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COMPREHENSIVE REVIEWS IN FOOD SCIENCE AND FOOD SAFETY

Functional implications of bound phenolic compounds and phenolics–food interaction: A review

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Abstract

Sizeable scientific evidence indicates the health benefits related to phenolic compounds and dietary fiber. Various phenolic compounds-rich foods or ingredients are also rich in dietary fiber, and these two health components may interrelate via noncovalent (reversible) and covalent (mostly irreversible) interactions. Notwithstanding, these interactions are responsible for the carrier effect ascribed to fiber toward the digestive system and can modulate the bioaccessibility of phenolics, thus shaping health-promoting effects in vivo. On this basis, the present review focuses on the nature, occurrence, and implications of the interactions between phenolics and food components. Covalent and noncovalent interactions are presented, their occurrence discussed, and the effect of food processing introduced. Once reaching the large intestine, fiber-bound phenolics undergo an intense transformation by the microbial community therein, encompassing reactions such as deglycosylation, dehydroxylation, α- and β-oxidation, dehydrogenation, demethylation, decarboxylation, C-ring fission, and cleavage to lower

molecular weight phenolics. Comparatively less information is still available on the consequences on gut microbiota. So far, the very most of the information on the ability of bound phenolics to modulate gut microbiota relates to in vitro models and single strains in culture medium. Despite offering promising information, such models provide limited information about the effect on gut microbes, and future research is deemed in this field.

KEYWORDS
bioaccessibility, bound phenolics, gut, microbial transformations, microbiota

1 | INTRODUCTION

Phenolic compounds (PCs) are secondary metabolites found in vegetal tissues such as flowers, seeds, roots, and edible parts (de la Rosa et al., 2019). PCs are involved in the plant defense system and adaptation response to the environment, also presenting a structural function. They also contribute to organoleptic traits of fruits, flowers, and vegetables (Ferreira et al., 2017; Luna-Guevara et al., 2018). Nonetheless, PCs are widely studied for their beneficial activities, including antioxidant, anti-inflammatory, antitumor, and antimicrobial properties (Acosta-Estrada et al., 2014; de la Rosa et al., 2019; Luna-Guevara et al., 2018). Different biochemical routes are involved in their production, shikimic acid being the main precursor (Ferreira et al., 2017). More than 8000 PCs, with a large variety of structures, have been identified. At least, all PCs contain in their chemical structure one aromatic ring with one or more hydroxyl groups joined (de la Rosa et al., 2019; Luna-Guevara et al., 2018). According to the number and arrangement of the carbon atoms, PCs are classified in flavonoids and nonflavonoids (namely, phenolic acids, lignans, stilbenes, and other lower molecular weight compounds) (de la Rosa et al., 2019). They can also be classified as free, conjugated (to sugars and low-molecular-weight compounds), and insoluble bound phenolics (BPs); these latter are covalently bound to structural components of the cell wall (Acosta-Estrada et al., 2014; Shahidi & Yeo, 2016). In the present review, the classification of flavonoids and nonflavonoids is used, as summarized in Figure 1. This review presents a summary definition of phenolics structural diversity and its relationship with characterization, occurrence, and distribution of BPs in food. Thereafter, the functional implications arising from phenolics–food interaction are presented in terms of bioaccessibility, transformation during digestion, and modulation of intestine microbiota. Overall, this work aims to comprehensively review the modulation of the health-promoting effects resulting from phenolics interaction with dietary fibers and food components in general.

1.1 | Structural diversity of PCs

1.1.1 | Phenolic acids

These compounds are usually divided into hydroxycinnamic and hydroxybenzoic acids. They are widely distributed in different vegetal products (Vuolo et al., 2019) and involved in several biochemical processes (Luna-Guevara et al., 2018). Phenolic acids are insoluble and usually bound to other molecules or components of the cell wall (de la Rosa et al., 2019). These compounds contain a phenyl group substituted by one carboxylic group and at least one OH group and could be divided into three types: hydroxybenzoic acids (C6–C1 backbone), acetophenones and phenylacetic acids (C6–C2 backbones), and hydroxycinnamic acids (C6–C3 backbone) (de la Rosa et al., 2019; Luna-Guevara et al., 2018; Vuolo et al., 2019). Common hydroxybenzoic acids include salicylic, protocatechuic, vanillic, and gallic acids. Regarding hydroxycinnamic acids, some examples are *p*-coumaric, caffeic, or chlorogenic acids (de la Rosa et al., 2019; Ferreira et al., 2017; Shahidi & Yeo, 2016).

1.1.2 | Flavonoids

Flavonoids are ubiquitous water-soluble compounds, usually found as glycoside conjugated forms in fruits, vegetables, and derived products (Acosta-Estrada et al., 2014; Vuolo et al., 2019). More than 6000 flavonoids have been identified, with a wide variety of chemical structures. Their basic structure consists of a phenyl benzopyran skeleton formed by two phenyl rings (A, B) joined by a heterocyclic pyran ring (C) (de la Rosa et al., 2019; Ferreira et al., 2017; Vuolo et al., 2019). Different classifications of flavonoids have been proposed but, usually, six families are considered: flavonols (e.g., kaempferol and quercetin), flavones (e.g., apigenin and luteolin), flavanones (e.g., hesperidin and naringenin), flavan-3-ols (e.g., catechin

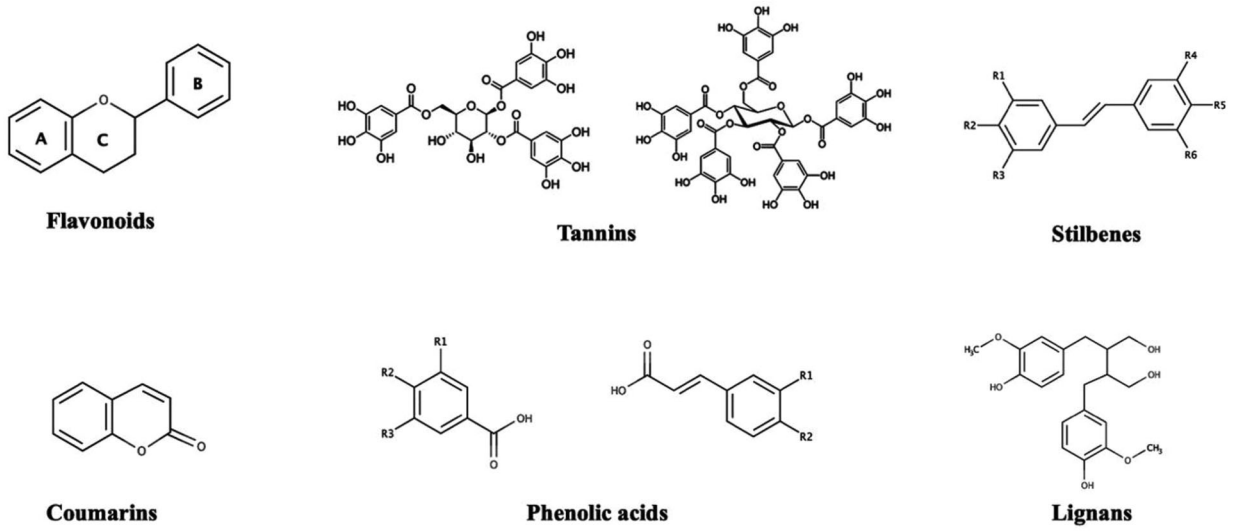

FIGURE 1 Basic structure of the main phenolic classes

and epicatechin), anthocyanidins (e.g., pelargonidin and cyanidin), and isoflavones (e.g., genistein and daidzein) (Ferreira et al., 2017; Luna-Guevara et al., 2018).

Flavonoids usually appear in nature after suffering glycosylation, esterification, and polymerization reactions. Hence, the polymerization of flavan-3-ols, such as catechin and epicatechin, leads to large molecules known as condensed tannins (Ferreira et al., 2017). Tannins are generally classified as condensed and hydrolysable compounds (Luna-Guevara et al., 2018). More than 500 different tannins have been described in plant roots, fruits, seeds, and leaves. Condensed tannins are usually found in berries, nuts, and cereals (de la Rosa et al., 2019; Ferreira et al., 2017). Hydrolysable tannins came from the esterification of ellagic and gallic acids (Vuolo et al., 2019). Red grapes, wines, and berries are a rich source of hydrolysable tannins (Luna-Guevara et al., 2018). Overall, weak acids, bases, and enzymes can break these compounds.

1.1.3 | Stilbenes

These compounds present two phenyl groups joined by a two-carbon bridge (C6–C2–C6) (Ferreira et al., 2017). They are part of the defense system of plants against pathogens and environmental factors, also known as phytoalexins. The most important stilbene is the resveratrol, found in wine and the skin of red grapes and other berries (de la Rosa et al., 2019; Ferreira et al., 2017).

