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REVIEW

Worldwide (poly)phenol intake: assessment methods and identified gaps

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Abstract

Introduction (Poly)phenols (PPs) are plant secondary metabolites widely distributed in dietary sources, and several evidences show that consumption of PP has a positive impact in human health. However, the correct estimation of food intake and the estimation of PP content of foods are essential to associate PPs intake with health effects.

Purpose This review aimed to gather information from several studies on PP intake in different countries, compare methods used for both assessment of food intake and PP quantification and highlight existing gaps and future directions.

Methods Twenty-four studies of PP intake from thirteen countries were selected for analysis. The selected studies included assessment of all plant food groups contributing to PP intake, total PP content and/or content of major classes (flavonoids or phenolic acids), a large study population and both genders.

Results and Conclusion Most studies presented daily intakes of extractable (poly)phenols. Very few studies have determined intake of non-extractable (poly)phenols, which is a very important fraction of PPs contributing to total PP intake. High heterogeneity was observed among countries regarding the intake of total PP intake and the two main PP classes. This may reflect not only different diet patterns, but also different methods used for collecting food consumption data and estimation of PP content. Thus, criteria of harmonization are suggested regarding assessment of food intake, determination of PP content in foods and validation with biomarkers.

Keywords Non-extractable polyphenols · Flavonoids · Phenolic acids · Food intake · Diet · Biomarkers

Introduction

Plants produce a great variety of secondary metabolites. Phenolic compounds, usually called (poly)phenols (PPs), are the most widely distributed in dietary sources. Although they are not essential for humans, PPs may have a potential positive impact on human health. Due to their abundance in certain foods, they are important candidates responsible for the beneficial effects, associated with vegetable and fruit-rich diets. Consumption of PPs in high amounts may present some adverse effects, mainly pharmacokinetic interactions and inhibition of non-heme iron absorption. However, this could be more relevant when PPs are consumed as supplements [1]. Moreover, there is growing evidence that a continuous and prolonged intake of PPs may be associated with a lower risk of several chronic non-communicable diseases, such as diabetes, cardiovascular diseases, neurodegenerative diseases and cancer, as well as low-grade inflammation and symptoms associated with ageing and menopause [2–6]. However, several limitations exist in epidemiological studies, and in most of the clinical

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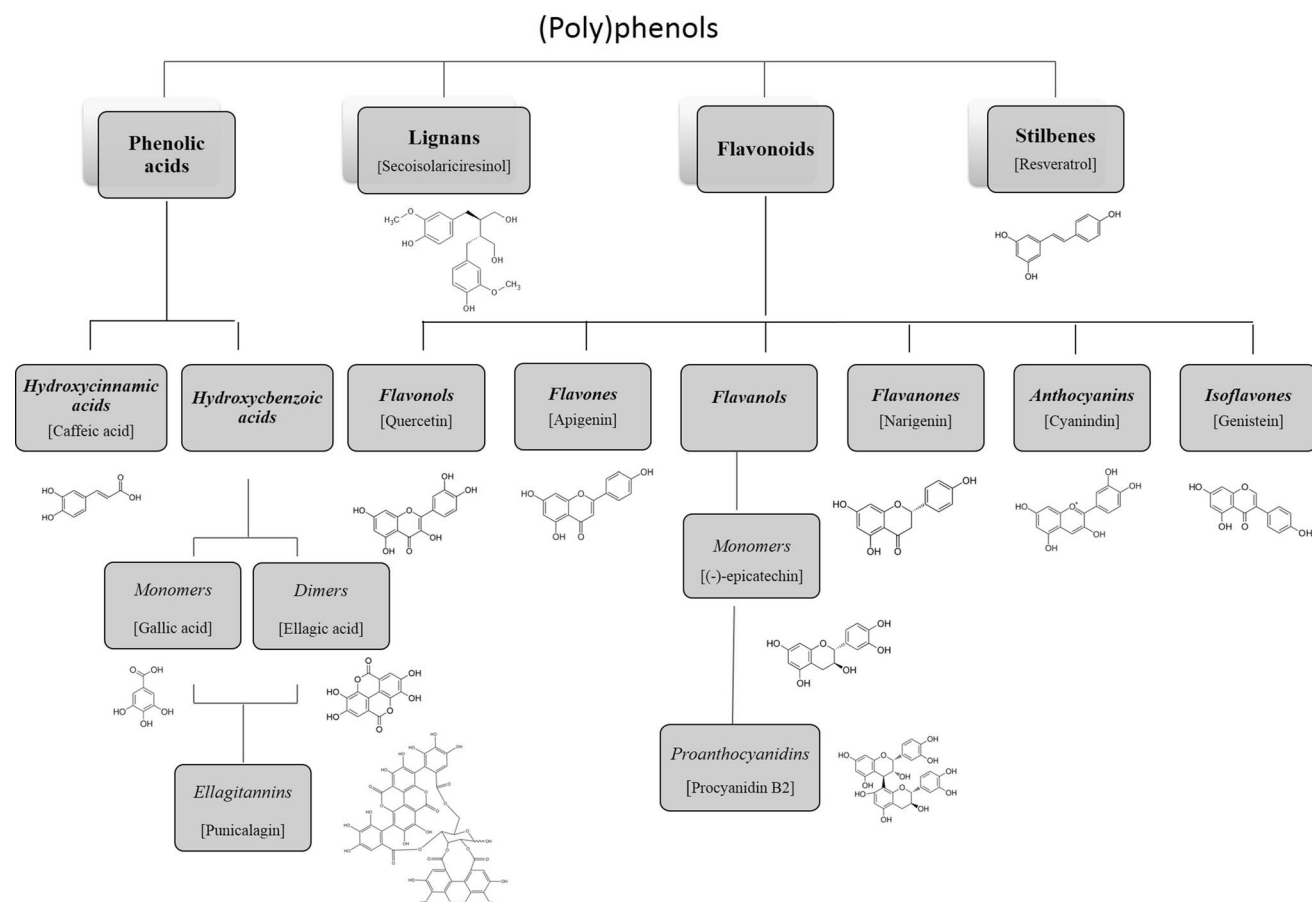
Fig. 1 Main (poly)phenol classes according with Phenol-Explorer database (http://phenol-explorer.eu/, accessed on June 2015). **Classes** are in bold, *subclasses* are in italic bold and *families* within sub-classes are in italic. A common aglycone is represented with the respective name in brackets (structures were drawn with ChemBio-Draw Ultra 14.0)

trials, and no conclusive answers linking dietary PP exposure, PP metabolites and disease biomarkers have yet been reached [7–9].

