

## REVIEW

# Polyphenols: A concise overview on the chemistry, occurrence, and human health

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This review gives an updated picture of each class of phenolic compounds and their properties. The most common classification implies the subdivision of phenolics in two main groups: flavonoids (e.g., anthocyanins, flavanols, flavanones, flavonols, flavonones, and isoflavones) and non-flavonoids (e.g., phenolic acids, xanthenes, stilbens, lignans, and tannins) polyphenols. The great interest in polyphenols is associated with their high potential application for food preservation and for therapeutic beneficial use. The relationship between polyphenol intake and human health has been exploited with special reference to cardiovascular diseases, hypertension, diabetes, metabolic syndrome, obesity, and cancer. The use of current existing databases of bioactive compounds including polyphenols is described as key tools for human health research.

## KEYWORDS

anthocyanins, cancer, flavonoids, Food Composition Databases, metabolic syndrome, phytoestrogens, polyphenol intake, proanthocyanidins, cardiovascular disease

## 1 | INTRODUCTION

Bioactive compounds are defined as compounds that occur in nature and are part of the food chain. They have the ability to interact with one or more compounds of the living tissue, by showing an effect on human health (Biesalski et al., 2009). The infinite combinations of functional groups, that is, hydroxyls, alcohols, aldehydes, alkyls, benzyl rings, and steroids, lead to a great diversity of plant compounds, each one with peculiar characteristics (Roessner & Beckles, 2009).

Within nutraceuticals (Andrew & Izzo, 2017; Daliu, Santini, & Novellino, 2019; Durazzo & Lucarini, 2018; Santini et al., 2018; Santini & Novellino, 2014; Santini & Novellino, 2018; Santini, Tenore, & Novellino, 2017), more than 8,000 different phenolics are identified in the plant kingdom and represent one of most numerous and widely distributed class of plant secondary metabolites (Cheynier, Comte, Davies, Lattanzio, & Martens, 2013; Kabera, Semana, Mussa, & He, 2014; Santini, Novellino, Armini, & Ritieni, 2013). Several outstanding reviews on polyphenols have been recently published (Amiot, Riva, & Vinet, 2016; Bernatoniene & Kopustinskiene, 2018; Białeck-

Florjańczyk, Fabiszewska, & Zieniuk, 2018; Clifford, Jaganath, Ludwig, & Crozier, 2017; Costa et al., 2017; Durazzo et al., 2018; Pervaiz, Songtao, Faghihi, Haider, & Fang, 2017; Roche et al., 2017; Xiao, Zhang, Tong, & Shi, 2018; H. Zhang & Tsao, 2016; Zhao et al., 2017), and the reader is referred to them for a more in-depth information. Here, we provide a concise introductory guide for the beginners in order to assist them in their initial entry into the chemistry and pharmacology of polyphenols. Specifically, we provide a concise overview on the chemistry and occurrence of the main classes of polyphenolic compounds as well as on the current evidence supporting (or not) an association between polyphenolic intake and the incidence of human chronic disease, with a special focus on cardiovascular diseases, metabolic syndrome (MetS), and cancer.

## 2 | PHENOLIC COMPOUNDS

Phenolics are own defined as compounds that possess an aromatic ring with at least one hydroxyl group, and their structure can vary

from simple molecule to complex polymer with high molecular weight (El Gharras, 2009). There is discordance concerning the way to classify them. The most adopted classification implies the subdivision of phenolics in two main groups: flavonoids and non-flavonoid polyphenols, and this classification has been commonly used in the literature (de la Rosa, Alvarez-Parrilla, & Gonzalez-Aguilar, 2010; Kabera et al., 2014).

## 2.1 | Phenolic acids—Hydroxycinnamic and hydroxybenzoic acids

Phenolic acids are non-flavonoid polyphenolic compounds present in foodstuffs and are characterized by a carboxyl group linked to benzene ring (Lafay & Gil-Izquierdo, 2008). They are derived from two main phenolic compounds, benzoic and cinnamic acids. Examples of hydroxybenzoic derivatives are gallic, p-hydroxybenzoic, vanillic, and syringic acids, whereas caffeic, ferulic, sinapic, and p-coumaric acids belong to hydroxycinnamic acids (Amarowicz et al., 2009; Proestos, Koutelidakis, Kapsokefalou, & Komaitis, 2011). It is worth mentioning the review of Khadem & Marles (2010) that remarked how the wide diversity of naturally occurring phenolic acids, at least 30 hydroxy- and polyhydroxybenzoic acids with biological activity, have been reported in the last 10 years. Recently, Roche et al. (2017) reported representative literature on the phytonutrients category of phenolic acids, with attention to the most prevalent ones, that is, gallic acid, tannic acid, and capsaicin. For example, ellagic acid, abundant in cranberries, strawberries, blueberries, and blackberries, has been shown to decrease blood pressure and high blood cholesterol, to exert antiinflammatory properties and even to reduce skin wrinkles from radiation. Another example is gallic acid, which can be found in tea, mango, rhubarb, and soy and which is known mainly for its antioxidant effect (Roche et al., 2017).

Fruits and vegetables are characterized mainly by the presence of free phenolic acids, whereas grains and derivatives by bound phenolic acids (Chandrasekara & Shahidi, 2010; D'Evoli et al., 2016; Dueñas et al., 2016; Stuper-Szablewska & Perkowski, 2017).

The hydroxycinnamic (Alam et al., 2016; El-Seedi et al., 2012) are present at high concentrations in many food products, including fruits (especially the red colored ones), vegetables, tea, cocoa, wine, tea leaves, coffee, and whole grains (El Gharras, 2009; El-Seedi et al., 2012; Santana-Gálvez, Cisneros-Zevallos, & Jacobo-Velázquez, 2017). Hydroxycinnamates can exist as monomers, dimers, or as (a) bound forms as ester (with hydroxy acids, mono/disaccharides, and polymers); (b) as amides (conjugated with mono- or polyamines, amino acids, or peptides). As instance, p-coumaric acid (4-hydroxycinnamic acid) (Pei, Ou, Huang, & Ou, 2016) is a phenolic acid that has low toxicity in mice ( $LD_{50} = 2,850 \text{ mg kg}^{-1}$  of body weight) and acts as a precursor of other phenolic compounds. It exists either in free or conjugated form in plants (Pei et al., 2016). Clifford et al. (2017) have reviewed nomenclature, quantification, characterisation by NMR and MS, biosynthesis, and role of chlorogenic acids and of acyl-quinic acids, with attention to coffee. Coffee is the major human

dietary source worldwide of acylquinic acids. Levels of total caffeoylquinic acids (including 3-caffeoylquinic acid A, 4-caffeoylquinic acid A, and 5-caffeoylquinic acid A) in espresso coffees purchased from 20 different coffee shops ranged from 24 to 423 mg (Romano et al., 2014; Santini et al., 2011).

In addition to hydroxycinnamic acids, phenolic compounds with C6–C3 carbon skeletons, also known as phenylpropanoids, includes curcuminoids, coumarins, and chromones. The most widely studied among the curcuminoids is curcumin (Tsuda, 2018). Curcumin, which represents by alone a constituent (up to ~5%) of the traditional olistic medicine, is known as turmeric (Nakmareong et al., 2011; Nelson et al., 2017). Curcumin exerts a number of pharmacological actions of potential therapeutic interest (Atkin, Katsiki, Derosa, Maffioli, & Sahebkar, 2017; Kocaadam & Şanlıer, 2017; Mantzourou, Pavlidou, Vasios, Tsagalioti, & Giaginis, 2018; Milani, Basirnejad, Shahbazi, & Bolhassani, 2017; Shen, Jiang, Yang, Wang, & Zhu, 2017; Soleimani, Sahebkar, & Hosseinzadeh, 2018), and it is extensively marketed worldwide as a nutraceutical (Santini & Novellino, 2017a). Starting from the first clinical trial published in *The Lancet* in 1937 (Oppenheimer, 1937), more than 1,200 clinical trials involving more than 6,000 subjects have been carried out, and many systematic reviews have been published (Kunnumakkara et al., 2017). A recent overview of systematic reviews identified 22 systematic reviews related to the clinical efficacy of curcumin-containing nutraceuticals that have been published (Pagano, Romano, Izzo, & Borrelli, 2018). On the basis of such analysis, there is evidence that curcumin might be useful for a number of health conditions including skin diseases, arthritis-related diseases, metabolic diseases and possibly—in a very preliminary fashion—depressive disorders, and ulcerative colitis (Pagano et al., 2018). Such collectively promising results should be interpreted with the due attention to the high risk of bias in many primary trials and to the low-moderate level of some analyses (Pagano et al., 2018).