1.1.4 | Coumarins

Coumarins represent a distinguished group of bioactive PCs formed by fusing a benzenic ring with an oxygen heterocycle (Ferreira et al., 2017; Luna-Guevara et al., 2018). They are found in different vegetal tissues and in angiosperms families' essential oils, such as Asteraceae, Apiaceae, or Rutaceae. Coumarins are further classified in simple coumarins, furocoumarins, pyranocoumarins, and substituted coumarins. Hydroxycoumarin, esculetin, bergamottin, deltoin, and khellactone are examples of the main coumarins found in plant foods (Luna-Guevara et al., 2018).

1.1.5 | Lignans

Their structure is formed by two phenylpropanoid units (C6–C3–C3–C6). Generally, lignans are found in cereals, fruits, and vegetables, with flaxseeds reported to be the richest source (Luna-Guevara et al., 2018). Some common examples are secoisolariciresinol, matairesinol, and sesamin (de la Rosa et al., 2019; Ferreira et al., 2017). Lignans are strictly related to lignin, a polymer found in the cell wall and woody tissues; they have also been found to mimic phytoestrogens.

1.2 | Covalent and noncovalent interactions with dietary fibers

PCs can intrinsically interact with food components rather than being combined with ingredients rich in dietary fiber during food formulation. The interaction(s) with dietary fiber in the food matrix modify their bioaccessibility and bioactivity and include noncovalent (reversible) interactions and covalent (mostly irreversible) interactions (Jakobek & Matić, 2019). Although van der Waals forces,

electrostatic attraction, hydrophobic contact, or covalent bonding (esterification) interactions play a role, these interactions are mainly driven by the hydrogen bonds (González-Aguilar et al., 2017). On these bases, the concept of "antioxidant dietary fiber" was introduced years ago based on the nonextractable PCs associated with dietary fibers but still displaying a range of different antioxidant capacities (Saura-Calixto, 1998).

A range of techniques can be used to characterize these interactions, such as isothermal titration calorimetry, confocal laser scanning microscopy, saturation transfer difference NMR spectroscopy, dynamic light scattering, and size-exclusion chromatography. Interestingly, PCs-–fiber binding has been thermodynamically characterized with adsorption or binding isothermal models, including Langmuir (the most used model), Redlich–Peterson, Toth equations, Clausius–Clapeyron, Dubinin–Radushkevich, Hill, and Freundlich equations (Jakobek et al., 2020). The structural properties, concentrations, and compositions of both fiber and PCs are critical factors to be considered to maximize/optimize these interactions (Jakobek & Matić, 2019). The effects of pH, temperature, and ionic strength on the degree of fiber–PC interactions have been discussed in different studies (Koh et al., 2020; Liu et al., 2019). On the other hand, the concentration of PCs is also critical; for example, Guo et al. (2018) reported that when the concentration of luteolin in the solution was increased from 0.2 to 1 mg/ml, the binding degree was significantly increased.

PCs vary in their degree of hydroxylation, methylation, methoxylation, esterification, glycosylation, hydrogenation, and molecular weight, in turn having significant differences in the formation of PCs–fiber complexes. In this regard, starting from previous evidence about a stronger binding affinity between pectin and pectinate beads of 3,4-dihydroxyphenylglycol, Bermúdez-Oria et al. (2019) investigated the interactions between 3,4-dihydroxyphenylglycol and pectin after in vitro digestion. They suggested that both noncovalent interactions, mostly hydrogen and covalent bonds, enhanced the formation of the 3,4-dihydroxyphenylglycol–pectin complex. Wang et al. (2013) investigated the effects of the chemical structure of PCs on their interactions with oat β-glucans. The presence of four or more hydroxyl groups decreased the binding interactions, whereas those with three or less favored the adsorption of flavonoids. They also observed that the efficiency of flavonoid for adsorption capacity was in the order: flavonol > flavone > flavanone > isoflavone. More recently, Jakobek et al. (2020) studied the interactions between β-glucan and three quercetin derivatives. They revealed that the adsorption was higher for quercetin-3-rhamnoside and quercetin-3-glucoside, when compared with quercetin-3-galactoside. This study also showed that the spatial arrangements of OH groups on the quercetin derivative molecules affect adsorption.

Zhu et al. (2018) also investigated the effects of hydroxylation, esterification, methylation, and methoxylation of phenolic acids on their adsorption capacities onto arabinan-rich pectic polysaccharides (ARPP) from rapeseed meal. They found that hydroxyl groups on phenolic acids increased their adsorption onto ARPP, whereas methyl groups on phenolic acids decreased their adsorption. In another study, Wang et al. (2013) showed that *O*-coumaric acid was bound to oat β-glucans higher than *p*- and *m*-coumaric acids. Lin et al. (2016) investigated the binding between pectin-rich fractions and anthocyanidins and reported that pelargonidin (one hydroxyl group on the aromatic B ring) solution had the highest reduction (−58%), whereas delphinidin (three hydroxyl groups on the aromatic B ring) had the lowest reduction (−22%). They also indicated that increased hydroxylation of the B ring of anthocyanidin stabilized anthocyanidins.

Besides PCs, the structure of dietary fibers as well as their branching degrees might also have an important effect on the binding affinity. For instance, Fernandes, Le Bourvelecc, et al. (2020) observed that a higher branching degree restricted the interaction of arabinan with PCs. On the other hand, Koh et al. (2020) investigated the effect of water-soluble fraction (more highly branched) and chelator-soluble fraction (more linear structure) of blueberry pectin on the stability of anthocyanins under in vitro digestion. They showed that chelator-soluble blueberry pectin protected anthocyanins against degradation, whereas water-soluble blueberry pectin prevented only cyanidin-3-glucoside during gastrointestinal digestion. This was likely induced by hydrogen bonds between hydroxyl or carboxyl groups of the α-1,4-linked-galacturonic acid backbone of blueberry pectin and hydroxyl groups of anthocyanins. More recently, Fernandes, Oliveira, et al. (2020) showed that low methylesterified pectic polysaccharides greatly bind to cyanidin-3-glucoside compared with the highly methylesterified ones. Similarly, the same researchers investigated the effect of blueberry pectin composition on anthocyanin adsorption, confirming that ionic interaction occurred between protonated anthocyanins (flavylium cations) and free carboxylated pectin.

It has also been reported that the molecular weight of either the dietary fiber or the PCs also affects their interaction. In a study performed by Guo et al. (2018), the interactions between flavonoids and three polysaccharides from corn silk with different molecular weights (43.3, 61.3, and 106.6 kDa) were investigated. They demonstrated that the maximum adsorbed amounts of flavonoids increased with an increase in the molecular weight of the

polysaccharides. They observed that luteolin (higher molecular weight) showed the strongest binding affinity to corn silk polysaccharides, whereas formononetin (smaller molecular weight) had the lowest affinity. On the other hand, Zhu et al. (2018) reported a maximum adsorption value of ferulic acid to the ARPP hydrolysate from rapeseed having a molecular weight of 76 kDa. The authors also assumed that ARPP hydrolysate having a molecular weight of 153 kDa had low chain flexibility (lower ferulic acid adsorptions). In contrast, ARPP hydrolysate having a molecular weight of 76 kDa had desirable chain flexibility, thus providing more adsorption sites to interact with ferulic acid.

On the other hand, the binding affinity varies depending on the type of dietary fibers. Liu et al. (2019) investigated and compared the adsorption behavior of catechin onto cellulose and pectin, showing that pectin (20.71 mg/g) showed increased adsorption capacity compared to cellulose (2.41 mg/g). This could be explained considering that pectin, a soluble fiber, had a long molecular chain structure, whereas cellulose, an insoluble fiber, was crystalline because of its extensive hydrogen bonding between the glucose chains. Therefore, pectin had more favored sites for catechin to bind, in comparison to cellulose. The binding behavior also varied depending on the incubation time. They also reported that the adsorption of catechin with cellulose required about 6 h to reach the adsorption saturation, which was longer than pectin for about 2.5 h.

Concerning covalent bonds, insoluble PCs have been reported to be linked to cell wall structural components, mainly structural polysaccharides (such as cellulose, hemicellulose, and other arabinoxylans, pectin and lignin) and rod-shaped proteins (Acosta-Estrada et al., 2014). In plants, they are important to serve as protection against pathogen insects and fungi and antioxidants. The PCs have been described to bind membrane components via covalent cross-linking, either ether bonds between lignins and hydroxyl groups of the phenolic ring or esters between their carboxy group and alcohol groups of polysaccharides and proteins (Acosta-Estrada et al., 2014).