PPs are characterized by the presence of one or more hydroxyl groups attached to an aromatic ring [10]. They can be classified into different classes according to the number of phenol rings that they contain and on the basis of structural elements that bind these rings to one another [11, 12] (Fig. 1). PPs may occur in a non-conjugated form (aglycone) or conjugated with sugars, carboxylic and organic acids, amines, lipids and other phenols. In addition, some PPs may also be linked to plant cell wall macromolecules. Larger PPs include hydrolysable phenols such as ellagitannins (ET) and condensed tannins such as proanthocyanidins (PA). Ellagitannins are oligomers of ellagic and gallic acid, which are only hydrolysed by various treatments such as hot water, acids and bases or enzymatically by tannases [13]. PA are dimers, oligomers and polymers of flavan-3-ols, mostly the aglycones catechin and epicatechin [14]. Main classes, subclasses and some common PPs are shown in Fig. 1. PPs that are not so common and are

not represented in Fig. 1 include other subclasses of flavonoids such as chalcones, hydroxychalcones and coumarins, and other phenols such as alkylphenols, cucurminoids, hydroxybenzaldehydes, hydrocinnamaldehydes, hydroxyphenylpropenes, methoxyphenols, naphtoquinones, phenolic terpenes and tyrosols [15].

Epidemiological studies can be very helpful in studying the association of PP intake with real disease endpoints. However, prediction of health effects of PPs in these studies is dependent on calculating the amount of ingested PPs by the studied population (PP exposure) and the bioavailable fraction of PPs. Exposure, on the one hand, relies on the correct estimation of food intake and, on another hand, on the correct estimation of PP content of foods. Moreover, estimation of amounts of circulating PP and/or its metabolites depend on reliable biomarkers. These should be compounds measured in a biological sample that reflect habitual intake of some PP rich food, or the individual PP, and should be subjected to little intraindividual variability [16]. This review aims to gather information from several studies focused on PP intake in different countries, compare

methods used for both assessment of food intake and PP quantification, discuss its nutritional relevance and point existing gaps and future directions.

Overview of (poly)phenol content in foods and its nutritional relevance

There are two main approaches to determine PP content in foods: (1) Folin–Ciocalteu colorimetric assay, based on the reducing properties of the phenolic groups, used to estimate total amount of PPs [17] and (2) chromatographic techniques, most commonly, HPLC linked with several possible detection systems, used to quantify individual compounds and also total PP content [18]. Two major public databases gather the (poly)phenol content of foods and beverages: the United States Department of Agriculture (USDA) databases for flavonoids [19], proanthocyanidins [14] and isoflavones [20], and the Phenol-Explorer database [15]. USDA databases only present values for PPs of the flavonoid class, expressed as aglycones, leaving out other classes that are abundant in many foods. On the other hand, Phenol-Explorer gathers information on all classes and types of PPs, including aglycones, conjugates and esters, being therefore more comprehensive. This database provides content values for individual PPs in three categories:

1. Chromatography, which presents data for extractable PPs (EPP), PPs extractable with aqueous/organic solvents (methanol/ethanol/acetone and water), determined normally by reverse-phase high-performance liquid chromatography (HPLC) and gas chromatography. EPPs are low molecular weight PPs from several classes and subclasses, including PA (dimers and trimers) and hydrolysable tannins of low molecular weight [21].
2. Normal-phase HPLC for PA from dimers to polymers.
3. Chromatography after hydrolysis, which contains data for those PPs that are attached to the food matrix and can only be solubilized and quantified after basic or acid hydrolysis, mostly lignans in many foods and phenolic acids in cereals [22]. PPs under this category are part of what is defined by Saura-Calixto as non-extractable PPs (NEPP), the residue of aqueous/organic extracts. As originally defined, NEPP includes high molecular weight proanthocyanidins and hydrolysable PPs (HPP) which are PPs linked to cell wall macromolecules or trapped within the food matrix and can only be released by hydrolysis treatments [21].

To highlight the nutritional relevance of PP in the human diet, we looked for the fifty richest foods in PPs and the distribution of the different subclasses of PPs among the selected foods (Tables 1, 2). Phenol-Explorer database was used to estimate the total PP content per common serving sizes for each food. The 50 richest foods were selected and ranked within each food group according to total PP content per portion normally consumed, to get a clear picture of the nutritional relevance of the PP intake per food. Some spices and herbs, particularly cloves, are foods with the highest contents in PPs per 100 g of fresh weight; however, serving sizes are very small, and thus, the actual PP intake is lower or equivalent to other foods less rich in PPs. Considering serving sizes, fruits are clearly the richest in PPs among food groups, accounting for 44% of the fifty selected foods. Within the selected fruits, 50% are berries, emphasizing the importance of these fruits to PP intake. Particularly, high values are observed for black chokeberry and elderberry, followed by blackcurrant and blueberry. Although apples and oranges do not have such a high PP content as berries, they are very important contributors to total PP intake, having a huge dietary relevance due to its high consumptions among the population [23, 24]. According to FAOSTAT food balance data of 2011, oranges account for 13.33 kg of the food supply per capita, followed by banana with 12.05 kg and apple 9.4 kg [25]. Despite being one of the most consumed fruits, banana is not included in the 50 richest foods in PPs presented in Table 1, because in Phenol-Explorer, its content in PPs is very low (5.4 mg/100 g fw of flavanols, including PAs up to 6 mers, and 1 mg/100 g fw of hydroxybenzoic acids). However, when considering NEPP, bananas scored values as high as 980 mg/100 g fw for PA [26]. Thus, this is a good example of a food that is highly consumed by the population and is an important contributor to overall PP intake, but may be underestimated due to incomplete information of the composition database on NEPP. Underestimation in total PP intake may therefore also happen for other foods with nutritional significance. Furthermore, PP contents may vary depending on species, seasonal variation, maturity, and various agricultural, food-processing and storage practices [27, 28].