Coumarin class of organic compounds consists of 1,2-benzopyrone ring system as a basic parent scaffold. Since the last few years, coumarins were synthesized in many of their derivative forms. On the other hand, coumarins are considered phytoalexins, because they are overaccumulated in plant tissues as a result of both pathogen attack and abiotic stresses. Their pharmacological properties are related to their substitution pattern (Venkata Sairam, Gurupadayya, Chandan, Nagesha, & Vishwanathan, 2016). The prototype of this class of molecules is coumarin, found in cinnamon and other plant, which can cause liver toxicity in several species, and it is considered a non-genotoxic carcinogen (Abraham, Wöhrlein, Lindtner, Heinemeyer, & Lampen, 2010). Coumarins are known for their anticoagulant effects. The observation of fatal hemorrhage in cattle eating mouldy sweet clover, as a result of impaired coagulation, led to the introduction in therapy of the anticoagulant drug dicoumarol, which is chemically related to warfarin (Andrew & Izzo, 2017). A Norwegian study has recently shown that children eating oatmeal porridge several times a week sprinkled with cinnamon could have a coumarin intake greatly exceeding the tolerable daily intake (Fotland, Paulsen, Sanner, Alexander, & Husøy, 2012). Similarly, adults drinking cinnamon-based

tea and consuming cinnamon supplements also can exceed the tolerable daily intake (Fotland, Paulsen, Sanner, Alexander, & Husøy, 2012).

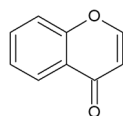
Among coumarins, auraptene, known also as 7-geranyloxycoumarin, is a natural prenyloxycoumarin present in plants of *Rutaceae* and *Apiaceae* families. Several biological activities such as antioxidant, anti-inflammatory, antibacterial, antifungal, and antigenotoxic are attributed to this compound (Genovese & Epifano, 2011).

Chromone is recognized as a privileged structure and a useful template for the design of novel compounds with potential pharmacological interest, particularly in the field of neurodegenerative, inflammatory, and infectious diseases as well as diabetes and cancer (Reis, Gaspar, Milhazes, & Borges, 2017). The chromone moiety (1,4-benzopyrone), shown in Figure 1, is the essential component of pharmacophores of a large number of bioactive molecules (Vanguru, Merugu, Garimella, & Laxminarayana, 2018). Khellin, found in the fruit of *Amni visnaga*, is a well-known chromone, formerly used as an antispasmodic drug. Efforts to find better drugs led to the chemical development and synthesis of sodium cromoglycate (Andrew & Izzo, 2017). The great interest in phenolic acids is associated with their high potential for food preservation and for therapeutic application (Białecka-Florjańczyk et al., 2018). Biological studies on hydroxycinnamic acids have been focused on their possible beneficial effects in neurodegenerative diseases, due to their anti-inflammatory, antioxidant, and neuroprotective actions (Zhang, Zhang, Ho, & Huang, 2019), as well as on endothelial functions, via attenuation of oxidative stress, improvement of nitric oxide bioavailability, and decrease of E-selectin, ICAM-1, and VCAM-1 expression (Fuentes & Palomo, 2014). Accordingly, association between phenolic acids intake and reduced blood pressure and triglycerides has been reported in observational studies (Grosso et al., 2018).

Hydroxybenzoic acids are known mainly due to their antioxidant properties with a potential in chronic diseases. Epidemiological studies have revealed inverse association between hydroxybenzoic acids intake and the risk of cardiovascular diseases and obesity (Guo et al., 2017; Tresserra-Rimbau et al., 2014a; Tresserra-Rimbau et al., 2014b).

## 2.2 | Flavonoids

Flavonoids are classified into the following subclasses: anthocyanins, flavanols, flavanones, flavonols, flavonones, and isoflavones (Amarowicz et al., 2009; Kabera et al., 2014; Kumar & Pandey, 2013). A wide range of pharmacological activities, including antioxidant, antibacterial, hepatoprotective, anti-inflammatory, and antihyperlipidemic effect, are attributed to flavonoids (Abenavoli et al., 2018; Azzini et al., 2016; Belwal, Nabavi, Nabavi, & Habtemariam, 2017; D'Evoli

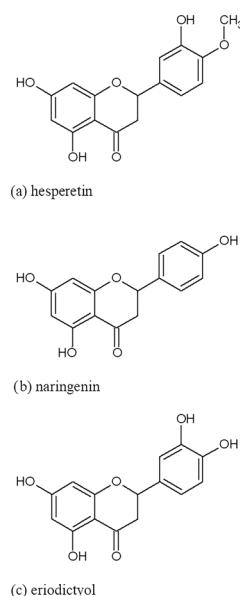


**FIGURE 1** The backbone structure of chromone

et al., 2013; Farhadi, Khameneh, Iranshahi, & Iranshahy, 2018; Farhat, Drummond, & Al-Dujaili, 2017; Iriti et al., 2017; Miccadei et al., 2008; Ninfali, Antonini, Frati, & Scarpa, 2017; Rasouli, Mohammad-Bagher Hosseini-Ghazvini, & Khodarahmi, 2018; Rees, Dodd, & Spencer, 2018; Riccio et al., 2018; Tungmunthum, Thongboonyou, Pholboon, & Yangsabai, 2018). The term flavonoid generally indicates a phenol compound having a phenylbenzopyran chemical structure with a carbon skeleton of a C<sub>6</sub>–C<sub>3</sub>–C<sub>6</sub> joined to a chroman ring (Pereira, Valentão, Pereira, & Andrade, 2009). In most of the cases, three or more –OH groups are linked to their backbone structure (Zhang & Tsao, 2016). Flavonoids can occur as aglycones or as conjugated to sugars and/or organic acids (Khoddami, Wilkes, & Roberts, 2013; Kumar & Pandey, 2013). Flavonoids derived from the aromatic amino acids, phenylalanine, and tyrosine are C<sub>15</sub> compounds arranged in three rings (C<sub>6</sub>–C<sub>3</sub>–C<sub>6</sub>) (Vermerris & Nicholson, 2008); the degree and pattern of hydroxylation, prenylation, alkalization, or glycosylation reactions modify the primary structure of the molecule (Khoddami et al., 2013). The substitution of chemical groups in the flavonoid structures is correlated to the corresponding biological and/or chemical properties and bioavailability (Cermak et al., 2009; Teng & Chen, 2019).

### 2.2.1 | Flavanones

Figure 2 shows the chemical structures of molecules belonging to flavanones, that is, hesperetin, naringenin, and eriodictyol. The work of Brahmachari (2008) describes more than 160 naturally occurring flavanones that belong to 36 plant families. Flavanones are present in vegetables, that is, tomato, potato (Durazzo et al., 2010), spices, that is, rosemary and peppermint (Bajkacz & Adamek, 2017), and particularly in fruits, that is, lemon, orange, strawberry, raspberry, and plum (W. Cao et al., 2015; Pavlović et al., 2013; Sablani et al., 2010). Khan, Huma, and Dangles (2014) showed that hesperetin (Figure 6a) and



**FIGURE 2** The chemical structures of (a) hesperetin, (b) naringenin, and (c) eriodictyol

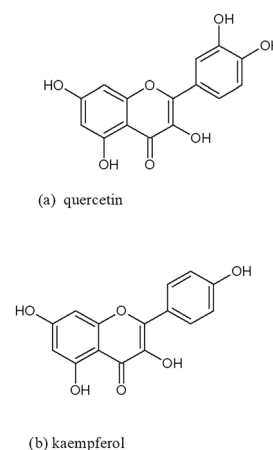
its derivatives are characteristic flavanones of sweet orange, tangelo, lemon, and lime, whereas naringenin (Figure 6b) and its derivatives are peculiar of grapefruit and sour orange. As instance, in citrus fruit, Barreca et al. (2017) reported quantities ranging from ~180 to 740 mg/L of this compound. The recent study of Barbosa, Ruviano, and Macedo (2018) is addressed on the comparison of different Brazilian citrus by-products as source of natural antioxidants, with focus on profile of flavanones: nine polyphenols were detected in the studied by-products, and hesperidin was the main compound found in the residues of citrus by-products after juice processing.