1.3 | The bioaccessibility of phenolics

The binding of PCs with dietary fibers can change the fraction released from the food matrix and potentially available (bioaccessibility) and the actual amount of PC metabolites absorbed in the intestine and detected in plasma (bioavailability) (Jakobek & Matić, 2019). The concept includes digestive transformations and involves the absorption into intestinal epithelium cells as well as presystemic metabolism. Interestingly, the nonabsorbed compounds can be delivered by fibers to the colon, where they might be processed and transformed by microbial activity. The presence of fibers might potentially decrease polyphenol bioaccessibility in the small intestine, in turn increasing PCs reaching the lower parts of the digestive tract (Jakobek & Matić, 2019; Tomas et al., 2020). Once in the large intestine, some PCs show potential beneficial effects, whereas others are catabolized and absorbed through enterocytes. This role played by bound PCs is included among the important functions of dietary fibers. Overall, fiber particle size and the nature of these interactions are reported to affect the PCs bioaccessibility (Jakobek & Matić, 2019). In particular, PCs bioaccessibility in the small intestine might be higher when considering dietary fiber with smaller particle size. Therefore, it is not possible to generalize to date, and further works in this area are strongly recommended to better understand the impact of different dietary fibers on PCs bioaccessibility.

Generally, in vitro digestion methods are the most exploited to simulate both gastric and small intestinal phases, followed or not by Caco-2 cells uptake evaluations (Rocchetti, Giuberti, et al., 2020; Rocchetti, Rizzi, et al., 2020). In this regard, PCs bioaccessibility is usually assessed using the in vitro static gastrointestinal method, first harmonized by Minekus et al. (2014), with further improvements (Brodkorb et al., 2019). This method represents a standardized guideline allowing to compare results from different research groups. This simulated method includes a three-stage process: (1) a simulated oral step based on amylase activity; (2) a simulated gastric step based on a pepsin activity; and (3) a simulated pancreatic treatment based on pancreatin. Besides, several other conditions (including composition and concentration of bile extract, simulated movement during digestion, temperature, food particle size, and dark anaerobic environment) represent critical factors to be carefully considered. Besides, in the last years, the dynamic gastrointestinal digestion method was used to measure PCs bioaccessibility. This method allows to include also a further colonic fermentation experiment to reach more and comprehensive information about the PCs bioaccessibility during a simulated consumption. For example, dynamic gastrointestinal digestion methods have been used to estimate the bioaccessibility of PCs characterizing different food matrices, such as grape pomace extracts (Gil-Sánchez et al., 2018) and potato (Ekbatan et al., 2018). Besides, to better characterize the transport and metabolism of phenolic metabolites following an in vitro digestion system (static or dynamic), studies using Caco-2 and hepatic HepG2 cells can be conducted. Interestingly, these latter cell models can be used to study glucuronidation, sulfation, and methylation reactions (typical for PCs). Regarding some examples of polyphenol-rich food sources, Gonçalves et al. (2019) investigated the bioaccessibility and bioavailability

of PCs characterizing sweet cherries (*Prunus avium* L.). These authors showed that after the simulated digestion process, PCs were able to be absorbed by the cell barrier, thus becoming bioavailable. However, native PCs were primarily transformed during the passage through the cell monolayer, thus suggesting profound cellular modifications. In another work, Hithamani et al. (2017) evaluated the uptake of PCs from millet and onion by human intestinal Caco-2 cells, showing a clear impact of sprouting and heat treatments on the transport of individual PCs from apical to the basolateral compartment across Caco-2 monolayer, with a higher permeability of phenolic acids than flavonoids.

2 | OCCURRENCE OF BPs IN PLANT FOODS

2.1 | Extraction and profiling of BPs

Plant PCs exist as free or bound forms. Free phenolics (FPs) do not physically/chemically interact with other molecules and are usually soluble in aqueous/organic solvents. Conjugated phenolics are covalently bound to low-molecular-mass compounds, such as sugars or fatty acids, and are also soluble in aqueous/organic solvents. On the other hand, BPs are not soluble due to possible interaction with macromolecules such as cellulose, protein, lignin, and sometimes due to covalent bonds (e.g., ester, ether, and C−C bonds) in the plant cell wall (Figure 2). To date, a great number of studies available in the scientific literature are based on the chemical characterization and evaluation of biological functions of FPs, whereas few comprehensive studies on BPs and their properties exist. Nonetheless, BPs can account for a relatively large amount of PCs in foods. To date, the most important methods to recover BPs can be classified in chemical, enzymatic, and physical methods.

2.1.1 | Alkaline and acidic hydrolysis (chemical extraction methods)

BPs are not extractable in aqueous and/or organic solvents; therefore, preventive hydrolysis based on alkaline or acidic treatments is one of the most valuable strategies for targeting these compounds. The alkali treatment can cleave the ester bonds linking the compounds to the cell wall, thus allowing the release of PCs (mainly phenolic acids) from the insoluble residues. Generally, NaOH and KOH solutions are the most used in alkaline extraction conditions; examples from different sources such as nuts and blackberry are provided in the literature (Rocchetti, Bhumireddy, et al., 2019; Tomas et al., 2020). The alkaline extraction requires strict conditions to be followed to ensure the good recovery of BPs (Wang et al., 2020). In particular, the reaction must be conducted in dark conditions for 60 min, usually under argon or nitrogen flows (i.e., inert gas atmosphere) and adding ascorbic acid or chelators to prevent oxidation. Also, following the preliminary extraction step, hydrochloric or citric acid is added to the extraction mixture to adjust the pH to neutral or acidic values (usually 3 or 4). The acidification is essential considering that the acidic pH can prevent quinone formation derived from the deprotonation of phenolic hydroxyl groups in a strong alkali environment. Besides, the food extract may contain large quantities of proteins that precipitate at strong basic pH conditions. The second option for the chemical extraction of BPs is based on acidic conditions, mainly exploiting HCl or H_2SO_4. Also, ester and glycosidic bonds between PCs and the cell wall can be removed when an acid treatment is adopted (Wang et al., 2020). Overall, both methods present advantages and drawbacks: the alkali method normally requires long extraction times and a more complicated sample pretreatment; on the other hand, the acid method often requires high processing temperature, likely responsible for the degradation of some PCs. Noteworthy, alkaline conditions ensure the irreversible hydrolysis of ester bonds. The correct extraction method should be chosen considering both targeted compounds and characteristics of the food matrix (e.g., dietary fiber content) under investigation.

2.1.2 | Enzymatic and physical extraction methods

Carbohydrate-hydrolyzing enzymes (e.g., pectinase, amylase, xylanase, β-glucosidase, cellulase, and hemicellulase) can promote the release of BPs from the plant cell wall. The examples of enzymatic hydrolysis reported in scientific literature demonstrated quite different recovery efficiencies according to the complexity of cell wall structure and the different phenolic composition. However, enzymatic extraction represents a valuable alternative to overcome the limitations previously reported for chemical extraction methods. The second alternative to conventional extraction methods is represented by nonconventional physical extraction technologies based on ultrasounds, microwave, and ultrahigh pressure. These methods mainly consist of heat treatments and mechanically assisted technologies able to accelerate the solubilization of plant matrices to improve the release of BPs (Barba et al., 2016).