Table 2 ascertains the relevance of the different classes and subclasses of PPs for the selected foods, according to the data extracted from Phenol-Explorer. Considering this classification, there is a clear differential distribution among foods, with some subclasses being generally more abundant than others. For example, within flavonoids, flavanones, flavones and isoflavones are the less abundant subclasses in the 50 richest foods. This, however, may not reflect their dietary relevance. They may be highly consumed, such as flavanones, which are present in oranges, one of the most consumed fruits. Other less common phenols are included in the general class "other" (Table 2). Some spices, for example cloves, stand out with enormous amounts of hydroxyphenylpropenes, and even though they are used in low quantities, they still contribute to a high phenol intake when

Table 1 Fifty most rich foods in PPs, ranked according to content per portion in the different food groups

Food group	Food[a]	mg PP/portion	Common portion[b] (g)	mg PP/100 g FW[c]
Fruits	Black chokeberry	2568.6	1 cup (145)	1771.4
	Black elderberry	2011.4	1 cup (145)	1387.1
	Blackcurrant	850.4	1 cup (112)	759.3
	Highbush blueberry	719.2	1 cup (148)	486.0
	Blackberry	389.9	1 cup (144)	270.8
	Sweet cherry	380.1	1 cup (138)	275.4
	Strawberry	364.0	1 cup (144)	252.8
	Red raspberry	254.9	1 cup (123)	207.3
	Plum, fresh	253.3	1 unit (66)	383.7
	Black grape	235.6	1 cup (151)	156.1
	Apple	193.7	1 unit (161)	128.29
	Lingonberry	159.6	1 cup (145)	110.1
	Gooseberry	144.6	1 cup (150)	96.4
	American cranberry	134.9	1 cup (100)	134.9
	Loquat	126.0	1 cup (149)	84.5
	Pear	106.2	1 unit (178)	59.6
	Peach	48.0	1 unit (150)	72.0
	Orange	70.6	1 unit (121)	58.33
	Nectarine	43.0	1 unit (142)	61.1
	Cloudberry	41.3	1 cup (123)	33.6
	Apricot	25.7	1 unit (35)	73.3
	Lemon	21.4	1 unit (58)	36.9
Vegetables	Artichoke head	332.8	1 unit (128)	260.0
	Red onion	161.0	1 cup (115)	140.0
	Broccoli	159.5	1 cup (91)	175.3
	Red chicory	68.1	1 cup (29)	234.8
	Black olive	47.8	1 tbsp (8.4)	569.2
	Spinach	36.1	1 cup (30)	120.4
	Asparagus	31.1	1 cup (134)	23.2
	Carrot	30.2	1 cup (128)	23.6
	Cauliflower	23.9	1 cup (107)	22.3
	Potato	23.4	1 cup, diced (75)	31.2
Cereal products	Breakfast cereals, bran	85.7	1 cup (30)	285.7
	Rye bread, whole grain	62.2	1 slice (32)	194.5
	pasta, whole grain	23.0	1 cup (105)	21.9
Seeds and products	Dark chocolate	2722.9	1 bar (101)	2696.0
	Common bean, whole	1329.1	1 cup (194)	685.1
	Cocoa powder	997.8	3 tsp (28)	3563.7
	Chestnut	344.9	1 handful (28.3)	1216.4
	Soy tempe	245.2	1 cup (166)	147.7
	Soybean, roasted	229.7	1 cup (93)	246.9
	Sesame seed (meal)	220.1	1 handful (28.3)	776.5
	Soy Yogurt	191.4	1 unit (227)	84.3
	Almond	52.5	1 handful (28.3)	185.2
Spices & Herbs	Cloves	319.0	1 tsp (2.1)	15,188.2
	Common sage, dried	64.0	1 tbsp (5.3)	1207.6
	Capers	56.3	1 tbsp (8.6)	654.7
	Oregano, dried	41.8	1 tsp (1.8)	2319.8

Table 1 continued

Food group	Food[a]	mg PP/portion	Common portion[b] (g)	mg PP/100 g FW[c]
Beverages	Coffee beverage (filter)	509.0	1 cup (237)	214.75
	Black Tea (infusion)	248.5	1 cup (245)	101.42
	Red wine	149.1	1 glass (147)	101.5

[a] Data on the polyphenol content in foods were extracted from the Phenol-Explorer database (http://phenol-explorer.eu, accessed June 2015). Selected foods and vegetables were all raw and whole. Foods that are normally used as ingredients for further processing were not considered (for example, flour). Whenever more than 1 item of a particular food was available, the one that was normally consumed and had the higher PP content was selected. Although Phenol-explorer also includes retention factors for some foods that are cooked or processed, these factors were not applied due to incomplete information of retention factors on many of the PPs present in some foods

[b] Common portions were obtained from USDA National Nutrient Database for Standard Reference (https://ndb.nal.usda.gov/, accessed June 2015); tsp, teaspoon; tbsp., tablespoon

[c] Total (poly)phenols per 100 g of fresh weight were calculated as the sum of individual phenols according to Perez-Jimenez [21]

consumed. In cereals, most phenols are alkylphenols, which occur mainly in whole grain products and are therefore lost during refining. Tyrosols are present in high amounts exclusively in olives, and stilbenes are found in low amounts in wine and lingonberry. Lignans, a class of NEPP, are the main PP found in fruits such as pear and apricot, in vegetables like broccoli and cauliflower and in sesame seeds. Other fruits and vegetables such as peach, orange, nectarine and carrot also include considerable percentages of lignans.

Common subclasses of flavonoids in the selected foods, include: anthocyanins, mostly present in red and black fruits, as well as in red wine; flavanols, abundant in fruits, tea and some seeds, particularly cocoa products; proanthocyanidins, which constitute more than 90% of the flavanols in apples, berries and seeds; flavonols, mostly abundant in vegetables and some herbs. Phenolic acids are also very abundant PPs, being present in all food groups. Foods with high percentages of hydroxycinnamic acids include coffee, the main contributor for the intake of this subclass of phenolic acids, some vegetables, particularly, potato and some fruits such as loquat and pear and rye bread. Hydroxybenzoic acids, on the other hand, are mainly present in chestnut, red raspberry and cloudberry.