Flavanones intake has been associated with a reduced risk of diabetes and obesity (Adriouch et al., 2018; Tresserra-Rimbau et al., 2016). Naringenin, that is, the aglycone of naringin, is one of the best studied among the flavanones. It is mainly found in *Citrus* fruits, and a number of papers has highlighted its potential use in health conditions such as oxidative stress, inflammation, neurological disorders, and particularly cardiovascular/metabolic diseases (Salehi, Fokou, et al., 2019; Zeng, Jin, Zhang, Zhang, & Liang, 2018). The daily mean intake of naringenin has been estimated to be 58.1 mg (Ranka et al., 2008). Studies have been performed in hypercholesterolemic and overweight patients, with a dosage ranging between 600 and 800  $\mu$ M/day (Salehi, Fokou, et al., 2019). Naringenin decreases low density lipoproteins and triglycerides, increases high density lipoproteins, and inhibits glucose uptake. At a molecular level, it suppresses protein oxidation and macrophage inflammation, protects against intercellular adhesion molecule-1 (ICAM-1), inhibits leukotriene B<sub>4</sub>, monocyte adhesion, and foam cell formation (Orhan et al., 2015).

## 2.2.2 | Flavonols

Flavonols are reported to be present in onions, apples, persimmon, saffron, berries, broccoli, lettuce, tea, and red wine (Bataglion, da Silva, Eberlin, & Koolen, 2015; Durazzo et al., 2014; Hoffmann-Ribani, Huber, & Rodriguez-Amaya, 2009; Sultana & Anwar, 2008; Valavanidis, Vlachogianni, Psomas, Zovoili, & Siatis, 2009). A meta-analysis of epidemiologic studies has shown that the intake of flavonols may reduce the risk of type-2 diabetes (Rienks, Barbaresko, Oluwagbemigun, Schmid, & Nöthlings, 2018). Quercetin and kaempferol are the main representative molecules (Figure 3). A recent work has described the role of quercetin exploiting the previous published papers on the effect of quercetin (Hirpara, Aggarwal, Mukherjee, Joshi, & Burman, 2009; L. Li, Zhang, & Du, 2018; Miltonprabu et al., 2017; Oboh, Ademosun, & Ogunsuyi, 2016; Rauf et al., 2018), and (Calderón-Montaña, Burgos-Morón, Pérez-Guerrero, & López-Lázaro, 2011; A. Y. Chen & Chen, 2013; Devi et al., 2015; Imran et al., 2019) against several chronic diseases.

Quercetin is mainly found in onions, apples, and berries; it has attracted researchers' attention for its activity against cancer prevention, chronic inflammation, and cardiovascular diseases. The estimated mean intakes of quercetin is 29.4 mg per day (Ranka et al., 2008). Evidence suggests that quercetin negatively regulates key signaling pathways associated with life-threatening diseases, such as NF- $\kappa$ B, MAPK, PI3K-AKT, and mTOR. In addition, several patents have been

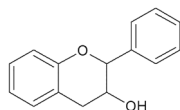


**FIGURE 3** The chemical structures of (a) quercetin and (b) kaempferol

recently reported on quercetin derivatives for wide therapeutic applications such as anticancer, antiaging, and as anti-inflammatory agent (Sharma, Kashyap, Sak, Tuli, & Sharma, 2018). Quercetin is also marketed as a dietary supplement, and it is suggested to be assumed a dose up to 1,000 mg/daily, an amount that exceeds the usual dietary intake levels (Andres et al., 2018). A recent meta-analysis of placebo-controlled randomized controlled trials showed a statistically significant effect of quercetin supplementation in the reduction of blood pressure, possibly at a dose higher than 500 mg/day (Serban et al., 2016). A further meta-analysis of RCTs did not suggest any clinically relevant effect of quercetin supplementation on plasma lipids, apart from a significant reduction of triglycerides at doses above 50 mg/day (Sahebkar, 2017). Finally, there is clinical evidence that quercetin provides benefits in human endurance exercise capacity and endurance exercise performance (Kressler, Millard-Stafford, & Warren, 2011). The antioxidant and anti-inflammatory actions of quercetin (Chen, Jiang, Wu, & Fang, 2016) may play a role in such clinical effect. Kaempferol is a natural flavonol present in different edible plants (e.g., tea, broccoli, cabbage, kale, beans, endive, leek, tomato, strawberries, and grapes). It has been described to possess anti-inflammatory, anticancer, and notably cardiovascular protective properties (Devi et al., 2015; Rajendran et al., 2014). A prospective American study aiming at investigating the effect of flavonols and flavones on coronary heart disease risk showed protective effect in women associated with the highest kaempferol intake. The lower risk associated with kaempferol intake was probably due to broccoli consumption (Lin, Gong, Song, & Cui, 2017). Similarly, kaempferol intake has been associated to the reduction of acute coronary syndrome (Rienks, Barbaresko, & Nöthlings, 2017).

## 2.2.3 | Flavanols

Epicatechin, and catechins belong to subgroup of monomeric flavanols. The backbone structure of this catechins subclass is shown in Figure 4. The name catechin derived from the term *catechu*, the extract of *Acacia catechu* L. (Braicu, Lodomery, Chedea, Irimie, & Berindan-Neagoe, 2013). The chemical structure is constituted by a



**FIGURE 4** The structure backbone of catechins subclass

3,3',4,5,7-pentahydroxyflavone with two steric forms of (+)-catechin and its enantiomer (Bernatoniene & Kopustinskiene, 2018). Flavanols can form gallic acid conjugates such as epicatechin gallate, epigallocatechin, and epigallocatechin gallate (Braicu et al., 2013; Rosen, 2012).

Catechins are major polyphenols in tea and have been related to the health beneficial health effects of tea (Annunziata et al., 2018; Zhang et al., 2019; Zhang, Tang, & Row, 2014). Epigallocatechin-3-gallate (EGCG) is abundant in tea (Lambert et al., 2003), whose consumption has been correlated with a low incidence of chronic cardiovascular disease and cancer (Peluso & Serafini, 2017). Recently, a unique O-methylated catechin, namely, the (-)-epigallocatechin 3-O-(3-O-methyl) gallate (EGCG3Me), has been identified in green and oolong tea varieties (Zhang et al., 2019). Cocoa-based products, that is, chocolate, are rich catechin and epicatechin (Kofink, Papagiannopoulos, & Galensa, 2007; Rodríguez-Carrasco, Gaspari, Graziani, Santini, & Ritieni, 2018).

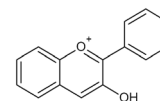
Other sources are fruits, such as grapes and blackberries, apples, or nuts like beans, almond, pistachos, and red wine (Bhagwat, Haytowitz, & Holden, 2014; Cassino, Tsolakis, Bonello, Gianotti, & Osella, 2019; Gadkari & Balaraman, 2015; Harnly et al., 2006; Martinez et al., 2016).

Cocoa and chocolate flavanols have attracted clinical attention for the prevention of cardiovascular and metabolic diseases. A systematic review and meta-analysis of RCTs, which included 19 RCTs for a total of 1,131 participants showed that cocoa flavanol intake had favorable effects on select cardiometabolic biomarkers among adults (Lin et al., 2016). A meta-analysis of ten RCTs comprising 297 individuals showed the blood pressure-lowering ability of flavanol-rich cocoa products (Desch et al., 2010). Such results have been confirmed by a more recent Cochrane review, which, on the basis of 35 randomized clinical trials, provided moderate-quality evidence that short-term intake of flavanol-rich chocolate and cocoa products cause a small (2 mmHg) blood pressure-lowering effect in healthy adults (Ried, Fakler, & Stocks, 2017).

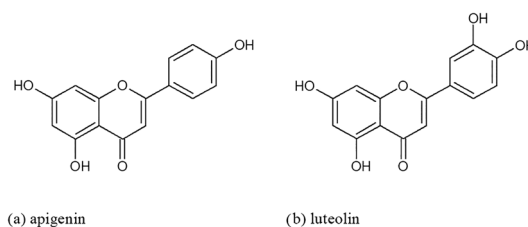
The anti-obesity potential of flavanols has been also explored. A meta-analysis based on 58 controlled clinical trials demonstrated that flavanol intake decreased body mass index and waist circumference (Akhlaghi, Ghobadi, Mohammad Hosseini, Gholami, & Mohammadian, 2018). Finally, a systematic review based on 13 clinical trials concluded that "cocoa flavanols intake may improve vascular function, reduce exercise-induced oxidative stress, and alter fat and carbohydrate utilization during exercise, but without affecting exercise performance" (Decroix, Soares, Meeusen, Heyman, & Tonoli, 2018).

