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Structural Diversity of Polyphenols and Distribution in Foods

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1.1 Introduction

(Poly)Phenolic compounds or polyphenols are the most common and ubiquitous groups of secondary metabolites widely distributed in the Plant Kingdom. These metabolites are involved in important roles in plants, such as pigmentation, growth and reproduction functions, protection against ultraviolet (UV) radiation, resistance to pathogens and herbivores, and many other functions. They also contribute substantially to the organoleptic characteristics of flowers, leaves, fruits, and vegetables such as bitterness, astringency, color, and flavor (Bravo, 1998; Lattanzio *et al*., 2008; Pandey and Rizvi, 2009; Tomás-Barberán and Espín, 2001). Apart from beneficial effects on plants, many of these nonnutrient metabolites have been attributed as the molecules potentially responsible for the health effects in humans. Vegetable- and fruit-rich diets exhibit a wide spectrum of potential biological activities related to the prevention of many of the major chronic diseases such as cardiovascular, neurodegenerative, and cancer diseases (D'Archivio *et al*., 2007; Espín *et al*., 2017; Rothwell *et al*., 2017). In this book, the most recent studies about metabolism and the current evidence on the health effects of the different group of

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polyphenols, as well as their bioavailable metabolites, will be reviewed and discussed.

1.2 Classification and Chemistry of Polyphenols

The structure of phenolic compounds varies extensively but presents as a common feature the presence of one (simple phenolics) or more (polyphenols) hydroxyl substituents attached directly to one or more aromatic or benzene rings. Therefore, they have been classified into different groups or classes according to the pattern of their basic skeleton, from relatively simple, such as phenolic acids, to polymerized molecules of relatively high molecular mass, such as hydrolyzable and condensed tannins (Manach *et al.*, 2004; Pereira *et al.*, 2010). In general, the phenolic compounds are found in plants in the conjugated form rather than as free compounds, with one or more sugar residues linked by β-glycosidic bonds to a hydroxyl group (*O*-glycosides) or a carbon atom of the aromatic ring (*C*-glycosides). The associated sugars can be monosaccharides, disaccharides or even oligosaccharides, glucose being the most common followed by others such as galactose, rhamnose, xylose, arabinose, etc. (Manach *et al.*, 2004).

Moreover, the wide structural diversity in phenolic compounds encompasses over 8000 compounds described in nature that traditionally are divided into two main groups based on their basic structure, flavonoids and nonflavonoids, that are subdivided into different subgroups according to the number of aromatic or phenol rings and the structural elements that bind these rings to one another (Bravo, 1998; D'Archivio *et al.*, 2007; Del Rio *et al.*, 2013; Waterhouse, 2002).

1.2.1 Flavonoids

Flavonoids are the largest group of phenolic compounds, accounting for more than 5000 different compounds present in dietary plant foods, although they usually occur as glycosides rather than aglycones, mostly linked to glucose, rhamnose, xylose or galactose (Harbone and Williams, 2000; Tsao, 2010).

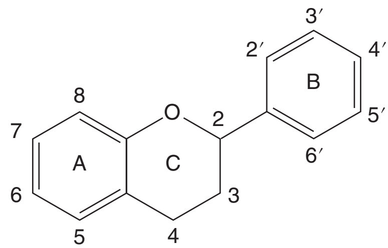


Figure 1.1 The basic structure of flavonoids.

The basic flavonoid structure is composed of two phenol rings (A and B) linked through a linear three-carbon chain that forms a heterocyclic pyran ring (C) containing one oxygen atom (Figure 1.1).

Based on the degree of oxidation, saturation, and hydroxylation of the central pyran ring, flavonoids can be divided into different subgroups as flavan-3-ols (catechins and proanthocyanidins), flavones, flavonols, flavanones, isoflavones, and anthocyanidins (Table 1.1) (Bravo, 1998). The diversity of each group of flavonoids depends on the different patterns of substitution of the hydroxyl groups in the basic flavonoid skeleton, mainly the conjugation with various mono- and disaccharides creating highly complex structures (Bravo, 1998). In addition to these major flavonoid groups, there are other minor ones such as chalcones, dihydrochalcones, dihydroflavonols, and flavan-3,4-diols. In Table 1.1, the most common examples of different flavonoid subgroups found in plant foods are listed.