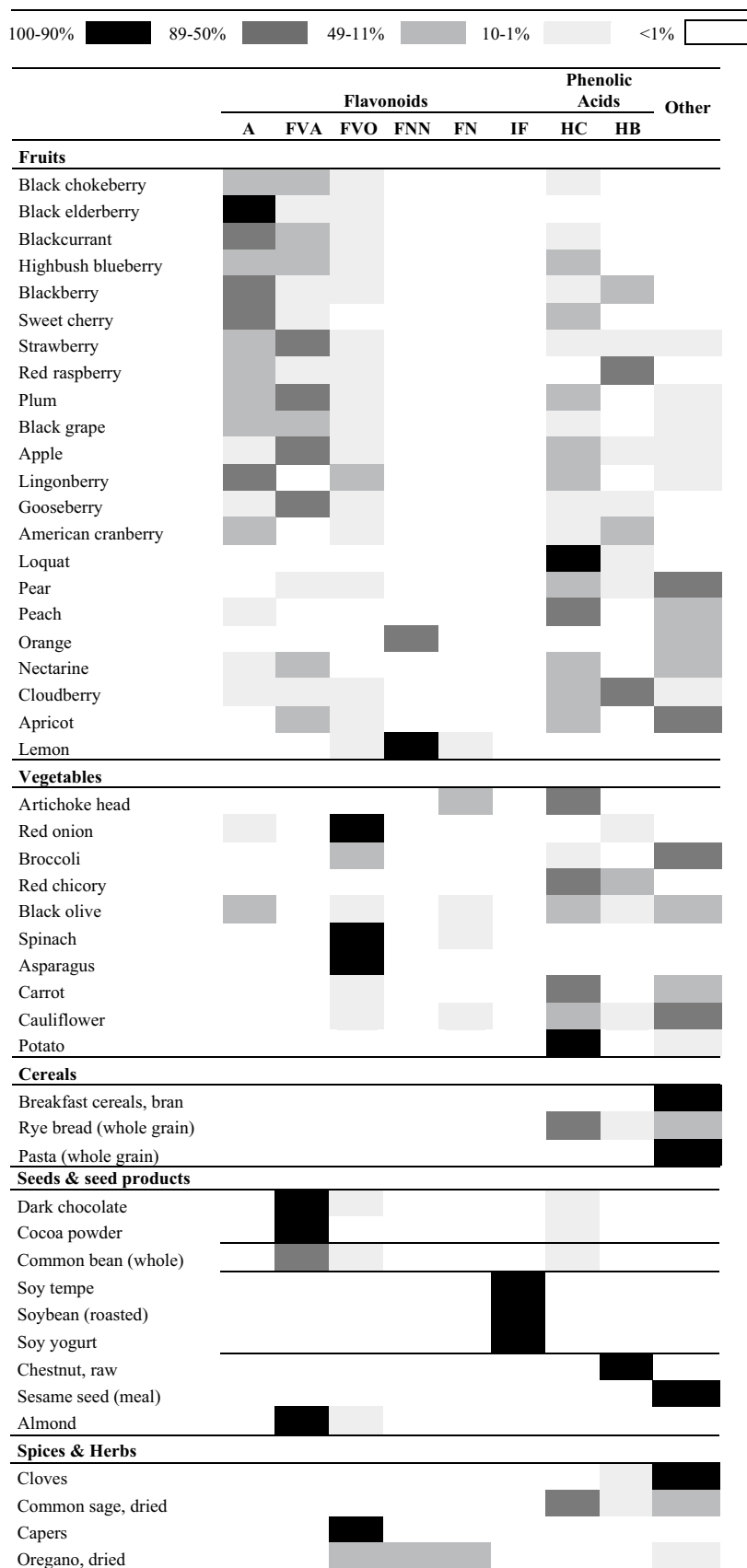## Overview of (Poly)phenol intake in the world

PP intake was assessed in many epidemiological studies and clinical trials studying the effect of PP on human health. However, in many of these studies, the study population was small, and the studies were difficult to compare due to different methods of assessment of food intake and calculation of PP intake. In this review, we gathered information on PP intake among different countries all over the world, to compare methodologies and values of PP intake. A systematic search was performed (Supplemental Fig. 1),

and the following criteria were used to select studies for analysis:

1. Assessment of intake of all plant based food groups contributing to PP intake: cereals, vegetables, legumes, fruits, wine, cocoa products, tea and coffee;
2. Large study population ($n \geq 1000$);
3. Both sexes included in the study;
4. Total PP content or total content of major classes (flavonoids or phenolic acids); studies assessing only a few subclasses were not considered;
5. In epidemiological studies assessing the association between PP intake and a disease, only healthy controls were considered.

Based on these criteria, 49 records were eligible for full text analysis, and 24 were selected for qualitative analysis (flow chart of study selection and search terms are presented on Supplemental Fig. 1). The selected studies (Table 3) were performed in thirteen different countries, from Europe (Spain [24, 29, 30], Finland [31], Poland [32, 33], France [34], Italy [35, 36], UK and Ireland [37]), Australia [38], USA [39–44], Brazil [45, 46], China [47], Korea [48] and Fiji [49]. One study was a large European cohort [50] involving 10 countries from Europe (Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, Netherlands and UK). Another study also analysed the polyphenol intake in Europe [51], based on a European food consumption database that included 14 countries from Europe (Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Spain, Sweden and UK). Comparative analysis of the selected studies highlights some important differences on the methods used for assessing dietary intake and conversion to PP intake.

Table 2 Percentage of the different classes and subclasses of (poly)phenols in the 50 most rich foods in PP

Legend: 100–90% (black) · 89–50% · 49–11% · 10–1% · <1% (white)

	Flavonoids						Phenolic Acids		Other
	A	FVA	FVO	FNN	FN	IF	HC	HB	
Fruits									
Black chokeberry									
Black elderberry									
Blackcurrant									
Highbush blueberry									
Blackberry									
Sweet cherry									
Strawberry									
Red raspberry									
Plum									
Black grape									
Apple									
Lingonberry									
Gooseberry									
American cranberry									
Loquat									
Pear									
Peach									
Orange									
Nectarine									
Cloudberry									
Apricot									
Lemon									
Vegetables									
Artichoke head									
Red onion									
Broccoli									
Red chicory									
Black olive									
Spinach									
Asparagus									
Carrot									
Cauliflower									
Potato									
Cereals									
Breakfast cereals, bran									
Rye bread (whole grain)									
Pasta (whole grain)									
Seeds & seed products									
Dark chocolate									
Cocoa powder									
Common bean (whole)									
Soy tempe									
Soybean (roasted)									
Soy yogurt									
Chestnut, raw									
Sesame seed (meal)									
Almond									
Spices & Herbs									
Cloves									
Common sage, dried									
Capers									
Oregano, dried									

Table 2 continued

	Flavonoids						Phenolic Acids		Other
	A	**FVA**	**FVO**	**FNN**	**FN**	**IF**	**HC**	**HB**	
Beverages									
Coffee beverage (filter)							▨		
Black Tea (infusion)		▨						▨	
Wine (Red)	▨								
Spices & Herbs									
Cloves									▨
Common sage, dried							▨		▨
Capers				▨					
Oregano, dried			▨						
Beverages									
Coffee beverage (filter)							▨		
Black Tea (infusion)		▨						▨	
Wine (Red)	▨								