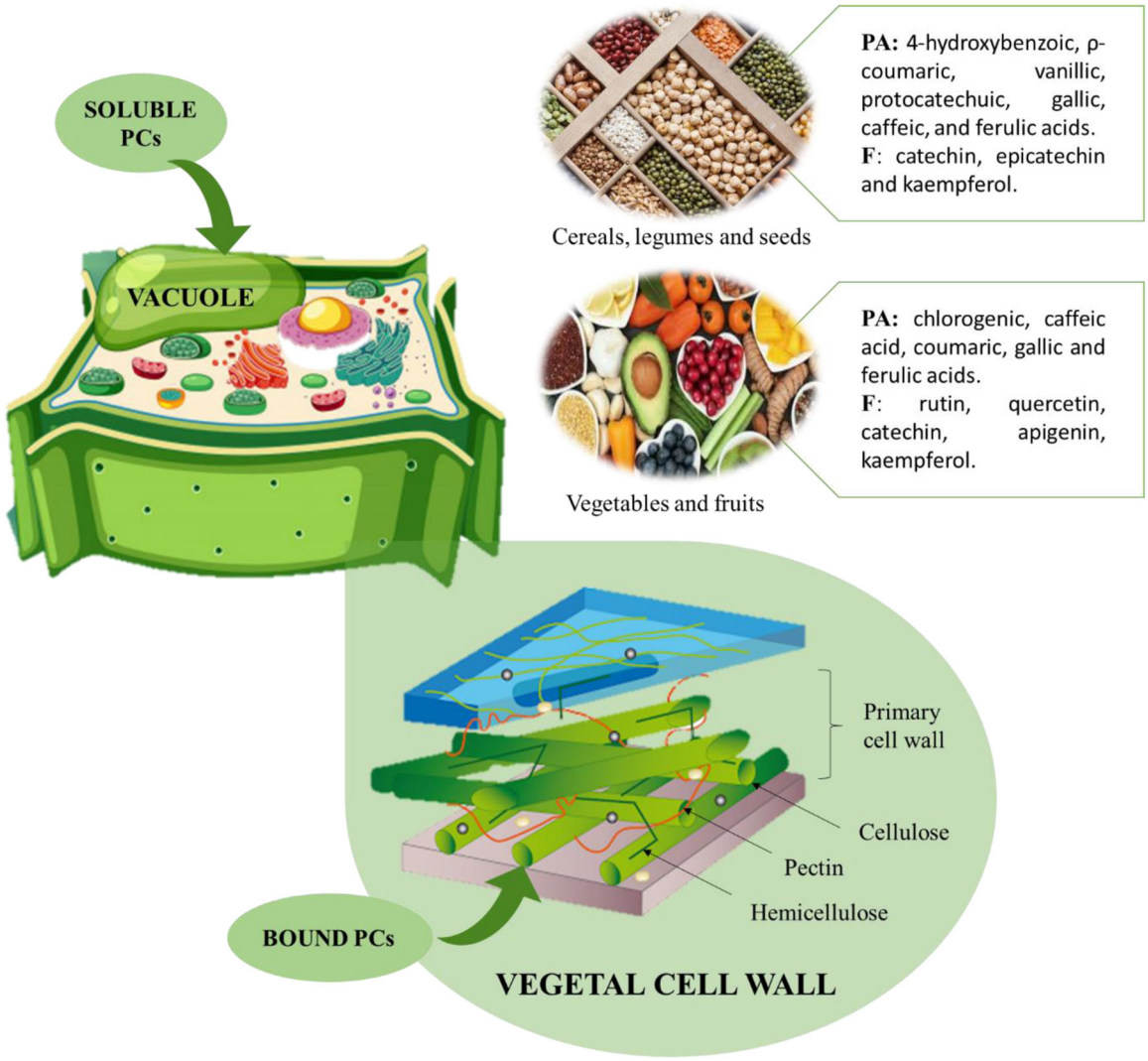

FIGURE 2 Distribution of soluble and insoluble bound phenolic compounds (PCs) and several of the phenolic acids (PA) and flavonoids (F) present in different plant foods

2.1.3 | Profiling and analysis of BPs by targeted/untargeted metabolomics

In most available scientific literature, BPs have been analyzed using two different strategies, namely, spectrophotometry and/or chromatography coupled with mass spectrometry. Overall, UV/Vis spectrophotometry offers a rapid chemical index to measure free, bound, and total phenolics, but chromatographic techniques followed by high-resolution mass spectrometry platforms provide higher specificity. In this regard, BPs extracted by alkaline hydrolysis from the bran of different rice varieties revealed a great abundance of *p*-coumaric and ferulic acids using HPLC–UV (Wu et al., 2018). Different food matrices were targeted in other works, to include tomato, nuts, gluten-free ingredients, gluten-free pasta, and pigmented cereals. Table 1 summarizes the extraction strategies of BPs from different food sources, together with the analytical techniques used for their comprehensive profiling and/or identification.

2.2 | Profile and distribution in cereals and pseudocereals, legumes, and vegetables

Although most of the studies available on PCs are based on their free fraction, BPs are gaining growing attention because they are emerging as important contributors to the total content and in vivo functional properties. Being insoluble BPs localized in the primary cell wall of vegetal cells (Acosta-Estrada et al., 2014; Shahidi & Yeo, 2016; Wang et al., 2020), they are more abundant in protective tissues (e.g., pericarp, seed coat, and hull), whereas nutritional tissues have lower amounts. In plants, these compounds play a fundamental role in response to stress conditions (such as UV radiation, pathogens, or herbivores)

TABLE 1 List of both hydrolysis types and identification methods of bound phenolics in different food sources according to recent published papers

Source of BPs	Hydrolysis type	Identification method	Reference
Blackberry	Alkaline hydrolysis	UHPLC–QTOF–MS	Tomas et al. (2020)
Nuts	Alkaline hydrolysis	UHPLC–QTOF–MS	Rocchetti, Bhumireddy, et al. (2019)
Quinoa and buckwheat seeds	Alkaline hydrolysis	UHPLC–QTOF–MS	Rocchetti, Miragoli, et al. (2019)
Pigmented sorghum	Alkaline hydrolysis	UHPLC–QTOF–MS	Rocchetti, Giuberti, Busconi, et al. (2020)
Gluten-free flours	Alkaline hydrolysis	UHPLC–QTOF–MS	Rocchetti, Lucini, et al. (2019)
Tomato berries	Alkaline hydrolysis	UHPLC–QTOF–MS	Rocchetti, Senizza, et al. (2019)
Lychee pulp	Alkaline hydrolysis	HPLC–DAD	Xu et al. (2020)
Millet flour	Acidic and alkaline hydrolysis	HPLC–DAD–MS	Balli et al. (2020)
Apple pomace	Sequential alkaline and acidic hydrolysis	UPLC–Q-Exactive Orbitrap–MS	Li et al. (2020)
Yellow and red araçá fruits	Acidic hydrolysis	HPLC–DAD–QTOF–MS/MS	Mallmann et al. (2020)
Cocoa beans	Acidic and alkaline hydrolysis	UHPLC–DAD–ESI–HR-MS/MS	Oracz et al. (2019)
Pickled olives, tomato, sweet, and hot peppers	Acidic and alkaline hydrolysis	RP-HPLC–UV	Alu'datt et al. (2019)

Abbreviations: BPs, bound phenolics.

and participate in morphogenesis and plant growth (Wang et al., 2020). Consequently, their actual content is rather variable and strongly related to genotype × environment interactions and other factors.

In general, BPs content has been estimated at about 20%–60% in vegetables, fruits, legumes, and seeds (Shahidi & Yeo, 2016). The content of BPs has been determined in several cereals, for example, in maize (87%–96%), rice (52%–91%), barley (62%–88%), oat (88%), or quinoa seeds (80%) (Acosta-Estrada et al., 2014). Regarding legumes such as lentils, they present a range of BPs between 10% and 63%. Also, in different beans, such as chickpeas, red beans, or pearl beans, the content varies between 33% and 56%. Some seeds, such as blackberry, black raspberry, and blueberry, present amounts of insoluble BPs higher than FPs (Ayoub et al., 2016). BPs have been found in the epidermis, hypodermis, chlorenchyma, palisade, and parenchyma cells (Shahidi & Yeo, 2016). Among BPs characterizing plant foods, phenolic acids and flavonoids are the most studied. In the first group, compounds such as 4-hydroxybenzoic, *p*-Hydroxybenzoic, *p*-coumaric, vanillic, caffeic, and ferulic acids have been found in different cereals. For example, the study carried out by Zavala-López and García-Lara (2017) indicated that *trans*-ferulic acid and *p*-coumaric acid (1029.9 and 138.6 μg/g DW, respectively) were the main BPs in maize kernel. Legumes and oilseeds (i.e., sunflower seeds, rapeseeds, or flaxseeds) are also rich in BP acids, such as protocatechuic, gallic, *p*-coumaric, and ferulic acids (Shahidi & Yeo, 2016). For instance, Gao et al. (2017) analyzed the BP profile of different legumes: kidney bean (*Phaseolus vulgaris* L.), cowpea (*Vigna unguiculata* [Linn.] Walp), snow pea (*Pisum sativum* var. *macrocarpon* L.), green soybean (*Glycine max* [L.] Merr), and soybean sprouts. Each food displayed a particular BP profile; only *p*-coumaric acid was identified in kidney bean and cowpea, whereas green soybean and soybean sprouts contained a mix of several PCs, such as *p*-coumaric acid, ferulic acid, *p*-hydroxybenzoic acid, syringic acid, and vanillic acid (in bound forms). Protocatechuic acid was the main BP in snow pea, whereas syringic acid was the major compound in green soybean and soybean sprouts (Gao et al., 2017). Some flavonoids and derivatives have also been identified as bound forms in cereals, legumes, and seeds, including catechins and kaempferol (Ayoub et al., 2016; Pająk et al., 2014; Shahidi & Yeo, 2016). Other BPs have been studied in these sources. For example, in the study of Ayoub et al. (2016), blueberries seeds contained bound anthocyanidins, such as cyanidin and delphinidin derivatives, and condensed tannins. Regarding vegetables and fruits, their BP content is usually lower than the observed in cereals (Song et al., 2020), as reported, for example, in carrot, onions, potatoes, apples, and orange (38%, 10%–23%, 40%, 7%, and 24%, respectively) (Acosta-Estrada et al., 2014). Several BP

acids, such as chlorogenic, caffeic, coumaric, gallic, and ferulic acids, have been identified in fruits and vegetables. For instance, few BPs were identified and quantified in four potato cultivars, with caffeic acid being the main compound in the four varieties (Ru et al., 2019). Other BPs obtained from these varieties were *p*-coumaric acid and ferulic acid. The profile of BPs indicated that *p*-coumaric acid (294.1 mg/g DW) was the main compound in carrots (Viacava et al., 2020), followed by 4-*O*-coumaroylquinic acid, caffeoyl glucose, and isocoumarin. Bound flavonoids, including rutin, quercetin, catechin, apigenin, kaempferol, luteoloside, or naringenin, have been reported as well (Kim, 2018). Finally, anthocyanins and condensed tannins have been found in apples, blueberries, cranberries, or pomegranates. Resveratrol has been found in the insoluble fraction of grapes and some berries, such as cranberries, raspberries, or blueberries (Kim, 2018). Table 2 summarizes several studies about the BPs profile in different plant foods.