Flavan-3-ols or flavanols are structurally characterized by the presence of a hydroxyl group in the heterocyclic ring C. Unlike other flavonoid subgroups, they cannot occur as glycosides in food sources, but exist as simple monomers such as catechin and epicatechin, to the oligomeric and polymeric condensed tannins, which are also known as proanthocyanidins. Proanthocyanidins are highly complex chemical structures formed by oligomerization or polymerization of up to 50 subunits of monomeric flavanols joined by one (type B proanthocyanidins) or two (type A proanthocyanidins) oxidative couplings between two monomers. Proanthocyanidins containing only catechin/epicatechin units are known as procyanidins, which are the most common in nature, while those formed by gallocatechin/epigallocatechin units are called prodelphinidins,

Table 1.1 Main flavonoid groups and distribution in foods

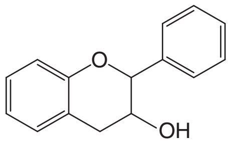
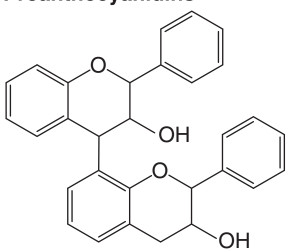
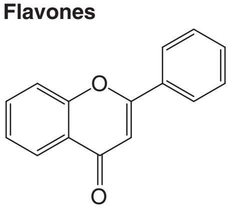
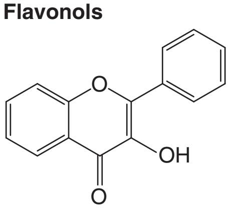
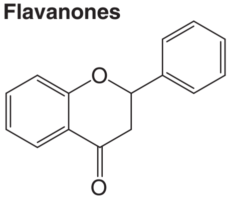
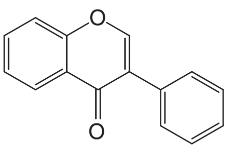
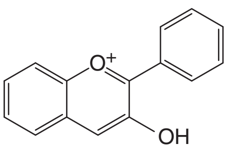
Structure	Main compounds	Food sources
Flavan-3-ols 	Catechin Epicatechin Epicatechin gallate Gallocatechin	Apple, apricot, peach, grape, berries, cereals, chocolate, red wine, nuts, black and green tea
Proanthocyanidins 	Procyanidin B1 Procyanidin B2	Red wine, beer, cider, apple, pear, grape, chocolate
Flavones 	Apigenin Luteolin Chrysin	Parsley, celery, lettuce, artichoke, herbs (rosemary, thyme, oregano, etc.), citrus fruits, cereal grains, sweet peppers
Flavonols 	Quercetin Kaempferol Myricetin Isorhamnetin	Yellow and red onion, caper, lettuce, parsley, berries, green and black tea, mango, carrot, pumpkin, kale, cabbage, broccoli, garlic
Flavanones 	Naringenin Hesperetin	Orange, grapefruit, lemon, lime

Table 1.1 (Continued)

Structure	Main compounds	Food sources
Isoflavones 	Daidzein Genistein Glycitein	Soybean, tofu, green bean, lentil, chickpea, pea, mung bean, broad bean, medicinal herbs
Anthocyanidins 	Cyanidin Delphinidin Pelargonidin Peonidin	Berries, currant, grape, aronia, cherries, plum, pomegranate, red wine, red cabbage, eggplant, red onion, radish, hazelnut, pistachio nut, black and red bean, medicinal herbs

and those with afzelechin/epiafzelechin units are known as propelargonidins (Smeriglio *et al*., 2017; Spranger *et al*., 2008).

Flavones are structurally characterized by a double bond and an oxygen atom in the heterocyclic ring C of the flavonoid skeleton. Flavones, such as apigenin and luteolin, can be found in plants showing a wide range of substitutions, including methylations, hydroxylations, acylations, and glycosylations leading mainly to *O*- or *C*-glycosides (Hostetler *et al*., 2017).

Flavonols contain a similar structure to flavones but with the presence of a hydroxyl group at carbon 3 of the flavone nucleus (3-hydroxyflavones). Flavonols are one of the most abundant flavonoid subgroups widely found in plants; they are commonly found as glycosides and the most common one is quercetin (Leo and Woodman, 2015).

Flavanones and dihydroflavonols contain a similar structure to that of flavones and flavonols in which the double bond in the heterocyclic ring C has been reduced (hydrogenated). Flavanones are one of the main flavonoid subgroups and are mostly found in the form of glycosylated derivatives through the formation of an *O*-glycosidic linkage usually with a rutinosyl (rhamnosyl 1-6 glucosyl-) or a neohesperidosyl (rhamnosyl 1-2 glucosyl-) moiety to the aglycone hydroxyl groups, the most common being glycosylation of the hydroxyl at C-7 of ring A (Barreca *et al.*, 2017).