Values in % are shown in a colour scale from black (higher) to white (lower)
A Anthocyanins; *FVA* Flavanols, including PA; *FVO* Flavonols; *FNN* Flavanones; *FN* Flavones; *IF* isoflavonoids; *HC* Hydroxycinnamic Acids; *HB* Hydroxybenzoic Acids.
Percentages were calculated with values obtained from Phenol-Explorer database (http://phenol-explorer.eu/, accessed June 2015)

Assessment of food intake

Selection of the dietary data collection method determines the accuracy of the result in terms of absolute estimates. The main methods of individual diet assessment were twenty-four hour diet recalls (24hR, 11 studies) and semi-quantitative food frequency questionnaires (FFQ, 8 studies). Other methods used to assess individual consumption were: a forty-eight hour recall (48hR, 1 study), a Diet History Questionnaire (DHQ, 1 study) and a National Survey Questionnaire (NSQ, 1 study) that assessed the foods present at home. One study relied on values from Food Balance Sheets (FBS) to estimate the national food consumption (Table 3). FBS give information on a country's food supply during a reference period. Although they show the amount of foods potentially available for consumption by the population, they may not cover all the foods and do not represent the actual consumption, providing only a gross estimate [52]. As such, they should not be considered an adequate instrument to base assessment of PP intake.

The food frequency questionnaire is normally used to obtain information on how often a food is consumed. Quantitative information is obtained if the questionnaire includes questions on portion sizes, but requires validation before use [53]. This is the most used method to collect long-term dietary intake data from large numbers of individuals, since it can be self-administered and is cost-effective. However, it is based on an individual's perceptions of usual intake over a large period, normally the previous year, and although shorter periods may be selected (such as previous month), it may lack detail about the consumed foods and is prone to large random errors [54]. Furthermore, the type of

information provided to participants on portion sizes may also influence individual perception, changing the report of consumed foods. Portion sizes are normally reported as natural units, household measures or grams and may be accompanied by photographs of different serving portions. In fact, portion sizes may be considered country-specific, and thus, questionnaires need to be adapted to culture habits, including the foods consumed in the country and the respective portion sizes. From the eight studies that used FFQ as the diet assessment method, seven were country-specific [24, 33, 35, 40, 41, 44, 47] and five were clearly validated (Table 3).

The 24-hour diet recall provides detailed information about all foods and beverages consumed over the previous day, recorded by a trained interviewer, face-to-face, by telephone or computer assisted. Although more accurate than the FFQ method, data from one single 24hR are not representative of habitual intake, and information from multiple recalls repeated in non-consecutive occasions should be collected [54]. Only two of the analysed studies provided multiple 24hR in non-consecutive days [34, 45]. This is particularly important when estimating PP intake since some of the foods providing PPs are consumed seasonally.

The DHQ is carried out in three steps to collect detailed information on both frequency and quantity of consumed foods over a determined period [55]. It is the most time consuming and expensive method, not being feasible for large populations.

Most of the analysed studies were based on diet assessment data from large epidemiological studies [24, 30, 33–36, 40, 41, 44, 47, 50] or national dietary surveys [29, 31, 32, 38, 39, 42, 43, 45, 46, 48, 49]. However, dietary data

Table 3 Polyphenol intake in several European and non-European countries: comparison of methodologies for diet assessment and PP quantification

Country/ Publication Year [Ref]	Year of survey/name Type of study	Study population	Diet assessment[a]	PP database	PP quantified[b,c,d]	mg/day (mean or range)	Main PP class/ subclass/family contributor[e]	Main food contributors[e,f]
Spain 2007 [29]	2001/MAPA National dietary survey	6900 households hotels and institutions	NSQ (last year; validation NR)	Analysed food	TPP EPP NEPP-PA NEPP-Hydrol	2591–3016 1106 449 1248	ND	Cereals, beverages, fruits *Beverages, cereals, fruits* *Fruits*, legumes *Cereals*, fruits, vegetables
Spain 2010 [30]	1992–1996/ EPIC-Spain Cohort	40,623 35–64 years	DHQ (last year, validated)	USDA	Flavonoids[c]	313	PA	Apple, red wine
Spain 2013 [24]	2003–2009/ PREDIMED Cohort	7200 53–82 years	FFQ (last year, validated)	Phenol-explorer	EPP Flavonoids[c] Phenolic acids	820 443 304	*Flavonoids* flavanones & PA HC	*Fruits*, Na-bev, vegetables *Fruits*, vegetables, A-bev *NA-bev*, fruit, vegetables
Finland 2008 [31]	2002/FINDIET National dietary survey	2007 25–64 years	48hR	Analysed food	TPP Flavonoids[c] Phenolic acids	863 208 641	*Phenolic acids* PA HC	*Coffee*, cereals *Fruit*, fruit juices *Coffee*, cereals
Poland 2012 [32]	2003–2005/ WOBASZ National dietary survey	6661 20–74 years	1x24hR	Analysed food	EPP	1102	ND	NA-bev, vegetables, fruits, cereals
Poland 2014 [33]	2002–2005/ HAPIEE Cohort	10,477 45–69 years	FFQ (last 3 months, validation NR)	Phenol-Explorer	EPP Flavonoids[c] Phenolic acids	1741/854[g] 898 800	*Flavonoids* Flavanols HC	Coffee, tea, fruit Tea, chocolate Coffee, tea
France 2011 [34]	1994–1996/ SU.VI.MAX Cohort	4942 45–60 years	6x24hR	Phenol-Explorer	EPP Flavonoids[c] Phenolic acids	1193 506 639	*Phenolic acids* PA & Flavan-3-ols HC	*NA-bev*, fruit Fruit, NA-bev, cocoa, A-bev *NA-bev*
Italy 2015 [35]	2005–2010/ Moli-sani Cohort	14,029 35–44 years	FFQ (last year, validation unclear[h])	Eurofir e-BASIS USDA	Flavonoids[c] Lignans	268 80	Anthocyanidins	*Fruit*, vegetables *Fruit*, vegetables
Italy 2015 [36]	2001–2003 Cohort	1658 45–64 years	FFQ (last year, Validation unclear[h])	Eurofir e-BASIS USDA	Flavonoids[c]	320[g]	PA & flavan-3-ols	Fruits, red wine
UK 2011 [37]	2011	na	FBS	USDA	Flavonoids[d]	182	Anthocyanidins	Grapes & oranges
Ireland 2011 [37]	2011	na	FBS	USDA	Flavonoids[d]	177	Anthocyanidins	Grapes & oranges, beer &wine
Europe 2015 [50]	2003 EPIC cohort calibration study	36,037 35–74 years	1x24hR	Phenol-Explorer	EPP Flavonoids[c] Phenolic acids	1184[g] 519[g] 609[g]	PA *Flavanols* HC	Coffee, fruits & tea, wine Fruits & tea, wine, choc *Coffee*
Europe 2015 [51]	1997–2009	30,790 18–64 years	EFSA database[i]	Flaviola	Flavonoids[c]	428	Flavan-3-ols & PA	*Tea & fruits*

