Improving the estimation of flavonoid intake for study of health outcomes

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Imprecision in estimating intakes of non-nutrient bioactive compounds such as flavonoids is a challenge in epidemiologic studies of health outcomes. The sources of this imprecision, using flavonoids as an example, include the variability of bioactive compounds in foods due to differences in growing conditions and processing, the challenges in laboratory quantification of flavonoids in foods, the incompleteness of flavonoid food composition tables, and the lack of adequate dietary assessment instruments. Steps to improve databases of bioactive compounds and to increase the accuracy and precision of the estimation of bioactive compound intakes in studies of health benefits and outcomes are suggested.

INTRODUCTION

Flavonoids are bioactive, polyphenolic, non-nutrients in plants[1,2] that are ubiquitous in diets.[3–5] Figure 1 shows the major classes of flavonoids commonly found in plant foods. Table 1 lists some common food sources of the various flavonoid classes and references figures illustrating some of these (Figure 2 and Figures S1–S3, which are available in the Supporting Information for this article online).[6–11] Although there are thousands of flavonoids found in nature, only several dozen are common in foods. Emerging science from some observational and metabolic studies suggests that flavonoid-rich diets may lower the risk of some diet-related chronic degenerative diseases, such as cardiovascular disease, type 2 diabetes, and certain cancers,[12–16] but a few clinical and laboratory reports indicate that very high doses of certain flavonoids may have adverse effects, such as interference with common medications and, for some green tea extracts, liver toxicity.[17–24] Therefore, it is important to accurately assess flavonoid intakes from the perspectives of both disease prevention and safety.[25–29] Adverse effects and safety issues, however, are beyond the scope of this article.

This article summarizes flavonoid intakes from recent observational epidemiologic studies in Europe and the United States. It explores some possible sources of flavonoid intake misestimation in these studies, including the variability of flavonoids in foods due to differences in growing conditions and processing, the challenges in laboratory quantification of flavonoids in foods, the incompleteness of flavonoid food composition tables, and the lack of adequate dietary assessment tools. It concludes with steps scientists can take to improve databases, reduce methodological misestimations, and increase the accuracy and precision of studies assessing the associations between flavonoids and health outcomes. This article does not address reporting requirements for studies of bioactive compounds such as flavonoids or the many pitfalls that must be avoided in experimental and clinical studies. These issues are covered in a recent article[30] documenting reporting

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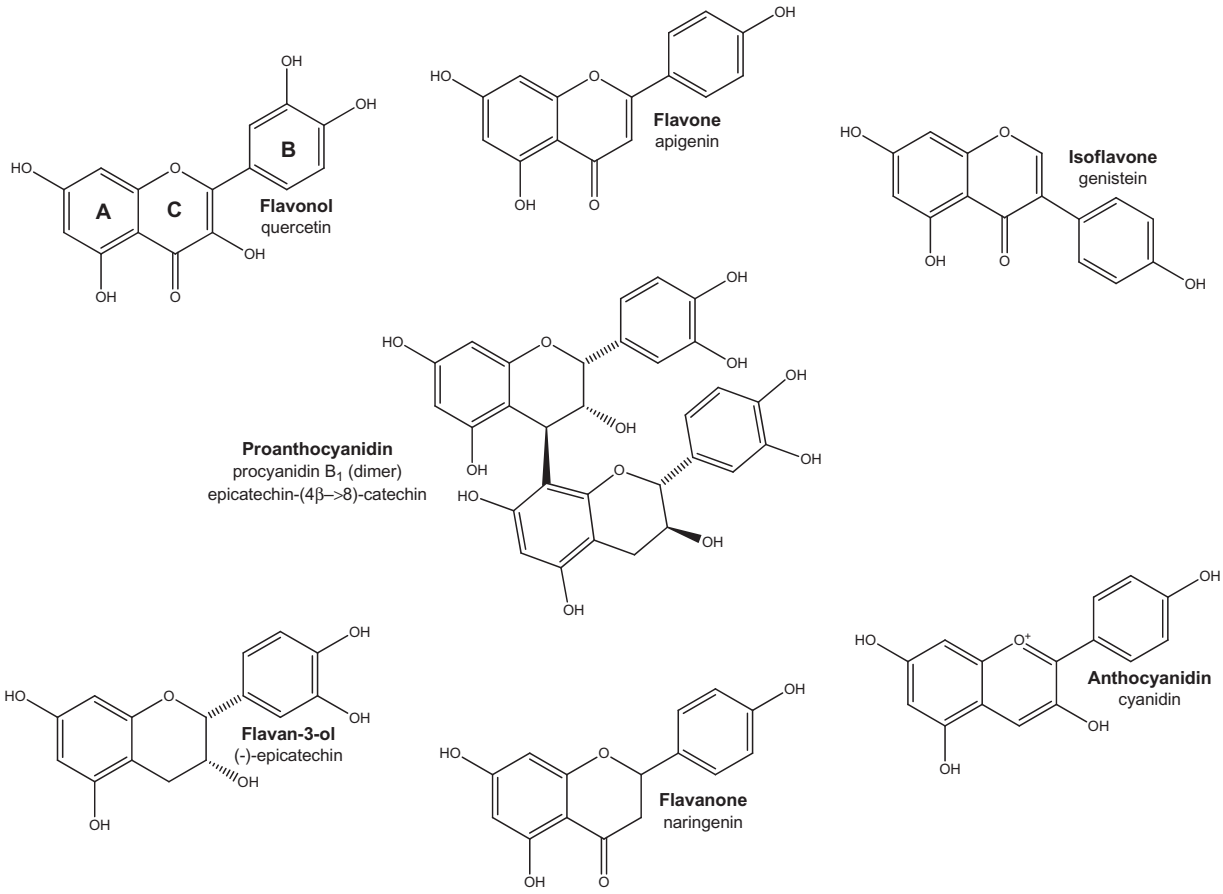

Figure 1 **Flavonoid classes commonly found in plant foods, with representative examples of each.** Except for flavan-3-ols and proanthocyanidins, most compounds in the other classes have sugars attached (flavonoid glycosides). Here, they are all presented as aglycones (without sugars).

requirements by the International Life Sciences Institute Bioactive Committee[31] using the CONSORT framework developed[32–33] and endorsed by leading researchers here and abroad.

FLAVONOID INTAKES IN EUROPEAN AND US COHORTS

Table 2[3,4,34–58] reports flavonoid intakes based on means and medians from recent US, European, and Australian cohort and population-based studies of adults. Only studies that measured intakes of proanthocyanidins[6,59] (condensed tannins, Figure 2) and at least 4 monomeric flavonoid classes were included (indicating that more complete flavonoid data were used). As seen in Table 2, intake estimates varied greatly across cohorts by country. Since flavonoid intake distributions are usually skewed to the right, mean intakes tended to be higher than median intakes. When proanthocyanidins, particularly the thearubigins[60] (derived tannins; see Figure S3 in the Supporting Information for this article available online), were not measured, total flavonoid intakes were usually lower by at least a third. Note that, in Table 2, values in boldface indicate thearubigins were included; in the remaining studies, these compounds were excluded.

Thus, intakes may not be directly comparable because the studies used various flavonoid databases and dietary assessment tools (food frequency questionnaires of varying length, histories, recalls, and records). Despite these variable approaches to measuring diet and assessing flavonoid intakes, some generalizations are possible. First, the range of mean total flavonoid intakes between and within these Australian, European, and US adult populations was wide, from 209 to 1017 mg/d (mean 435 mg/d). The highest mean intake (1017 mg/d) was reported in studies by Knaze et al.[39] and Zamora-Ros et al.[46–49] for a British cohort, and the lowest mean intake (209 mg/d) reported was for the National Findiet cohort.[41] Both of these studies used a single 24-hour recall, which may be too short in duration to reflect usual diets and may have captured unrepresentative (outlier) days that do not reflect usual diets.[61] Four studies[35,40,44,45] provided means and medians for many of the flavonoid classes, and 3 of these

Table 1 **Flavonoid classes, common compounds, and their plant sources**

Flavonoid class (compounds)	Common plant sources (botanical families)
Anthocyanidins (cyanidin, delphinidin, malvidin, pelargonidin, peonidin, petunidin)	Blueberries (Ericaceae), red wine (Vitaceae), strawberries (Rosaceae). Usually present in any pink to purple fruit or vegetable[a]
Flavonols (isorhamnetin, kaempferol, myricetin, quercetin)	Blueberries (Ericaceae), garlic and onions (Amaryllidaceae), kale and broccoli (Brassicaceae), spinach (Chenopodiaceae), red wine (Vitaceae), tea (Theaceae), tomatoes (Solanaceae). Ubiquitous in plant families
Flavones (apigenin, luteolin)	Celery (Apiaceae), garlic (Amaryllidaceae), green peppers (Solanaceae), peppermint (Lamiaceae). Common in any leafy plant, particularly the parsley family (Apiaceae)
Isoflavones (daidzein, genistein, glycitein, biochanin A, coumestrol,[b] formononetin)	Soy products, peanuts, beans (Fabaceae). Present in members of the legume family (Fabaceae), especially the genus *Glycine* (soy), but also in small amounts in other plants[7–11]
Flavanones (eriodictyol, hesperetin, naringenin)	Citrus fruits and juices (Rutaceae), peppermint (Lamiaceae)
Flavan-3-ols (epicatechin, epicatechin 3-gallate, epigallocatechin, epigallocatechin gallate, catechin, gallocatechin)	Apples, apricots, peaches, pears, strawberries (Rosaceae), black and green tea (Theaceae), blueberries and cranberries (Ericaceae), chocolate (Malvaceae), grapes and red wine (Vitaceae)
Proanthocyanidins (monomers,[c] dimers, trimers, 4–6 mers, 7–10 mers, polymers)	Apples, apricots, peaches, pears, strawberries (Rosaceae), blueberries and cranberries (Ericaceae), chocolate (Malvaceae), grapes and red wine (Vitaceae), peanuts (Fabaceae), pecans and walnuts (Juglandaceae)
Theaflavins and thearubigins. Theaflavins are flavan-3-ol dimers, and thearubigins are flavan-3-ol polymers. Both are derived tannins[6]	Formed during the processing of tea (Theaceae). Theaflavins (Figure 2) are red, and thearubigins (Figure S3) are reddish brown

[a]Other pink to red to violet pigments are lycopene (a tetraterpene or carotenoid) in tomatoes and red peppers (Solanaceae, potato family, where eggplant has anthocyanins), watermelon (Cucurbitaceae, squash family), and grapefruit (Rutaceae, citrus family, where blood oranges have anthocyanins), and the betalains (indole alkaloids) in the Chenopodiaceae family (beets, quinoa, spinach, Swiss chard, etc.) (Figure S1 in the Supporting Information online)
[b]Coumestrol is a coumestan; coumestans are structurally similar to isoflavones (Figure S2 in the Supporting Information online).
[c]Monomers are flavan-3-ols that are free flavan-3-ols or cleaved from oligomers and polymers during analysis (extraction and/or isolation)

provided mean and median total flavonoid intakes. The median total intakes in these 3 studies were 44 mg/d, 57 mg/d, and 66 mg/d, lower than the means reported, illustrating that estimates tend to be skewed to the right (Table S1).

Second, the flavonoids consumed in the greatest amounts in these studies were the polymeric proanthocyanidins (ranging from 48 to 706 mg/d, with a mean of 242 mg/d). Proanthocyanidins were rarely included in studies before 2004,[62] when a provisional database on the proanthocyanidin content of foods first became available.[58,59,63–65] In these recent studies, the mean total intake of the monomeric flavonoid classes was 193 mg/d (range, 83–560 mg/d). Intakes of the monomeric flavonoids in these studies were as follows: flavan-3-ols, 102 mg/d (range, 12–431 mg/d); flavanones, 34 mg/d (range, 13–53 mg/d); anthocyanidins, 27 mg/d (range, 3–59 mg/d); flavonols, 27 mg/d (range, 5–52 mg/d); flavones, 5 mg/d (range, 0.2–34 mg/d); and isoflavones 1 mg/day (range, 0.1–5 mg/d) (Table S1).

Third, it should be noted that mean isoflavone intakes of individuals in these European and US cohorts (<2 mg/d) differed strikingly from intakes reported in studies of Asian populations (≈26 mg/d).[66–69] Mean intakes of other classes of flavonoids appear to be more similar among European,[35,36,38,39,41,42,44,46–49] US,[3,4,34,40,43] and possibly Asian populations.[70–74] However, very few Asian studies[70–74] have measured intakes of the other flavonoid classes, and none appear to have included proanthocyanidins. It is not known whether intakes from other classes of flavonoids differ between Asian and Western populations.[13,75]

Fourth, even the highest flavonoid intake levels for individual compounds or classes in these cohorts were typically lower than those in intervention studies that have achieved clinical effects.[76] For example the dose used in most intervention studies exceeded the usual intakes from diets by ≈3- to 15-fold.[77–83] In the recent FLAVURS intervention study, doses ranging from 20 to 70 mg flavonoids over baseline flavonoid intake levels (that were stated to be low but not reported) showed some effects on microvascular reactivity.[84]

POSSIBLE REASONS FOR ACROSS-STUDY VARIATIONS IN ESTIMATED FLAVONOID INTAKE

Flavonoid intakes vary greatly within and between populations, owing not only to real differences in intakes[85] but also to other causes of variability. These variations may lead to inconsistent associations with health outcomes.[12,86–95] Sources of variability include the variability of plants themselves, the methods of processing plant foods for consumption, the chemical analyses

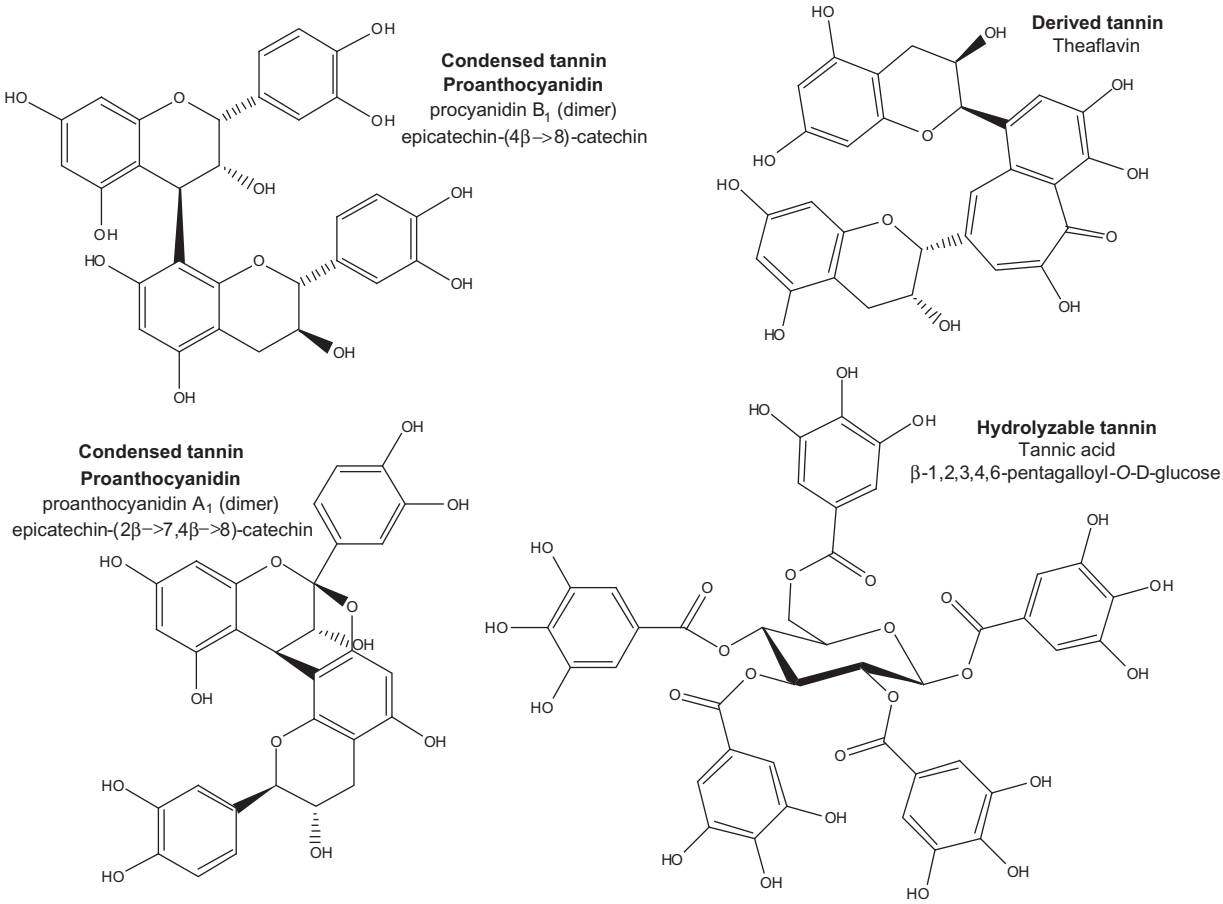

Figure 2 **Tannins: condensed (proanthocyanidins), derived (theaflavin), and hydrolyzable (tannic acid).** Until or unless databases that include the condensed, derived, and hydrolyzable tannins are developed,[6] it is probably wise to include theaflavins with proanthocyanidin dimers and thearubigins with proanthocyanidin polymers. There are a few flavone dimers, particularly in medicinal plants, as well as a few flavan-3-ol-anthocyanin and proanthocyanidin–anthocyanin pairs in wine.

used to measure the flavonoids present, and the completeness of flavonoid databases. In addition, inadequate dietary assessment tools can cause variability between studies. Each source of misestimation is discussed in greater detail below.