Isoflavones or isoflavonoids differ from the other flavonoid subgroups because the ring B is bound to the heterocyclic ring C at C-3 position instead of C-2. Unlike other flavonoid subgroups, the occurrence of isoflavones in plants is limited, almost exclusively, to leguminous plants, mainly found in the form of β-glucosides and their acetyl- or malonyl-derivatives. However, there is a large structural variation of isoflavones according to the oxidation level of their skeleton. Isoflavones, like lignans, and stilbenes are also classified as phytoestrogens due to their structural similarities to estrogens and, therefore, their capacity to bind to estrogen receptors (Heinonen *et al.*, 2002). The dietary glucosylated isoflavones, such as daidzin or genistin, are poorly absorbed after consumption. However, they are cleaved to their aglycones, daidzein and genistein, which are readily absorbed into the circulatory system and/or further metabolized in the colon by the action of the intestinal microbiota to other bioactive metabolites such as equol, *O*-desmethylangolensin (ODMA), and dihydrogenistein (Frankenfeld *et al.*, 2014; Heinonen *et al.*, 2002; Zaheer and Humayoun Akhtar, 2017). Thus, it is well established that interindividual differences in the conversion of the isoflavone daidzein to equol and ODMA are associated with the heterogeneity of individual biological responsiveness to the consumption of isoflavones-containing products (Frankenfeld *et al.*, 2014; Heinonen *et al.*, 2002).

Anthocyanidins are water-soluble pigments responsible for the red, blue, and purple-colored plant organs, mainly flowers, fruits, and leaves, depending on the light, pH, and temperature (Khoo *et al.*, 2017; Laleh *et al.*, 2006). They differ from other flavonoid subgroups because they have a positive charge at the oxygen atom of the heterocyclic ring C of the basic flavonoid structure, also called the flavylium (2-phenylchromenylium) cation. They lead to a wide variety of pigments in plants and are commonly found as glycosides, called anthocyanins, which are bonded to various sugar residues mainly attached to the hydroxyl at C-3 on the heterocyclic ring C or attached to the hydroxyl groups of the ring A at C-5 and C-7 position. Among monosaccharides, such as glucose, xylose or galactose, and disaccharides, such as rutinose or neohesperidose, glucose is the most common glycosyl unit found in anthocyanins. These sugar moieties can also be acylated with different aromatic (*p*-coumaric, ferulic, caffeic, sinapic) or aliphatic acids (malonic, acetic) (D'Archivio *et al.*, 2007; Khoo *et al.*, 2017; Krga and Milenkovic, 2019; Wallace and Giusti, 2015).

1.2.2 Nonflavonoids

Nonflavonoids are the other principal group of phenolic compounds with dietary importance which generally have both a simpler chemical structure than that of the flavonoids as well as large and complex polyphenols. The main nonflavonoid phenolics include the simple phenolic acids (hydroxycinnamic and hydroxybenzoic acids), the hydrolyzable tannins (ellagitannins and gallotannins), stilbenes, coumarins, and lignans (Bravo, 1998). Table 1.2 shows the most common examples of nonflavonoid phenolics found in plant foods.

Phenolic acids are simple phenols that contain a carboxyl group and occur mainly as hydroxybenzoic (C6-C1 skeleton) and hydroxycinnamic acids (C6-C3 skeleton) which derive from benzoic or cinnamic acid, respectively. They can occur in plant foods either in their free or conjugated form attached to different functional groups or esterified to organic acids (Razzaghi-Asl *et al.*, 2013; Robbins, 2003).

The hydrolyzable tannins have a high molecular weight and are formed by a carbohydrate moiety, usually glucose, partially or totally esterified with phenolic residues such as gallic acid in the case of gallotannins or hexahydroxydiphenic acid (precursor of ellagic acid after hydrolysis) for ellagitannins. Unlike the flavonoid-derived condensed tannins, they are readily hydrolyzed under acid hydrolysis (Okuda *et al.*, 1995; Smeriglio *et al.*, 2017; Tomás-Barberán *et al.*, 2008). It is well documented that ellagitannins and ellagic acid have limited bioavailability. Indeed, when ellagic acid, either released from ellagitannins or free ellagic acid occurring naturally in foods, reaches the distal part of the gastrointestinal tract, it is further hydrolyzed

Table 1.2 Nonflavonoid (poly)phenols and main dietary sources

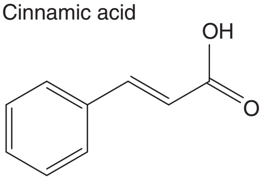
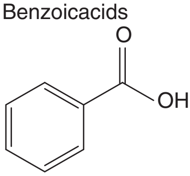
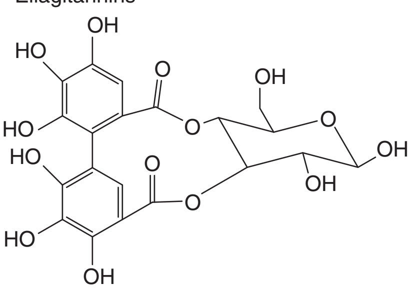
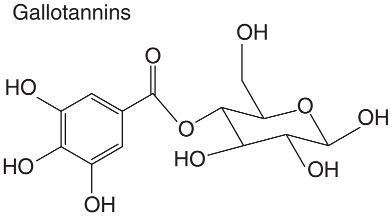
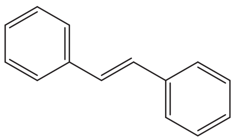
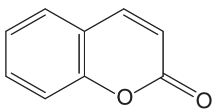
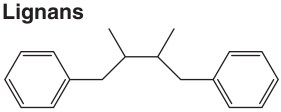
Structure	Main compounds	Food sources
Phenolic acids Cinnamic acid 	*p*-Coumaric acid Caffeic acid Ferulic acid Sinapic acid	Coffee, potato, broccoli, spinach, lettuce, cabbage, apple, pear, cherries, apricot, peach, blackcurrant, blueberry, asparagus, wine, rye bread
Benzoicacids 	Gallic acid Protocatechuic acid Syringic acid Vanillic acid	Cloudberry, raspberry, red cabbage, chestnut, tea
Hydrolyzable tannins Ellagitannins 	Sanguiin H6 Punicalagin Pedunculagin	Strawberry, raspberry, blackberry, pomegranate, walnut, chestnut, hazelnut, mango, green and black tea, oak-aged beverages
Gallotannins 	Galloyl-hexoside Digalloyl-hexoside	Mango, chestnut, red sword bean