## 2.2.4 | Anthocyanins

Anthocyanins (named from the Greek *anthos*, flower and *kyáneos*, blue), are shown in Figure 5. They are water-soluble flavonoids



**FIGURE 5** The structure backbone of anthocyanins



**FIGURE 6** The chemical structures of (a) apigenin and (b) luteolin

responsible for the color of fruits and flowers, which varies from red-orange to blue-violet. The basic structural unit of anthocyanins is the flavylium ion (2-phenylchromenylium; Pascual-Theresa & Sanchez-Ballesta, 2008; Pervaiz et al., 2017). Most of the anthocyanins occur as acylated by organic acids (p-coumaric, sinapic, caffeic, ferulic, or sinapic acids) via ester bonds (Zhao et al., 2017). The common anthocyanins are cyanidin, delphinidin, malvidin, and peonidin. Black currants, red raspberry, elderberries, chokeberries, or strawberry, plums, pomegranates, blood orange, beans, cabbage, and red onions, are examples of anthocyanins sources (Albuquerque, Silva, Oliveira, & Costa, 2018; Weber & Larsen, 2017).

Anthocyanin clinical research has explored their possible relevance in cardiovascular diseases and complications, cognitive outcomes, and cancer. Promising, although not compelling clinical data, based on systematic review and meta-analysis, seem to suggest that anthocyanin supplementation may positively affect cholesterol and lipoprotein metabolism in patients with dyslipidaemia (Liu, Sun, Lu, & Bo, 2016; Wallace, Slavin, & Frankenfeld, 2016). Inhibition of lipid and glucose absorption from the gut, increase of cholesterol fecal excretion, and inhibition of cholesterol synthesis are the potential mechanisms involved. Also, a systematic review and meta-analysis of a prospective cohort studies has recently shown an inverse correlation between dietary intake of anthocyanins and risk of type-2 diabetes mellitus (Guo, Yang, Tan, Jiang, & Li, 2016). The antioxidant and anti-inflammatory effects of anthocyanins are believed to be relevant for retarding the progression of type-2 diabetes (Liobikas, Skemiene, Trumbeckaite, & Borutaite, 2016; Smeriglio, Barreca, Bellocco, & Trombetta, 2016). More recently, a meta-analysis suggested a correlation between intake of dietary anthocyanins and reduced risk cardiovascular disease mortality (Kimble, Keane, Lodge, & Howatson, 2018).

Robust preclinical evidence supports a beneficial role for anthocyanins in cognitive functions (Spencer, 2010). A recent systematic review, which included acute trials ( $n = 4$ ) and longer term ( $n = 3$ ) interventions that assessed multiple cognitive outcomes in



subjects with cognitive impairment found improvements in six of seven studies retrieved after anthocyanin-rich food consumption. Improvements of the cognitive outcomes included verbal learning and memory after anthocyanin-rich food consumption (Kent, Charlton, Netzel, & Fanning, 2017).

Finally, although anthocyanins experimentally inhibit cell growth, induce cell cycle arrest, stimulate apoptosis (or autophagy), and exerts anti-invasion and anti-metastatic actions, there are conflicting clinical results concerning the possible intake of anthocyanins and cancer prevention in humans (B. W. Lin et al., 2017).

### 2.2.5 | Flavones

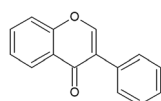
The basic chemical structure of flavones consists of two benzene rings linked through a heterocyclic pyrone ring and the main flavones found in foods, luteolin, and apigenin (Figure 6). They are mainly present in their glycoside forms. Recently, Hostetler, Ralston, and Schwartz (2017) summarized, on the basis of existing studies, the concentration of flavones in teas and dry herbs, in juices and wines, in fruits, vegetables, olive oil, and honey. As instance, for wheat grain apigenin-c-glycosides, a value of 2.1-mg/100-g dry weight has been observed (Wijaya & Mares, 2012) and for black olives values of 6.5 and in the range 3.2–17.5-mg/100-g fresh weight for apigenin and luteolin, respectively (Bhagwat et al., 2014; Owen et al., 2003).

Examples of food sources are acerola, apricot, cashew, bean, cabbage, cardon, dandelion, apple, artichoke, mango, papaya, and onion (Bataglion et al., 2015; Colla et al., 2013; Hussain et al., 2013; Siriamornpun & Kaewseejan, 2017). There is evidence that dietary flavones intake may help reduce weight gain over time in population (Adriouch et al., 2018). Furthermore, a systematic review of epidemiological studies retrieved a cohort study in which a significant reduction between ovarian cancer incidence and kaempferol and luteolin intake was observed (Mohammadi, Dehghani, Larijani, & Azadbakht, 2016).

Health-promoting and therapeutic beneficial effects, that is, on diabetes, amnesia, Alzheimer's disease, depression, insomnia, and cancer related to apigenin have been recently reported with reference to in vivo research, chemistry, and nutraceutical features (Salehi, Venditti, et al., 2019).

### 2.2.6 | Isoflavones

Isoflavones, shown in Figure 7, are biologically active compounds with estrogenic properties and often referred as phytoestrogen (Anandhi Senthilkumar, Fata, & Kennelly, 2018; Xiao et al., 2018; Zaheer & Humayoun Akhtar, 2017). The main representative components are genistein, daidzein, biochanin A, and glycitein.



**FIGURE 7** The structure backbone of isoflavones subclass

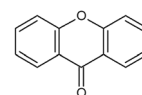
Isoflavones are found almost exclusively in the leguminous family of plants. Other sources are reported in apple, apricot, blackcurrant, cherry, cabbage, sweet potato, plum, date, onion, wheat, and melon pineapple (Abrankó, Nagy, Szilvássy, Stefanovits-Bányai, & Hegedus, 2015; Bustamante-Rangel, Delgado-Zamarreño, Pérez-Martín, Rodríguez-Gonzalo, & Domínguez-Álvarez, 2018; Konar, Poyrazoglu, Demir, & Artik, 2012; Kuhnle et al., 2009). Isoflavone-containing preparations are promoted for alleviating menopausal symptoms. Accordingly, a systematic reviews and meta-analysis of the clinical data have been recently published on the potential beneficial effects of phytoestrogens on menopause and cancer prevention (Andrew & Izzo, 2017). A systematic review and meta-analysis of clinical trials recently observed that specific phytoestrogen supplementation is associated with modest reductions of some menopausal symptoms such as hot flashes and vaginal dryness (Franco et al., 2016). There is also some evidence that phytoestrogens intake might exert cancer chemopreventive effects. A systematic review of observational data concluded that, despite some shortcomings, soy consumption consistent with a traditional Japanese diet, could reduce the risk of breast cancer incidence and recurrence (Fritz et al., 2013). A similar protective trend has been observed for prostate cancer risk reduction, although a firm conclusion cannot be drawn, given the size (number of patients) and duration of the individual trials (van Die, Bone, Williams, & Pirotta, 2014).

In summary, the available evidences suggest that phytoestrogens may have a beneficial effect—although modest—on menopausal symptoms. Nonetheless, there is preliminary evidence that phytoestrogen intake could reduce the incidence of prostate and breast cancer.

### 2.3 | Xanthon, stilbens, lignans, and tannins

Xanthon, stilbenes, lignans, and tannins belong to non-flavonoids phenolic compounds (Durazzo, Lucarini, et al., 2018; González-Laredo, Rocha-Guzmán, Gallegos-Infante, Moreno-Jiménez, & Gómez, 2018; Gutiérrez-Grijalva, Ambriz-Pérez, Leyva-López, Castillo-López, & Heredia, 2016; Kabera et al., 2014). They are compounds with at least two aromatic rings in the structure, whereas only tannins have more aromatic rings.

Xanthon, whose chemical structure is shown in Figure 8, are very stable molecules; they comprise a family of O-heterocycle symmetrical compounds with a dibenzo-γ-pyrone scaffold and are known as xanthone, xanthene-9-one, or dibenzo-γ-pyrone (Negi, Bisht, Singh, Rawat, & Joshi, 2013). They have recently received more attention from food (Li, Thomas, & Johnson, 2013) and pharmaceutical industries, involved in drug development because of their chemical structure, which allows them to interact with different drug targets (Gutierrez-Orozco & Failla, 2013).



**FIGURE 8** The structure backbone of xanthon subclass

The principal natural sources of xanthenes are the mangosteen fruit (*Garcinia mangostana* L.) and the mango fruit (*Mangifera indica* L.) (Gutierrez-Orozco & Failla, 2013).

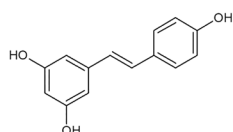
Their distinctive tricyclic aromatic ring exhibits a wide range of physiological properties and a protective potential as anticancer, antibacterial, anti-inflammatory, and antidiabetic (Li et al., 2013; Miura et al., 2001; Wezeman, Brase, & Masters, 2015; Yasunaka et al., 2005).

The basic chemical structure of stilbenes (González-Laredo et al., 2018) consists into two benzene rings linked by a double bond, the E isomer being the most common configuration.