Nevertheless, as mentioned before, the BPs content is influenced by several factors, including stress conditions, cultivar, plant organ, cultivation techniques, cooking, or storage conditions (Viacava et al., 2020). For example, the study carried out by Giusti et al. (2019) showed the influence of processing on the composition and content of BPs in coat and cotyledon of selected plant foods. The authors indicated that ferulic acid was the main BP in black beans (190.8 mg/100 g DW in the raw sample), whereas catechin was the principal polyphenol in black lentils (5.1 mg/100 g DW in the cooked sample) and chickpeas (2.6 mg/100 g DW in the raw sample). Besides, a notable effect of cooking was found, with lower contents in both coat and cotyledons of these vegetables, which were removed from plant tissue and lost in the cooking water. In another study, the application of postharvest wounding stress alone or in combination with extrusion leads to an increase in both FP content and BPs in carrots. Specifically, caffeic acid, *p*-coumaric acid, luteolin, and isocoumarin were the BPs that increased the most due to wounding stress (Viacava et al., 2020). The profile of BPs in black rice can be modified by hydrolysis (Alves et al., 2016). This outcome was observed after applying either chemical or enzymatic hydrolysis at different temperatures. Overall, relevant BPs found in black rice were protocatechuic and ferulic acids, but the maximum extraction yield was obtained by enzymatic hydrolysis plus alkaline hydrolysis for protocatechuic acid, whereas alkaline hydrolysis was optimal for ferulic acid (Alves et al., 2016). The study carried out by Yeo and Shahidi (2020) characterized the influence of four lentil varieties on the profile of PCs located in hulls. The authors observed that the variety influenced the presence and amount of each identified BP. Besides, the differences in the composition and content of BPs depend also on the pedoclimatic condition of cultivation. A study evaluated the effect of harvesting location among vegetables and legumes consumed in China. The results showed that the harvesting location significantly influenced the amount of BPs such as *p*-coumaric, ferulic, or sinapic acids (Gao et al., 2017).

2.3 | Effect of processing on BPs

So far, the potential of both thermal and nonthermal (i.e., high pressure or pulsed electric fields) processing was exploited to release bioactives such as PCs from their natural entrapment, to promote their bioaccessibility and absorption (Khan et al., 2018). Indeed, the inclusion of bioactives in the cell wall (dietary fiber) can promote limited access to digestive enzymes. In this sense, processing can facilitate the disruption of the food matrix and dietary fiber in particular, thus promoting the decrease of particle size (Calvo-Lerma et al., 2020) as well as the release of bioactives and nutrients present by the raw matrix. Overall, the processing of cereals and pulses into ready-to-eat matrices was found to have a positive impact on the release of PCs in the upper gastrointestinal tract, thus promoting their bioaccessibility (Oghbaei & Prakash, 2016). Processing can also be used for the selective modification of natural barriers and, consequently, to change the different responses at the digestive level, thus controlling bioaccessibility and bioavailability on demand (Barba et al., 2016).

Although there is a lack of studies dealing with the application of thermal and nonthermal processing to improve the bioaccessibility and bioavailability of PCs, an increase of bioaccessibility after cooking, frying, and pasteurization can be observed. Also, the number of studies evaluating the effect of high pressure and pulsed electric field on PCs bioaccessibility and bioavailability is also limited, reporting contradictory findings (Barba et al., 2016). This might be due to the lack of analytical determinations of the individual PCs after processing. Considering the modifications in PCs observed after high pressure and pulsed electric field (Barba et al., 2015), a study focusing on individual PCs immediately after processing and subsequent storage and after simulated in vitro digestion methods is advisable.

On the other hand, the use of fermentation assisted by lactic acid bacteria implies changes occurring both in the content and in the profile of the different bioactive compounds. For example, by the action of bacteria, bioactive peptides, short-chain fatty acids, or polysaccharides can be produced, whereas the content of sugar and/or some antinutritional compounds can decrease. In this sense, changes in PCs have also been observed, thus determining modifications of the parent compounds in metabolites with a different biological value. These modifications may lead to a

TABLE 2 Profile of insoluble bound phenolic compounds in different plant foods

Food source	Total BPs (μg/g)	Main BPs	References
Cereals			
Barley	485.06	PA: Gallic acid, protocatechuic acid, 4-hydroxybenzoic acid, vanillic acid, caffeic acid, syringic acid, *p*-coumaric acid, ferulic acid, synaptic acid, salicylic acid, cinnamic acid	Alves et al. (2016); Zavala-López and García-Lara (2017); Zhu et al. (2019)
Oat	1776.09	PA: 4-Hydroxybenzoic acid, vanillic acid, caffeic acid, syringic acid, *p*-coumaric acid, ferulic acid, synaptic acid, cinnamic acid	
Rye	316.42	PA: Gallic acid, protocatechuic acid, 4-hydroxybenzoic acid, vanillic acid, caffeic acid, syringic acid, *p*-coumaric acid, ferulic acid, synaptic acid, cinnamic acid	
Rice	128.60	PA: Gallic acid, 4-hydroxybenzoic acid, vanillic acid, syringic acid, *p*-coumaric acid, ferulic acid, synaptic acid, cinnamic acid	
Black rice	189.90	PA: Protocatechuic acid, 4-hydroxybenzoic acid, vanillic acid, *p*-coumaric acid, ferulic acid	
Corn	1152.82	PA: 4-Hydroxybenzoic acid, vanillic acid, caffeic acid, syringic acid, *p*-coumaric acid, ferulic acid, synaptic acid, cinnamic acid	
Triticale	457.19	PA: Gallic acid, protocatechuic acid, 4-hydroxybenzoic acid, vanillic acid, caffeic acid, syringic acid, *p*-coumaric acid, ferulic acid, synaptic acid, salicylic acid, cinnamic acid	
Buckwheat	1090.65	PA: Ferulic acid derivatives, gallic acid, 4-hydroxybenzoic acid, 5-caffeoylquinic acid, syringic acidF: Rutin, kaempferol-3-*O*-rutinoside, quercetin, apigenin, kaempferol, dihydromyricetin	
Quinoa • White • Red • Black	25.96–411.09 127.69–468.08 141.52–658.27	PA: 4-Hydroxybenzoic acid, caffeic acid, protocatechuic acid, *p*-coumaric acid, ferulic acid, sinapic acid, rosmarinic acid, and othersF: Catechin, quercetin, kaempferol	
Legumes			
Chickpea	193.82	PA: Gallic acid, protocatechuic acid, 4-hhydroxybenzoic acid, syringic acid	Gao et al. (2017); Giusti et al. (2019); Wang et al. (2016); Yeo and Shahidi (2020)
Black bean	1388.71	PA: Protocatechuic acid, vanillic acid, *p*-coumaric acid, ferulic acidF: Catechin, epicatechin, rutin, isoquercitrin, quercitrin	
Soybean	1285.56	PA: Gallic acid, protocatechuic acid, vanillic acid, syringic acid, *p*-coumaric acid, ferulic acid, *p*-hydroxybenzoic acid, sinapic acidF: Epicatechin, rutin, isoquercitrin, quercitrin	

(Continues)

TABLE 2 (Continued)