Table 1.2 (Continued)

Structure	Main compounds	Food sources
Stilbenes 	Resveratrol	Red wine, grape
Coumarins 	Umbelliferona Esculetina Scoparone	Citrus, parsley, celery, medicinal herbs
Lignans 	Secoisolariciresinol Matairesinol Pinoresinol Lariciresinol	Flaxseed, sesame seeds

and/or metabolized by the colonizing microbiota into a family of dibenzo[*b,d*]pyran-6-one derivatives known as urolithins that can reach systemic tissues (Cerdá *et al.*, 2004; Tomás-Barberán *et al.*, 2017). Urolithins are bioavailable microbial metabolites characterized by a nucleus of a dibenzo [*b,d*]pyran6-one with different hydroxylation patterns. In recent years, three different ellagitannin-metabolizing metabotypes have been described in humans associated with interindividual variability in urolithin production, which depends on gut microbiota composition (Tomás-Barberán *et al.*, 2014).

Stilbenes are structurally characterized by the presence of two phenyl moieties connected by a two-carbon methylene bridge (C6-C2-C6). They can be found as both monomeric and oligomeric forms that are produced by oxidative coupling between monomeric stilbenes such as *trans*-resveratrol (Rivière *et al.*, 2012; Shen *et al.*, 2009). Since there are more than 400 natural stilbenes in the plant kingdon, low quantities of stilbenes are present in the human diet, resveratrol being the most representative which occurs in both *cis* and *trans* isomers as well as in glycosylated forms such as its glucoside, piceid (D'Archivio *et al.*, 2007; Del Rio *et al.*, 2013; Shen *et al.*, 2009).

Coumarins are a family of benzopyrones derived from hydroxycinnamic acids (C6-C3) by lactonization. The most common are coumarins, isocoumarins, furanocoumarins, and benzocoumarins. They are highly bioactive, and even toxic, compounds that are seldom found in foods (Matos *et al.*, 2015).

Finally, lignans are nonflavonoid phytoestrogens whose structure derives from oxidative dimerization of two phenyl-propanoid units (C6-C3) linked at the central carbon (C8-C8′). Lignans are generally found in free forms, although to a lesser extent they can be coupled to sugars as glycosidic derivatives. It is well established that dietary lignans are metabolized by intestinal microbiota to the bioactive mammalian lignans or enterolignans, enterodiol and enterolactone, that contain a structure with only two phenolic hydroxyl groups, at the metaposition of each aromatic ring (D'Archivio *et al.*, 2007; Raffaelli *et al.*, 2002; Saleem *et al.*, 2005).

1.3 Dietary Intake and Food Sources of Polyphenols

As indicated above, phenolic compounds or polyphenols are nonnutrient secondary metabolites widely spread throughout the plant kingdom as constituents of almost all vegetables, fruits, cereals, beverages such as tea, coffee, and red wine, and other plant-derived foods, and therefore, they represent an important source of bioactive compounds in the human diet (Pérez-Jiménez *et al.*, 2010a; Scalbert and Williamson, 2000). Moreover, polyphenols are involved, both positively and negatively, in the sensory and organoleptic properties of fruits and vegetables such as color, flavor, and astringency (Ignat *et al.*, 2011; Tomás-Barberán and Espín, 2001).

According to several observational studies conducted in different cohorts, the estimated mean total daily intake of polyphenols can reach over 1 g, becoming the most abundant micronutrients present in a regular diet (Manach *et al.*, 2004; Miranda *et al.*, 2016; Ovaskainen *et al.*, 2008; Pérez-Jiménez *et al.*, 2011; Pinto and Santos, 2017; Tresserra-Rimbau *et al.*, 2013; Zamora-Ros *et al*., 2016). Over 500 different polyphenols are found in low or high amounts in most of the over 400 plant species regularly consumed in the human diet. One-third of dietary polyphenols is dominated by phenolic acids and the remaining two-thirds by the largest subgroup of flavonoids (Gupta *et al*., 2013; Pérez-Jiménez *et al*., 2010b). It is well known that fruit and beverages such as tea, coffee, and red wine are the most relevant from their content in the diet, but vegetables, cereals, and leguminous plants are also important sources. However, their polyphenol content may significantly differ among different varieties of a specific plant food based on genotype and ecophysiological factors as well as environmental and agronomic conditions (high or low temperature, UV exposure, insect attack, postharvest handling, water supply) and food processing-related factors (type of storage, culinary preparation, type of processing) (D'Archivio *et al*., 2007; Manach *et al*., 2004; Schreiner, 2005).