Stilbenes are reported to be present in grapes, almond, bean, blueberries, bilberries, peanuts, grapevine, cranberries, mulberries, plum, and wine (Arraki et al., 2017; Błaszczuk, Sady, & Sielicka, 2019; Chang, Alasalvar, Bolling, & Shahidi, 2017; Hassan, Saleh, & AbdElgawad, 2018; Shrikanta, Kumar, & Govindaswamy, 2015). The recent review of El Khawand, Courtois, Valls, Richard, and Krisa (2018) remarked how stilbenes present a high diversity in their phenolic structures (various chemical substituents and polymerization), which is a determining factor for their absorption and metabolism rates (El Khawand et al., 2018). The review of Reinisalo, Kärund, Koskela, Kaamiranta, and Karjalainen (2015) summarized studies on the molecular mechanisms involved in the stilbene-mediated protection against oxidative stress in age-related diseases; the Nrf2/ARE pathway and cAMP second messenger system together are the key regulators of cellular antioxidant defence. Stilbenes can activate nuclear localization of Nrf2 and activation of Nrf2 target genes associated with antioxidant defence and autophagy (Reinisalo et al., 2015).

Stilbenes intake has been associated to a reduced all-cause mortality (Tresserra-Rimbau et al., 2014a) as well as to a reduced the risk of hypertension onset (Miranda, Steluti, Fisberg, & Marchioni, 2016), diabetes (Tresserra-Rimbau et al., 2016), and obesity (Grosso et al., 2017; Grosso et al., 2018). The most known and studied among stilbenes is resveratrol, shown in Figure 9 (Annunziata, Tenore, & Novellino, 2018; Koushki, Amiri-Dashatan, Ahmadi, Abbaszadeh, & Rezaei-Tavirani, 2018; Ramírez-Garza et al., 2018; Tabeshpour, Mehri, Shaebani Behbahani, & Hosseinzadeh, 2018). Although resveratrol exerts cardioprotective effects, a recent meta-analysis of available RCTs does not suggest any benefit of its supplementation on cardiovascular risk factors (Sahebkar et al., 2015). However, a further meta-analysis of 36 RCTs demonstrated that resveratrol intake significantly reduced weight, body mass index, WC, and fat mass and significantly increased lean mass (Tabrizi et al., 2018).

Lignans are diphenolic compounds derived from the combination of two phenylpropanoid C6-C3 units at the  $\beta$  and  $\beta'$  carbon atoms and can be linked to additional ether, lactone, or carbon bonds; they have a 1,4-diarylbutan like chemical structure (Lewis & Davin, 1999)



**FIGURE 9** The chemical structure of resveratrol

and are derived from the shikimic acid biosynthetic pathway (Imai, Nomura, & Fukushima, 2006). Lignans are vascular plant secondary metabolites, with widespread occurrence in the plant kingdom and to which are attributed a wide range of physiological properties, positively influencing human health (Durazzo, 2018a). As reported by Durazzo, Lucarini, et al. (2018), in a review on the occurrence of lignans in food groups, which also summarizes the main national databases of lignans, the main sources of dietary lignans are oilseeds (i.e., flax, soy, rapeseed, and sesame), whole-grain cereals (i.e., wheat, oats, rye, and barley), legumes, various vegetables, and fruit (particularly berries), as well as beverages, such as coffee, tea, and wine, and, recently, lignans are also reported in dairy products, meat, and fish. The main dietary lignans are secoisolariciresinol, matairesinol, lariciresinol, pinoresinol, medioresinol, and syringaresinol (shown in Figure 10).

The intake of lignans has been mostly related to their possible cancer chemopreventive actions (due to their phytoestrogen properties) and in the prevention of cardiovascular diseases (Anandhi Senthilkumar et al., 2018; Xiao et al., 2018).

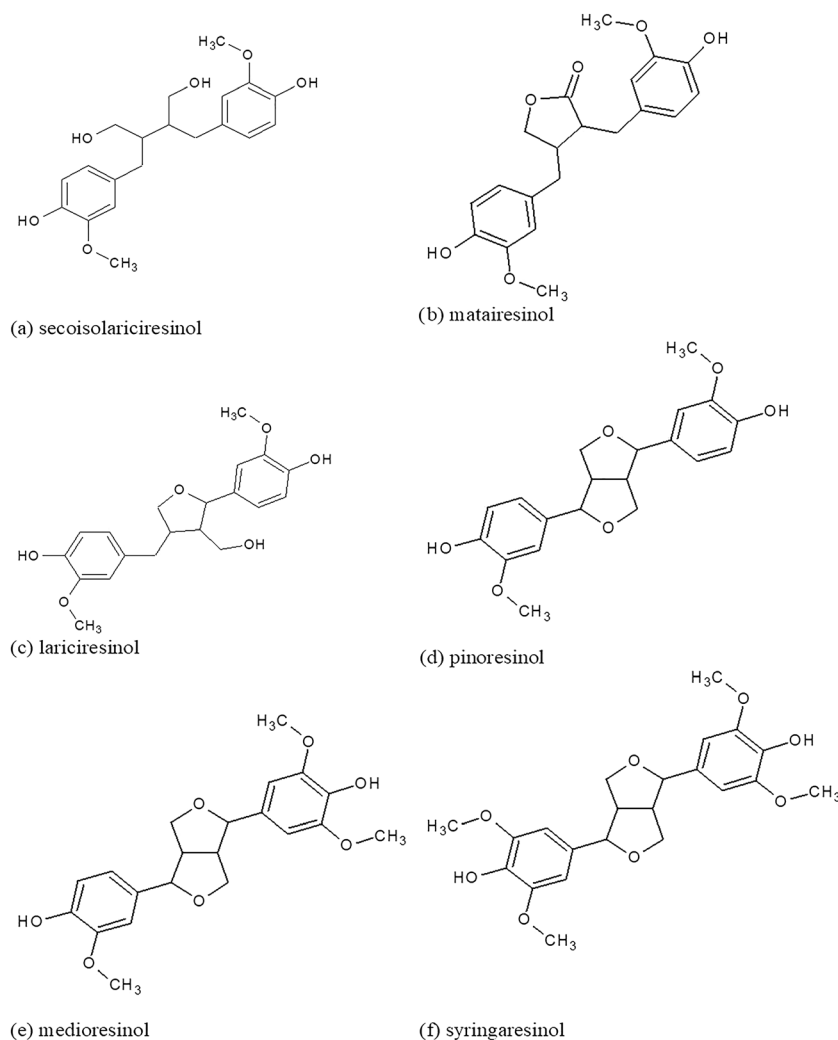
A meta-analysis, which included 21 studies (11 prospective cohort studies and 10 case-control studies), found that high lignan exposure may be associated with a reduced breast cancer risk in postmenopausal women (Buck, Zaineddin, Vrieling, Linseisen, & Chang-Claude, 2010). However, a further and more recent meta-analysis of 143 of prospective supports the need for a more conservative evaluation of the clinical aspects (Grosso et al., 2017).

A study aiming at examining total and individual lignan intakes in 2,599 postmenopausal women found that total and individual lignan intake (i.e., matairesinol, pinoresinol, and secoisolariciresinol) were not associated with the prevalence of cardiovascular diseases and its risk factors, whereas the intake of lariciresinol was linked to a reduced hypercholesterolemia (Witkowska et al., 2018).

Also, a meta-analysis assessed the association between dietary flavonoid and lignan intake with all-cause and cardiovascular disease mortality in prospective cohort studies. As a result, only limited evidence for lignans intake and all-cause mortality was evidenced (Grosso et al., 2017).

Tannins are classified into two major groups: hydrolyzable and non-hydrolyzable tannins, also called condensed tannins or proanthocyanidins (Durazzo, 2018b; Kabera et al., 2014; Smeriglio, Barreca, Bellocchio, & Trombetta, 2017). Proanthocyanidins, namely, condensed tannins, are oligomers and polymers consisting from two to more than 200 monomers of flavan-3-ol units (M. H. Chen, McClung, & Bergman, 2016; Serrano, Puupponen-Pimiä, Dauer, Aura, & Saura-Calixto, 2009). Hydrolyzable tannins are further categorized into gallotannins and ellagitannins (Arapitsas, 2012; Jakobek, 2015). As instance, numerous studies are present on biological and biomedical functions of penta-O-galloyl-D-glucose and its derivatives (Cao et al., 2014; Zhang, Li, Kim, Hagerman, & Lü, 2009). Another study of Ma et al. (2015) showed how the hydrolyzable gallotannin, penta-O-galloyl- $\beta$ -D-glucopyranoside, inhibits the formation of advanced glycation endproducts by protecting the protein structure.