Inherent variability of flavonoid content in plants

A plant's capacity to produce flavonoids varies intrinsically by its genus, species, family, and even within subspecies and cultivars or varieties.[96–101] Most plants contain more than one class of flavonoids. Table 3 shows some particularly rich sources (e.g., total flavonoids $\geq$50 mg/serving) common in US diets,[102] including apples, blueberries, dark chocolate, grapefruit juice, grapes, oranges, pears, red wine, strawberries, and tea (black, black decaffeinated, and green). Variability in flavonoid content, even within the same family, genus, and species, occurs because flavonoids are secondary metabolites produced in varying amounts in response to stressors such as invading microorganisms, insects, plant diseases, season, climate, geography, or other environmental influences.[103–110]

Animals do not synthesize flavonoids. The few flavonoids present in animal foods are usually due to the animal's diet (e.g., isoflavones in milk due to alfalfa, clover, other Fabaceae plants, and soy meal eaten by cows)[111] or to processing.[11]

Flavonoids in foods are often conjugated with gallates, glycosides, or methoxy groups (Figures S4–S6 available in the Supporting Information online), which may affect bioavailability.[112–116] Although plant genera and species differ in the specific aglycones, sugars, and the amount of compounds that are present (which are affected in turn by the degree of ripeness and other environmental factors),[9,117–122] each genus and species is fairly consistent in the type and amount of one or more "signature" flavonoid classes it contains. For example, blueberries[101] are rich in anthocyanins and proanthocyanidins, dark chocolate[123,124] is rich in flavan-3-ols and proanthocyanidins, and citrus[125,126] is rich in flavanones. This considerable variability in food flavonoid

Table 2 **Mean and median flavonoid intakes reported in recent European, US, and Australian cross-sectional and cohort studies**

Country	Year	Cohort	Sex	No.	Diet method	Databases used[a]	Total flavonoids[b] (mg per day)	Monomeric flavonoids[b] (mg per day)	Reference
Means									
Australia	2013	CIFOARES	F	1063	FFQ	f2007 i2008, PE	**775**	**560**	Ivey et al. (2013)[37]
Denmark	2012	EPIC[c]	M + F	3917	24-h recall	f2007 i2008, PE	**599**	200	Knaze et al. (2012)[39]; Zamora-Ros et al. (2011, 2011, 2012, 2013)[46–49]
Finland	2008	Findiet 2002	M + F	2007	24-h recall	f2007, local	209	92	Ovaskainen et al. (2008)[41]
France	2011	SU.VI.MAX	M + F	4942	24-h recall	PE	423	187	Perez-Jimenez et al. (2011)[42]
France	2012	EPIC[c]	F	4735	24-h recall	f2007 i2008, PE	**529**	189	Knaze et al. (2012)[39]; Zamora-Ros et al. (2011, 2011, 2012, 2013)[46–49]
France	2012	SU.VI.MAX	M + F	2574	24-h recall	PE	528	274	Kesse-Guyot et al. (2012)[38]
Germany	2012	EPIC[c]	M + F	4415	24-h recall	f2007 i2008, PE	**482**	203	Knaze et al. (2012)[39]; Zamora-Ros et al. (2011, 2011, 2012, 2013)[46–49]
Greece	2012	EPIC[c]	M + F	2687	24-h recall	f2007 i2008, PE	**236**	108	Knaze et al. (2012)[39]; Zamora-Ros et al. (2011, 2011, 2012, 2013)[46–49]
Italy	2012	EPIC[c]	M + F	3953	24-h recall	f2007 i2008, PE	**429**	163	Knaze et al. (2012)[39]; Zamora-Ros et al. (2011, 2011, 2012, 2013)[46–49]
Norway	2012	EPIC[c]	F	1797	24-h recall	f2007 i2008, PE	**483**	151	Knaze et al. (2012)[39]; Zamora-Ros et al. (2011, 2011, 2012, 2013)[46–49]
Scotland	2011	LBC	M + F	882	FFQ	Kyle	302	250	Butchart et al. (2011)[35]
Scotland	2011	BMD	F	3226	FFQ	f2004, Kyle	307	259	Hardcastle et al. (2011)[36]
Spain	2010	EPIC[c]	M + F	40 683	History	f2007 i2007	**313**	122	Zamora-Ros et al. (2010)[44]
Spain	2012	EPIC[c]	M + F	3220	24-h recall	f2007 i2008, PE	**410**	150	Knaze et al. (2012)[39]; Zamora-Ros et al. (2011, 2011, 2012, 2013)[46–49]
Spain	2013	EPIC[c]	M + F	40 622	History	f2007 i2008, PE	387	133	Zamora-Ros et al. (2013)[45]
Sweden	2012	EPIC[c]	M + F	6050	24-h recall	f2007 i2008, PE	**378**	166	Knaze et al. (2012)[39]; Zamora-Ros et al. (2011, 2011, 2012, 2013)[46–49]
The Netherlands	2012	EPIC[c]	M + F	3980	24-h recall	f2007 i2008, PE	**576**	202	Knaze et al. (2012)[39]; Zamora-Ros et al. (2011, 2011, 2012, 2013)[46–49]
United Kingdom	2012	EPIC[c]	M + F	974	24-h recall	f2007 i2008, PE	**1017**	311	Knaze et al. (2012)[39]; Zamora-Ros et al. (2011, 2011, 2012, 2013)[46–49]
United States	2007	NHANES	M + F	8809	24-h recall, FFQ	f2003 i2002	**285**	**190**	Chun et al. (2007),[4] Wang et al. (2011)[43]
United States	2011	NHS I	F	46 672	FFQ	f2007	**357**	124	Cassidy et al. (2011)[3]
United States	2011	HPS	M	23 043	FFQ	f2007	**377**	139	Cassidy et al. (2011)[3]
United States	2011	NHS II	F	87 242	FFQ	f2007	**412**	129	Cassidy et al. (2011)[3]
United States	2012	ACS CPSII	M + F	98 469	FFQ	f2007 i2002	**268**	83	McCullough et al. (2012)[40]
United States	2014	NHANES III	M + F	17 900	24-h recall	f2011 i2008	353	245	Bai et al. (2014)[34]
Mean							435	193	
Range							209–1,017	83–560	
Medians									
Greece	2010	EPIC[c]	M + F	28 572	FFQ	f2007, i2007	161[d]	86[d]	Dilis et al. (2010)[51]
United States	2007	Iowa	F	34 489	FFQ	f2003, i1999	**239**	**70**[d]	Mink et al. (2007)[53]
United States	2012	NHS	F	69 622	FFQ	f2007	**232**	100[d]	Cassidy et al. (2012)[50]
United States	2013	Framingham	M + F	2915	FFQ	f2007	**225**	87[d]	Jacques et al. (2013)[52]
Mean							214	86	
Range							161–239	70–100	

Abbreviations: ACS CPSII, American Cancer Society Cancer Prevention Study II Nutrition; BMD, bone mineral density population study; CIFOARES, Calcium Intake Fracture Outcome Age-Related Extension Study; EPIC, European Prospective Investigation into Cancer and Nutrition; Findiet 2002, National Findiet 2002; Framingham, Framingham Offspring Study; FFQ, food frequency questionnaire; HPS, Health Professionals Follow-up Study; Iowa, Iowa Women's Health Study; LBC, Lothian Birth Cohort 1936; NHANES, National Health and Nutrition Examination Survey 1999–2002; NHANES III, National Health and Nutrition Examination Survey 1988–1994; NHS, Nurse's Health Study; NHS I, Nurses' Health Study I; NHS II, Nurses' Health Study II; SU.VI.MAX, Supplémentation en Vitamines et Minéraux Antioxydants Cohort.

[a]Databases: f2003, f2007, f2011 – versions of the USDA flavonoid database[55]; i1999, i2002, i2003, i2007, i2008 – versions of the USDA isoflavone database[54]; Kyle – Kyle & Duthie (2006)[57]; local – local flavonoid data[41]; PE – Phenol Explorer;[56] proanthocyanidin data are from the USDA 2004 database.[58]

[b]Boldface indicates thearubigins are included (see Figure S3).

[c]EPIC 10 countries: Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden, and the United Kingdom.

[d]Median values summed for illustrative purposes.

Table 3 **Flavonoid content of individual foods commonly listed in food frequency questionnaires**[a]

Food	Serving	Total flavonoids (mg per serving)	Total flavonoids (mg per 100 g)	Anthocyanins (mg per 100 g)	Flavonols (mg per 100 g)	Flavones (mg per 100 g)	Isoflavones (mg per 100 g)	Flavanones (mg per 100 g)	Flavan-3-ols (mg per 100 g)	Proanthocyanidins (mg per 100 g)	Genus	Species	Botanical family
Beverages													
Tea, black[b]	1 c (8 fl oz)	315	133		4	0	0		28	101	*Camellia*	*sinensis*	Theaceae
Tea, decaffeinated black[b]	1 c (8 fl oz)	137	58		5	0			3	50	*Camellia*	*sinensis*	Theaceae
Tea, green[b]	1 c (8 fl oz)	339	143		5	0	0		132	7	*Camellia*	*sinensis*	Theaceae
Wine, red	5 fl oz serving	141	96	19	2	0.2	0.01	2	11	62	*Vitis*	*vinifera*	Vitaceae
Fruit													
Apples	1 medium	218	120	2	4	0.1	0	0	9	105	*Malus*	*domestica*	Rosaceae
Blueberries	1 c fresh	529	357	163	11	0.2	0	0	7	176	*Vaccinium*	*augustifolium*	Ericaceae
Grapefruit juice	1 c	54	22		0.4	0	0	21			*Citrus*	*X paradisi*	Rutaceae
Grapefruit	White, 0.5 medium	28	22		0	0	0.17	22		0	*Citrus*	*X paradisi*	Rutaceae
Grapes	Red, 1 c fresh	144	114	48	1	1	0		2	62	*Vitis*	*vinifera*	Vitaceae
Orange juice	1 c	37	15	0	0.3	0	0.11	14			*Citrus*	*sinensis*	Rutaceae
Oranges	1 medium	57	43		1	0.2	0	43	0	0	*Citrus*	*sinensis*	Rutaceae
Pears	1 medium	66	40	2	1	0	0	0	5	32	*Pyrus*	*communis*	Rosaceae
Raisins	1 sm box, 1.5 oz	0.4	1	0.05	0.3	0.01	0.1	0	1	0	*Vitis*	*vinifera*	Vitaceae
Strawberries	1 c fresh halves	258	175	27	2	0	0	0.26	5	142	*Fragaria*	× *ananassa*	Rosaceae
Candy, nuts, soy													
Dark chocolate	0.5 bar (1.75 oz)	144	287						53	234	*Theobroma*	*cacao*	Malvaceae
Milk chocolate	0.5 bar (1.75 oz)	84	167						15	152	*Theobroma*	*cacao*	Malvaceae
Peanuts	1 c halves & whole	12	16	0	0	0	0	0	1	16	*Arachis*	*hypogaea*	Fabaceae
Walnuts	0.5 c pieces or chips	42	70	3	0	0	0.03	0	0	67	*Juglans*	*regia*	Juglandaceae
Soy milk	1 c	24	10				10				*Glycine*	*max*	Fabaceae
Soy tofu	0.5 c tofu firm	40	32		1	0	31				*Glycine*	*max*	Fabaceae
Vegetables													
Broccoli	0.5 c chopped, cooked	9	12	0	11	1	0	0	0	0	*Brassica*	*oleracea* var. *italica*	Brassicaceae
Celery	1 c chopped, raw	5	5	0	1	4	0	0	0	0	*Apium*	*graveolens* var. *dulce*	Apiaceae
Garlic clove	1 clove	0.1	4		4		0.1				*Allium*	*sativum*	Amaryllidaceae
Garlic powder	1 tsp powder	0.3	8		8		0.2				*Allium*	*sativum*	Amaryllidaceae
Onion as garnish	1 medium slice	4	26		26	0.03	0		0	0	*Allium*	*cepa* var *cepa*	Amaryllidaceae
Onion as vegetable	0.5 c raw	21	26		26	0.03	0		0	0	*Allium*	*cepa* var *cepa*	Amaryllidaceae
Pepper, green	1 medium	8	7	0	2	5	0		0	0	*Capsicum*	*annuum*	Solanaceae
Spinach, raw	1 c raw	3	11		11	1	0			0	*Spinacia*	*oleracea*	Chenopodiaceae
Squash	0.5 c mashed, cooked	1	1		1		0		0		*Cucurbita*	*maxima*	Cucurbitaceae
Tomato sauce	0.5 c	1	1		1						*Lycopersicon*	*esculentum*	Solanaceae
Tomato	1 medium fresh	2	1	0	1	0	0	1	0	0	*Lycopersicon*	*esculentum*	Solanaceae

Abbreviations: c, cup; fl, fluid; oz, ounces; sm, small; tsp, teaspoon.
[a]Sources: USDA databases[54,55,58]; foods listed are from a modified version of the Willett Food Frequency Questionnaire,[102] except green tea. Serving sizes are predefined on the food frequency questionnaire (available at www.cancer.org) and are generally similar to those in the USDA Nutrient Database for Standard Reference. Blanks mean no chemical analysis was available for that particular class of flavonoids in that food item.
[b]For black and green teas, the proanthocyanidins include theaflavins and thearubigins.

content, even within specific species and varieties, cannot be entirely eliminated. For example, in the US Department of Agriculture (USDA) databases, the mean (weighted by number of data points), number of data points, standard error of the mean, minimum value from data points, maximum value from data points, and confidence estimate for the quality of the data, along with sources of data, are all provided for each item and compound. As databases grow to include more and better flavonoid analyses, the variability of estimated values should decrease, improving precision in measuring intakes.

Processing of foods

Flavonoid content is also affected by food processing. Ignoring processing losses leads to overestimates of food flavonoid content. Processing losses depend on the individual flavonoid and its chemical properties, the food and its matrix, and the processing method used.[127–144] Milling (particularly for grains) often removes flavonoids.[145–147] Boiling may leach flavonoids into water that is discarded, decreasing the flavonoid content.[127,148] Microwaving, freezing, and frying appear to have less effect on flavonoid content.[127,131,149–152] Juicing may increase the citrus flavonoid content, if the processing techniques that are used extract flavonoids from the peel and deposit them into the juice.[144,153,154]

Databases sometimes provide data only on the raw food item because that is what was analyzed. Now, the USDA's Nutrient Data Laboratory and the Food Composition and Methods Development Laboratory[155] and scientists compiling Phenol-Explorer[156] are providing flavonoid "retention factors" that account for common processing techniques for foods and flavonoids so that food tables in the future will contain improved food flavonoid composition estimates for both raw and cooked items by type of cooking method.

Although a detailed discussion of the influence of food preparation and processing methods on flavonoid values is outside the scope of this article, it is important to mention that the lack of quantitative data on nonnutrient bioactive compounds such as flavonoids in processed foods potentially lessens the ability to detect associations between flavonoid intakes and health outcomes.[8] Dekker and Verkirk[157] investigated the data on bioactive glucosinolates from the broccoli family (Brassicaceae). With the data and computer modeling, they estimated that, if information about home preparation of foods was quantified, the statistical power of a study could at least be doubled.[157] If all variation of the food production chain could be accounted for, a study's statistical power could be increased by a factor of 5.

For the flavonoids, values are needed for processed foods such as cereals, breads, and crackers. This might improve the estimated relative risks observed in studies of flavonoids and health.

Varying precision of chemical analyses used to determine flavonoid content

Until recently, the gaps that existed in food composition data were major impediments to accurate estimation of flavonoid intake. Today, better chemical analytic methods are available and databases are more complete, with duplicate analyses of more compounds and a wider variety of foods, including cooked and processed items.

The laboratory methods used to determine flavonoid content affect the precision and accuracy of the values in and the quality of databases.[158] The analytical methods for measuring flavonoids involve extraction, separation, characterization (i.e., detection and identification), and quantification. Newer extraction methods reduce the amount of solvent used as well as flavonoid losses due to degradation. Although solvent extraction systems are effective, no single extraction or separation system is suitable for all the flavonoid compounds in any one class or group of classes because of differences in polarity among individual compounds.[1,159,160]

Acid hydrolysis is used for reliable identification of aglycones because mass spectroscopy fragmentation may not identify some similar flavonoids. It also separates the *O*-glycosides (Figure S5 in the Supporting Information online), which are easily hydrolyzed from *C*-glycosides (Figure S6 in the Supporting Information online), which are not hydrolyzed.[161] Alkaline (basic) hydrolysis is used to determine where an acyl group (acetyl, malonyl, *p*-coumaryl, etc.) is attached to a sugar (Figure S6 in the Supporting Information online).[1,160,162–166] High-performance liquid chromatography is the most robust method for separation and quantification, and better separation is now available using ultra high-performance liquid chromatography. Ultraviolet detection, fluorimetry (for flavonoids with natural fluorescence), and mass spectroscopy are used for characterization and quantification.