Most plant foods contain complex mixtures of polyphenols. Some of them, however, are mainly present in particular foods such as flavanones in citrus fruit, isoflavones in legumes (soybean and derived foods), dihydrochalcones (phloridzin) in apples, or flavones in celery and parsley. Other polyphenols, such as quercetin or catechin, are, however, found in many food products (fruit, vegetables, cereals, tea, wine). In Tables 1.1 and 1.2, the most common sources of each phenolic subgroup are presented.

1.3.1 Flavonoids

Flavonoids (see Table 1.1) are extensively found in most foodstuffs of plant origin but mainly in fruits such as apples, berries, and citrus fruits, vegetables such as onions and parsley, together with red wine, green and black tea, cocoa, nuts and certain spices (Beecher, 2003; Crozier *et al*., 2009; Manach *et al*., 2004; Marzocchella *et al*., 2011).

Regarding flavanols, mainly catechin and epicatechin, the main representative sources are fruits such as apples, apricots, peaches, grapes, and some berries, cereals, chocolate, red wine, and nuts, whereas flavanols such as epigallocatechin gallate, gallocatechin or epigallocatechin are found especially in

Camellia sinensis teas (black, green, etc.) (Arts *et al.*, 2000a,b; Manach *et al.*, 2004). On the other hand, the most abundant type of proanthocyanidins found in plant foods is the dimeric procyanidins B1, B2, B3, and B4, that consist exclusively of epicatechin/catechin units. These procyanidins have been reported to be responsible for the astringent character of beverages (red wine, beer, and cider) and fruits (apples, pears, grapes, etc.) and the bitterness of chocolate (D'Archivio *et al.*, 2007; Crozier *et al.*, 2009; Gu *et al.*, 2004; Rasmussen *et al.*, 2005).

Flavones are the least common flavonoids in food. They occur in relatively high amounts in parsley and celery (apigenin and luteolin). They are also present as *O*-glycosides and *C*-glycosides in many different food products of the family Asteraceae (lettuce and artichoke) and Lamiaceae (herbs such as rosemary, thyme, oregano, mint, sage, etc.). They also occur in citrus fruits (vicenin-2, orientin), and cereal grains, (tricetin, tricin, luteolin, and apigenin *C*- and di-*C*-glycosides) as well as in sweet peppers (D'Archivio *et al.*, 2007; Del Rio *et al.*, 2013; Hostetler *et al.*, 2017). In addition, low amounts of methylated flavones such as diosmetin-, acacetin-, and chrysoeriol-*C*-glycosides are also found in citrus juices, mainly in mandarin orange, orange, citron, and bergamot juices, as well as low quantities of luteolin and apigenin in red and white wine (Del Rio *et al.*, 2013; Hostetler *et al.*, 2017). Finally, lesser amounts are found in other food sources such as blue fruits, pumpkin, chicory, kumquat, olive oil, honey, etc. as well as in some cereals and legumes such as wheat grain, black rice, fava bean, chickpea, etc. (Hostetler *et al.*, 2017).

Flavonols constitute the most ubiquitous flavonoid subgroup in our diet, with quercetin as the most consumed type of flavonols, typically found as glycosides. The main food sources of quercetin are yellow and red onions, capers, lettuce, parsley, and some types of berries, and in lesser amounts also found in apples, figs, Brussels sprouts, and buckwheat (Bhagwat *et al.*, 2011; D'Archivio *et al.*, 2007; Del Rio *et al.*, 2013). Other dietary flavonols also commonly found as *O*-glycosides are kaempferol and myricetin, found in green and black tea as well as in fruits and vegetables such as mango, carrot or pumpkin, and Brassicaceae such as kale, cabbage, and broccoli or Alliaceae such as garlic (Crozier *et al.*, 2009; Miean and Mohamed, 2001).

Flavanones are found in high concentrations mainly in citrus fruits and their juices (orange, grapefruit, lemon, lime, kumquat, etc.) where they account for approximately 95% of the flavonoids in the *Citrus* genus (Bhagwat *et al.*, 2011; Peterson *et al.*, 2006). They are also found in artichokes, tomatoes, and certain aromatic plants such as oregano (Bhagwat *et al.*, 2011; Crozier *et al.*, 2009; Ignat *et al.*, 2011). The main flavanone glycosides (rhamnosyl-glucosides) are hesperidin (hesperetin-7-*O*-rutinoside) found in oranges, naringin (naringenin-7-*O*-neohesperidoside) found in grapefruit, neohesperidin (hesperetin-7-*O*-neohesperidoside) found in bitter oranges, and eriocitrin (eriodictyol-7-*O*-rutinoside) found in lemons (D'Archivio *et al.*, 2007; Peterson *et al.*, 2006).