Table 3 continued

Country/ Publication Year [Ref]	Year of survey/name Type of study	Study population	Diet assessment[a]	PP database	PP quantified[b,c,d]	mg/day (mean or range)	Main PP class/ subclass/family contributor[e]	Main food contributors[e,f]
Australia 2006 [38]	1995 NNS95 National dietary survey	16,326 ≥2 years	1x 24hR	USDA	Flavonoids[d]	454	Flavan-3-ols	*Tea*
Fiji 2006 [49]	1993 National dietary survey	4606 Age NR	1x 24hR	Analysed food	EPP	267	ND	nr
USA 2007 [39]	1999–2002 NHANES National dietary survey	8809 ≥19 years	1x24hR	USDA	Flavonoids[d]	190	Flavan-3-ols	*Tea*
USA 2011 [40]	1990–2005 NHS I, II, HPFS Cohorts	15,6957 25–75 years	Multiple FFQ (last year, validated)	USDA EuroFIR Other	Flavonoids[c]	382[g]	PA	*Tea*, apples, orange juice
USA 2013 [41]	1998–2001 Framingham Cohort	2915 54 years (mean)	FFQ (last year, validated)	USDA EuroFIR Other	Flavonoids[c]	225	*PA*	Tea, apples, pears
USA 2014 [42]	1988–1994 NHANES National dietary survey	17,899 ≥19 years	1x24hR	USDA	Flavonoids[c]	345[g]	Flavan-3-ols & PA	Tea, wine
USA 2015 [43]	2007–2008 WWEIA/ NHANES National dietary survey	5420 ≥20 years	1x24hR	FNDS flavonoid addendum	Flavonoids[c]	251[g]	*Flavanols*	*Tea*
USA 2016 [44]	2003–2007 REGARDS Cohort	16,678 >45 years	Block98-FFQ (period NR, validated)	FNDS flavonoid addendum	Flavonoids[c]	230[g]	NR	Tea
Brazil 2015 [45]	2008–2009 National dietary survey	34,003 ≥10 years	2x24hR	Phenol Explorer	EPP Flavonoids[c] Phenolic acids	460 133 314	Phenolic acids ND ND	Coffee, legumes, cereals Legumes, fruits, NA-bev, cocoa *Coffee*, cereals, legumes
Brazil 2016 [46]	2008 ISA-capital National Dietary survey	1103 ≥18 years	1x24hR	Phenol Explorer	EPP Flavonoids[c] Phenolic acids	377 55 245	*Phenolic acids* Flavanones, flavonols & flavanols *HC*	*Coffee* Citrus fruits and juices, beans *Coffee*
China 2015 [47]	2008–2001 Cohort	3317 56–67 years	FFQ (different periods[j], validated)	USDA Hong-Kong	Flavonoids[c]	258[g]	*Flavan-3-ols* & PA	*Tea*, pome fruits

Table 3 continued

Country/ Publication Year [Ref]	Year of survey/name Type of study	Study population	Diet assessment[a]	PP database	PP quantified[b,c,d]	mg/day (mean or range)	Main PP class/ subclass/family contributor[e]	Main food contributors[e,f]
Korea 2016 [48]	2007–2012 KNHANES National dietary survey	33 581 ≥19 years	1x24 hR	Korean	Flavonoids[c]	318	PA, flavonols, isoflavones & flavan-3-ols	*Fruits*, vegetables, legumes

ND not determined; *NR* not reported

[a] NSQ, National Survey Questionnaire (daily record of foods present at home for households and purchases of foods 4x per year for hotels, restaurants and institutions); FFQ, Semiquantitative Food Frequency Questionnaire; DHQ, Diet History Questionnaire; 24hR, 24-h Recall; FBS, Food Balance Sheets

[b] TPP, Total (Poly)phenols (extractable and non-extractable); EPP, extractable (poly)phenols; NEPP-PA, non-extractable PA; NEPP-Hydrol, non-extractable (poly)phenols obtained after hydrolysis

[c] PA included

[d] PA excluded

[e] PP class contributing with more than 50% in italic; PA, Proanthocyanidins; HC, hydroxycinnamic acids. Flavanols is used when there is no differentiation between flavan-3-ols monomers and PA

[f] Foods contributing with more than 10% to daily intake, presented from the most representative to the less representative; foods contributing with more than 50% in italic; NA-bev, Non-alcoholic beverages; A-bev, Alcoholic beverages; choc, chocolate

[g] Energy adjusted

[h] FFQ was described in a previous paper; the authors concluded that FFQ had an acceptable relative validity [72, 73]

[i] Food consumption values were obtained from EFSA consumption database, which included several studies; main diet assessment methods were 24-h recalls and food records

[j] Participants could choose to report food consumed per day, per week, per month or per year

from many of these studies report to consumption 10 years ago or more [30, 34, 36, 38, 41–43, 49, 50]. Dietary habits of the population may have changed meanwhile, and these data may thus not represent actual food intake.

Since all methods have some limitations, the use of a combination of different types of dietary assessment methods has been suggested to improve accuracy and facilitate interpretation of the dietary data. However, for estimation of PP intake most, studies rely only on just one method.

Calculation of (poly)phenol intake

Converting food consumption data to PP intake requires a food composition database with specific characteristics. A realistic calculation of PP intake depends on a complete and accurate database, with all possible foods contributing to PP intake, as well as accurate values for all existing classes and subclasses of PPs. This goal could be hampered not only by assessment of food intake, but also by an incorrect estimation of PP content in foods. The most representative databases of PP content in foods used worldwide were already discussed in the previous section. Although Phenol-Explorer is more inclusive, it is not complete and any missing value for a food consumed by the population limits the estimation. Another neglected aspect is values for foods eaten after cooking. In particular, PP bioaccessibility and bioavailability are seriously affected by food processing, failing to predict raw-to-cook differences in PP yield as well as PP losses [56].