Mass spectroscopy can determine the following: 1) molecular mass (and, if high-resolution mass spectroscopy is used,[162] even more accurate identification of a compound's molecular formula and structure is possible); 2) structure of the aglycone (pattern of hydroxylation, attachment of ring B to ring C [see Figure 1]); 3) information about acylation of sugar hydroxyl groups and possible methylation or sulfation of aglycone hydroxyl(s); and 4) the number and the configuration of sugars and, sometimes, the glycosidic bond positions. However, mass spectroscopy does not provide

Table 4 **Current methods used for chemical analyses of flavonoid classes in foods and dietary supplements**

Flavonoid class	Extraction	Hydrolysis	Separation	Identification	Quantification	Comments
Anthocyanidins[146,162,165,170,171,173,177,179,202,217–219]	Acidic alcoholic such as methanol/water/acetic acid 85:15:0.5 v/v	Sugars present, but hydrolysis not usually done due to rearrangement and degradation	RP-HPLC: Binary elution usually either 1) aqueous 5% formic acid and methanol or 2) water-formic acid, 9:1 (v/v), and acetonitrile formic acid 9:1 (v/v)	UV maxima 265–275 and 465–560 nm. MS – peaks for compound and aglycone; very poorly ionized in negative ion mode, quantified in positive ion mode	An individual anthocyanin standard is often used to quantify several anthocyanins. MS can be employed for qualitative and quantitative analysis of anthocyanins in foods	Acid medium stabilizes anthocyanins. Anthocyanins more stable than anthocyanidins (aglycones) because of sugars
Flavonols[1,160,162,170,175,178,187,189,190,195,200,202,210,213]	Flavonoid glycosides more soluble in water and flavonoid aglycones more soluble in methanol. 50% aqueous ethanol most efficient; 60% or 70% methanol often used	Sugars usually present; hydrolysis often done using 1.2 MHCl, 50% methanol/water (v/v). *C*-glycosides are not appreciably acid hydrolyzed, and no glycosidase is yet known to hydrolyze carbon-carbon linked sugars	RP-HPLC: Binary eluant usually water with 1% formic acid, 0.01% trifluoracetic acid, or 10% acetic acid and acetonitrile with the same acid and percentage	UV maxima 240–280 and 300–380 nm. Fluorimetry (more sensitive) used for some flavonols. MS – compound ion usually most intense peak; *O*- and *C*-glycosides fragment by losing their sugars; better ionized in negative ion mode	Individual standards for aglycones are common. Usually quantified using UV at 270 nm and 360–370 nm or using MS. Quantitative analyses of flavonol monoglycosides can be done using calibration curves of quercetin 3-*O*-glucoside	*C*-glycosides are sometimes present but not often separated, identified, and quantified
Flavones[125,160,161,167,181,183,189,194,195,200,202]	Flavone glycosides usually extracted with flavonol glycosides. Methanol–water (60:40, v/v) has high extraction efficiency for glycosylated flavonoids, greatest simplicity, and least cost	Sugars usually present; often done with HCl in 50% aqueous methanol and, at appropriate temperatures, aglycones stable in acid medium. The major drawback of acid hydrolysis is isomerization of unsymmetrically substituted flavones (e.g., vitexin and isovitexin, Figure S6). *C*-glycosides resistant to hydrolysis	RP-HPLC: Binary eluant usually aqueous acetic or formic acid and acetonitrile (or methanol) with the same acid and percentage (e.g., 5% aqueous formic acid and methanol with 5% formic acid)	UV maxima 240–280 and 300–380 nm. 334–338 nm for apigenin, 342–350 nm for luteolin, 213–216 nm for polymethoxyflavones (Figure S4). Fluorimetry used for polymethoxyflavones. MS – *O*- and *C*-glycosides fragment by losing their sugars. Compound ion most intense peak; better ionized in negative ion mode	Individual standards for apigenin and luteolin available	*C*-glycosides very common but not often separated, identified, and quantified; usually only apigenin and luteolin determined out of at least 20 flavone aglycones found in food
Isoflavones[166,179,180,197,199,203–205,207,208,211,212,214]	80% methanol or aqueous acetonitrile. 58% acetonitrile extracts significantly higher amounts of malonyl glucosides than 80% methanol or 83% acetonitrile	Sugars usually present; commonly done because aglycones are stable during heat and acid treatment. Coumestrol (Figure S2) and genistein most sensitive to acid treatment. Most aglycones are liberated using enzyme hydrolysis	RP-HPLC: Binary eluant usually acetonitrile and water, both with acid (0.1–1% acetic, formic, or trifluoroacetic acid)	UV maxima 250–275 and 300–340 or 465–560 nm. Fluorimetry only for daidzein, formononetin, and coumestrol. MS usually removes sugars from the isoflavone glycoside. In other words the isoflavone aglycones tend to remain intact when subjected to MS.	Individual standards for aglycones common. Standard curves for most isoflavones show high linearity when standard concentration is plotted as function of peak area from HPLC analysis. Internal standards commonly used	Legume-containing foods (such as lentil soup and baked beans) are rarely analyzed for their isoflavone content or for other flavonoids

(continued)

Table 4 **Continued**

Flavonoid class	Extraction	Hydrolysis	Separation	Identification	Quantification	Comments
Flavanones[1,125,160,165,169,178,179,181,194,198,201,202]	Methanol, ethanol, acetone, water, ethyl acetate (to a lesser extent, propanol, dimethylformamide) solvent combinations frequently used for extraction. Using methanol–water (e.g., 60:40, v/v), extraction efficiencies for glycosylated flavanones in orange peel were <80%	Sugars present, but hydrolysis not usually done. Acid hydrolysis destroys flavanone aglycones nearly as fast as the flavanone glycosides are hydrolyzed. Alkaline hydrolysis can cause the formation of chalcones (Figure S7)	RP-HPLC: Binary eluant usually acetonitrile and water, both with acid (0.1–1% acetic, formic, or trifluoroacetic acid)	UV maxima 270–295 and a weak peak or shoulder at 300–360 nm. MS – flavanone glycosides provide parent and aglycone ions, and aglycone fragments in both positive and negative ion mode. Rutinosides (Figure S5) tend to fragment easier than neohesperidosides	Individual standards for most glycosides readily available	Presence of sugars needed for stability during analysis. Analyses are usually limited to certain glycosides, so aglycones may be underestimated. Flavanones have diastereoisomers that require chiral columns to separate
Flavan-3-ols[169,171,174,176,182,183,192,200,201,206,208]	Commonly, methanol–water or acetone/water/acetic acid (e.g., 70:28:2 v/v/v). 90% aqueous methanol most efficient compared with 90% ethanol, 90% acetone, or water-saturated ethyl acetate	Not done; sugars not present but can be gallated. If flavan-3-ols are present in an extract exposed to acidic hydrolysis, destruction and/or rearrangement can occur	RP-HPLC: Binary eluant usually acetonitrile (and/or methanol) and water, both with acid (0.05–2% acetic, formic, or trifluoroacetic acid)	UV detection at 210, 240–280 nm. Fluorimetry also used. MS – catechin gallate esters cleave at the gallate (Figure S4). In negative-ion mode, mass spectra dominated by the molecular ion	Individual standards available. Quantified by comparing peak height of sample with those of standards	Each compound is separated and quantified
Proanthocyanidins[159,168,172,184–186,188,191,193,196,206,215,216,220]	Aqueous acetone (e.g., 70% v/v) or methanol–water (e.g., 60:40 v/v). Use of acidified aqueous acetone increases extraction of procyanidins by weakening hydrogen bonds between procyanidins and polar fibrous matrixes	Not done intentionally. Acid degradation can occur due to organic acids present in separation and extraction	NP-HPLC: Ternary eluant most common, usually dichloromethane, methanol, and acetic acid/water (e.g., 1:1 v/v); separates proanthocyanidins according to degree of polymerization up to decamers. RP-HPLC: For lower-molecular-weight proanthocyanidins, order of elution not related to degree of polymerization. Binary eluant is acetonitrile (or methanol) and water, both with acid (acetic, formic, or trifluoroacetic acid)	UV maxima at 200–220 nm, 240–280 nm, and 300–380 nm. UV detection commonly done at 280 nm and is not specific in presence of other polyphenols. Fluorimetry also used. MS – fragments are formed by loss of monomeric residues, and only low-molecular-mass procyanidins are quantified. The positive mode is successful in detecting procyanidin oligomers through pentamers. MS does not distinguish different stereoisomers	For NP-HPLC, quantification is based on area under the curves using cocoa standards and does not use individual compound standards. Area summation of peak grouping is used to include contributions from all isomers within an oligomeric class. Peak breadth of certain oligomers is due to number of isomers. For RP-HPLC, each compound is separated and quantified	Individual compounds are not separated and quantified in NP-HPLC; monomers may be free flavan-3-ols or cleaved from oligomers and polymers during analysis (extraction and/or isolation). Neither NP-HPLC nor MS separates isomers

Abbreviations: HPLC, high-performance liquid chromatography; MS, mass spectrometry; NP-HPLC, normal-phase high-performance liquid chromatography; RP-HPLC, reverse-phase high-performance liquid chromatography; UV, ultraviolet.

information about the stereochemistry of the glycosidic linkage or distinguish between diastereomeric sugar units, even though such characteristics may be important for biological activity.[167] Mass spectroscopy can be used to quantify monomeric flavonoids in foods but not polymeric proanthocyanidins because the number and similarity of all their isomers, both structurally and in mass spectroscopy fragmentation, is so great.[160,168–171]

Table 4[1,125,146,159–162,165–220] summarizes some of the preferred analytical methods used today. Particular analytical challenges remain for each flavonoid class,[216,217,221–223] including the lack of standards for many individual flavonoid compounds in foods and the cost of developing and using standards. The quantification difficulties involving flavonoids are being resolved with the use of one standard for several similar compounds,[173,217,219] mass spectroscopy extractable chromatogram methods,[216] and ultraviolet molar relative response factors.[160,169] When evaluating the chemical data on foods and plants in the literature for inclusion in databases, database developers must determine if the analytical methods used were appropriate.

Completeness of flavonoid databases

The primary, or core, flavonoid databases provide extensive and precise data on the compounds in many foods, with a great deal of detail on variability, preparation, and processing. Table 5 compares the three primary flavonoid databases currently available: the USDA databases[203,224,225] for flavonoids,[55] isoflavones,[54] and proanthocyanidins[58] and the Phenol-Explorer[56,114,156,226–228] and EuroFIR-eBASIS[229–234] databases. The values in these USDA and European databases are generally similar because they are based largely on a common group of analytical data for food flavonoids in the literature. The most recently updated databases contain the greatest number of foods and the greatest amount of flavonoid analytical data points for each food.

For example, the first USDA release in 2003 had 225 food items, the release in 2007, 385 food items, and the release in 2011, 500 food items for 26 predominant flavonoids. The 2013 update includes 506 foods. Using blueberries as an example, in 2003 the USDA release had 2 items, in 2007 it had 4 items, in 2011 it had 5 items, and in 2013 it had 5 items but more data points. As a result, the total anthocyanidin value of raw blueberries (USDA National Nutrient Database for Standard Reference #09050) has varied: 113 mg/100 g in 2003, 164 mg/100 g in 2007, 131 mg/100 g in 2011, and 163 mg/100 g in 2013. Table 3 shows some common foods, which vary both in their flavonoid content and in the frequency with which they are consumed. Flavonoid intake estimates using updated databases tend to be higher than older estimates. Omissions of certain foods very rich in flavonoids, such as tea, cocoa, and berries, and also foods that are lower in flavonoid content but are eaten frequently in large amounts, such as tomatoes and potatoes, may lead to underestimates of flavonoid intakes.[227,228]

Flavonoid-rich dietary supplements are often not included in dietary assessment instruments or, if they are included, only a generic question on supplement use is asked (e.g., use of vitamin-mineral or botanical supplements). Detailed information on form and dose is needed when individuals report the use of flavonoid-containing dietary supplements.[10]

Flavonoid-rich supplements include black cohosh, blueberry extracts, chaste tree, citrus extracts, dong quai, evening primrose, *Gingko biloba*, green tea extracts, kava, lemon balm, licorice root, red clover, St. John's wort, saw palmetto, soy, and valerian. Although single-ingredient flavonoid products (such as chrysin, daidzein, diosmin, genistein, hesperidin, quercetin, and rutin) are sold over the counter, most supplements, including soy, green tea, citrus, or bioflavonoids, are blends, extracts, or mixtures containing several flavonoids (often in more than one class). Regulations do not require the precise composition of blends to be validated by chemical analysis and stated on labels. Supplement products are reformulated often, making it difficult to know what is actually present. A dietary supplement label database that provides information on labeled ingredients for many products sold in the United States is now available.[235] At present, survey data are insufficient to estimate the prevalence of the use of flavonoid-rich dietary supplements, but if it is high in certain groups[236,237] such as postmenopausal women,[26,238–240] this would be an incentive to include specific questions in surveys of such groups.

Inadequacy of dietary assessment tools

Dietary assessment of flavonoid intakes is unique because there are so many flavonoids in foods and the food composition tables upon which assessment depends are still quite incomplete, particularly for flavones and proanthocyanidins. Inadequate dietary assessment tools also contribute to misestimation in exposure assessment.[61,95,241–249]

In most epidemiologic studies, very large numbers of participants (often tens of thousands) report their usual diets using semiquantitative food frequency questionnaires that maximize information while reducing both participant burden and the costs of coding and analysis. Even so, food frequency questionnaires are particularly challenging for the assessment of flavonoid intakes. Most food lists for food frequency

Table 5 **Characteristics of the different primary flavonoid databases as of 2014**

	USDA database[54,55,58,224]	Phenol Explorer[56,114,156,226–228]	EuroFIR ePlantLIBRA and eBasis[a] [229–234]
Coverage	Flavonoids, isoflavones, proanthocyanidins	All phenols	All major bioactive compounds in food plants and supplements
Specific classes included	Anthocyanidins, flavan-3-ols, flavanones, flavones, flavonols, proanthocyanidins; isoflavones, and 1 coumestan	Anthocyanins; chalcones; dihydrochalcones; flavan-3-ols; flavanones; flavones; flavonols; isoflavonoids; phenolic acids, lignans, stilbenes, other polyphenols (curcuminoids, furanocoumarins, tyrosols, etc.)	30 classes, including: flavonoids, proanthocyanidins, biogenic amines, carotenoids, cyanogenic glycosides, glucosinolates, oligosaccharides, oxalates, phytosterols, and other polyphenols
Total no. of compounds included	26 individual flavonoids; 3 major and 2 minor isoflavones and the coumestan coumestrol; proanthocyanidins grouped by degree of polymerization monomers, dimers, trimers, 4–6 mers, 7–10 mers, and >10 mers; >24 132 original data points[b]	518 polyphenols (282 flavonoids) in 6 classes and 31 subclasses, >37 636 original data points; >20 347 data points for flavonoids	>25 000 data points covering 240 plants, and >500 distinct compounds in 30 classes
Date released	Flavonoids: March 2003; latest version (3.1) May 2014, with glycoside data in MS Access Isoflavones: April 1999; latest version (2.0) September 2008 Proanthocyanidins: August 2004	2009	EuroFIR eBASIS started in 2005, ePlantLIBRA started in 2010
Total no. of foods included	Flavonoids: 506 food items Isoflavones: 557 foods Proanthocyanidins 205 foods	>455 foods	Database includes 370 plants and plant food supplement ingredients commonly consumed in Europe
Available as	Free pdf or MS Access database	Free, by Internet in MySQL or MS Access database, reports exported in Excel spreadsheets	By subscription, reports exported in Excel spreadsheets
Database data sources	CALS, FSTA	Article citations, FSTA, Web of Knowledge	CAS SciFinder, Embase, PubMed, WoS
Sources	Flavonoids: 307 articles, 1 industry source Isoflavones: 102 articles, 2 unpublished academic data Proanthocyanidins: 30 articles	>636 articles in peer-reviewed journals	Composition data extracted from primary research in peer-reviewed journals
Acceptable chemical methods	Flavonoids: HPLC, CC, capillary zone electrophoresis, micellar electrokinetic capillary chromatography Isoflavones: Murphy et al.[203] reference method Proanthocyanidins: NP-HPLC for all oligomers, RP-HPLC only to trimers	HPLC, GC, capillary electrophoresis; Folin assay, pH differential method for anthocyanins. For chromatographic methods, content values are reported separately as glycosides and esters (without hydrolysis) or as aglycones (after hydrolysis)	Chromatography, colorimetry, fluorimetry, GC, GC-MS, high-performance thin-layer chromatography, HPLC, LC-MS, near-infrared spectroscopy, NMR
Data	mg/100 g fresh weight of edible portion of food; beverages as mg/100 g	mg/100 g fresh weight for solid foods and oils, and mg/100 ml for beverages, sauces, and seasonings.	mg/kg dry or fresh weight
Trace values[c]	Limit of quantification, if available, is multiplied by 0.71[225]		Trace amounts listed
Lack of values[d]	If zero value is provided, it is a true zero; if data are unavailable, compound is not listed	True zeros available if selected	If zero value is provided, it is a true zero; if data are unavailable, compound is not listed
Variability	By cultivar, location, agricultural practices, processing and storage conditions, preparation methods, environmental stress	By plant varieties, environmental factors, agricultural practices, food processing, food storage, and cooking	Subspecies/cultivar, maturity, country of origin, region, season, growing condition, processing