Isoflavones occur almost exclusively in legumes (Leguminosae), with the highest amount found in the cultivated soybean (*Glycine max* (L.)). Thus, soybean, also referred to as soy or soya, and its processed products including soy flour, soy flakes, miso, tempeh, natto, tofu, and soy milk, represent the main source of isoflavones (Danciu *et al.*, 2018; D'Archivio *et al.*, 2007; Zaheer and Humayoun Akhtar, 2017). The main isoflavones, referred to as phytoestrogens to indicate their estrogenic properties, are genistein, daidzein, and glycitein that occur as aglycones, mainly in processed soy products, or more often as glycosidic forms, mainly in grains, that are less well absorbed (Danciu *et al.*, 2018; Mazur *et al.*, 1998; Zaheer and Humayoun Akhtar, 2017). In addition to soybean, other legumes also contain significant amount of isoflavones such as green beans, lentils, chickpeas, peas, mung beans, and broad beans, as well as several medicinal plants including red clover, lucerne, and sohphlang flax (Danciu *et al.*, 2018; Ko, 2014; Zaheer and Humayoun Akhtar, 2017).

Finally, anthocyanins represent one of the most important components of flavonoids in the human diet. Anthocyanins are widely distributed in vegetables and fruits and are responsible for the blue, purple, and red pigments found in flowers, fruits, leaves, and roots. They are also increasing being used as colorants for the food industry (D'Archivio *et al.*, 2007; Khoo *et al.*, 2017; Krga and Milenkovic, 2019). The most common types of anthocyanidins widespread in fruits and vegetables are cyanidin (responsible for reddish-purple pigment), delphinidin (responsible for blue-reddish or purple pigment), pelargonidin (responsible for red and orange pigment), peonidin (responsible for reddish-purple pigment), malvidin (responsible for purple-blue and red pigment), and petunidin (responsible for dark red or purple pigment) (Bąkowska-Barczak, 2005; Katsumoto *et al*., 2007; Khoo *et al*., 2017). Among colored fruits, the main dietary sources are berries (elderberries, bilberries, blueberries, blackberries, strawberries, raspberries), currants, grapes, aronia, cherries, plums, pomegranates, some tropical fruits, and fruit-derived products (red wine, fruit juices, and jams). Among dark-colored vegetables and cereals, anthocyanins are found in red cabbage, eggplant, red onions, radishes, hazelnuts, pistachio nut, and black and red beans, as well as certain varieties of herbal medicinal plants including red clover, red hibiscus, and purple passion flower (Bhagwat *et al*., 2011; D'Archivio *et al*., 2007; Khoo *et al*., 2017).

1.3.2 Nonflavonoids

The nonflavonoid polyphenols group (see Table 1.2) is rich and diverse. It includes the phenolic acids, commonly found in many foods such as coffee and many types of fruits, the hydrolyzable tannins found in pomegranate, berries, nuts, tropical fruits, the stilbenes such as resveratrol found mostly in red wine, and the lignans found in flaxseed, sesame, and many grains and fruits (D'Archivio *et al*., 2007; Del Rio *et al*., 2013; Manach *et al*., 2004; Robbins, 2003).

Phenolic acids are abundant in the human diet, being present in all plant food groups. Phenolic acids can be distinguished in two main classes: cinnamic acid derivatives (hydroxycinnamic acids) and benzoic acid derivatives (hydroxybenzoic acids). Hydroxycinnamic acids such as *p*-coumaric, caffeic, ferulic, and sinapic acids are more abundant in plant foods and are commonly found as glycosides, esters of glucose, and esters of quinic acid. They are rich in coffee and some vegetables, fruits, and cereals, particularly in potatoes, broccoli, spinach, lettuce, cabbage, apples, pears, cherries, apricots, peaches, blackcurrants, blueberries, asparagus, wine, and rye bread (Bravo, 1998; D'Archivio *et al*., 2007; Del Rio *et al*., 2013; El Gharras, 2009;

Manach *et al.*, 2004). Regarding hydroxybenzoic acids, in particular, gallic, protocatechuic, syringic and vanillic acids, they are found in very few edible plant foods, mainly in some berries such as cloudberry or raspberry, red cabbage, chestnut, and tea (D'Archivio *et al.*, 2007; El Gharras, 2009; Manach *et al.*, 2004). Hydroxybenzoic acids, such as gallic or hexahydroxydiphenic acids, are constituents of hydrolyzable tannins such as the gallotannins found in mango and the ellagitannins of various types of fruit, such as strawberries, raspberries, blackberries and pomegranate, and in nuts (Manach *et al.*, 2004).