Six of the selected studies relied merely on USDA database, only estimating values for flavonoid intake (Table 3) [30, 37–39, 42, 47]. Furthermore, three of the studies did not include proanthocyanidins [37–39], thus not having a realistic estimation of flavonoid intake. In fact, as shown in Table 3, within flavonoids, the main subclasses contributing to PP intake were flavanols, mainly proanthocyanidins. A study in the USA that estimated PA intake has reported that PA oligomers and polymers may be responsible for half or more of flavanol intake [57]. Some common foods, such as fruits like strawberry and apple, beans and cocoa products, are rich in flavanols (Table 2), with low contents of flavanol monomers and high contents of PA (90% or more of flavanols being dimers, oligomers and polymers [15]). Therefore, in diets rich in these types of foods, PA may well be the main contributors to flavonoid intake, as well as to total PP intake (Table 3).

Whenever other classes of PPs, in addition to flavonoids, are to be considered, the Phenol-Explorer database should be used or food should be analysed in the laboratory. Nine of the twenty-four analysed studies presented EPP intake; six of them used the Phenol-Explorer database and included values for both flavonoids and phenolic acids [24, 33, 34, 45, 46, 50]; and three presented only total

content in EPP, quantified by the Folin–Ciocalteu method [29, 32, 49]. Only two studies have determined total PP intake, including EPP and NEPP—Spain [29] and Finland [31]. EPP values for Europe [50, 51], Spain [24], France [34] and Poland [33] were not very different, ranging from 820 to 1741 mg of PP/day. Brazil shows lower values (377 and 460 mg of PP/day), probably due to the low consumption of fruits and vegetables by the population [45, 46]. The lowest values were reported for Fiji Islands (267 mg/day); as refereed by the authors, this was due to a dietary shift away from fruits and vegetables, as well as limitations in reporting techniques [49]. The studies that consider EPP+NEPP present values ranging from 2591 to 3016 mg/day [29] and 863 mg/day [31]. The much higher values found in one of the studies from Spain may reflect an overestimation of food intake by the assessment method (questionnaire assessing the quantity of foods present at homes or purchased by hotels and institutions, instead of the actual consumed foods), and also the utilization of a less accurate method such as Folin–Ciocalteu for the quantification of total PP [29]. On the other hand, the process followed for extraction of NEPP includes both enzymatic and chemical hydrolysis of the residue after aqueous-organic extraction of EPP, allowing a higher release of PPs from the food matrix. Furthermore, the contribution of NEPP to total PP content in food may be between 60 and 90% in some fruits and nuts [26], emphasizing the importance of including NEPP analysis to estimate total PP intake. In the study from Finland, a more realistic information on food assessment was performed with two 24hR in consecutive days, specific methods were used to extract and quantify different PPs and total PP was calculated as the sum of individual PPs. However, enzymatic hydrolysis was not performed, which may explain a lower content of PP in foods.

Another important issue that should be addressed is the energy adjustment of intake values. PP intake may be associated with total energy intake, both by amount of consumed food and by type of consumed food, as shown in the cohort studies of Poland [33] and Italy [35]. Adjustment of nutrient and PP intake for total energy intake is particularly important in epidemiologic studies, because diseases may be influenced by caloric intake, and thus, the effects of the studied PPs may be distorted or confounded by energy intake [58, 59]. Although in some studies energy adjustment does not seem to have an influence on PP intake [24, 60], in others, values may be about 50% lower after energy adjustment [33]. Most of the recent studies shown in Table 3 already present energy adjusted PP intake [33, 42–44, 47, 50].

When considering the estimation by PP classes, only seven of the analysed studies estimated the intake of two main PP classes: flavonoids and phenolic acids [24, 31,

33, 34, 45, 46, 50]. High variations were observed in flavonoid intake (including PA), the lowest was 55 mg/day, in Brazil, and the highest was 898 mg/day, in Poland (Table 3). Flavonoid values for Spain, France and Europe were similar (443, 506 and 519 or 428 mg/day, respectively, Table 3). Regarding phenolic acids intake in Europe, Spain showed the lowest intake (304 mg/day), Finland, France and Europe had similar values (641, 639 and 609 mg/day, respectively) and Poland had the highest values (800 mg/day) (Table 3). The high heterogeneity clearly reflects different diet patterns that ultimately are the reflection of cultural differences associated with traditional food production and availability. Diets richer in coffee will tend to have higher phenolic acid intake, mainly hydroxycinnamic acids (Tables 2 and 3). Coffee consumption may contribute to as high as 52% of total EPP intake [50]. On the other hand, diets richer in fruits and tea will tend to have higher flavonoid intake, with tea contributing to intake of flavanol monomers and fruits to intake of PA (Tables 2 and 3). If NEPP are considered, cereals become important contributors to total PP intake due to its high content in hydrolysable PP, which comprise hydrolysable tannins, phenolic acids and hydroxycinnamic acids that are released from the food matrix by strong acidic hydrolysis [29]. Fruits and legumes also raise its importance as contributors due to its content in condensed tannins [29].

Biomarkers for (poly)phenol intake

Until now, most of the studies on PP intake reflect data based on dietary questionnaires. However, this approach is subjected, as discussed, to important biases and errors associated with dietary assessment and inaccuracies in food composition databases. Therefore, biomarkers may be chosen as objective measures not depending on dietary assessment methods. Due to large interindividual variability in absorption and metabolism, biomarkers should also reflect tissue exposure to PP more precisely [3]. Moreover, PP exposure also depends on factors such as microbiota, oxidative stress, presence of other xenobiotics, inflammation and disease.

Consequently, developing biomarkers of PP intake, measured in blood and urine, is essential to correctly identify associations between PP intake and health-related outcomes, in epidemiologic and clinical studies. However, the relationship between PP intake and specific biomarkers is often highly complex. The PPs most commonly ingested in the human diet are not necessarily the most active within the body, either because of their low intrinsic activity or due to one or several of the following factors [61]:

1. Poor digestion, which may result from difficult release of PPs from the food matrix, interactions with other food compounds present in the meal, or simply because the individual PPs are not digested by enzymes present in stomach and small intestine;
2. Poor absorption in small intestine;
3. Metabolizing by colon microbiota, with the production of metabolites that are absorbed and may be more active than parent compounds;
4. Extensive biotransformation by phase I and II reactions (mainly phase II) in enterocytes upon uptake, or in liver after bloodstream transport;
5. Rapid excretion.