(continued)

Table 5 **Continued**

	USDA database[54,55,58,224]	Phenol Explorer[56,114,156,226–228]	EuroFIR ePlantLIBRA and eBasis[a] [229–234]
Data evaluation	5 criteria: sampling plan, sample handling, no. of samples, analytical method, analytical quality control to generate a quality index and confidence code	3 criteria (inclusion/exclusion criteria): samples, analytical methods, expression of results	6 criteria: food description, component description, sample plan, sample handling, analytical methodology, and analytical performance
Botanical names	Botanical name or Nutrient Databank no. provided	Botanical name and family provided	Botanical name, family, plant part used as food, common name (15 languages), and a color image provided
Presentation of flavonoid food data	Description, mean (weighted) mg/100 g, total no. of data points, SEM, minimum value from data points, maximum value from data points, confidence code, sources, standardized food item no. (NDB no. or other no.)	Weighted mean value, standard deviation, minimum and maximum, no. of original data points for mean value, total no. of individual samples analyzed, no. of papers. Data sorted according to analytical methods	User chooses fields: plant information (cultivar, part, origin), processing, analytical method, compound class, extraction and preparation, identification, mean, standard deviation, standard error, maximum level, minimum level
Ease of use	The USDA databases are the easiest databases to use in developing food flavonoid databases for epidemiologic studies because all amounts are in mg/100 g and all data calculations are done appropriately (e.g., glycoside to aglycone, dry weight to fresh weight, etc.). Information for individual data such as glycosides, dry weight, fresh weight, etc., is available in a separate file	Phenol Explorer has the most complete flavonoid glycoside data, which can be converted to aglycone values. Provides flavonoid data in mg/100 ml (volume) for liquid items. Includes metabolic, retention, structural, and other chemical data on flavonoids and other polyphenols. Data sources are easily and directly accessed	The EuroFIR-eBASIS database provides raw data from the literature in mg/kg dry or fresh weight. The investigator must parse, aggregate, and compile the data
Comments	Flavonoid database release 3.1 and isoflavone database release 2.1 are now expanded to include ≈2900 foods in the FSRG's FNDDS 4.1, released September 2014. An updated proanthocyanidin database is in process, and retention factors for flavonoids are in process	Phenol Explorer includes structures and chemical data. All compounds are linked to other chemical databases (CAS, ChEBI, PubMed). All mean values are linked to original publications. Original data used to calculate mean values are available. Of the 3 databases, it is the richest	This database contains information on beneficial and adverse bioeffects. It includes data on plant food supplements as well as plant foods. It also lists the individual compounds found in each plant
URL	https://www.ars.usda.gov/Services/docs.htm?docid=24953	http://phenol-explorer.eu/	http://eplantlibra.eurofir.org/ http://ebasis.eurofir.org/

Abbreviations: CALS, Current Awareness Literature Service; CAS, Chemical Abstracts Service; CC, column chromatography; ChEBI, Chemical Entities of Biological Interest; Embase, Excerpta Medica dataBASE; FNDDS, Food and Nutrient Database for Dietary Studies; FSRG, Food Surveys Research Group; FSTA, Food Science and Technology Abstracts; GC, gas chromatography; HPLC, high-performance liquid chromatography; LC, liquid chromatography; MS, mass spectrometry; NMR, nuclear magnetic resonance; NP, normal-phase; PubMed, public access to MEDLINE (Medical Literature Analysis and Retrieval System Online, or MEDLARS Online); RP, reverse-phase; SEM, standard error of the mean; USDA, US Department of Agriculture; WoS, Web of Science.
[a]eBasis (BioActive Substances in Food Information System) database, which covers bioactive compounds in food plants, has been enlarged and extended to ePlantLIBRA (PLANT food supplements: Levels of Intake, Benefit and Risk Assessment), which includes data on plant food supplements. All eBASIS composition data are included within ePlantLIBRA.
[b]Data point: one value for one compound in one food item.
[c]Trace values or trace amounts: the item is analyzed, but the flavonoid values are below the limit of quantification of the method
[d]Lack of values: value is unknown or is missing because no analyses have been reported or published for that item and flavonoid class. True zeros: a zero where the absence of a flavonoid class or compound is based on chemical analyses.

questionnaires used in US cohort studies were constructed on the basis of contributions to energy intakes or other key micro- or macronutrients of foods and beverages consumed by the study population or a sample of the entire US population (e.g., National Health and Nutrition Examination Survey [NHANES]) without consideration of bioactive compounds. Since analytical data on flavonoids were not available during the construction of the original lists used in most food frequency questionnaires, older questionnaires still in use today may not be optimal to reflect the variability in dietary flavonoid intake in a population. This is primarily due to the paucity of information that would have allowed earlier researchers to identify key contributors of different flavonoids in the diet and place them in food frequency questionnaire food lists. Moreover, early food frequency questionnaires were designed to provide a rank order of usual intakes and not to provide quantitative estimates of absolute amounts of flavonoid intakes. Data from food frequency questionnaires developed in this way were often later used for studies of the association between flavonoids and health outcomes.[250–252]

Thus, the content of food frequency questionnaires is important. Some major flavonoid sources have been added to updated food frequency questionnaires as scientific interest in them has grown (e.g., tofu, tea, soy milk, blueberries). Some investigators have developed questions that focus on foods or dietary supplements that are known to be high in the bioactive compounds of particular interest, such as isoflavones in soy products (tofu and soy milk), or that contribute high amounts of flavonoids because they are consumed very frequently (e.g., potatoes, which are low in flavonoid content but are eaten very frequently in large amounts).[252–254] Some questionnaires now include questions on seasonally available fruits (apricots, blueberries, cherries, nectarines, strawberries). The appropriateness of questions on seasonality will depend upon the food availability in the populations studied.

A common problem in food frequency questionnaires is the combination of multiple foods with varying flavonoid content in the same line item. On some generic food frequency questionnaires designed to assess the intakes of many nutrients and not specifically the intakes of flavonoids, the criteria for combining certain foods in one line item were based on similar content for other nutrients (carotenoids, vitamin C, etc.) rather than for flavonoids. Such food groupings for composite items may not be appropriate for the precise assessment of flavonoid intake. For example, one early food frequency questionnaire grouped melons with berries, which would lead to underestimates of anthocyanidins, flavonols, and proanthocyanidins.[255] Similarly, composites such as "citrus fruits" and "wines" may vary greatly in their flavonoid values. Another issue with composite items is that the weights given to the different items may vary from questionnaire to questionnaire (based on underlying intake in the study), so researchers should be careful to apply appropriate weights when deriving flavonoid values.

Table 6 illustrates how descriptions of some composite items (weighted equally for illustrative purposes) differ on existing food frequency questionnaires. For example, depending on which fruits are included, values for total flavonoids may vary from 113 mg/100 g (for peaches, apricots, and plums) to 60 mg/100 g (for peaches and nectarines) to 48 mg/100 g (for peaches, apricots, and nectarines). The differences are also notable for composites of the mustard family (Brassicaceae), ranging from 61 mg/100 g for kale, chard (actually in the beet or Chenopodiaceae family), and mustard greens, to 45 mg/100 g for kale, collards, mustard, and turnip greens, to 29 mg/100 g for collards, mustard, and turnip greens. For squashes and other vegetables, the values for the composites ranged from 29 mg/100 g (summer squash, eggplant, zucchini) to 10 mg/100 g (summer squash, okra, green pepper) down to 1 mg/100 g (summer squash, yellow squash, zucchini). Protocols for weighting the foods in a composite item vary and may increase the differences between values on food frequency questionnaires for individual foods and composite items. Standardization would facilitate comparisons across studies.[246]

Several investigators have developed food frequency questionnaires to assess isoflavone intakes more specifically.[256–263] In the United States, the Block phytoestrogen questionnaire[260,264,265] has been used in the Study of Women's Health Across the Nation,[252] the Women's Health Initiative (Fred Hutchinson Cancer Center),[257] the Cancer Research Center of Hawaii,[266] and the Adventist Health Study[261] to measure isoflavonoid intakes. Some specialized questionnaires with a few flavonoid classes and compounds have been developed and used in some studies,[254,267–271] and other more complete flavonoid questionnaires[272–274] are being developed. Recently, the USDA released flavonoid data from the NHANES surveys for foods reported in 24-hour recalls, starting with the 2007–2008 survey years,[275,276] simplifying the task of identifying foods that are important contributors of flavonoids in the US diet.[4,43,277] Similar data are, or soon will be, available for populations in European countries, Australia, and elsewhere.[85,278,279] This information is critical for identifying important sources of flavonoids to modify food frequency questionnaires and to develop food lists for targeted interviews. More work is needed in food frequency questionnaire development to capture important sources of additional flavonoids in US and other Western diets.

Table 6 **Examples of composite items listed on three food frequency questionnaires commonly used in epidemiologic studies**

Composite items and questionnaire source						All items in one botanical family?	Comments
Harvard (Willett) food frequency questionnaire[a]	Total flavonoids, mg/100 g	Block food frequency questionnaire, 1998[b]	Total flavonoids, mg/100 g	National Cancer Institute[c]	Total flavonoids, mg/100 g		
Fresh apples or pears	80[d]	Apples or pears	80	Raw apples or pears	80	Yes	Same botanical family (Rosaceae)
Orange juice	15	Real 100% orange juice or grapefruit juice, including fresh, frozen, or bottled	18	Fresh or frozen orange or grapefruit juice	18	Yes	Same botanical family (Rutaceae) but very different flavanone content, both in aglycones and in sugars
Peaches, apricots, or plums[e]	113	Raw peaches, apricots, or nectarines, while in season	48	Fresh peaches or nectarines, in season	60	Yes	Same botanical family (Rosaceae)
Kale, mustard, or chard greens	61	Mustard greens, turnip greens, collards	29	Collards, mustard or turnip greens, or kale	45	No	All belong to Brassicaceae family except chard (spinach family, Chenopodiaceae)
Eggplant, zucchini, or other summer squash	29	Any other vegetable, like okra, squash, or cooked green peppers	10	Zucchini, yellow, or summer squash in season	1	No	All belong to Cucurbitaceae family except eggplant and green peppers (Solanaceae) and okra (Malvaceae)

[a]Three sources of the Willett food frequency questionnaire. 1) Diet Assessment. Copyright 1988, Brigham and Women's Hospital. All rights reserved worldwide; 2) Harvard Medical School Nurses' Health Study. Copyright 1998, Brigham and Women's Hospital. All rights reserved worldwide; and 3) Harvard Medical School 2002 Nurses' Health Study Questionnaire.
[b]Food questionnaire. Block 98.2. Copyright 1998, Block Dietary Data System. www.nutritionquest.com.
[c]Esophagus questionnaire. National Cancer Institute (oldest questionnaire; appears to have been administered by an interviewer).
[d]Total flavonoids (mg/100 g) for raw food items weighted equally for illustrative purposes using USDA databases.[54,55,58]
[e]A 2007 Harvard food frequency questionnaire has peaches or plums (with apricots listed separately). Total flavonoids for "peaches or plums" average 159 mg/100 g.

The alternative to food frequency questionnaires is the use of multiple food recalls and records to gather reports of all foods and beverages consumed. Multiple dietary recalls or records have the advantage that all foods and dietary supplements eaten are reported and quantified in 1-day time periods in replicate. Such data provide an estimate of intraindividual variation of intakes. Depending on the size of the study, however, this type of dietary assessment may not always be feasible, as daily recalls and records can be expensive and time intensive. Newer online technologies may make the use of multiple dietary recalls more acceptable.[280,281] A few studies, such as the European Prospective Investigation Into Cancer and Nutrition–Norfolk[61,269] and the Women's Health Initiative,[282] have collected both multiple food recalls and food frequency questionnaires. This use of dual assessments is helpful for capturing infrequently consumed flavonoid-rich foods and for developing even more complete food frequency questionnaires in the future.

OTHER ISSUES UNRELATED TO DATABASES: BIOAVAILABILITY AND BIOMARKERS OF INTAKE

Other sources of variation in exposure include the unknown bioavailability of flavonoid compounds.[283] The bioavailability of flavonoids is thought to differ depending on the flavonoid, the food matrix, and the influence of intestinal bacteria in biotransforming the compounds in the gut, all of which contribute to intra- and interindividual variability of biological flavonoid exposure.[284–294] The gallate, methoxy, or sugar groups (Figures S4–S6) as well as the structure of the aglycone are important in determining flavonoid bioavailability.[112–115,295] The Phenol-Explorer database provides pharmacokinetic data from animal and human studies of various compounds.[114]

The lack of biomarkers of flavonoid intake is another problem. Although work is continuing and consensus is developing on the best candidates, at present there are no agreed upon biomarkers of intake for all the various flavonoid classes, owing in part to the interindividual variation in the metabolism of flavonoid compounds.[95,249,296,297]

RECOMMENDATIONS FOR IMPROVING ESTIMATES OF FLAVONOID EXPOSURE

It is clear that the estimated flavonoid intakes in US and European cohorts vary greatly, owing in part to databases that vary in their completeness and to the use of different dietary assessment tools that were not designed to estimate flavonoid intakes precisely. In addition, there are difficult-to-quantify influences of cultivar, cooking method, degree of fruit or plant maturity at consumption, etc. These methodological limitations may obscure true differences in intakes, limit the ability to observe associations between flavonoid intakes and chronic degenerative diseases, and contribute to inconclusive findings in published studies.

Many of the shortcomings of flavonoid food and dietary supplement composition tables are remediable. For example, the development of improved chemical analyses and more complete flavonoid food and supplement databases is advised. Dietary assessment can be improved by adding flavonoid foods and supplements to food frequency questionnaires and using checklists to probe dietary recall and record responses to make sure all flavonoid-rich sources were mentioned and sources of variability ascertained (e.g., cooking method). The recommendations in Table 7 provide cross-disciplinary suggestions to advance the knowledge of food flavonoids,[298–301] starting with suggestions to improve methods of analyzing the flavonoid content of foods and supplements. In addition, standardization across laboratory methods is recommended. More complete data on the flavonoid content of foods and dietary supplements should be included in the available databases, and researchers should use these up-to-date flavonoid databases. Major food and supplement sources of flavonoids included in dietary assessment instruments should be based on population-based studies (such as NHANES) and reflect the consumption patterns of the study population.

Ideally, future work would provide estimates of the impact of food form, processing, and preparation on flavonoid values (as is provided by Phenol-Explorer). Randomized intervention studies should also examine the doses and forms of compounds consumed in a flavonoid-rich diet, along with their impact on blood biomarkers. Food frequency questionnaire line items with more than one food should consider flavonoid content whenever possible and be appropriately weighted for the study population. Clearly, decisions in the development of dietary assessment instruments will be difficult because researchers must balance the need to assess multiple dietary factors with keeping the instrument relatively brief so as not to tire or overwhelm participants.