The hydrolyzable tannins are divided into two classes: those composed of ellagic and gallic acid esters of glucose or related sugars (ellagitannins and galotannins, respectively) (Okuda *et al.*, 1995; Tomás-Barberán *et al.*, 2008). Ellagitannins such as sanguiin H6, punicalagin or pedunculagin are found in significant amounts in many berries, in particular strawberries and raspberries, as well as in other fruits and nuts such as pomegranate, muscadine grapes, walnuts, chestnuts, hazelnuts, mango, green and black tea, and are also present in oak-aged beverages (wine, whiskey, etc.) (Crozier *et al.*, 2009; Tomás-Barberán *et al.*, 2008, 2016). Gallotannins, unlike ellagitannins, are rarely found in plant foods, and occur almost exclusively in mango, chestnuts, and red sword bean (Gan *et al.*, 2018; Luo *et al.*, 2014; Smeriglio *et al.*, 2017).

Stilbenes are present in low quantities in the human diet, resveratrol being the most characteristic, mainly found in grapes and red wine, mostly in glycosylated forms rather than its *cis*/*trans* isomers, as well as oligomers containing different resveratrol units such as δ-viniferin and ε-viniferin (Burns *et al.*, 2002; D'Archivio *et al.*, 2007; Vitrac *et al.*, 2005). Other dietary sources with lesser amounts of stilbenes, mainly resveratrol, are peanuts, pistachios, some berries, red cabbage, and spinach (Crozier *et al.*, 2009; D'Archivio *et al.*, 2007; Rivière *et al.*, 2012), as well as certain medicinal remedies such as *Polygonum cuspidatum* that contains very high levels of resveratrol and its glucoside piceid (Vastano *et al.*, 2000).

Coumarins and derivatives are common in members of the Rutaceae (citrus), and Apiaceae (parsley, celery, etc.) families. They are also found in several species belonging to different botanical families used as herbal medicinal remedies such as

Aesculus hippocastanum (horse chestnut), *Passiflora incarnata* (passion flower), and *Hypericum perforatum* (St John's wort) (Matos *et al.*, 2015).

Lignans have been found in many plant foods, commonly as glycosides. They are receiving growing attention as precursors of the enterolignans (enterolactone and enterodiol), microbial metabolites that exert potential biological effects (Aehle *et al.*, 2011; Raffaelli *et al.*, 2002). The richest dietary source of lignans, mainly of secoisolariciresinol diglucoside and matairesinol, in lesser amount, is flaxseed (also called linseed). Relatively high amounts of other lignans, such as pinoresinol and lariciresinol, are found in sesame seeds (Milder *et al.*, 2005). Other minor sources include several cereals (triticale and wheat), legumes (soybeans and lentils), vegetables (garlic, asparagus, broccoli, carrots), and fruits (pears, prunes, strawberries, lingonberries, blackcurrants) (Aehle *et al.*, 2011; Gerstenmeyer *et al.*, 2013; Mazur *et al.*, 2000; Raffaelli *et al.*, 2002; Smeds *et al.*, 2007).

1.4 Databases Used to Assess Dietary Exposure to Polyphenols

One of the main tasks in nutritional studies with plant food products is determination of the dietary intake of specific food phytochemicals, and particularly polyphenols, due to the large structural diversity and variability among food products, and the changes occurring with processing, storage, and culinary practices. To help with this task, there are several free access internet-based databases, two of which are described here.

- *Phenol Explorer* (http://phenol-explorer.eu/). This database is freely accessible and describes the polyphenol content of food, with more than 500 polyphenols and their occurrence in 400 foods. The database also contains a comprehensive description of polyphenol metabolism, including pharmacokinetics data, as well as a description of the effect of food processing and cooking on these metabolites.
- *Phytohub* (http://phytohub.eu/). Phytohub is a comprehensive database of food phytochemicals. It is linked with FooDB

(http://foodb.ca/) and ITIS (Integrated Taxonomic Information System) (www.itis.gov//) which provides interesting and relevant information regarding the origin of plant foods and food sources. It is the first inventory of all phytochemicals present in foods (>350) commonly ingested in human diets and also includes >560 human and animal metabolites. Phytohub includes a connection with a mass search and structure application, as well as a food search link, which is very useful for metabolomic studies, and identification of discriminant metabolites in nutri-metabolomic studies.