Food source	Total BPs (μg/g)	Main BPs	References
Mung bean	949.67	PA: Gallic acid, protocatechuic acid, caffeic acid, *p*-coumaric acid, ferulic acidF: Catechin, rutin, isoquercitrin	
Kidney bean	413.97	PA: Protocatechuic acid, vanillic acid, ferulic acidFlavonoids: Catechin, rutin	
Lentil	73.1–458	PA: Gallic acid, methyl vanillate, protocatechuic acid, caffeic acid, *p*-coumaric acid, ferulic acid, synaptic acid, syringic acidF: Catechin-3-glucoside, catechin, epicatechin, luteolin 3′−7-diclucoside, kaempferol 3-*O*-glucosideProanthocyanidins: Procyanidin dimer A and B, prodelphinidin dimer A, procyanidin trimer C1 and A	
Lentil hulls	13[b]	PA: Protocatechuic acid derivativesF: Catechin, epicatechin, luteolin 7-*O*-glucoside, quercetin glucoside, quercetin, kaempferol, apigenin, kaempferol derivatives	
Snow pea	1.4	PA: Ferulic acid, *p*-coumaric acid, sinapic acid	
Cow pea	4.4–9.5	PA: *p*-Coumaric acid	
Seeds			
Blackberry	7.93[a]	PA: Protocatechuic acid, *p*-coumaric acid, gallic acid, caffeic acid, gallic hexosideF: Catechin, epicatechin, quercetin, epigallocatechin, myricetin, quercetin pentose, epicatechin gallate, quercetin-3-*O*-glucuronideProanthocyanidins: Procyanidin dimers B1, B3, and B4	Ayoub et al. (2016)
Black raspberry	4.60[a]	PA: Protocatechuic acid, *p*-coumaric acid, gallic acid, caffeic acid, gallic hexosideF: Catechin, epicatechin, quercetin, epigallocatechin, myricetin, epicatechin gallate, quercetin-3-*O*-glucuronideProanthocyanidins: Procyanidin dimers B1, B2, and B4Anthocyanins: Peonidin-3-*O*-glucoside	
Blueberry	1.05[a]	PA: Protocatechuic acid, *p*-coumaric acid, gallic acid, caffeic acid, syringic acid, gallic hexosideF: Myricetin, quercetin pentose, kaempferol hexosideProanthocyanidins: Procyanidin dimers B1 and B3Anthocyanins: Peonidin-3-*O*-arabinoside, petunidin-3-*O*-arabinoside, peonidin-3-*O*-glucoside, delphinidin-3-*O*-hexoside, petunidin-3-*O*-galactoside, cyanidin-3-(6-acetyl)-glucoside	

(Continues)

TABLE 2 (Continued)

Food source	Total BPs (μg/g)	Main BPs	References
Sunflower	127.4	PA: Gallic acid, protocatechuic, *p*-coumaric acid, ferulic acid, sinapic acidF: Quercetin, kaempferol, apigenin	Pająk et al. (2014)
Flaxseeds	4.69[a]	PA: Gallic acid, protocatechuic acid, hydroxybenzoic acid, vanillic acid, syringic acid, sinapic acid, ferulic acid, *p*-coumaric acid, cinnamic acid	
Vegetables and fruits			
Radish	275.1	PA: Gallic acid, protocatechuic acid, caffeic acid, *p*-coumaric acid, ferulic acid, sinapic acidF: Quercetin, kaempferol	Pająk et al. (2014); Ru et al. (2019)
Potatoes	292.5	PA: Caffeic acid, *p*-coumaric acid, ferulic acid	
Broccoli	427.1	PA: Gallic acid, protocatechuic acid, caffeic acid, *p*-coumaric acid, ferulic acid, chlorogenic acid, sinapic acidFlavonoids: Quercetin, kaempferol, luteolin, apigenin	
Onion (two varieties)	0.75; 1.03	PA: Gallic acid, vanillic acid, *p*-coumaric acid, sinapic acidF: Luteolin, quercetin, rutin	
Carrot	380.29	PA: Caffeic acid, *p*-coumaric acid, caffeoyl glucose, 5-*O*-caffeoylquinic acid, and 4-*O*-caffeoylquinic acidF: Rutin, quercetin, apigenin, luteolin, isocoumarin	Viacava et al. (2020)
Tomato	1.0	PA: *p*-Hydroxybenzoic acid, caffeic acid, ferulic acid, chlorogenic acid, *p*-coumaric acid, sinapic acidF: Naringenin, hesperidin, luteolin, quercetin, rutin	Alu'datt et al. (2019)
Hot peppers (three varieties)	1.40; 0.69; 1.22	PA: *p*-Hydroxybenzoic acid, gallic acid, caffeic acid, ferulic acid, vanillic acid, chlorogenic acid, *p*-coumaric acid, syringic acid, sinapic acidF: Luteolin, quercetin, rutin	
Sweet peppers (two varieties)	1.14; 0.83	PA: *p*-Hydroxybenzoic acid, gallic acid, caffeic acid, ferulic acid, vanillic acid, chlorogenic acid, *p*-coumaric acid, sinapic acidF: Luteolin, quercetin, rutin	
Olives (two varieties)	4.71; 7.32	PA: *p*-Hydroxybenzoic acid, gallic acid, ferulic acid, vanillic acid, chlorogenic acid, *p*-coumaric acid, sinapic acidOthers: Tyrosol, hydroxytyrosolF: Apigenin, hesperidin, luteolin, quercetin, rutinOthers: Oleuropein	

(Continues)

TABLE 2 (Continued)

Food source	Total BPs (μg/g)	Main BPs	References
Apple (two varieties)	0.71; 0.45	PA: Chlorogenic acid, *p*-coumaric acid, sinapic acidF: Epicatechin, naringenin, luteolin, quercetin, rutin	
Grape (three varieties)	3.52; 2.73; 1.08	PA: *p*-Hydroxybenzoic acid, gallic acid, ferulic acid, vanillic acid, chlorogenic acid, *p*-coumaric acid, sinapic acidFlavonoids: Epicatechin, luteolin, quercetin, rutin	
Pomegranate (two varieties)	1.17; 0.82	PA: Gallic acid, ferulic acid, vanillic acid, chlorogenic acid, *p*-coumaric acid, syringic acid, sinapic acidF: Epicatechin, rutin	
Raspberry	354.97	PA: Gallic acid, chlorogenic acid, caffeic acid, *p*-, *m*-, and *O*-coumaric acid, ferulic acid, vanillic acidF: Catechin, epicatechin, epigallocatechin gallate, quercetin, myricetin, morin, naringenin, apigenin, kaempferolStilbenes: Resveratrol	Kim (2018)
Cranberry	161.52	PA: *p*-Hydroxybenzoic acid, chlorogenic acid, caffeic acid, *p*- and *O*-coumaric acid, ferulic acid, vanillic acidF: Catechin, epicatechin, epigallocatechin gallate, quercetin, morin, naringenin, apigenin, kaempferolStilbenes: Resveratrol	
Blueberry	241.04	PA: *p*-Hydroxybenzoic acid, chlorogenic acid, caffeic acid, *p*-coumaric acid, ferulic acid, vanillic acidF: Catechin, epicatechin, epigallocatechin gallate, quercetin, morin, naringenin, apigenin, kaempferolStilbenes: Resveratrol	

Abbreviations: F, flavonoids; PA, phenolic acids.

[a]mg gallic acid equivalent/g

[b]mg/g

change in their bioaccessibility and bioavailability, which may directly affect their healthy properties.

Food processing usually focuses on inactivating pathogens and enzymes, prolonging shelf-life, making products available out of season, and providing a better nutritional profile. However, food processing might also be critical for the bioaccessibility of PCs, as it may have either a positive or a negative impact (Cilla et al., 2018). Both traditional processing technologies such as pasteurization, sterilization, grinding, cooking, baking, drying, and so forth and nonthermal technologies such as high-pressure processing, high-intensity pulsed electric field, and ultrasound may affect the phenolic content and/or profile of the food materials (Cilla et al., 2018). Even though many fruits and vegetables have already been investigated for changes in PCs bioaccessibility due to processing, data dealing with the effect of processing and fermentation on PCs associated with fiber after in vitro gastrointestinal digestion remain limited.

Overall, a schematic summary of the impact of processing conditions on the bioaccessibility and bioavailability of bound PCs in different food systems can be found in Table 3. Regarding the impact of cooking conditions on the BPs profile, Rocchetti, Lucini, Chiodelli, Giuberti, Montesano, et al. (2017) showed that cooking by boiling lowered the bound-to-free ratio of phenolics in gluten-free pasta formulated with alternative nonwheat flours. In this regard, flavonoids showed the highest reduction among bound phenolics compared to the other classes (Rocchetti, Lucini, Chiodelli, Giuberti, Montesano, et al., 2017). Therefore, in a health-promotion perspective, the cooking process may also alter the bioaccessibility of PCs at both small and large intestinal levels via the reduction of their bound fraction (Rocchetti, Lucini, Chiodelli, Giuberti, Gallo, et al., 2017). Still concerning cereals, Zhao et al. (2018) investigated the PCs bioaccessibility in defatted rice bran as well as its soluble and insoluble dietary fibers. Their results revealed that insoluble dietary fiber from defatted rice bran showed lower phenolic bioaccessibility than the defatted rice bran itself and the soluble dietary fiber from the same matrix. This can be explained by the fact that fiber–BPs interactions also affected bioaccessibility. These results suggested that the bioaccessibility of BPs was significantly lower when compared to FPs. More recently, Chen et al. (2019) evaluated the effect of extrusion on the phenolic bioaccessibility of defatted rice bran, showing an increase of phenolic bioaccessibility of 40.5% in extruded defatted rice bran compared to the unprocessed sample. On the other hand, Kurek et al. (2018) observed that the phenolic bioaccessibility values of bread fortified with oat, apple, and flax were 43.4%, 45.3%, and 67.7%, respectively. Oat and apple dietary fibers showed lower bioaccessibility values than the control bread (52.1%), whereas flax dietary