The harmonization of dietary assessment instruments across studies will facilitate future pooling of data, improve statistical power, and enable examination of rarer outcomes and disease phenotypes. Prespecification of hypotheses, the judicious use of statistical tests, and corrections for multiple testing are also recommended because of the multiple compounds involved and the many exposures of interest in flavonoid research. Finally, researchers should include more complete descriptions of the methodology used in assessing and analyzing

Table 7 **Recommendations to improve the assessment of flavonoid exposure**

Investigators	Recommended action	Comment
Analytical chemists	Use up-to-date and appropriate chemical analyses of flavonoids	For flavonoids, HPLC is currently the most robust method for separation and quantification. Analyses that include the *C*-glycosides and methoxylated flavonoids as well as the *O*-glycosides are needed. More data on flavonoid glycosides are now becoming available
	Utilize standard reference materials (when available) for quality control	Reference materials for flavonoids are usually developed in-house. Some external standard reference materials are now being provided through the National Institute of Standards and Technology and other agencies
Food composition database developers	Fill existing gaps on commonly eaten foods that contribute to total flavonoid intakes	Include the most popular varieties of each food item (e.g., Delicious, Granny Smith, McIntosh varieties of apples) due to variability by cultivar and variety
	Ensure that all appropriate foods are included in flavonoid databases	All food items and recipe constituents must be identified botanically. Some foods with the same name not only are different plants but are often in different botanical families, depending on the community. For example, "spinach" is usually *Spinacea oleracea* (Chenopodiaceae) in the United States, *Rumex patientia* (Polygonaceae) in Europe, and *Ipomea aquatica* (Convolvulaceae) in Asia
		Use an up-to-date primary database that is relatively complete and based on current analytical methods. Teas and other foods vary in their flavonoid content, depending on their preparation; values should be included for commonly used varieties and variants
Nutritional epidemiologists	Ensure that dietary assessment tools are appropriate for obtaining estimates of flavonoid intakes	When serial 24-h recalls or diet records are available and representative groups queried, use the data to construct purpose-built FFQ food lists if those foods are consumed at least weekly in the population. 24-h recalls and food records are most useful if they are obtained randomly on numerous occasions so that factors such as seasonality are taken into account. However, this may not always be feasible
		Check the scientific literature for flavonoid content of foods not listed in primary databases. A food's absence from a primary database does not mean it does not contain flavonoids. In some cases, flavonoid data for a specific food can be imputed from another botanically related food
		Focus on greater precision of estimated intakes. If possible, standardize FFQs across studies to optimize pooled analyses and replication. Develop new and better purpose-built FFQs that focus on flavonoid-rich or commonly eaten foods. Commonly consumed flavonoid-rich foods or supplements that capture variation across the population are particularly important and should be added to FFQs whenever possible. See Tables 1 and 3 for sources of flavonoid-rich foods
		Certain details such as cultivar, herbs, and spices may be less feasible to assess using a FFQ except with a flavonoid-focused survey. In this case, significant sources of flavonoid intake (foods, supplements, and medicines), including recipes and composite items, may be queried (see Tables 1 and 3 for some key food sources)

(continued)

Table 7 **Continued**

Investigators	Recommended action	Comment
	Validate estimates of flavonoid intakes with biomarkers when possible	Whenever available, biomarkers of flavonoid intakes should be used to validate intake estimates. Continue to identify new and improved biomarkers of flavonoid intake
	Use additional statistical techniques in assessing the relationship between flavonoid exposures and health outcomes	Avoid multiple statistical testing of dozens or even hundreds of individual flavonoid compounds, as this increases the likelihood of false-positive findings, particularly if adjustments such as the Bonferroni correction are not done
		Because associations of risk for flavonoids and other nutrients or non-nutrients may not be linear, consider statistical techniques (e.g., restricted cubic splines) to evaluate the shape of the association and to evaluate the linearity assumption
	Explore the gains to be made by controlling misestimations in flavonoid exposure estimates	Estimate the effects of improving flavonoid exposure estimates on relative risks and health outcomes in epidemiologic studies. It would be useful to carry out simulations to determine how much effect sizes and risk estimates improve by doing so
	Conduct both observational and intervention studies of flavonoids and disease risk	Observational studies are useful for examining associations between relative flavonoid consumption and chronic disease outcomes that require years to develop. Randomized double-blinded clinical trials of foods or components rich in flavonoids will be needed to prove causality but may not be feasible for studying chronic disease outcomes. Intervention studies are more feasible for studying shorter-term, modifiable biomarkers such as blood lipids, intermediate markers of disease such as blood pressure, and markers of glucose homeostasis and inflammation. Intervention research requires careful consideration of exposure form, dose, and length of intervention
	Devise flavonoid-rich dietary patterns associated with decreased health risks	Recently, health recommendations from the American Institute of Cancer Research,[298] the USDA,[299] the American Cancer Society,[300] and other organizations have focused on food patterns or groupings rather than specific nutrients in order to simplify communications and to deal with the issue of intercorrelated nutrients.[301] With computer programs that permit categorization of food intakes by family, genus, and species, it may be possible to better identify flavonoid-rich dietary intake patterns that are most beneficial for health

Abbreviations: FFQ, food frequency questionnaire; HPLC, high-performance liquid chromatography; USDA, US Department of Agriculture.

flavonoid data, including the procedures used in estimating and categorizing flavonoid and proanthocyanidin classes and individual compounds.

CONCLUSION

Better food composition tables can strengthen studies of the links between intakes of bioactive compounds, such as flavonoids, and health outcomes. However, to determine whether flavonoid intakes (or intakes of other bioactive compounds) lower the risk of chronic degenerative diseases, the aggregate evidence from many types of data must be examined. These data include in vitro, animal, clinical, and observational data and, when feasible, the results of randomized intervention studies. Complete food and supplement composition databases for flavonoids and appropriate dietary assessment methods are vital to any food-based research on flavonoids. The recently available flavonoid data from NHANES 24-hour recalls and other such studies highlight flavonoid-rich food and supplement sources for epidemiologic research. If these methodological issues are addressed, more precise estimates of flavonoid consumption can be evaluated in relation to health outcomes, and recommendations on optimal intakes for health can proceed more rapidly from speculative to evidence-based advice.

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Declaration of interest. The authors have no relevant interests to declare.

SUPPORTING INFORMATION

The following Supporting Information is available through the online version of this article at the publisher's website.

Table S1 Mean and median flavonoid intakes (all classes) reported in recent European, US, and Australian cross-sectional and cohort studies

Figure S1 Other naturally occurring pink to red or violet pigments in foods. Betalains are indole alkaloids and found predominantly in the Chenopodiaceae family (amaranth, beet, spinach family). Lycopene, a tetraterpene or carotenoid, is present in watermelon (Cucurbitaceae, squash family where many carotenoids are found), tomato (Solanaceae, potato family where anthocyanins are found in eggplant), and pink and red grapefruit (Rutaceae, citrus family where anthocyanins are found in blood oranges).

Figure S2 Coumestrol, a coumestan. Coumestans are found predominantly in Fabaceae, the soy family, particularly clover. Coumestrol is often included in the chemical analyses of isoflavones.

Figure S3 Proanthocyanidin pentamer and possible partial thearubigin structure. Proanthocyanidins, condensed tannins, are oligomers and polymers of flavan-3-ols. Thearubigins, derived tannins, are polymers or oligomers of flavan-3-ols formed during the fermentation of tea. Thearubigin structures are not known but may differ from proanthocyanidins due to flavan-3-ol gallates (Figure S4) and theaflavins (Figure 2) present in tea. Above is just a possible partial structure for thearubigins (Scaled down 33% from other chemical structures).

Figure S4 Examples of gallated and methoxylated flavonoids. Gallated flavan-3-ols are predominant in black, green, and oolong tea (Theaceae). Polymethoxylated flavones are found in citrus (Rutaceae) and peppermint (Lamiaceae).

Figure S5 Flavanone *O*-glycosides. The only difference between these two flavanones is the attachment of the second sugar to the first sugar. The neohesperidose confers a bitter taste to the flavanone whereas the rutinose makes the flavanone tasteless.

Figure S6 Flavone *C*-glycosides, isovitexin and vitexin, and an isoflavone acylated *O*-glycoside. Note that in daidzin 6"-*O*-acetate the sugar is acylated not the aglycone.

Figure S7 A chalcone and a dihydrochalcone. Some chalcones can easily cyclyze to form flavanones. Some dihydrochalcones are artificial sweeteners.

REFERENCES

1. Corradini E, Foglia P, Giansanti P, et al. Flavonoids: chemical properties and analytical methodologies of identification and quantitation in foods and plants. Nat Prod Res. 2011;25:469–495.

2. Crozier A, Jaganath IB, Clifford MN. Dietary phenolics: chemistry, bioavailability and effects on health. Nat Prod Rep. 2009;26:1001–1043.
3. Cassidy A, O'Reilly EJ, Kay C, et al. Habitual intake of flavonoid subclasses and incident hypertension in adults. Am J Clin Nutr. 2011;93:338–347.
4. Chun OK, Chung SJ, Song WO. Estimated dietary flavonoid intake and major food sources of U.S. adults. J Nutr. 2007;137:1244–1252.
5. Corcoran MP, McKay DL, Blumberg JB. Flavonoid basics: chemistry, sources, mechanisms of action, and safety. J Nutr Gerontol Geriatr. 2012;31:176–189.
6. Beecher GR. Overview of dietary flavonoids: nomenclature, occurrence and intake. J Nutr. 2003;133:3248S–3254S.
7. Kuhnle GG, Dell'Aquila C, Aspinall SM, et al. Phytoestrogen content of beverages, nuts, seeds, and oils. J Agric Food Chem. 2008;56:7311–7315.
8. Kuhnle GG, Dell'Aquila C, Aspinall SM, et al. Phytoestrogen content of cereals and cereal-based foods consumed in the UK. Nutr Cancer. 2009;61:302–309.
9. Lapcik O. Isoflavonoids in non-leguminous taxa: a rarity or a rule? Phytochemistry. 2007;68:2909–2916.
10. Thompson LU, Boucher BA, Cotterchio M, et al. Dietary phytoestrogens, including isoflavones, lignans, and coumestrol, in nonvitamin, nonmineral supplements commonly consumed by women in Canada. Nutr Cancer. 2007;59: 176–184.
11. Thompson LU, Boucher BA, Liu Z, et al. Phytoestrogen content of foods consumed in Canada, including isoflavones, lignans, and coumestan. Nutr Cancer. 2006;54:184–201.
12. Arab L, Liebeskind DS. Tea, flavonoids and stroke in man and mouse. Arch Biochem Biophys. 2010;501:31–36.
13. Beking K, Vieira A. Flavonoid intake and disability-adjusted life years due to Alzheimer's and related dementias: a population-based study involving twenty-three developed countries. Public Health Nutr. 2010;13:1403–1409.
14. Hooper L, Kay C, Abdelhamid A, et al. Effects of chocolate, cocoa, and flavan-3-ols on cardiovascular health: a systematic review and meta-analysis of randomized trials. Am J Clin Nutr. 2012;95:740–751.
15. Rossi M, Bosetti C, Negri E, et al. Flavonoids, proanthocyanidins, and cancer risk: a network of case-control studies from Italy. Nutr Cancer. 2010;62:871–877.
16. Wedick NM, Pan A, Cassidy A, et al. Dietary flavonoid intakes and risk of type 2 diabetes in US men and women. Am J Clin Nutr. 2012;95:925–933.
17. Akazome Y, Kametani N, Kanda T, et al. Evaluation of safety of excessive intake and efficacy of long-term intake of beverages containing apple polyphenols. J Oleo Sci. 2010;59:321–338.
18. Bousova I, Skalova L. Inhibition and induction of glutathione S-transferases by flavonoids: possible pharmacological and toxicological consequences. Drug Metab Rev. 2012;44:267–286.
19. Cermak R, Wein S, Wolffram S, et al. Effects of the flavonol quercetin on the bioavailability of simvastatin in pigs. Eur J Pharm Sci. 2009;38:519–524.
20. de Souza dos Santos MC, Goncalves CF, Vaisman M, et al. Impact of flavonoids on thyroid function. Food Chem Toxicol. 2011;49:2495–2502.
21. National Toxicology Program. Green tea extract – M030008. http://ntp.niehs.nih.gov/testing/status/agents/ts-m030008.html. Modified April 15, 2015. Accessed April 28, 2015.
22. Navarro VJ, Bonkovsky HL, Hwang SI, et al. Catechins in dietary supplements and hepatotoxicity. Dig Dis Sci. 2013;58:2682–2690.
23. Schonthal AH. Adverse effects of concentrated green tea extracts. Mol Nutr Food Res. 2011;55:874–885.
24. Wuttke W, Jarry H, Seidlova-Wuttke D. Isoflavones – safe food additives or dangerous drugs? Ageing Res Rev. 2007;6:150–188.
25. Andres S, Abraham K, Appel KE, et al. Risks and benefits of dietary isoflavones for cancer. Crit Rev Toxicol. 2011;41:463–506.
26. Egert S, Rimbach G. Which sources of flavonoids: complex diets or dietary supplements? Adv Nutr. 2011;2:8–14.
27. Erdman JW Jr, Balentine D, Arab L, et al. Flavonoids and heart health: proceedings of the ILSI North America Flavonoids Workshop, May 31–June 1, 2005, Washington, DC. J Nutr. 2007;137(3 suppl 1):718S–737S.
28. Prochazkova D, Bousova I, Wilhelmova N. Antioxidant and prooxidant properties of flavonoids. Fitoterapia. 2011;82:513–523.
29. Williamson G, Holst B. Dietary reference intake (DRI) value for dietary polyphenols: are we heading in the right direction? Brit J Nutr. 2008;99(suppl 3): S55–S58.
30. Balentine DA, Dwyer JT, Erdman JW, et al. Recommendations on reporting requirements for flavonoids in research. Am J Clin Nutr. 2015;101:1113–1125.
31. Ellwood K, Balentine DA, Dwyer JT, et al. Considerations on an approach for establishing a framework for bioactive food components. Adv Nutr. 2014;5: 693–701.
32. Gagnier JJ, Boon H, Rochon P, et al. Recommendations for reporting randomized controlled trials of herbal interventions: explanation and elaboration. J Clin Epidemiol. 2006;59:1134–1149.
33. Piaggio G, Elbourne DR, Pocock SJ, et al. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 Statement. JAMA. 2012;308:2594–2604.
34. Bai W, Wang C, Ren C. Intakes of total and individual flavonoids by US adults. Int J Food Sci Nutr. 2014;65:9–20.
35. Butchart C, Kyle J, McNeill G, et al. Flavonoid intake in relation to cognitive function in later life in the Lothian Birth Cohort 1936. Brit J Nutr. 2011;106:141–148.
36. Hardcastle AC, Aucott L, Reid DM, et al. Associations between dietary flavonoid intakes and bone health in a Scottish population. J Bone Miner Res. 2011;26: 941–947.
37. Ivey KL, Lewis JR, Prince RL, et al. Tea and non-tea flavonol intakes in relation to atherosclerotic vascular disease mortality in older women. Brit J Nutr. 2013;110: 1648–1655.
38. Kesse-Guyot E, Fezeu L, Andreeva VA, et al. Total and specific polyphenol intakes in midlife are associated with cognitive function measured 13 years later. J Nutr. 2012;142:76–83.
39. Knaze V, Zamora-Ros R, Lujan-Barroso L, et al. Intake estimation of total and individual flavan-3-ols, proanthocyanidins and theaflavins, their food sources and determinants in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Brit J Nutr. 2012;108:1095–1108.
40. McCullough ML, Peterson JJ, Patel R, et al. Flavonoid intake and cardiovascular disease mortality in a prospective cohort of US adults. Am J Clin Nutr. 2012;95: 454–464.
41. Ovaskainen ML, Torronen R, Koponen JM, et al. Dietary intake and major food sources of polyphenols in Finnish adults. J Nutr. 2008;138:562–566.
42. Pérez-Jiménez J, Fezeu L, Touvier M, et al. Dietary intake of 337 polyphenols in French adults. Am J Clin Nutr. 2011;93:1220–1228.
43. Wang Y, Chung SJ, Song WO, et al. Estimation of daily proanthocyanidin intake and major food sources in the U.S. diet. J Nutr. 2011;141:447–452.
44. Zamora-Ros R, Andres-Lacueva C, Lamuela-Raventos RM, et al. Estimation of dietary sources and flavonoid intake in a Spanish adult population (EPIC–Spain). J Am Diet Assoc. 2010;110:390–398.
45. Zamora-Ros R, Jimenez C, Cleries R, et al. Dietary flavonoid and lignan intake and mortality in a Spanish cohort. Epidemiology. 2013;24:726–733.
46. Zamora-Ros R, Knaze V, Lujan-Barroso L, et al. Estimation of the intake of anthocyanidins and their food sources in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Brit J Nutr. 2011;106:1090–1099.
47. Zamora-Ros R, Knaze V, Lujan-Barroso L, et al. Estimated dietary intakes of flavonols, flavanones and flavones in the European Prospective Investigation into Cancer and Nutrition (EPIC) 24 hour dietary recall cohort. Brit J Nutr. 2011;106: 1915–1925.
48. Zamora-Ros R, Knaze V, Lujan-Barroso L, et al. Dietary intakes and food sources of phytoestrogens in the European Prospective Investigation into Cancer and Nutrition (EPIC) 24-hour dietary recall cohort. Eur J Clin Nutr. 2012;66:932–941.
49. Zamora-Ros R, Knaze V, Romieu I, et al. Impact of thearubigins on the estimation of total dietary flavonoids in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Eur J Clin Nutr. 2013;67:779–782.
50. Cassidy A, Rimm EB, O'Reilly EJ, et al. Dietary flavonoids and risk of stroke in women. Stroke. 2012;43:946–951.
51. Dilis V, Trichopoulou A. Antioxidant intakes and food sources in Greek adults. J Nutr. 2010;140:1274–1279.
52. Jacques PF, Cassidy A, Rogers G, et al. Higher dietary flavonol intake is associated with lower incidence of type 2 diabetes. J Nutr. 2013;143:1474–1480.
53. Mink PJ, Scrafford CG, Barraj LM, et al. Flavonoid intake and cardiovascular disease mortality: a prospective study in postmenopausal women. Am J Clin Nutr. 2007;85:895–909.
54. Bhagwat S, Haytowitz DB, Holden JM. USDA database for the isoflavone content of selected foods, release 2.0. http://www.ars.usda.gov/Services/docs.htm?docid=24953. Published September 2008. Last modified December 31, 2014. Accessed April 28, 2015.
55. Bhagwat S, Haytowitz DB, Holden JM. USDA database for the flavonoid content of selected foods, release 3.1. http://www.ars.usda.gov/nutrientdata/flav. Published December 2013. Last modified December 31, 2014. Accessed April 28, 2015
56. Institut National de la Recherche Agronomique (INRA). Phenol-Explorer 3.6: database on polyphenol content in foods. http://www.phenol-explorer.eu/. Released June 2013. Accessed April 28, 2015.
57. Kyle JAM, Duthie GG. Flavonoids in foods. In: OM Andersen, KR Markham, eds. Flavonoids: Chemistry, Biochemistry and Applications. Boca Raton, FL: CRC Press; 2006:219–263.
58. US Department of Agriculture, Agricultural Research Service, Nutrient Data Laboratory. USDA database for the proanthocyanidin content of selected foods, 2004. https://www.ars.usda.gov/Services/docs.htm?docid=5843. Published August 2004. Last modified September 17, 2014. Accessed April 28, 2015.
59. Santos-Buelga C, Scalbert A. Proanthocyanidins and tannin-like compounds – nature, occurrence, dietary intake and effects on nutrition and health. J Sci Food Agric. 2000;80:1094–1117.
60. Drynan JW, Clifford MN, Obuchowicz J, et al. MALDI-TOF mass spectrometry: avoidance of artifacts and analysis of caffeine-precipitated SII thearubigins from 15 commercial black teas. [published correction appears in *J Agric Food Chem*. 2013;61:1418]. J Agric Food Chem. 2012;60:4514–4525.
61. Lentjes MA, McTaggart A, Mulligan AA, et al. Dietary intake measurement using 7 d diet diaries in British men and women in the European Prospective