1.5 Bioavailability, Metabolism, and Bioactivity of Dietary Polyphenols

Over recent decades, spectacular advances have been made through in our understanding of the possible role of dietary polyphenols in preventive nutrition. In fact, for decades, epidemiological and observational studies have been pointing out that dietary polyphenols present in a fruit- and vegetable-rich diet exert protective effects against several chronic degenerative diseases including cardiovascular diseases, diabetes, cancer, and neurodegenerative conditions such as Alzheimer's and Parkinson's diseases, mainly in the context of regular or long-term intake (Bravo, 1998; Cory *et al.*, 2018; Espín and Tomás-Barberán, 2005; Fraga *et al.*, 2019; Tresserra-Rimbau *et al.*, 2014). Moreover, in parallel, extensive preclinical research in animal and cell models has described a wide spectrum of biological activities for many dietary polyphenols beyond the antioxidant properties classically attributed to plants, including antimicrobial, antiinflammatory, and anticarcinogenic properties, displayed in both the digestive tract and systemic tissues (Bravo, 1998; Espín and Tomás-Barberán, 2005; Del Rio *et al.*, 2013; Fraga *et al.*, 2019; Quideau *et al.*, 2011; Vauzour *et al.*, 2010).

According to these findings and with the aim of responding to consumer demands, many dietary polyphenols are being used in so-called functional foods as well as nutraceuticals according to their presumably favorable effect on health and to contribute to the prevention of certain chronic diseases (González-Sarrías *et al.*, 2013; Liu, 2003). However, it is important to note that there is still not enough convincing evidence from human studies to fully support the link between dietary polyphenols intake and health benefits, mainly due to inaccurate *in vitro–in vivo* extrapolation (Ávila-Gálvez *et al.*, 2018a; Espín *et al.*, 2017; Hollman, 2014). Thus, to date, unlike vitamins and minerals, only cocoa flavanols and olive oil hydroxytyrosol have gained approval from the European Food Safety Authority (EFSA) for their cardioprotective action (EFSA, 2011, 2014).

Moreover, despite outstanding progress in our understanding of the association between polyphenol-rich food intake and the potential effects on chronic diseases and general health, it is important to note that the beneficial effects depend on bioavailability and metabolism. Thus, the identification and measurement of physiologically relevant polyphenol metabolites, that might exert higher or lower beneficial biological activities than their precursors, represent a crucial requisite for the understanding of the role of dietary polyphenols in human health (D'Archivio *et al.*, 2007; Espín *et al.*, 2017; González-Sarrías *et al.*, 2017; Manach *et al.*, 2004).

In this regard, most dietary polyphenols occur as glycosides and as complex oligomeric structures in plant foods, that are poorly bioavailable and cannot reach systemic tissues in their native form. Once they reach the distal gastrointestinal tract, they are further hydrolyzed and metabolized by either the intestinal enzymes or the gut microbiota. The resulting polyphenol metabolites are then absorbed, and rapidly undergo extensive phase II metabolism by glucuronyl transferases, sulfate transferases, and catechol methyl transferases, yielding sulfate, glucuronide, and methyl conjugates that appear in the circulatory system and can be detected in urine up to 3–4 days after intake. Significant concentrations of the metabolites, in the range from nM to low μM, are present in plasma and these metabolites can target systemic tissues, and therefore, they may trigger beneficial effects attributed to dietary polyphenols (Del Rio *et al.*, 2013; Espín *et al.*, 2017; González-Sarrías *et al.*, 2017; Selma *et al.*, 2009). In recent years, it has been reported that once the polyphenol-derived metabolites are absorbed, they are conjugated by phase II metabolism enzymes to favor excretion. These metabolites do not always demonstrate relevant health effects as the conjugates often show lower bioactivity in different models than that of their deconjugated counterparts (Aires *et al*., 2013; Ávila-Gálvez *et al*., 2018b; Giménez-Bastida *et al*., 2016; González-Sarrías *et al*., 2014).

In relation to this, it is important to consider several factors that may directly or indirectly affect the bioavailability of dietary polyphenols. These include the food matrix, that involves bonds with food constituents as proteins or lipids, as well as food processing-related factors such as storage and cooking that can significantly limit the release needed to be potentially bioavailable and bioactive (D'Archivio *et al*., 2007). Growing evidence also suggests that interindividual variability in the absorption, distribution, metabolism, and excretion (ADME) of bioactive compounds may be one of the main reasons behind the heterogeneity found in individual biological responsiveness after intake. This variability is determined by genetic and nongenetic factors, such as age, gender, (epi)genotype, and gut microbiota composition (Manach *et al*., 2017; Milenkovic *et al*., 2017).

Regarding microbiota, it is important to point out the two-way interaction existing with dietary polyphenols. Thus, dietary polyphenols not only undergo transformations by specific bacteria, but they can also modulate the gut microbiota composition and even their activity, acting as a prebiotic conferring a potential beneficial effect (Espín *et al*., 2017; Selma *et al*., 2009). In this regard, recently, Tomás-Barberán *et al*. (2018) critically suggested that polyphenol gut microbiota metabolites could be considered either as well-known bioactives or as biomarkers regarding gut microbiota composition and functionality, which might be related to the potential response to dietary interventions.

In conclusion, it is becoming more and more important to understand the bioavailability, metabolism, and tissue distribution of dietary polyphenols to establish an association of their metabolites with their biological effects, rather than with the original dietary polyphenol counterparts.

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