TABLE 3 Impact of processing conditions on the bioaccessibility of bound phenolic compounds from different food systems

Food matrix	Processing conditions	Phenolic bioaccessibility	Reference
Rice bran	Defatting step	Lower bound phenolic bioaccessibility from insoluble fiber of defatted rice bran.	Zhao et al. (2018)
Rice bran	Defatting and extrusion steps	The combined processing conditions accounted for an increase (+40.5%) of phenolic bioaccessibility.	Chen et al. (2019)
Bread	Fortification with oat, apple, and flax	The highest phenolic bioaccessibility (+67.7%) observed with flax fortification.	Kurek et al. (2018)
Strawberry juice	Ultrasound processing of fiber added to the juice	Increase of phenolic bioaccessibility during in vitro gastrointestinal digestion.	Cassani et al. (2018)
Tomato sauce	Addition of different % of dietary fiber (inulin)	The addition of 10% inulin resulted in a decrease of in vitro bioaccessibility of polyphenols.	Tomas et al. (2018)
Blackberry puree	Addition of different % of dietary fibers (inulin and pectin)	Overall reduction of phenolic bioaccessibility during in vitro gastrointestinal digestion.	Tomas et al. (2020)
White and pigmented rice	Solid-state fermentation method	Increase of phenolic bioaccessibility.	Janarny and Gunathilake (2020)
Okara	Microbial fermentation with *Lactobacillus plantarum*	Decrease of phenolic bioavailability because of fiber–phenolic interactions.	Quintana et al. (2020)
Gluten-free pasta	Cooking by boiling	The cooking process altered the potential bioaccessibility of polyphenols lowering their bound-to-free ratio.	Rocchetti et al. (2017)

fiber had higher values. These findings suggest that different dietary fiber sources may affect the bioaccessibility of PCs differently. Also, Cassani et al. (2018) investigated the impact of ultrasound processing (7.5 min, 40 kHz, 180 W) of fiber-, inulin-, and oligofructose-enriched strawberry juices on the phenolic bioaccessibility after in vitro gastrointestinal digestion. Overall, processing was found to increase the in vitro bioaccessibility of PCs. The trend observed is related to the release of ellagic acid from its ester form, likely deriving from the hydrolysis of ellagitannins, a mechanism related to the alkaline pH of the intestinal environment. Another reason was that the processing conditions resulted in the degradation of dietary fiber, likely determining the release of ellagic acid in the small intestine during the digestion of fiber-enriched strawberry juices (Cassani et al., 2018). These authors suggested that bioaccessible compounds of strawberry juices can be protected with the combination of fiber enrichment and nonthermal processing. In a previous study (Tomas et al., 2018), tomato sauce containing inulin (5% and 10% w/w) significantly affected the PCs content and total antioxidant capacity after in vitro gastrointestinal digestion due to the interaction between inulin and PCs. More recently, the addition of inulin and pectin to blackberry puree decreased the PCs bioaccessibility (Tomas et al., 2020). A possible explanation for the trends observed could be the incomplete release of PCs due to the presence of fiber, and the interactions between PCs and fiber, likely limiting their bioaccessibility (Cassani et al., 2018). The particle size of the dietary fiber was also observed to affect the bioaccessibility of PCs. In a recent study by Janarny and Gunathilake (2020), solid-state fermentation was carried out using *Rhizopus oryzae*, and the bioaccessibility and bioavailability of bioactives in four different varieties of white and red rice bran were investigated. The results indicated that phenolic bioaccessibility increased with solid-state fermentation. This trend was explained by the structural breakdown of the bran matrix related to the increase in the extracellular enzymes produced by fungal metabolism. Another explanation was that fermentation improved the conversion of bioactive compounds into more absorbable forms by transformation. In another study, Chen et al. (2019) evaluated the impact of fermentation with *R. oryzae* on the bioaccessibility of PCs in defatted rice bran. It was observed that the amount of bioaccessible PCs in fermented defatted rice bran increased during the gastric phase from 347.04 to 567.16 mg GAE/100 g, and from 395.11 to 649.55 mg GAE/100 g after the pancreatic phase. Also, Quintana et al. (2020) in vitro digested okara and okara fermented with *Lactobacillus plantarum*. The authors observed a strong decrease in the antioxidant activity of okara and fermented okara after gastric and intestinal digestion. The researchers concluded that high amounts of fiber in okara interacted greatly with these compounds, limiting their bioavailability and antioxidant activity.

In short, bioprocessing and fermentation may enhance the content of FPs by leading to their liberation from fiber. However, to obtain more concrete and significant results, additional studies are required in order to specifically investigate the fate of dietary fiber–phenolic interactions during processing.

3 | FUNCTIONAL IMPLICATIONS OF PHENOLICS–FOOD INTERACTION

3.1 | Interaction between PCs and other food components

In the last years, PCs are receiving prominent interest from food manufacturers and consumers for their correlation with the prevention of several diseases. These compounds are ingested through the diet in significant amounts, around 1 g/day, an amount that may be increased through supplements. However, their healthful effects and their role in modulating the prevalence of noncommunicated diseases are intricate to validate due to (1) the wide variability of chemical structures and bioactive actions; (2) the high variability between vegetable varieties, the presence of nonextractable PCs usually link to fiber, and the effect of technological and culinary treatment difficult to estimate the actual content in foods; (3) the effect of food matrices as modulators in PCs actions and the interaction between PCs and other food components could lead to synergistic or antagonists effects; (4) the interaction between PCs with cell-membrane receptors, digestive enzymes, or gut microbiota during the gastrointestinal digestion and absorption; and (5) their metabolism by the human body and the polyphenol gut microbiota metabolism in each metabotype. All of the mentioned intricacies could finally influence PCs bioavailability and the further biological effect. Besides, the chemical structure of PCs can affect their biological properties, such as bioavailability or antioxidant activity. Still, besides these, PCs can bind with cell receptors or digestive enzymes and could exert specific interactions with other food components. These aspects are discussed in this section.

3.1.1 | Matrix effect: Interaction with other food components

PCs have the ability to interact not only with fiber but also with other compounds present in foods, such as carbohydrates, proteins, or lipids. Paradoxically, the interaction between PCs and these food macromolecules and the

related effects on the bioactivity of PCs have been poorly investigated. For example, the systematic consumption of tea (Bøhn et al., 2012) and coffee (Crippa et al., 2014) was related to a lower risk of cardiovascular disease. Considering that the consumption of these two beverages is usually accompanied by milk, research has been focused on evaluating the impact of milk proteins on the health-promoting properties of these beverages. In fact, it is well known that PCs can bind to proteins, thus affecting both protein and PCs activities. Despite the limited information available, it seems that the addition of bovine, whey, or soymilk completely suppresses the cardiovascular caring effect of tea (van der Burg-Koorevaar et al., 2011; Von Staszewski et al., 2011). PCs–protein interactions could affect not only the bioavailability of both proteins and PCs, but also protein functions and PCs antioxidant potential. Pessato et al. (2018) reported that whey proteins could interact with phenolics via noncovalent bonds, as highlighted by the reduction of surface hydrophobicity and by a negative exothermic enthalpy using calorimetry. Consistently, the radical scavenging activity of epigallocatechin gallate (EGCG) was found to be higher in the absence of milk proteins. Telmo et al. (2021) evaluated the ability of yeast proteins to bind phenolics during the fining process of phenolics, showing the highest binding ability for tannins, followed by anthocyanins and phenolics acids. Similarly, both collagen and caseins could bind polyphenols, in turn presenting lower degrees of in vitro digestion following interaction with phenolics (Zhao et al., 2020). Nonetheless, other studies showed controversial information because no differences were found in the digestive catechin recoveries (or bioaccessibility) of black tea consumed with or without milk (5.6%−40%) (Dubeau et al., 2010; van der Burg-Koorevaar et al., 2011). These studies used in vitro antioxidant assays (prone to interference by reducing agents) and organic solvents such as methanol for catechin measurement purposes. However, the presence of organic solvents could break down the interaction between PCs and proteins, leaving bare the reliability of these conclusions. The lack of standardized protocols for the evaluation of antioxidant profiles of a sample for in vitro studies could explain the reported discrepancies.

Nonetheless, considering the previous evidence on significant PCs–protein interactions, the actual antioxidant potential can be consequently affected, as in vitro studies suggested. Adding milk, sugar, or milk with sugar in tea could increase and stabilize PCs' in vitro antioxidant activity, although with a corresponding reduction of the radical scavenging activity. With regard to this, it is advisable to harmonize the debate related to the available in vitro methods to assess PCs antioxidant properties, considering the wide variety of existing protocols.

The research progress in the field of PCs–protein interaction (in solution phase) at the molecular level is not sufficient to fully explain the effects on antioxidant capacity in vitro or bioactivity in vivo.

