	35

Results are adjusted for confounding factors, but methods of adjustment varied in different studies. [1]Sum of kaempferol, quercetin, myricetin, isorhamnetin (flavonols), apigenin, luteolin (flavones), hesperetin, naringenin and eriodictyol (flavanones). [2]Sum of quercetin, kaempferol and myricetin. [3]Sum of quercetin, kaempferol, myricetin, luteolin and apigenin. [4]Sum of quercetin, kaempferol, myricetin and luteolin. [5]Sum of kaempferol, quercetin, myricetin (flavonols) and hesperetin, naringenin (flavanones). ●, significant result; ○, not significant result.

Table 7. Effect of dietary flavonoids on asthma, cataract, diabetes and rheumatoid arthritis-epidemiological study

Country	Study population	Flavonoid intake/d	Compared with	Incidence	Relative risk (95% CI)	Reference
Finland	Finnish Mobile Clinic Health Examination Survey n=10,054, >15 y 28 y follow-up	>33 mg total[1] flavonols (4) flavones (2) flavanones (3)	<6 mg	Rheumatoid arthritis	1.18 (0.62, 2.26) ○	21
				Diabetes	0.98 (0.77, 1.24) ○	
				Cataract	1.36 (0.84, 2.21) ○	
				Asthma	0.65 (0.47, 0.90) ●	
		>4.3 mg quercetin	<1.7 mg	Rheumatoid arthritis	2.64 (1.30, 5.36) ○	
				Diabetes	0.81 (0.64, 1.02) ●	
				Cataract	0.94 (0.57, 1.56) ○	
				Asthma	0.76 (0.56, 1.01) ●	
		>0.9 mg kaempferol	<0.2 mg	Rheumatoid arthritis	1.91 (1.01, 3.62) ●	
				Diabetes	0.92 (0.72, 1.18) ○	
				Cataract	1.16 (0.69, 1.95) ○	
				Asthma	0.86 (0.64, 1.14) ○	
		>0.2 mg myricetin		Rheumatoid arthritis	0.83 (0.44, 1.55) ○	
				Diabetes	0.79 (0.62, 1.00) ○	
				Cataract	1.10 (0.69, 1.76) ○	
				Asthma	1.13 (0.86, 1.49) ○	
		>21 mg hesperetin	<2 mg	Rheumatoid arthritis	1.10 (0.59, 2.07) ○	
				Diabetes	0.96 (0.76, 1.22) ○	
				Cataract	1.66 (1.04, 2.66) ○	
				Asthma	0.64 (0.46, 0.88) ●	
		>6 mg naringenin	<0.5 mg	Rheumatoid arthritis	0.99 (0.52, 1.88) ○	
				Diabetes	0.98 (0.78, 1.24) ○	
				Cataract	1.53 (0.95, 2.46) ○	
				Asthma	0.69 (0.50, 0.94) ○	

Results are adjusted for confounding factors. [1]Sum of kaempferol, quercetin, myricetin, isorhamnetin (flavonols), apigenin, luteolin (flavones), hesperetin, naringenin and eriodictyol (flavanones). ●, significant result; ○, not significant result.

DISCUSSION

Though certainly not definitive, the potential preventive action of flavonols, flavones, and flavanones against a variety of chronic diseases reflects findings not only from observational studies but from basic research studies of their multifunctional capabilities as antioxidants, chelators of transition metals, modulators of signal transduction pathways, and other actions that may beneficially affect disease etiology and pathophysiology.[39] As with all investigations of nutrients and health, a range of in vitro, cell culture, animal model, and human studies are necessary to fully understand the relationship between one or more related compounds and the prevention of chronic diseases. While observational studies have proven a driving force in generating many hypotheses about diet-health relationships, this approach is problematic for flavonoids and many other phytochemicals.

Analytic and descriptive epidemiological investigations are critically dependent on an accurate measurement of food intake through the use of dietary assessment instruments, most often food frequency questionnaires in large cohort studies. However, beyond the participants in the cohort or case-control groups completing these instruments accurately, this approach depends on inclusion of foods most relevant to the hypothesis and validated nutrient databases. With regard to assessing flavonoid intake, many food frequency questionnaires are absent these items or fail to distinguish sufficiently between important food sources, e.g., types of berry fruit, red vs. white wine, *Ca-*

mellia sinensis teas vs. herb teas. As suggested by this review, the dietary assessment of flavonoid subclasses and even individual flavonoids must be considered important as opposed to earlier efforts examining total flavonoid intake to health outcomes.

Due to the vast number of individual flavonoids created by the variety of glycosides, often estimated at over 4000 different compounds, the lack of a truly comprehensive food composition database is not surprising. Further, the variation of flavonoids in foods and beverages is substantially dependent on factors such as cultivar, growth conditions, ripeness, post-harvest processing, cooking, and storage.[9,10,40] For example, yellow onions may contain between 9~81 mg quercetin/100 g fresh weight depending on the cultivar and red onions can contain up to 139 mg quercetin/100 g.[10,12] Loss of flavonoids may also occur during food preparation; though these compounds are relatively resistant to heat and stable in lightly fried vegetables, significant losses (up to 75%) may occur in cooking water due to their solubility.[9,10]

Complicating the difficulty of adequately determining flavonoid intake is the very limited information available on the bioavailability of these compounds and the suggestion that the degree and rate of absorption from different food matrices may prove as or more important than the quantity consumed. Illustrating this challenge is the fact that the principal flavonols in onion (quercetin-3-glucoside, quercetin-3,4'-glucoside, quercetin-4'-glucoside) are more readily absorbed then the major flavonols in green and black tea (quercetin-3-rhamnoglucoside or rutin).[41] Further complexity to this matter is added by the apparently large inter-individual differences in flavonoid bioavailability and biotransformation.[42,43]

Advances in observational studies may occur through the correlation of disease outcomes with flavonoid status in plasma and urine,[44,45] although a better understanding and consideration of flavonoid pharmacokinetics is essential. Several studies have reported positive correlations between plasma and/or urinary concentrations of hesperetin, kaempferol, naringenin and/or quercetin and their dietary intake through food or supplements.[42,46-49] In contrast, Erlund et al. (2001 and 2002)[43,50] reported that hesperetin and naringenin status in plasma and urine were not correlated with intake, though such discrepancies may be accounted for by inter-individual differences or by use of different test foods. Because flavonoid concentrations in plasma are typically cleared rapidly, levels in urine may prove a more reliable, integrated biomarker of flavonoid intake.

In conclusion, caution is warranted in the interpretation of epidemiological studies because accurate and complete information about daily intake and bioavailability need to be more fully developed. Nonetheless, the available epidemiological studies, together with data from animal models and clinical trials suggest that flavonoids, including flavonols, flavones and flavanones, may beneficially affect disease etiology and pathophysiology.

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