Investigation into Cancer-Norfolk study: a focus on methodological issues. Brit J Nutr. 2014;111:516–526.
62. Linseisen J, Radtke J, Wolfram G. Flavonoid intake of adults in a Bavarian subgroup of the national food consumption survey [in German]. Z Ernährungswiss. 1997;36:403–412.
63. Auger C, Al-Awwadi N, Bornet A, et al. Catechins and procyanidins in Mediterranean diets. Food Res Int. 2004;37:233–245.
64. Gu L, Kelm MA, Hammerstone JF, et al. Concentrations of proanthocyanidins in common foods and estimations of normal consumption. J Nutr. 2004;134: 613–617.
65. Hellstrom JK, Torronen AR, Mattila PH. Proanthocyanidins in common food products of plant origin. J Agric Food Chem. 2009;57:7899–7906.
66. Chan SG, Ho SC, Kreiger N, et al. Dietary sources and determinants of soy isoflavone intake among midlife Chinese women in Hong Kong. J Nutr. 2007;137: 2451–2455.
67. Kokubo Y, Iso H, Ishihara J, et al. Association of dietary intake of soy, beans, and isoflavones with risk of cerebral and myocardial infarctions in Japanese populations: the Japan Public Health Center-based (JPHC) study cohort I. Circulation. 2007;116:2553–2562.
68. Messina M, Nagata C, Wu AH. Estimated Asian adult soy protein and isoflavone intakes. Nutr Cancer. 2006;55:1–12.
69. Surh J, Kim MJ, Koh E, et al. Estimated intakes of isoflavones and coumestrol in Korean population. Int J Food Sci Nutr. 2006;57:325–344.
70. Arai Y, Watanabe S, Kimira M, et al. Dietary intakes of flavonols, flavones and isoflavones by Japanese women and the inverse correlation between quercetin intake and plasma LDL cholesterol concentration. J Nutr. 2000;130:2243–2250.
71. Kimira M, Arai Y, Shimoi K, et al. Japanese intake of flavonoids and isoflavonoids from foods. J Epidemiol. 1998;8:168–175.
72. Kita J, Tada J, Ito M, et al. Intake of phytochemicals among Japanese, calculated by the new FFF database. Biofactors. 2004;22:259–263.
73. Li G, Zhu Y, Zhang Y, et al. Estimated daily flavonoid and stilbene intake from fruits, vegetables, and nuts and associations with lipid profiles in Chinese adults. J Acad Nutr Diet. 2013;113:786–794.
74. Zhang Y, Li Y, Cao C, et al. Dietary flavonol and flavone intakes and their major food sources in Chinese adults. Nutr Cancer. 2010;62:1120–1127.
75. Chun OK, Lee SG, Wang Y, et al. Estimated flavonoid intake of the elderly in the United States and around the world. J Nutr Gerontol Geriatr. 2012;31:190–205.
76. Hooper L, Kroon PA, Rimm EB, et al. Flavonoids, flavonoid-rich foods, and cardiovascular risk: a meta-analysis of randomized controlled trials. Am J Clin Nutr. 2008;88:38–50.
77. Ameer B, Weintraub RA, Johnson JV, et al. Flavanone absorption after naringin, hesperidin, and citrus administration. Clin Pharmacol Ther. 1996;60:34–40.
78. Ishii K, Furuta T, Kasuya Y. Mass spectrometric identification and high-performance liquid chromatographic determination of a flavonoid glycoside naringin in human urine. J Agric Food Chem. 2000;48:56–59.
79. Meng X, Sang S, Zhu N, et al. Identification and characterization of methylated and ring-fission metabolites of tea catechins formed in humans, mice, and rats. Chem Res Toxicol. 2002;15:1042–1050.
80. Olthof MR, Hollman PC, Buijsman MN, et al. Chlorogenic acid, quercetin-3-rutinoside and black tea phenols are extensively metabolized in humans. [published correction appears in *J Nutr*. 2003;133:2692]. J Nutr. 2003;133:1806–1814.
81. Peluso I, Raguzzini A, Serafini M. Effect of flavonoids on circulating levels of TNF-α and IL-6 in humans: a systematic review and meta-analysis. Mol Nutr Food Res. 2013;57:784–801.
82. Sesink AL, O'Leary KA, Hollman PC. Quercetin glucuronides but not glucosides are present in human plasma after consumption of quercetin-3-glucoside or quercetin-4′-glucoside. J Nutr. 2001;131:1938–1941.
83. Soleas GJ, Yan J, Goldberg DM. Measurement of trans-resveratrol, (+)-catechin, and quercetin in rat and human blood and urine by gas chromatography with mass selective detection. Methods Enzymol. 2001;335:130–145.
84. Macready AL, George TW, Chong MF, et al. Flavonoid-rich fruit and vegetables improve microvascular reactivity and inflammatory status in men at risk of cardiovascular disease–FLAVURS: a randomized controlled trial. Am J Clin Nutr. 2014;99:479–489.
85. Zamora-Ros R, Knaze V, Lujan-Barroso L, et al. Differences in dietary intakes, food sources and determinants of total flavonoids between Mediterranean and non-Mediterranean countries participating in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Brit J Nutr. 2013;109:1498–1507.
86. Hui C, Qi X, Qianyong Z, et al. Flavonoids, flavonoid subclasses and breast cancer risk: a meta-analysis of epidemiologic studies. PLoS One. 2013;8:e54318. doi: 10.1371/journal.pone.0054318.
87. Jin H, Leng Q, Li C. Dietary flavonoid for preventing colorectal neoplasms. Cochrane Database Syst Rev. 2012;8:CD009350. doi: 10.1002/14651858.CD009350.pub2.
88. Liu YJ, Zhan J, Liu XL, et al. Dietary flavonoids intake and risk of type 2 diabetes: a meta-analysis of prospective cohort studies. Clin Nutr. 2014;33:59–63.
89. Peterson JJ, Dwyer JT, Jacques PF, et al. Associations between flavonoids and cardiovascular disease incidence or mortality in European and US populations. Nutr Rev. 2012;70:491–508.
90. Romagnolo DF, Selmin OI. Flavonoids and cancer prevention: a review of the evidence. J Nutr Gerontol Geriatr. 2012;31:206–238.
91. Wang X, Ouyang YY, Liu J, et al. Flavonoid intake and risk of CVD: a systematic review and meta-analysis of prospective cohort studies. Brit J Nutr. 2014;111:1–11.
92. Wang Y, Stevens VL, Shah R, et al. Dietary flavonoid and proanthocyanidin intakes and prostate cancer risk in a prospective cohort of US men. Am J Epidemiol. 2014;179:974–986.
93. Woo HD, Kim J. Dietary flavonoid intake and smoking-related cancer risk: a meta-analysis. PLoS One. 2013;8:e75604. doi: 10.1371/journal.pone.0075604.
94. Woo HD, Kim J. Dietary flavonoid intake and risk of stomach and colorectal cancer. World J Gastroenterol. 2013;19:1011–1019.
95. Zamora-Ros R, Touillaud M, Rothwell JA, et al. Measuring exposure to the polyphenol metabolome in observational epidemiologic studies: current tools and applications and their limits. Am J Clin Nutr. 2014;100:11–26.
96. Gao L, Mazza G. Characterization, quantitation, and distribution of anthocyanins and colorless phenolics in sweet cherries. J Agric Food Chem. 1995;43: 343–346.
97. Harbaum B, Hubbermann EM, Wolff C, et al. Identification of flavonoids and hydroxycinnamic acids in pak choi varieties (*Brassica campestris* L. ssp. *chinensis* var. *communis*) by HPLC-ESI-MSn and NMR and their quantification by HPLC-DAD. J Agric Food Chem. 2007;55:8251–8260.
98. Lin LZ, Chen P, Harnly JM. New phenolic components and chromatographic profiles of green and fermented teas. J Agric Food Chem. 2008;56:8130–8140.
99. Lin LZ, Harnly JM, Pastor-Corrales MS, et al. The polyphenolic profiles of common bean (*Phaseolus vulgaris* L.). Food Chem. 2008;107:399–410.
100. Maatta-Riihinen KR, Kamal-Eldin A, Mattila PH, et al. Distribution and contents of phenolic compounds in eighteen Scandinavian berry species. J Agric Food Chem. 2004;52:4477–4486.
101. Wang SY, Chen HJ, Camp MJ, et al. Flavonoid constituents and their contribution to antioxidant activity in cultivars and hybrids of rabbiteye blueberry (*Vaccinium ashei* Reade). Food Chem. 2012;132:855–864.
102. Calle EE, Rodriguez C, Jacobs EJ, et al. The American Cancer Society Cancer Prevention Study II Nutrition Cohort: rationale, study design, and baseline characteristics [published correction appears in *Cancer.* 2002;94:2490–2501]. Cancer. 2002;94:500–511.
103. Bjorkman M, Klingen I, Birch AN, et al. Phytochemicals of Brassicaceae in plant protection and human health – influences of climate, environment and agronomic practice. Phytochemistry. 2011;72:538–556.
104. Butcher JD, Crosby KM, Yoo KS, et al. Environmental and genotypic variation of capsaicinoid and flavonoid concentrations in Habanero (*Capsicum chinense*) peppers. HortScience. 2012;47:574–579.
105. Carbone F, Preuss A, De Vos RC, et al. Developmental, genetic and environmental factors affect the expression of flavonoid genes, enzymes and metabolites in strawberry fruits. Plant Cell Environ. 2009;32:1117–1131.
106. Crupi P, Pichierri A, Basile T, et al. Postharvest stilbenes and flavonoids enrichment of table grape cv Redglobe (*Vitis vinifera* L.) as affected by interactive UV-C exposure and storage conditions. Food Chem. 2013;141:802–808.
107. Gonzalez-Molina E, Moreno DA, Garcia-Viguera C. Genotype and harvest time influence the phytochemical quality of Fino lemon juice (*Citrus limon* (L.) Burm. F.) for industrial use. J Agric Food Chem. 2008;56:1669–1675.
108. Jaakola L, Hohtola A. Effect of latitude on flavonoid biosynthesis in plants. Plant Cell Environ. 2010;33:1239–1247.
109. Jiang B, Zhang ZW. Comparison on phenolic compounds and antioxidant properties of Cabernet Sauvignon and Merlot wines from four wine grape-growing regions in China. Molecules. 2012;17:8804–8821.
110. Khlestkina EK. The adaptive role of flavonoids: emphasis on cereals. Cereal Res Commun. 2013;41:185–198.
111. Kuhnle GG, Dell'Aquila C, Aspinall SM, et al. Phytoestrogen content of foods of animal origin: dairy products, eggs, meat, fish, and seafood. J Agric Food Chem. 2008;56:10099–10104.
112. Arts IC, Sesink AL, Faassen-Peters M, et al. The type of sugar moiety is a major determinant of the small intestinal uptake and subsequent biliary excretion of dietary quercetin glycosides. Brit J Nutr. 2004;91:841–847.
113. Das S, Rosazza JP. Microbial and enzymatic transformations of flavonoids. J Nat Prod. 2006;69:499–508.
114. Rothwell JA, Urpi-Sarda M, Boto-Ordonez M, et al. Phenol-Explorer 2.0: a major update of the Phenol-Explorer database integrating data on polyphenol metabolism and pharmacokinetics in humans and experimental animals. Database. 2012;2012:bas031. doi: 10.1093/database/bas031.
115. Simonetti P, Gardana C, Riso P, et al. Glycosylated flavonoids from tomato puree are bioavailable in humans. Nutr Res. 2005;25:717–726.
116. Ullmann U, Haller J, Decourt JP, et al. A single ascending dose study of epigallocatechin gallate in healthy volunteers. J Int Med Res. 2003;31:88–101.
117. Belviso S, Scursatone B, Re G, Zeppa G. Novel data on the polyphenol composition of Italian ancient apple cultivars. Int J Food Prop. 2013;16:1507–1515.
118. Koponen JM, Happonen AM, Mattila PH, et al. Contents of anthocyanins and ellagitannins in selected foods consumed in Finland. J Agric Food Chem. 2007;55: 1612–1619.