Tannins can also be divided, according to their constitutive monomers and chemical structures, into four groups: proanthocyanidins,



**FIGURE 10** The chemical structures of main dietary lignans, (a) secoisolariciresinol, (b) matairesinol, (c) lariciresinol, (d) pinoresinol, (e) medioresinol, (f) syringaresinol

hydrolyzable tannins, phlorotannins, and complex tannins (Serrano et al., 2009). Phlorotannins are oligomers, or polymers of phloroglucinol (1,3,5-trihydroxybenzene), that are produced by brown algae (*Phaeophyceae*; Corona et al., 2016; Leyton et al., 2016). They consist in subgroups: fualos and phlorethols (ether linkage), fucols (phenyl linkage), fucophlorethols (ether and phenyl linkage), eckols, and carmalols (dibenzodioxin linkage; Corona et al., 2016).

Complex tannins present a complex structural of different groups as examples gallotannin or ellagitannin units linked to catechin or epicatechin (Serrano et al., 2009).

Tannins are reported to be constituent of legumes such as beans (Boudjou, Oomah, Zaidi, & Hosseinian, 2013; Campos-Vega et al., 2009; Chen et al., 2018), fruits, particularly berries (Fischer, Jaksch, Carle, & Kammerer, 2013; Hellström & Mattila, 2008; Kalili, Vestner, Stander, & de Villiers, 2013), and nuts (Bittner, Rzeppa, & Humpf, 2013).

Dietary supplements containing proanthocyanidins include cranberry juice (*Vaccinium macrocarpon*), a top-selling herbal supplement used for the prevention of urinary tract infections, pine bark (*Pinus pinaster*, *subsp. atlantica*) extracts, marketed for preventing/treating a wide range of chronic conditions without compelling evidence of efficacy (Andrew & Izzo, 2017), and grape (*Vitis vinifera*) seeds, which,

based on a meta-analysis of nine small randomized clinical trials ( $n = 390$  patients in total), appeared to lower heart rate and systolic blood pressure (Feringa, Laskey, Dickson, & Coleman, 2011).

An Italian case-control study, including a total of 1,294 case studies, showed that proanthocyanidin consumption was inversely associated to prostate cancer risk (Praud et al., 2018). Also, in a population of 948 women aged over 75 years, proanthocyanidin intake was associated with better renal function and reduced renal associated events (Ivey et al., 2013).

### 3 | POLYPHENOL INTAKE AND HUMAN HEALTH

#### 3.1 | Cardiovascular diseases

Cardiovascular diseases, including coronary artery diseases, stroke, heart failure, and hypertension, are the first cause of death in Western countries. A large number of naturally occurring compounds and foods are promoted for the prevention of such diseases (Allawadhi, Khurana, Sayed, Kumari, & Godugu, 2018; Tapsell, Neale, & Probst, 2019).



Accordingly, a number of observational and intervention studies has explored the possible association between the intake of polyphenol-rich foods (e.g., beverages such as cocoa, fruit and vegetables, tea, extra virgin/virgin olive oil, and wine) and cardiovascular diseases.

In a 7,447 participants, parallel group, randomized, multicenter, controlled 5-year feeding trial, Tresserra-Rimbau et al. (2014a) showed a 37% relative reduction in all-cause mortality comparing the highest with the lowest quintiles of total polyphenol intake (Tresserra-Rimbau et al., 2014a; Tresserra-Rimbau et al., 2014b). Among the polyphenol subclasses, stilbenes and lignans were significantly associated with reduced all-cause mortality (Tresserra-Rimbau et al., 2014a). Similarly, a population-based cohort-study, which included 807 men and women aged 65 years and older, from the Italian Chianti region of Tuscany (Italy), suggested that an high dietary intake of polyphenols in the diet may be associated with longevity (Tresserra-Rimbau et al., 2013).

An observational study assessing the association between intakes of total polyphenol and polyphenol subgroups and the risk of major cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes) revealed a 46% reduction of cardiovascular diseases risk comparing the population with the highest intake of polyphenols versus the population with the lowest intake. The polyphenols with the strongest inverse associations were flavanols, lignans, and hydroxybenzoic acids (Tresserra-Rimbau et al., 2014b).

### 3.2 | Inflammatory cardiovascular risk

Medina-Remón et al. (2017) found that an increase in polyphenol intake, measured as urinary total polyphenol excretion, was associated to decreased inflammatory biomarkers (i.e., vascular cell adhesion molecule, intercellular adhesion molecule, interleukin, tumor necrosis factor alpha, and monocyte chemotactic protein). Furthermore, high polyphenol intake reduced cardiovascular risk factors, with a positive effect on blood pressure and lipid profile (Medina-Remón et al., 2017).

In summary, clinical evidence suggests that polyphenols intake may reduce the risk of cardiovascular diseases. Although it is not completely clear how polyphenols exerts their protective effects, it is believed that modulation of nitric oxide production and induction of antioxidant defences may play an important role (Costa et al., 2017).

### 3.3 | Hypertension

High blood pressure is the major risk factor for cardiovascular diseases. Consumption of polyphenol-rich food has been associated with an improvement in endothelial function via the NO-cGMP pathway and ACE inhibition (Hügel, Jackson, May, Zhang, & Xue, 2016).

A cross-sectional study of 589 elderly at high cardiovascular risk revealed an inverse association between urinary total polyphenol excretion and the prevalence of hypertension. Specifically, participants in the highest quartile of urinary total polyphenol excretion had a reduced prevalence of hypertension compared with those in the lowest quartile (Medina-Remon et al., 2011). An analysis of individual subclasses of polyphenols revealed an inverse association between the

highest tertile of tyrosols, alkylphenols, lignans, and stilbene and hypertension in a general Brazilian population (Miranda et al., 2016). A meta-analysis specifically focused on grape polyphenols showed, on the basis of ten retrieved studies, that daily grape polyphenol consumption reduced systolic blood pressure by 1.48 mmHg when compared with control participants. Diastolic blood pressure was unmodified (Li, Zhao, Tian, Chen, & Cui, 2015).

There is also clinical evidence that gender may influence the beneficial properties of polyphenols (Bacchetti, Turco, Urbano, Morresi, & Ferretti, 2018). Grosso et al. (2018) found that subjects with the highest quartile of total polyphenol consumption have a 31% decreased risk of hypertension compared with the lowest intake in women, but this has not been observed in men. Associations were found also with hydroxycinnamic acids and flavanols intake (Grosso et al., 2018).

Finally, a randomized study in which subjects were randomized to receive either a low-polyphenol diet for 8 weeks or to consume a high-polyphenol diet (based on the intake of fruits, vegetables, berries, and dark chocolate) showed that increasing the dietary polyphenol intake caused a significant improvement in microvascular function in hypertensive participants (Noad et al., 2016).

### 3.4 | Diabetes

There is evidence that high intake of polyphenols may reduce the risk of diabetes. Tresserra-Rimbau et al. (2016) prospectively examined the associations between the intake of polyphenols on the risk of incident diabetes in an observational cohort analysis including 18,900 non-diabetic elderly at high risk of cardiovascular disease. It was observed a 28% reduction in new-onset diabetes in the highest compared with the lowest tertile of total polyphenol intake. Among polyphenol subclasses, stilbenes and flavanones intake was associated with a reduced risk (Tresserra-Rimbau et al., 2016).

Recently, a meta-analysis of 18 prospective epidemiologic studies, which investigated the association between polyphenols (51 different compounds in total) and type 2 diabetes, revealed inverse associations for intakes of different subclasses and individual polyphenols, including flavonoids, flavanols, flavan-3-ols, catechins, anthocyanidins, isoflavones, daidzein, genistein, and stilbenes (Rienks et al., 2018).

### 3.5 | MetS and obesity

MetS is a clustering of metabolic abnormalities that may include hypertension, central obesity, insulin resistance, hypertension, and dyslipidemia. It is strongly associated with an increased risk for developing cardiovascular diseases and type-2 diabetes. Management of MetS includes lifestyle modifications, pharmacotherapy, and a nutraceutical approach (Finicelli et al., 2019; Rochlani, Pothineni, Kovelamudi, & Mehta, 2017; Santini et al., 2017; Santini & Novellino, 2017b).