It would thus be very valuable to have biomarkers for PP intake, especially if we could distinguish between metabolites arising from different classes or subclasses of PPs. This specificity is very important since some PPs present in urine may arise from the ingestion of their main dietary source or may be formed when other consumed PPs are metabolized. For example, the presence of ferulic acid in urine may derive from both consumption of foods rich in ferulic acid, such as cereals, and when caffeic acid is metabolized to ferulic acid [62]. Moreover, other metabolites, such as hippuric acid, may arise from different PPs and also from endogenous metabolism of other substances [63].

It has been suggested that urine biomarkers are more suitable to assess PP intake, since absorbed metabolites may be rapidly removed from circulation, either by entering tissues, or by excretion in urine, in amounts that are higher than the metabolites found in plasma [64]. Another advantage is that urine is a noninvasive method. On the other hand, time of appearance of metabolites in urine varies widely; for example, after ingestion of a berry-fruit pure rich in PPs, different metabolites could be identified in urine collected at different interval times [65]. Thus, determination of urinary metabolites in pooled 24-h urine collection may provide a more realistic assessment of total PP intake. A meta-analysis performed with forty PPs has shown that daidzein, glycitein, enterolactone and hydroxytyrosol, had both a high recovery yield in urine and a high correlation with the dose of consumed PP or food (isoflavones from supplements or soy products, lignans from flaxseed and olive oil, respectively), suggesting good sensitivity and robustness as biomarkers for intake [63].

Results obtained from other studies may suggest biomarkers for dietary exposures of other PP classes or subclasses, or for intake of PP rich foods: Dihydrocaffeic acid-3′-O-sulphate and feruloylglycine were pointed as suitable urine biomarkers for coffee ingestion [64]; conjugates of the flavanones hesperidin and naringenin for orange juice [66]; (epi)gallocatechin, (epi)catechin and methyl-(epi)catechin metabolites for flavan-3-ols [64], and free and

conjugated forms of urolithins may be used as markers of ellagitannins [13, 67]. However, some flavonoid subclasses give rise to a broad range of urine metabolites, such as anthocyanins [68] and flavonols [64], thus making it difficult to ascertain the determination of a compound or a few urine compounds to this subclass of ingested PPs. This may be further complicated by sample processing before analysis, leading to different yields in recoveries of metabolites and, therefore, differences in their relative abundances. In some cases, sample preparation methods may lead to losses of unstable metabolites. Moreover, discrepancies could also be associated with the enzymatic treatment of samples; for example, the extent of hydrolysis of sulphates metabolites may be different, depending on the origin of the enzymes utilized [69]. The method of analysis, sensibility of instrumentation and availability of standards are other factors that may influence the accuracy of metabolite analysis and identification. An easier and faster method may be used, based on Folin–Ciocalteu that determines total PPs in urine collected after overnight fast [70]. Although a high variability was observed, total PP excreted has shown a positive association with total PP food intake [4, 70].

Recently, a metabolomics approach applied to a European cohort has identified specific sets of metabolites correlated with consumption of coffee, red wine, tea, citrus fruit, apples and chocolate, suggesting that measurement of food metabolome in future epidemiologic studies should be used as a complement or substitute to the traditional methods based on questionnaires, thus improving PP dietary exposure assessment [71]. This, however, may be difficult in studies with large populations; therefore, the use of questionnaires for the entire population, together with food metabolome analysis for a subset of the population as a validation procedure, could be a feasible alternative.

Conclusions

Nowadays, a broad perception of PP intake in the world and a comparison of intakes among different countries are not possible with the available data. Few countries have conducted reliable national surveys with the specific aim of estimating PP intake. We could identify some major limitations related to the accuracy of available data on PP intake: (1) Different methods are used for dietary assessment, mostly FFQs and 24-h recalls. Although easier to use, FFQs lack detail about consumed foods, must be country-specific and are prone to large random errors. On the other hand, the 24-h recall is considered as a reference method, has detailed and specific information on food consumption, but information on habitual intake requires multiple recalls; (2) Many studies are based on data collected a long time ago, not reflecting actual diet; (3) Different databases are used for calculating PP intake from consumed food, and information on some foods or PPs, particularly NEPP, is missing; (4) Lacking of reliable tools for food metabolome analysis, as a complement to the traditional questionnaires, either by lack of robust biomarkers or analytic limitations. This is a very important gap due to the large interindividual variability in PP absorption and metabolism.

Furthermore, different methods for collecting data on food consumption and calculation of PP intake make it very difficult to compare intakes among countries. Additionally, PP contents are not available for some foods or specific varieties characteristically consumed in some countries, decreasing the reliability of PP intake estimation. This, however, is important if we want to fully understand the relevance of the effect of PPs in human health and design new foods with bioactive compounds targeted to the needs of specific populations in different countries.

To minimize all the factors that may influence the study of the effect of PPs on health, it is essential to have some guidelines harmonizing data collection for such studies. National surveys should be conducted in each country, with the following criteria:

1. Data on food intake should be collected by multiple 24-h recalls distributed along the year (at least one per trimester). Whenever a cohort is covering several years, initial and concluding year should be covered;
2. Total PP intake should include extractable and non-extractable PPs. A harmonized protocol for extraction and determination of PPs must be developed and used for construction of national databases regarding the foods actually consumed by the population. These data should then be included on a wider database, such as Phenol-Explorer.
3. PP content in food should be calculated as the sum of individual components for the main different PP classes: flavonoids (extractable and non-extractable); phenolic acids (extractable and non-extractable); lignans; stilbenes; and tyrosols. Values should be adjusted for energy intake.
4. If possible, PP metabolome in human urine should be determined, at least for a subset of the population, to validate overall PP intake. A less accurate alternative could be total urine PP, which showed a positive association with PP intake.

Many small population studies are also conducted to address health effects of individual or specific mixtures of foods or (poly)phenols. In such studies, the same criteria should be applied concerning the methods to assess food intake and PP content in the consumed food. In addition, when available, they should include validated biomarkers, either individual compounds or panel of compounds, for the food or PP under study.

Compliance with ethical standard

Conflict of interest On behalf of all authors, the corresponding author declares that there is no conflict of interest.

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