119. Jin A, Ozga JA, Lopes-Lutz D, et al. Characterization of proanthocyanidins in pea (*Pisum sativum* L.), lentil (*Lens culinaris* L.), and faba bean (*Vicia faba* L.) seeds. Food Res Int. 2012;46:528–535.
120. Ojwang LO, Dykes L, Awika JM. Ultra performance liquid chromatography-tandem quadrupole mass spectrometry profiling of anthocyanins and flavonols in cowpea (*Vigna unguiculata*) of varying genotypes. J Agric Food Chem. 2012;60:3735–3744.
121. Rajarathnam E, Narpinder S, Shagun S, et al. Beneficial phytochemicals in potato – a review. Food Res Int. 2013;50:487–496.
122. Vorsa N, Polashock JJ. Alteration of anthocyanin glycosylation in cranberry through interspecific hybridization. J Am Soc Hortic Sci. 2005;130:711–715.
123. Cooper KA, Campos-Gimenez E, Jimenez Alvarez D, et al. Rapid reversed phase ultra-performance liquid chromatography analysis of the major cocoa polyphenols and inter-relationships of their concentrations in chocolate. J Agric Food Chem. 2007;55:2841–2847.
124. Hurst WJ, Payne MJ, Miller KB, et al. Stability of cocoa antioxidants and flavan-3-ols over time. J Agric Food Chem. 2009;57:9547–9550.
125. Gattuso G, Barreca D, Gargiulli C, et al. Flavonoid composition of citrus juices. Molecules. 2007;12:1641–1673.
126. Roowi S, Crozier A. Flavonoids in tropical citrus species. J Agric Food Chem. 2011;59:12217–12225.
127. Abida T, Ismat N, Atif K. Identification and quantitaion of flavonoid in fresh and processed potatoes. Electron J Environ Agric Food Chem. 2011;10:2206–2215.
128. Amarowicz R, Carle R, Dongowski G, et al. Influence of postharvest processing and storage on the content of phenolic acids and flavonoids in foods. Mol Nutr Food Res. 2009;53(suppl 2):S151–S183.
129. Andres-Lacueva C, Monagas M, Khan N, et al. Flavanol and flavonol contents of cocoa powder products: influence of the manufacturing process. J Agric Food Chem. 2008;56:3111–3117.
130. Bergquist SAM, Gertsson UE, Nordmark LYG, et al. Effects of shade nettings, sowing time and storage on baby spinach flavonoids. J Sci Food Agric. 2007;87:2464–2471.
131. Gorinstein S, Leontowicz H, Leontowicz M, et al. Comparison of the main bioactive compounds and antioxidant activities in garlic and white and red onions after treatment protocols. J Agric Food Chem. 2008;56:4418–4426.
132. Grace MH, Massey AR, Mbeunkui F, et al. Comparison of health-relevant flavonoids in commonly consumed cranberry products. J Food Sci. 2012;77:H176–H183.
133. Ieri F, Innocenti M, Andrenelli L, et al. Rapid HPLC/DAD/MS method to determine phenolic acids, glycoalkaloids and anthocyanins in pigmented potatoes (*Solanum tuberosum* L.) and correlations with variety and geographical origin. Food Chem. 2011;125:750–759.
134. Ioannou I, Hafsa I, Hamdi S, et al. Review of the effects of food processing and formulation on flavonol and anthocyanin behaviour. J Food Eng. 2012;111:208–217.
135. Lee SU, Lee JH, Choi SH, et al. Flavonoid content in fresh, home-processed, and light-exposed onions and in dehydrated commercial onion products. J Agric Food Chem. 2008;56:8541–8548.
136. Moreno-Perez A, Fernandez-Fernandez JI, Bautista-Ortin AB, et al. Influence of winemaking techniques on proanthocyanidin extraction in Monastrell wines from four different areas. Eur Food Res Technol. 2013;236:473–481.
137. Neilson AP, Ferruzzi MG. Influence of formulation and processing on absorption and metabolism of flavan-3-ols from tea and cocoa. Ann Rev Food Sci Technol. 2011;2:125–151.
138. Obuchowicz J, Engelhardt UH, Donnelly K. Flavanol database for green and black teas utilising ISO 14502-1 and ISO 14502-2 as analytical tools. J Food Comp Anal. 2011;24:411–417.
139. Oliveira C, Amaro LF, Pinho O, et al. Cooked blueberries: anthocyanin and anthocyanidin degradation and their radical-scavenging activity. J Agric Food Chem. 2010;58:9006–9012.
140. Pappas E, Schaich KM. Phytochemicals of cranberries and cranberry products: characterization, potential health effects, and processing stability. Crit Rev Food Sci Nutr. 2009;49:741–781.
141. Payne MJ, Hurst WJ, Miller KB, et al. Impact of fermentation, drying, roasting, and Dutch processing on epicatechin and catechin content of cacao beans and cocoa ingredients. J Agric Food Chem. 2010;58:10518–10527.
142. Perez-Gregorio MR, Garcia-Falcon MS, Simal-Gandara J. Flavonoids changes in fresh-cut onions during storage in different packaging systems. Food Chem. 2011;124:652–658.
143. Rodrigues AS, Perez-Gregorio MR, Garcia-Falcon MS, et al. Effect of post-harvest practices on flavonoid content of red and white onion cultivars. Food Control. 2010;21:878–884.
144. Sentandreu E, Navarro JL, Sendra JM. Effect of technological processes and storage on flavonoids content and total, cumulative fast-kinetics and cumulative slow-kinetics antiradical activities of citrus juices. Eur Food Res Technol. 2007;225:905–912.
145. Asenstorfer RE, Wang Y, Mares DJ. Chemical structure of flavonoid compounds in wheat (*Triticum aestivum* L.) flour that contribute to the yellow colour of Asian alkaline noodles. J Cereal Sci. 2006;43:108–119.
146. Escribano-Bailon MT, Santos-Buelga C, Rivas-Gonzalo JC. Anthocyanins in cereals. J Chromatogr A. 2004;1054:129–141.
147. Guo X, Wu C, Ma Y, et al. Comparison of milling fractions of tartary buckwheat for their phenolics and antioxidant properties. Food Res Int. 2012;49:53–59.
148. Nemeth K, Piskula MK, Takacsova M. Effect of boiling on yellow onion quercetin (glucosides). Czech J Food Sci. 2004;22:170–172.
149. Igual M, Garcia-Martinez E, Camacho MM, et al. Changes in flavonoid content of grapefruit juice caused by thermal treatment and storage. Innov Food Sci Emerg Technol. 2011;12:153–162.
150. Oszmianski J, Wojdylo A, Kolniak J. Effect of L-ascorbic acid, sugar, pectin and freeze-thaw treatment on polyphenol content of frozen strawberries. LWT Food Sci Technol. 2009;42:581–586.
151. Rodrigues AS, Perez-Gregorio MR, Garcia-Falcon MS, et al. Effect of curing and cooking on flavonols and anthocyanins in traditional varieties of onion bulbs. Food Res Int. 2009;42:1331–1336.
152. Vallejo F, Tomas-Barberan FA, Garcia-Viguera C. Phenolic compound contents in edible parts of broccoli inflorescences after domestic cooking. J Sci Food Agric. 2003;83:1511–1516.
153. Bai JH, Manthey JA, Ford BL, et al. Effect of extraction, pasteurization and cold storage on flavonoids and other secondary metabolites in fresh orange juice. J Sci Food Agric. 2013;93:2771–2781.
154. Manthey JA, Grohmann K. Phenols in citrus peel byproducts. Concentrations of hydroxycinnamates and polymethoxylated flavones in citrus peel molasses. J Agric Food Chem. 2001;49:3268–3273.
155. US Department of Agriculture, Agricultural Research Service, Food Composition and Methods Development Lab. Research Project 8040-52000-063-15: flavonoid content of selected dietary supplements and foods. http://www.ars.usda.gov/research/projects/projects.htm?ACCN_NO=425594. Last modified April 22, 2015. Accessed April 28, 2015.
156. Rothwell JA, Perez-Jimenez J, Neveu V, et al. Phenol-Explorer 3.0: a major update of the Phenol-Explorer database to incorporate data on the effects of food processing on polyphenol content. Database. 2013;2013:bat070. doi: 10.1093/database/bat070.
157. Dekker M, Verkerk R. Dealing with variability in food production chains: a tool to enhance the sensitivity of epidemiological studies on phytochemicals. Eur J Nutr. 2003;42:67–72.
158. Harnly JM, Bhagwat S, Lin LZ. Profiling methods for the determination of phenolic compounds in foods and dietary supplements. Anal Bioanal Chem. 2007;389:47–61.
159. Cote J, Caillet S, Doyon G, et al. Analyzing cranberry bioactive compounds. Crit Rev Food Sci Nutr. 2010;50:872–888.
160. Lin LZ, Harnly JM. A screening method for the identification of glycosylated flavonoids and other phenolic compounds using a standard analytical approach for all plant materials. J Agric Food Chem. 2007;55:1084–1096.
161. Engelhardt UH, Finger A, Kuhr S. Determination of flavone C-glycosides in tea. Z Lebensm Unters Forsch 1993;197:239–244.
162. Lin LZ, Sun J, Chen P, et al. UHPLC-PDA-ESI/HRMS/MS^n analysis of anthocyanins, flavonol glycosides, and hydroxycinnamic acid derivatives in red mustard greens (*Brassica juncea* Coss variety). J Agric Food Chem. 2011;59:12059–12072.
163. Mortensen A, Kulling SE, Schwartz H, et al. Analytical and compositional aspects of isoflavones in food and their biological effects. Mol Nutr Food Res. 2009;53(suppl 2):S266–S309.
164. Rostagno MA, Villares A, Guillamon E, et al. Sample preparation for the analysis of isoflavones from soybeans and soy foods. J Chromatogr A. 2009;1216:2–29.
165. Stalikas CD. Extraction, separation, and detection methods for phenolic acids and flavonoids. J Sep Sci. 2007;30:3268–3295.
166. Vacek J, Klejdus B, Lojkova L, et al. Current trends in isolation, separation, determination and identification of isoflavones: a review. J Sep Sci. 2008;31:2054–2067.
167. Stobiecki M. Application of mass spectrometry for identification and structural studies of flavonoid glycosides. Phytochemistry. 2000;54:237–256.
168. Kelm MA, Hammerstone JF, Schmitz HH. Identification and quantitation of flavanols and proanthocyanidins in foods: how good are the datas? Clin Dev Immunol. 2005;12:35–41.
169. Lin LZ, Harnly JM. Quantitation of flavanols, proanthocyanidins, isoflavones, flavanones, dihydrochalcones, stilbenes, benzoic acid derivatives using ultraviolet absorbance after identification by liquid chromatography-mass spectrometry. J Agric Food Chem. 2012;60:5832–5840.
170. Tolonen A, Uusitalo J. Fast screening method for the analysis of total flavonoid content in plants and foodstuffs by high-performance liquid chromatography/electrospray ionization time-of-flight mass spectrometry with polarity switching. Rapid Commun Mass Spectrom. 2004;18:3113–3122.
171. Valls J, Millan S, Marti MP, et al. Advanced separation methods of food anthocyanins, isoflavones and flavanols. J Chromatogr A. 2009;1216:7143–7172.
172. Adamson GE, Lazarus SA, Mitchell AE, et al. HPLC method for the quantification of procyanidins in cocoa and chocolate samples and correlation to total antioxidant capacity. J Agric Food Chem. 1999;47:4184–4188.

173. Amico V, Chillemi R, Mangiafico S, et al. Polyphenol-enriched fractions from Sicilian grape pomace: HPLC-DAD analysis and antioxidant activity. Biores Technol. 2008;99:5960–5966.
174. Arts ICW, Hollman PCH. Optimization of a quantitative method for the determination of catechins in fruits and legumes. J Agric Food Chem. 1998;46: 5156–5162.
175. Bilyk A, Sapers GM. Varietal differences in the quercetin, kaempferol, and myricetin contents of highbush blueberry, cranberry, and thornless blackberry fruits. J Agric Food Chem. 1986;34:585–588.
176. Castro J, Pregibon T, Chumanov K, et al. Determination of catechins and caffeine in proposed green tea standard reference materials by liquid chromatography-particle beam/electron ionization mass spectrometry (LC-PB/EIMS). Talanta. 2010;82:1687–1695.
177. Chandra A, Rana J, Li Y. Separation, identification, quantification, and method validation of anthocyanins in botanical supplement raw materials by HPLC and HPLC-MS. J Agric Food Chem. 2001;49:3515–3521.
178. Cuyckens F, Claeys M. Mass spectrometry in the structural analysis of flavonoids. J Mass Spectrom. 2004;39:1–15.
179. de Rijke E, Out P, Niessen WM, et al. Analytical separation and detection methods for flavonoids. J Chromatogr A. 2006;1112:31–63.
180. Dentith S, Lockwood B. Development of techniques for the analysis of isoflavones in soy foods and nutraceuticals. Curr Opin Clin Nutr Metabol Care. 2008; 11:242–247.
181. Dugo P, Presti ML, Ohman M, et al. Determination of flavonoids in citrus juices by micro-HPLC-ESI/MS. J Sep Sci. 2005;28:1149–1156.
182. Fernandez de Simon B, Perez-Ilzarbe J, Hernandez T, et al. Importance of phenolic compounds for the characterization of fruit juices. J Agric Food Chem. 1992; 40:1531–1535.
183. Finger A, Kuhr S, Engelhardt UH. Chromatography of tea constituents. J Chromatogr A. 1992;624:293–315.
184. Gu L, Kelm M, Hammerstone JF, et al. Fractionation of polymeric procyanidins from lowbush blueberry and quantification of procyanidins in selected foods with an optimized normal-phase HPLC-MS fluorescent detection method. J Agric Food Chem. 2002;50:4852–4860.
185. Gu L, Kelm MA, Hammerstone JF, et al. Screening of foods containing proanthocyanidins and their structural characterization using LC-MS/MS and thiolytic degradation. J Agric Food Chem. 2003;51:7513–7521.
186. Gu L, Kelm MA, Hammerstone JF, et al. Liquid chromatographic/electrospray ionization mass spectrometric studies of proanthocyanidins in foods. J Mass Spectrom. 2003;38:1272–1280.
187. Hakkinen SH, Karenlampi SO, Heinonen IM, et al. Content of the flavonols quercetin, myricetin, and kaempferol in 25 edible berries. J Agric Food Chem. 1999; 47:2274–2279.
188. Hammerstone JF, Lazarus SA, Schmitz HH. Procyanidin content and variation in some commonly consumed foods. J Nutr. 2000;130(suppl):2086S–2092S.
189. Harborne JB. Plant polyphenols–XIV. Characterization of flavonoid glycosides by acidic and enzymic hydrolyses. Phytochemistry. 1965;4:107–120.
190. Hertog MGL, Hollman PCH, Venema DP. Optimization of a quantitative HPLC determination of potentially anticarcinogenic flavonoids in vegetables and fruits. J Agric Food Chem. 1992;40:1591–1598.
191. Hummer W, Schreier P. Analysis of proanthocyanidins. Mol Nutr Food Res. 2008; 52:1381–1398.
192. Kim H, Keeney PG. Method of analysis for (-)-epicatechin in cocoa beans by high performance liquid chromatography. J Food Sci. 1983;48:548–551.
193. Lazarus SA, Adamson GE, Hammerstone JF, et al. High-performance liquid chromatography/mass spectrometry analysis of proanthocyanidins in foods and beverages. J Agric Food Chem. 1999;47:3693–3701.
194. Leuzzi U, Caristi C, Panzera V, et al. Flavonoids in pigmented orange juice and second-pressure extracts. J Agric Food Chem. 2000;48:5501–5506.
195. Lin LZ, Harnly J, Zhang R, et al. Quantitation of the hydroxycinnamic acid derivatives and the glycosides of flavonols and flavones by UV absorbance after identification by LC-MS. J Agric Food Chem. 2012;60:544–553.
196. Lin L-Z, Sun J, Chen P, et al. UHPLC-PDA-ESI/HRMS^n profiling method to identify and quantify oligomeric proanthocyanidins in plant-derived foods. J Agric Food Chem. 2014;62:9387–9400.
197. Luthria DL, Natarajan SS. Influence of sample preparation on the assay of isoflavones. Planta Medica. 2009;75:704–710.
198. Makawi SZA, Gadkariem EA, Ayoub SMH. Determination of antioxidant flavonoids in Sudanese honey samples by solid phase extraction and high performance liquid chromatography. E-Journal of Chemistry. 2009;6(suppl 1): S429–S437.
199. Mazur W, Fotsis T, Wahala K, et al. Isotope dilution gas chromatographic-mass spectrometric method for the determination of isoflavonoids, coumestrol, and lignans in food samples. Anal Biochem. 1996;233:169–180.
200. Merken HM, Beecher GR. Liquid chromatographic method for the separation and quantification of prominent flavonoid aglycones. J Chromatogr A. 2000;897: 177–184.
201. Merken HM, Beecher GR. Measurement of food flavonoids by high-performance liquid chromatography: A review. J Agric Food Chem. 2000;48:577–599.
202. Merken HM, Merken CD, Beecher GR. Kinetics method for the quantitation of anthocyanidins, flavonols, and flavones in foods. J Agric Food Chem. 2001;49: 2727–2732.
203. Murphy PA, Song T, Buseman G, et al. Isoflavones in soy-based infant formulas. J Agric Food Chem. 1997;45:4635–4638.
204. Nguyenle T, Wang E, Cheung AP. An investigation on the extraction and concentration of isoflavones in soy-based products. J Pharm Biomed Anal. 1995; 14:221–232.
205. Penalvo JL, Nurmi T. Application of coulometric electrode array detection to the analysis of isoflavonoids and lignans. J Pharm Biomed Anal. 2006;41:1497–1507.
206. Robbins RJ, Leonczak J, Johnson JC, et al. Method performance and multilaboratory assessment of a normal phase high pressure liquid chromatography-fluorescence detection method for the quantitation of flavanols and procyanidins in cocoa and chocolate containing samples. J Chromatogr A. 2009; 1216:4831–4840.
207. Schwartz H, Sontag G. Comparison of sample preparation methods for analysis of isoflavones in foodstuffs. Analytica Chimica Acta. 2009;633:204–215.
208. Song T, Barua K, Buseman G, et al. Soy isoflavone analysis: quality control and a new internal standard. Am J Clin Nutr. 1998;68(suppl 6):1474S–1479S.
209. Sultana T, Stecher G, Mayer R, et al. Quality assessment and quantitative analysis of flavonoids from tea samples of different origins by HPLC-DAD-ESI-MS. J Agric Food Chem. 2008;56:3444–3453.
210. Vukics V, Guttman A. Structural characterization of flavonoid glycosides by multistage mass spectrometry. Mass Spectrom Rev. 2010;29:1–16.
211. Wang CC, Prasain JK, Barnes S. Review of the methods used in the determination of phytoestrogens. J Chromatogr B Analyt Technol Biomed Life Sci. 2002; 777:3–28.
212. Wang J, Sporns P. MALDI-TOF MS analysis of isoflavones in soy products. J Agric Food Chem. 2000;48:5887–5892.
213. Wang J, Sporns P. MALDI-TOF MS analysis of food flavonol glycosides. J Agric Food Chem. 2000;48:1657–1662.
214. Wilkinson AP, Wahala K, Williamson G. Identification and quantification of polyphenol phytoestrogens in foods and human biological fluids. J Chromatogr B Analyt Technol Biomed Life Sci. 2002;777:93–109.
215. Wollgast J, Pallaroni L, Agazzi ME, et al. Analysis of procyanidins in chocolate by reversed-phase high-performance liquid chromatography with electrospray ionisation mass spectrometric and tandem mass spectrometric detection. J Chromatogr A. 2001;926:211–220.
216. Wu Q, Wang M, Simon JE. Determination of proanthocyanidins in fresh grapes and grape products using liquid chromatography with mass spectrometric detection. Rapid Commun Mass Spectrom. 2005;19:2062–2068.
217. Wu X, Beecher GR, Holden JM, et al. Concentrations of anthocyanins in common foods in the United States and estimation of normal consumption. J Agric Food Chem. 2006;54:4069–4075.
218. Wu X, Gu L, Prior RL, et al. Characterization of anthocyanins and proanthocyanidins in some cultivars of Ribes, Aronia, and Sambucus and their antioxidant capacity. J Agric Food Chem. 2004;52:7846–7856.
219. Wu X, Prior RL. Systematic identification and characterization of anthocyanins by HPLC-ESI-MS/MS in common foods in the United States: fruits and berries. J Agric Food Chem. 2005;53:2589–2599.
220. Yanagida A, Shoji T, Shibusawa Y. Separation of proanthocyanidins by degree of polymerization by means of size-exclusion chromatography and related techniques. J Biochem Biophys Methods. 2003;56:311–322.
221. Kuhnert N. Unraveling the structure of the black tea thearubigins. Arch Biochem Biophys. 2010;501:37–51.
222. Kuhnert N, Drynan JW, Obuchowicz J, et al. Mass spectrometric characterization of black tea thearubigins leading to an oxidative cascade hypothesis for thearubigin formation. Rapid Commun Mass Spectrom. 2010;24:3387–3404.
223. Menet MC, Sang S, Yang CS, et al. Analysis of theaflavins and thearubigins from black tea extract by MALDI-TOF mass spectrometry. J Agric Food Chem. 2004;52: 2455–2461.
224. Holden JM, Bhagwat SA, Haytowitz DB, et al. Development of a database of critically evaluated flavonoids data: application of USDA's data quality evaluation system. J Food Comp Anal. 2005;18:829–844.
225. Mangels AR, Holden JM, Beecher GR, et al. Carotenoid content of fruits and vegetables: an evaluation of analytic data. [published correction appears in *J Am Diet Assoc* 1993;93:527]. J Am Diet Assoc. 1993;93:284–296.
226. Neveu V, Perez-Jimenez J, Vos F, et al. Phenol-Explorer: an online comprehensive database on polyphenol contents in foods. Database. 2010;2010:bap024. doi: 10.1093/database/bap024.
227. Perez-Jimenez J, Neveu V, Vos F, et al. Identification of the 100 richest dietary sources of polyphenols: an application of the Phenol-Explorer database. Eur J Clin Nutr. 2010;64(suppl 3):S112–S120.
228. Perez-Jimenez J, Neveu V, Vos F, et al. Systematic analysis of the content of 502 polyphenols in 452 foods and beverages: an application of the Phenol-Explorer database. J Agric Food Chem. 2010;58:4959–4969.
229. European Food Information Resource AISBL. eBASIS: bioactive substances in food information system. eBASIS database. http://ebasis.eurofir.org/Default.asp. Accessed April 29, 2015.