Evidence regarding the effectiveness of polyphenols in preventing or delaying the physiopathological components accountable for MetS onset has been provided (Amiot et al., 2016; Finicelli et al., 2019). In an

observational Iranian study, higher intake of flavonoids—but not total polyphenol intake and other subclasses of polyphenol—was inversely associated with risk of developing MetS and hypertriglyceridemia (Sohrab et al., 2018). Furthermore, a cohort study cross-sectional population-based survey including 8,821 adults in Eastern Europe found that dietary polyphenols intake was inversely associated with MetS and its effects such as waist circumference, blood pressure, high lipoprotein cholesterol, and triglycerides in women. It was found also to be associated with fasting plasma glucose in both genders (Grosso et al., 2018). Among polyphenol subclasses, phenolic acids have been associated with blood pressure and triglycerides, whereas phenolic acids and stilbenes with MetS. Flavonoids have been related with fasting plasma glucose and lignans and stilbenes with waist circumference. Hydroxycinnamic acids, flavanols, and dihydrochalcones had the most prominent effect (Grosso et al., 2018).

Adriouch et al. (2018) provided evidence that dietary polyphenol consumption might have favorable effect on weight gain in the general population over a 6-year period of time (Adriouch et al., 2018). Waist circumference and body mass index were differently affected by the diverse polyphenol subclasses. Specifically, flavanones, flavones and lignans intake resulted in less notable increase in body mass index; flavanones, flavones, hydroxycinnamic acids, and lignans intake was associated to a less notable increase in waist circumference (Adriouch et al., 2018). A cross-sectional study was performed with 573 participants at high cardiovascular risk; after 5-year follow-up, significant inverse correlation between total urinary polyphenol excretion and body weight, body mass index, waist circumference, and waist-to-height ratio was observed (Guo et al., 2017).

Finally, a systematic review of 19 randomized controlled trials concluded that further research is required before suggesting a role of polyphenol intake in reducing weight in overweight and obese individuals. Only nine out of 19 trials studies showed a significant decrease in weight (Farhat et al., 2017). Further larger trials with a duration of 12 months or more are needed to elucidate the effect of polyphenols on body weight status.

### 3.6 | Cancer

Most naturally occurring ingredients with consistently reported anticancer efficacy contains high levels of polyphenols (Oyenihi & Smith, 2019; Tariq et al., 2017). Polyphenols have demonstrated chemopreventive efficacy against experimental tumors, via anti-initiating, anti-promoting, anti-progression, and anti-angiogenesis actions, as well as by modulating the immune system (Asadi-Samani, Bagheri, Rafieian-Kopaei, & Shirzad, 2017; Erices, Torres, Niechi, Bernales, & Quezada, 2018; Mileo & Miccadei, 2016; Rengasamy et al., 2019; Salehi et al., 2018; Xing, Zhang, Qi, Tsao, & Mine, 2019).

Also, polyphenol anticancer actions involve redox changes, modulation of enzymes, and signaling kinases resulting to effects on multiple genes and cell signaling pathways (Maru, Hudlikar, Kumar, Gandhi, & Mahimkar, 2016; Mileo & Miccadei, 2016). Despite encouraging experimental data, clinical results have not provided univocal

results and should be also mentioned that some polyphenols, such as genistein and daidzein, might adversely affect hormone-related cancer (Zhou et al., 2016).

The dietary assessment and the role in the prevention of cancer by polyphenols have been systematically reviewed (Grosso, Godos, et al., 2017) in an analysis including 143 clinical studies. Meta-analyses of prospective studies showed that isoflavones intake was significantly associated with decreased risk of lung and gastric cancer and, to a lesser extent, to breast and colorectal cancers (Grosso, Godos, et al., 2017). Meta-analyses of case-control studies showed that flavonoids intake was associated with a decreased risk of gastrointestinal, breast, and lung cancer. However, despite a large number of epidemiological studies have investigated the relation between dietary polyphenols and cancer, the evidence is not fully consistent, and further larger studies are needed.

Similar conclusions were given by Rothwell, Knaze, and Zamora-Ros (2017), who have recently summarized the epidemiological evidence for associations between cancer risk and polyphenol intake (Rothwell et al., 2017). Epidemiological studies have found that the intake of flavonoids, the most studied subgroup of polyphenols with regard to cancer risk, have been rarely associated with a reduction in cancer risk itself. There is some evidence that isoflavones, whose main dietary sources are soy foods, might possibly reduce the risk of some type of cancer (i.e., colorectal, breast, and prostate cancers), particularly in Asian countries (Rothwell et al., 2017).

## 4 | PHENOLIC COMPOUNDS AND DATABASES

The need for categorization of polyphenols and for the implementation of specific and dedicated databases emerged, based on both analytical data and collected data taken from literature throughout a harmonized and standardized approach for the evaluation of an adequate dietary intake (Durazzo et al., 2018; Durazzo, Lucarini, et al., 2018).

Nowadays, the main core public databases, gathering extensive data on the polyphenol content of foods and beverages are (a) the United States Department of Agriculture (USDA) databases (USDA website <https://www.usda.gov/>); (b) the Phenol-Explorer (Phenol-Explore website <http://phenol-explorer.eu/>; Neveu et al., 2010); (c) the eBASIS-Bioactive Substances in Food Information Systems (eBASIS website <http://www.eurofir.org/our-tools/ebasis/>; Kiely et al., 2010; Plumb et al., 2017).

Phenol-Explorer was the first comprehensive web-based open-access database on polyphenol content in foods, including data on pharmacokinetic and metabolites, the effect of food processing and cooking throughout several updates (Rothwell et al., 2012; Rothwell et al., 2013) and including lignans data in the current version 3.6; data were collected from peer-reviewed scientific publications and evaluated before they were aggregated to produce final representative mean content values.

**TABLE 1** Examples of sources of main class of polyphenol throughout existing databases

Phenol class	Target compounds	Example of source	Content	Database websites	Source of data
Phenolic acids	4-Hydroxybenzoic acid	Coffee	420–610 mg/kg FW	eBASIS	Yilmaz and Kolak (2017)
	Ferulic acid	Hard wheat, whole grain flour	72.21 mg/100 g FW	Phenol-Explorer	Lempereur, Rouau, and Abecassis (1997)
Flavanones	Eriocitrin	Peppermint, dried	8,051.58 mg/100 g FW	Phenol-Explorer	Areias, Valentao, Andrade, Ferreres, and Seabra (2001); Guedon and Pasquier (1994)
	Eriocitrin	Fennel	1,851 mg/kg DW	eBASIS	Parejo, Viladomat, Bastida, and Codina (2004)
	Naringenin	Mandarin	64.8 mg/kg FW	eBASIS	Frankle, Custer, Arakaki, and Murphy (2004)
	Naringenin	Rosemary, fresh ( <i>Rosmarinus officinalis</i> )	24.86 mg/100 g, edible portion	Haytowitz, Wu, & Bhagwat, (2018b), USDA Database for the Flavonoid Content of Selected Foods, Release 3.3	Zheng and Wang (2001)
	Myricetin	Apricot	406.9 mg/kg DW	eBASIS	Sultana and Anwar (2008)
Flavonols	Quercetin	Capers, raw	233.84 mg/100 g edible portion	Haytowitz, et al. (2018b), USDA Database for the Flavonoid Content of Selected Foods, Release 3.3	Inocencio, Rivera, Alcaraz, and Tomás-Barberán (2000); Giuffrida, Salvo, Ziino, Toscano, and Dugo (2002)
	Kaempferol	Cloves	23.80 mg/100 g FW	Phenol-Explorer	Shan, Cai, Sun, and Corke (2005)
	Kaempferol	Saffron	205.48 mg/100 g edible portion	Haytowitz, et al. (2018b), USDA Database for the Flavonoid Content of Selected Foods, Release 3.3	Carmona et al. (2007)
	Kaempferol	Arugula	34.89 mg/100 g edible portion	Haytowitz, et al. (2018b), USDA Database for the Flavonoid Content of Selected Foods, Release 3.3	Arabbi, Genovese, and Lajolo (2004); Martínez-Sánchez, Gil-Izquierdo, Gil and Ferreres (2008); Huber, Hoffmann-Ribani, and Rodríguez-Amaya (2009)
	(+)-catechin	Cocoa, powder	107.75 mg/100 g FW	Phenol-Explorer	Gu, House, Wu, Ou, and Prior (2006), Tomas-Barberan et al. (2007)
Anthocyanins	(-)-Epigallocatechin 3-gallate	Carob flour ( <i>Ceratonia siliqua</i> )	109.46 mg/100 g, edible portion	Haytowitz, et al. (2018b), USDA Database for the Flavonoid Content of Selected Foods, Release 3.3	Sakakibara, Honda, Nakagawa, Ashida, and Kanazawa (2003)
	Epigallocatechin	Bean, Faba	46.5–140.3 mg/kg FW	eBASIS	Arts, van de Putte, and Hollman (2000)
	Epigallocatechin	Tea, raw	742–1,451.9 mg/Kg FW	eBASIS	Yixiang et al. (2011)
	Cyanidin	Raspberries, black	669.01 mg/100 g, edible portion	Haytowitz, et al. (2018b), USDA Database for the Flavonoid Content of Selected Foods, Release 3.3	Wu et al. (2006)

(Continues)

TABLE 1 (Continued)

Phenol class	Target compounds	Example of source	Content	Database websites	Source of data
Flavones	Cyanidin	Cabbage, red, raw ( <i>Brassica oleracea</i> , <i>Capitata Group</i> )	209.83 mg/100 g, edible portion	Haytowitz, et al. (2018b). USDA Database for the Flavonoid Content of Selected Foods, Release 3.3	Chun, Smith, Sakagawa, and Lee (2004); Franke et al. (2004); Wu et al. (2006)
	Delphinidin	Eggplant, raw ( <i>Solanum melongena</i> )	85.69 mg/100 g, edible portion	Haytowitz, et al. (2018b). USDA Database for the Flavonoid Content of Selected Foods, Release 3.3	Wu et al. (2006)
	Pelargonidin Pelargonidin	Radish Strawberry	250 mg/kg FW 4.31 mg/100 g FW	eBASIS Phenol-Explorer	Harnly et al. (2006) Skupien and Oszmianski (2004)
	Apigenin	Parsley, dried ( <i>Petroselinum crispum</i> )	4,503.50 mg/100 g, edible portion	Haytowitz, et al. (2018b). USDA Database for the Flavonoid Content of Selected Foods, Release 3.3	Mattila, Astola and Kumpulainen (2000); Huber et al. (2009)
	Apigenin	Parsley, fresh ( <i>Petroselinum crispum</i> )	215.46 mg/100 g, edible portion	Haytowitz, et al. (2018b). USDA Database for the Flavonoid Content of Selected Foods, Release 3.3	Justesen, Knuthsen and Leth (1998); Justesen and Knuthsen (2001); Lugasi and Hovari (2000); Sakakibara et al. (2003); Huber et al. (2009)
	Luteolin	Globe artichoke, heads, raw	42.10 mg/100 g FW	Phenol-Explorer	Romani, Pinelli, Cantini, Cimato, and Heimler (2006)
Isoflavones	Luteolin	Oregano, Mexican, dried	1,028.75 mg/100 g, edible portion	Haytowitz, Wu, & Bhagwat, (2018b). USDA Database for the Flavonoid Content of Selected Foods, Release 3.3	Lin et al. (2007)
	Luteolin	Common thyme, fresh	39.50 mg/100 g FW	Phenol-Explorer	Zheng and Wang (2001)
	Luteolin	Common sage, fresh	33.40 mg/100 g FW	Phenol-Explorer	Zheng and Wang (2001)
	Luteolin	Black olive, raw	3.43 mg/100 g FW	Phenol-Explorer	Romani, Mulinacci, Pinelli, Vincieri, and Cimato (1999); Blekas, Vassilakis, Harizanis, Tsimidou, and Boskou (2002)
	Biochanin A	Red clover	2,980–3,750 mg/kg DW	eBASIS	Hoerger et al. (2011)
	Genistein	Soy, flour	46.43 mg/100 g FW	Phenol-Explorer	Mazur et al. (1996); Preinerstorfer and Sontag (2004); Umphress, Murphy, Franke, Custer, and Blitz (2005); Akitha Devi et al. (2009); Kuhnle et al. (2009)
Stilbenes	Daizein	Soy, flour	50.22 mg/100 g FW	Phenol-Explorer	Mazur et al. (1996); Preinerstorfer and Sontag (2004); Umphress et al. (2005); Akitha Devi et al. (2009); Kuhnle et al., 2009
	trans-Piceatannol	Red wine Grape	193–1748 µg/kg FW	eBASIS	Cantos, Tomas-Barberan, Martinez, and Espin (2003)
	Resveratrol	Muscadine grape, red wine	3.02 mg/100 ml	Phenol-Explorer	Lamikanra, Grimm, Rodin, and Inyang (1996)

(Continues)

TABLE 1 (Continued)

Phenol class	Target compounds	Example of source	Content	Database websites	Source of data
Lignans	<i>Resveratrol</i>	Lingonberry, raw	3.00 mg/100 g FW	Phenol-Explorer	Ehala, Vaher, and Kalljurand (2005)
	<i>Lariciresinol</i>	Broccoli, raw	97.20 mg/100 g FW	Phenol-Explorer	Milder, Arts, van de Putte, Venema, and Hollman (2005)
	<i>Lariciresinol</i>	Kale, raw	59.90 mg/100 g FW	Phenol-Explorer	Milder et al. (2005)
	<i>Lariciresinol</i>	Lentil, flour	1,638.9–1,768.7 µg/kg DW	eBASIS	Durazzo, Turfani, Azzini, Maiani, and Carcea (2013)
	<i>Secoisolariciresinol</i>	Flaxseed, meal	257.60 mg/100 g FW	Phenol-Explorer	Obermeyer et al. (1995); Milder et al. (2005); Penalvo, Haajanen, Botting, and Adlercreutz (2005)
	<i>Matariresinol</i>	Sesameseed, meal	29.79 mg/100 g FW	Phenol-Explorer	Milder et al. (2005); Smeds et al. (2007)

Abbreviations: DW, dry weight; FW, fresh weight.

The USDA database, based on a compilation of data from literature, was developed in 2004 and expanded in recent years with inclusion of flavonoids, proanthocyanidins, and isoflavones (Bhagwat et al., 2014; Haytowitz, Wu, & Bhagwat, 2018a, b).

eBASIS should be defined as the first European Union (EU) harmonized food composition database: contains composition data and biological effects of over 300 major European plant foods of 24 compound classes, such as glucosinolates, phytosterols, polyphenols, isoflavones, glycoalkaloids, and xanthine alkaloids in 15 EU languages (Plumb et al., 2017). It is based on the compilation of expert, who critically evaluated data extracted from peer-reviewed literature as raw data. Currently, data points inserted in eBASIS for phenolic compounds were 639 for simple phenols, 3,616 for flavanols, 1,039 for flavones, 1,733 for flavanones, 3,669 for flavonols, 4,541 for anthocyanins, 6,543 for isoflavones, 2,695 for lignans, 405 for stilbenes, and 533 for proanthocyanidins (eBASIS website <http://www.eurofir.org/our-tools/ebasis/>; Plumb et al., 2017). Table 1 reports examples of the sources of the main class of polyphenol as reported throughout existing databases.

Indeed, related to the role of biologically active compounds in humans, it is worth mentioning the Human Metabolome Database or HMDB 4.0 (HMDB website <http://www.hmdb.ca/>), a web metabolomic database on human metabolites (Wishart et al., 2018), and PhytoHub (Phytohub website <http://phytohub.eu/>), a freely electronic database on phytochemicals commonly ingested in diets, and their metabolites (Bento da Silva et al., 2016).

## 5 | CONCLUSION

This updated picture reports key concepts in polyphenol research and highlights new frontiers of polyphenols in nutrition and health. In summary, clinical evidence suggests that polyphenols intake could possibly reduce the risk of cardiovascular diseases. Concerning the association between polyphenols and type 2 diabetes, it is worth mentioning a recent meta-analysis of 18 prospective epidemiologic studies, which revealed inverse associations for intakes of different subclasses and individual polyphenols (Rienks et al., 2018). Further research is required before suggesting a role of polyphenol intake in reducing weight in overweight and obese individuals. Regarding the relation between dietary polyphenols and cancer, despite a large number of epidemiological studies, the evidence is not fully consistent, and further larger studies are needed.

The research end point on polyphenols should be addressed towards two main directions: (a) the identification of new structures of polyphenols throughout innovative advanced technologies; (b) the studies of bioactivities, starting from the evaluation of interactions between compounds by in vitro assays, throughout studies on cell lines and animal models, to bioavailability and intervention studies until epidemiological and clinical trials in humans. Both studies pathways are interconnected, and an integrated and multidisciplinary approach of research, in terms of health benefits, must be considered necessary to achieve the above mentioned end point. In this regard, the use of nanotechnologies for micro and nanodelivery polyphenol-



target formulations represent a new frontier for better target tissues and organs and enhance the therapeutic efficacy of polyphenols.

Ultimately, considering the potential beneficial health effect of polyphenols, the exploitation of food waste and of different/unconventional matrixes as alternative sources in terms of polyphenols should be pursued.

## CONFLICT OF INTEREST

The authors declare that they do not have any conflict of interest to disclose.

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