230. European Food Information Resource AISBL and PlantLIBRA. PlantLIBRA database. http://eplantlibra.eurofir.org/Default.asp. Updated 2013. Accessed April 29, 2015.
231. Black L, Kiely M, Kroon P, et al. Development of EuroFIR-BASIS – a composition and biological effects database for plant-based bioactive compounds. Nutr Bull. 2008;33:58–61.
232. Gry J, Black L, Eriksen FD, et al. EuroFIR-BASIS – a combined composition and biological activity database for bioactive compounds in plant-based foods. Trends Food Sci Technol. 2007;18:434–444.
233. Kiely M, Black LJ, Plumb J, et al. EuroFIR eBASIS: application for health claims submissions and evaluations. Eur J Clin Nutr. 2010;64(suppl 3):S101–S107.
234. Westenbrink S, Oseredczuk M, Castanheira I, et al. Food composition databases: the EuroFIR approach to develop tools to assure the quality of the data compilation process. Food Chem. 2009;113:759–767.
235. National Institutes of Health, Office of Dietary Supplements. Dietary Supplement Label Database (DSLD). http://www.dsld.nlm.nih.gov/dsld/. Accessed April 29, 2015.
236. Pocobelli G, Kristal AR, Patterson RE, et al. Total mortality risk in relation to use of less-common dietary supplements. Am J Clin Nutr. 2010;91:1791–1800.
237. Skeie G, Braaten T, Hjartaker A, et al. Use of dietary supplements in the European Prospective Investigation into Cancer and Nutrition calibration study. Eur J Clin Nutr. 2009;63(suppl 4):S226–S238.
238. Boucher BA, Cotterchio M, Anderson LN, et al. Use of isoflavone supplements is associated with reduced postmenopausal breast cancer risk. Int J Cancer. 2013; 132:1439–1450.
239. Boucher BA, Cotterchio M, Curca IA, et al. Intake of phytoestrogen foods and supplements among women recently diagnosed with breast cancer in Ontario, Canada. Nutr Cancer. 2012;64:695–703.
240. Geller SE, Studee L. Botanical and dietary supplements for menopausal symptoms: what works, what does not. J Womens Health. 2005;14:634–649.
241. Dodd KW, Guenther PM, Freedman LS, et al. Statistical methods for estimating usual intake of nutrients and foods: a review of the theory. J Am Diet Assoc. 2006;106:1640–1650.
242. Freedman LS, Guenther PM, Dodd KW, et al. The population distribution of ratios of usual intakes of dietary components that are consumed every day can be estimated from repeated 24-hour recalls. J Nutr. 2010;140:111–116.
243. Kirkpatrick SI, Reedy J, Butler EN, et al. Dietary assessment in food environment research: a systematic review. Am J Preven Med. 2014;46:94–102.
244. Lieffers JR, Hanning RM. Dietary assessment and self-monitoring with nutrition applications for mobile devices. Can J Diet Pract Res. 2012;73:e253–e260.
245. Rutishauser IH. Dietary intake measurements. Public Health Nutr. 2005;8: 1100–1107.
246. Slimani N, Deharveng G, Unwin I, et al. The EPIC Nutrient DataBase project (ENDB): a first attempt to standardize nutrient databases across the 10 European countries participating in the EPIC study. Eur J Clin Nutr. 2007;61:1037–1056.
247. Subar AF, Dodd KW, Guenther PM, et al. The food propensity questionnaire: concept, development, and validation for use as a covariate in a model to estimate usual food intake. J Am Diet Assoc. 2006;106:1556–1563.
248. Webb D, Leahy MM, Milner JA, et al. Strategies to optimize the impact of nutritional surveys and epidemiological studies. Adv Nutr. 2013;4:545–547.
249. Zamora-Ros R, Rabassa M, Llorach R, et al. Application of dietary phenolic biomarkers in epidemiology: past, present, and future. J Agric Food Chem. 2012;60: 6648–6657.
250. Fink BN, Steck SE, Wolff MS, et al. Construction of a flavonoid database for assessing intake in a population-based sample of women on Long Island, New York. Nutr Cancer. 2006;56:57–66.
251. Gao X, Cassidy A, Schwarzschild MA, et al. Habitual intake of dietary flavonoids and risk of Parkinson disease. Neurology. 2012;78:1138–1145.
252. Huang MH, Norris J, Han W, et al. Development of an updated phytoestrogen database for use with the SWAN food frequency questionnaire: intakes and food sources in a community-based, multiethnic cohort study. Nutr Cancer. 2012;64: 228–244.
253. Guha N, Kwan ML, Quesenberry CP Jr, et al. Soy isoflavones and risk of cancer recurrence in a cohort of breast cancer survivors: the Life After Cancer Epidemiology study. Breast Cancer Res Treat. 2009;118:395–405.
254. Ranka S, Gee JM, Biro L, et al. Development of a food frequency questionnaire for the assessment of quercetin and naringenin intake. Eur J Clin Nutr. 2008;62: 1131–1138.
255. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol. 1985;122:51–65.
256. Chan SG, Ho SC, Kreiger N, et al. Validation of a food frequency questionnaire for assessing dietary soy isoflavone intake among midlife Chinese women in Hong Kong. J Nutr. 2008;138:567–573.
257. Frankenfeld CL, Lampe JW, Shannon J, et al. Frequency of soy food consumption and serum isoflavone concentrations among Chinese women in Shanghai. Public Health Nutr. 2004;7:765–772.
258. French MR, Thompson LU, Hawker GA. Validation of a phytoestrogen food frequency questionnaire with urinary concentrations of isoflavones and lignan metabolites in premenopausal women. J Am Coll Nutr. 2007;26:76–82.
259. Heald CL, Bolton-Smith C, Ritchie MR, et al. Phyto-oestrogen intake in Scottish men: use of serum to validate a self-administered food-frequency questionnaire in older men. Eur J Clin Nutr. 2006;60:129–135.
260. Huang MH, Harrison GG, Mohamed MM, et al. Assessing the accuracy of a food frequency questionnaire for estimating usual intake of phytoestrogens. Nutr Cancer. 2000;37:145–154.
261. Jaceldo-Siegl K, Fraser GE, Chan J, et al. Validation of soy protein estimates from a food-frequency questionnaire with repeated 24-h recalls and isoflavonoid excretion in overnight urine in a Western population with a wide range of soy intakes. Am J Clin Nutr. 2008;87:1422–1427.
262. Lee SA, Wen W, Xiang YB, et al. Assessment of dietary isoflavone intake among middle-aged Chinese men. J Nutr. 2007;137:1011–1016.
263. Tseng M, Olufade T, Kurzer MS, et al. Food frequency questionnaires and overnight urines are valid indicators of daidzein and genistein intake in U.S. women relative to multiple 24-h urine samples. Nutr Cancer. 2008;60:619–626.
264. Block G, Hartman AM, Dresser CM, et al. A data-based approach to diet questionnaire design and testing. Am J Epidemiol. 1986;124:453–469.
265. Kirk P, Patterson RE, Lampe J. Development of a soy food frequency questionnaire to estimate isoflavone consumption in US adults. J Am Diet Assoc. 1999;99: 558–563.
266. Maskarinec G, Robbins C, Riola B, et al. Three measures show high compliance in a soy intervention among premenopausal women. J Am Diet Assoc. 2003;103: 861–866.
267. Hakim IA, Hartz V, Harris RB, et al. Reproducibility and relative validity of a questionnaire to assess intake of black tea polyphenols in epidemiological studies. Cancer Epidemiol Biomarkers Prev. 2001;10:667–678.
268. Mullie P, Clarys P, Deriemaeker P, et al. Estimation of daily human intake of food flavonoids. Int J Food Sci Nutr. 2008;59:291–298.
269. Mulligan AA, Kuhnle GG, Lentjes MA, et al. Intakes and sources of isoflavones, lignans, enterolignans, coumestrol and soya-containing foods in the Norfolk arm of the European Prospective Investigation into Cancer and Nutrition (EPIC–Norfolk), from 7 d food diaries, using a newly updated database. Public Health Nutr. 2013; 16:1454–1462.
270. Ward HA, Kuhnle GG, Mulligan AA, et al. Breast, colorectal, and prostate cancer risk in the European Prospective Investigation into Cancer and Nutrition – Norfolk in relation to phytoestrogen intake derived from an improved database. Am J Clin Nutr. 2010;91:440–448.
271. Zhang Y, Cao J, Chen W, et al. Reproducibility and relative validity of a food frequency questionnaire to assess intake of dietary flavonol and flavone in Chinese university campus population. Nutr Res. 2010;30:520–526.
272. Blair CK, Kelly AS, Steinberger J, et al. Feasibility and preliminary efficacy of the effects of flavanoid-rich purple grape juice on the vascular health of childhood cancer survivors: a randomized, controlled crossover trial. Pediatr Blood Cancer. 2014;61:2290–2296.
273. Somerset S, Papier K. A food frequency questionnaire validated for estimating dietary flavonoid intake in an Australian population. Nutr Cancer. 2014;66:1200–1210.
274. Venter I, Nel D, Herselman M, et al. Development and Evaluation of a Food Frequency Questionnaire to Assess Daily Total Flavonoid Intake Using a Rooibos Intervention Study Model [Dissertation]. Stellenbosch: Faculty of Medicine and Health Sciences, Stellenbosch University; 2013.
275. Bhagwat S, Haytowitz DB, Wasswa-Kintu S. USDA's Expanded Flavonoid Database for the assessment of Dietary Intakes, 2014. http://www.ars.usda.gov/Services/docs.htm?docid=24953. Last modified December 31, 2014. Accessed April 29, 2015.
276. Sebastian RS, Goldman JD, Enns CW, et al. Food sources of flavonoids for adults in the United States: What We Eat in America, NHANES 2007–2008. FASEB J. 2014;28(suppl 369.5). doi:10.1096/fj.1530–6860.
277. Song WO, Chun OK. Tea is the major source of flavan-3-ol and flavonol in the U.S. diet. J Nutr. 2008;138(suppl):1543S–1547S.
278. Christensen KY, Naidu A, Parent ME, et al. The risk of lung cancer related to dietary intake of flavonoids. Nutr Cancer. 2012;64:964–974.
279. Somerset SM, Johannot L. Dietary flavonoid sources in Australian adults. Nutr Cancer. 2008;60:442–449.
280. Subar AF, Kirkpatrick SI, Mittl B, et al. The Automated Self-Administered 24-hour dietary recall (ASA24): a resource for researchers, clinicians, and educators from the National Cancer Institute. J Acad Nutr Diet. 2012;112:1134–1137.
281. Brustad M, Skeie G, Braaten T, et al. Comparison of telephone *vs* face-to-face interviews in the assessment of dietary intake by the 24 h recall EPIC SOFT program – the Norwegian calibration study. Eur J Clin Nutr. 2003;57:107–113.
282. Kolar AS, Patterson RE, White E, et al. A practical method for collecting 3-day food records in a large cohort. Epidemiology. 2005;16:579–583.
283. Loke WM, Jenner AM, Proudfoot JM, et al. A metabolite profiling approach to identify biomarkers of flavonoid intake in humans. J Nutr. 2009;139:2309–2314.
284. Del Rio D, Borges G, Crozier A. Berry flavonoids and phenolics: bioavailability and evidence of protective effects. Brit J Nutr. 2010;104(suppl 3):S67–S90.
285. Del Rio D, Rodriguez-Mateos A, Spencer JP, et al. Dietary (poly)phenolics in human health: structures, bioavailability, and evidence of protective effects against chronic diseases. Antioxid Redox Sign. 2013;18:1818–1892.

286. Graefe EU, Wittig J, Mueller S, et al. Pharmacokinetics and bioavailability of quercetin glycosides in humans. J Clin Pharmacol. 2001;41:492–499.
287. Holst B, Williamson G. Nutrients and phytochemicals: from bioavailability to bioefficacy beyond antioxidants. Curr Opin Biotechnol. 2008;19:73–82.
288. Neilson AP, George JC, Janle EM, et al. Influence of chocolate matrix composition on cocoa flavan-3-ol bioaccessibility in vitro and bioavailability in humans. J Agric Food Chem. 2009;57:9418–9426.
289. Richelle M, Tavazzi I, Enslen M, et al. Plasma kinetics in man of epicatechin from black chocolate. Eur J Clin Nutr. 1999;53:22–26.
290. Roowi S, Stalmach A, Mullen W, et al. Green tea flavan-3-ols: colonic degradation and urinary excretion of catabolites by humans. J Agric Food Chem. 2010;58:1296–1304.
291. Scalbert A, Morand C, Manach C, et al. Absorption and metabolism of polyphenols in the gut and impact on health. Biomed Pharmacother. 2002;56:276–282.
292. Scalbert A, Williamson G. Dietary intake and bioavailability of polyphenols. J Nutr. 2000;130(suppl):2073S–2085S.
293. Stalmach A, Mullen W, Steiling H, et al. Absorption, metabolism, and excretion of green tea flavan-3-ols in humans with an ileostomy. Mol Nutr Food Res. 2010;54:323–334.
294. Manach C, Williamson G, Morand C, Scalbert A, Remesy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. Am J Clin Nutr. Jan 2005;81(suppl 1):230S–242S.
295. Viskupicova J, Ondrejovic M, Sturdik E. Bioavailability and metabolism of flavonoids. J Food Nutr Res. 2008;47:151–162.
296. Carlsen MH, Karlsen A, Lillegaard IT, et al. Relative validity of fruit and vegetable intake estimated from an FFQ, using carotenoid and flavonoid biomarkers and the method of triads. Brit J Nutr. 2011;105:1530–1538.
297. Perez-Jimenez J, Hubert J, Hooper L, et al. Urinary metabolites as biomarkers of polyphenol intake in humans: a systematic review. Am J Clin Nutr. 2010;92:801–809.
298. American Institute for Cancer Research. Recommendations for cancer prevention. http://www.aicr.org/reduce-your-cancer-risk/recommendations-for-cancer-prevention/. Published September 12, 2014. Accessed April 29, 2015.
299. United States Department of Agriculture, US Department of Health and Human Services. *Dietary Guidelines for Americans, 2010*. 7th ed. Washington, DC: US Government Printing Office; 2010.
300. Kushi LH, Doyle C, McCullough M, et al. American Cancer Society guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity [Summary for patients in *CA Cancer J Clin*. 2012;62:68–69]. CA Cancer J Clin. 2012;62:30–67.
301. Wiseman M. The second World Cancer Research Fund/American Institute for Cancer Research Expert Report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Proc Nutr Soc. 2008;67:253–256.