3.1.2 | Interaction between PCs and enzymes

Digestion is a crucial step for understanding the bioavailability, metabolism, and pharmacokinetics of PCs. The digestion process may be influenced by the interactions between food components and digestive enzymes, thus affecting human health (Giuberti et al., 2020). Hence, understanding how food components interact during digestion is essential for elaborating nutritional interventions based on PCs. For example, previous works indicated that EGCG can interact with heme oxygenase-1 (HO-1), which is shown to be cytoprotective through its antioxidant activities. Besides, the action of EGCG on HO-1 is reduced by pharmacological inhibitors of phosphatidylinositol 3-kinase (PI3K) and MEK1/2, which implies its action may be through PI3 kinase/Akt and ERK cascade pathways. EGCG is also able to activate eNOS expression through these pathways. The ability of EGCG as an antioxidant compound has been widely studied in different cellular tissues such as macrophages, colon carcinoma cells, mammalian carcinoma cells, and hepatic tissues, among other (Sharifi-Rad et al., 2020). The vast majority of the in vitro or in vivo studies used EGCG and other PCs as pure standards. EGCG activity could be affected by the administration form and by the interaction with other food components. Furthermore, after EGCG ingestion, several metabolic modifications could occur, and the compound will not reach the stomach or colon in the same structural form as the liver or cardiomyocytes. As previously discussed, PCs can interact with various proteins based on their structure, ratio of protein/polyphenol, pH of the medium, among others. PCs' binding to the protein chain usually occurs through hydrogen bonding or hydrophobic attraction (formation of soluble protein–polyphenol aggregates) as the first step in the onset of PCs–protein interactions, followed by self-association of soluble PCs–protein complexes to produce large and insoluble aggregates. The protein three-dimensional structure is usually lost as resulting of PCs–protein interaction, with potential influence on their biological activity. For the same reason, interactions of PCs with digestive enzymes (glucosidases such as α-amylase and α-amyloglucosidase; proteases such as trypsin) or other enzymes such as tyrosinase, peroxidase, decarboxylase, squalene epoxidase, and ribonuclease are known to reduce their activities (Giuberti et al.,

2020). Indeed, the interactions between PCs and several proteins related to oxidative stress and cell damage could be exploited to provide a radical scavenging mechanism, thus promoting human health. Moreover, the effect toward digestive enzymes was related to a protective effect toward metabolic disorders such as diabetes or obesity.

3.1.3 | Interaction between PCs and cell membranes

The physicochemical properties of PCs allow them to participate in different metabolic cellular reactions. However, these latter are dependent on the ability of PCs to cross the biological membranes. In this context, previous studies demonstrated that PCs reach plasma following ingestion of PCs-rich foods, and the transport across the cell membranes is strictly influenced by PCs' structure and nature. Indeed, although aglycon PCs could cross the membranes to passive diffusion, PCs glycosides are mainly transported through specific transporters.

In the last years, the in vitro studies on the transport of PC glycosides generally assumed no modification until they reached the colon, where gut microbiota enzymes mediate a deglycosylation process. However, intervention studies highlighted that the primary site of absorption of flavonoid glycosides was the small intestine (Hostetler et al., 2017). In the specific case of quercetin and its glucosides, they can be absorbed earlier, thus resulting in a higher plasma peak concentration of total quercetin. In this regard, increasing scientific evidence highlighted that epithelial brush border membrane transporters play a pivotal role in the absorption of dietary PCs. In this regard, the ability of flavonoids to interact with the polar/nonpolar regions of the lipid bilayer characterizing cell membranes was demonstrated by various experimental approaches (such as X-ray scattering and molecular simulations), revealing that the flavonoids quercetin, genistein, and daidzein are mainly located close to the polar area of the bilayer in the region composed of the phosphate and carbonyl groups of fatty acids. Overall, the transporter-dependent translocation of quercetin glucosides was found to be more efficient than the spontaneous penetration of quercetin aglycones through the lipid bilayer (Tarahovsky et al., 2014). Also, the main insulin-regulated glucose transporter (GLUT4) may also participate in the translocation of hydrophobic flavonoid aglycones, with genistein being able to inhibit this transporter and regulating the insulin-dependent glucose transport in adipocytes (Tarahovsky et al., 2014). On the other hand, flavonoids can inhibit the monocarboxylate transporters MST2 and SLC-16, which are responsible for the translocation of lactates, pyruvates, ketone bodies, and various drugs (Tarahovsky et al., 2014); however, further studies are required to better understand the involvement of these transporters in flavonoid translocation across the membrane. Anthocyanins stand out as faster flavonoid compounds able to permeate the gastric mucosa, as some pharmacokinetics studies showed in rats and humans. In this regard, malvidin 3-glucoside and malvidin-3-galactoside were reported as the predominant compounds detected in both plasma and tissues of mice after both a single dose and long-term feeding of bilberry anthocyanins (Kalt, 2019). From the wide diversity of PCs, flavonoids have been the most widely studied. Among procyanidins, the flavan-3-ols monomers have been extensively studied, whereas oligomers have received much less attention. Procyanidins are generally poorly absorbed, whereas dimers and trimers have been detected in rat plasma, with a maximum concentration reached 1 h after oral intake of a grape seed extract (Serra et al., 2009). Phenolic acids such as caffeic acid are easily absorbed through the gut barrier, where the monocarboxylic acid transporter is involved. The bioavailability of PCs was usually studied in vitro at the intestinal level by using a Caco-2 cell model, but the involvement of gastric conditions has been recently implicated in the absorption of PCs. It is important to notice that PCs are normally metabolized in the gut, but most studies are made in the intact structures of PCs. After the absorption, PCs are conjugated to glucuronide, sulfate, and methyl groups in the gut mucosa and inner tissues. Among PCs, procyanidins remain stable under digestion conditions; their metabolism is limited even at the colon compartment, and their bioavailability has been widely studied by combining in vitro and in vivo models. Furthermore, the PCs that reach the colon are extensively metabolized by the gut microbiota into a wide array of low-molecular-weight phenolic acids.

Notwithstanding, according to literature, the major PCs are absorbed in the intestine, and brush-border membranes and gut microbiota are responsible for their metabolism. However, the presence of digestive enzymes and the pH conditions of the stomach seem to exert a structural effect on PCs. Also, PCs can bind to cellular membranes. As referred, PCs interact with proteins and lipids, which open the possibility to act as a bond between neighboring bilayer surfaces, as the first step in membrane aggregation. These phenomena could also affect the lateral compartmentalization and segregation of cell surface compounds and the signal transduction and cell–cell interaction. The lack of water solubility of some PCs could also influence the PCs accumulation in biological membranes, where they could interact with different signal transducers or receptors modulating the lipid-phase behavior and finally influencing their function.

3.2 | Microbial transformation of phenolics in the large intestine

The expected health efficacy of dietary PCs depends on two crucial and interconnected aspects: bioaccessibility and bioavailability, both defined during the digestion process. The physiological conditions in the stomach and small intestine are insufficient to de-compartmentalize some phenol–food macromolecules complexes that are moved into the large intestine, where they are exposed to the catabolic action of a vast mass of microorganisms, commonly known as intestinal microbiota (Phan et al., 2020). The amount of BPs reaching the colon and the rate of microbial transformation are markedly influenced by the characteristics of the food matrix, the type of phenol–food macromolecule interaction, and the chemical nature of the PC. In turn, the release kinetic of food components to the lumen can be manipulated by the addition of certain ingredients (enriched food) or technological process (heat, fractionation, fermentation) (Juániz et al., 2017; Koistinen et al., 2017; Le Bourvellec et al., 2019; Phan et al., 2020). The catabolic activity of microbiota is commonly referred to as colonic/microbial fermentation and encompasses phase I reactions such as deglycosylation, dehydroxylation, α- and β-oxidation, dehydrogenation, demethylation, decarboxylation, C-ring fission, and C-ring cleavage (Juániz et al., 2017; Mosele, Macià, Romero, et al., 2016). As a consequence of colonic fermentation, the parent PC undergoes several structural modifications resulting in the generation of microbial metabolites. Colonic fermentation occurs as the bolus moves through the gut following a logical line of sequential transformations (Phan et al., 2020). BPs should be firstly released from the food network, and then the released compounds can be absorbed by colonocytes or are metabolized further by bacteria. In sum, we can imagine the colon lumen as a mixture of different but related phenolic derivatives, some of them being intermediates and other produced at a different rate according to the time of exposition and the microbiota composition (Juániz et al., 2017; Le Bourvellec et al., 2019; Mosele, Macià, Romero, et al., 2016). Below, we provide an overview of the colonic fate of PCs, focusing on the subclasses frequently present in the BPs fraction of foods.

3.2.1 | Phenolic acids

Ferulic acid

Its bound form is abundant in whole grains, fruits, and vegetables (Bresciani et al., 2016; Koistinen et al., 2017; Rocchetti, Bhumireddy, et al., 2019). Under *in vitro* conditions, dihydroferulic, caffeic, and 3-(3′,4′-dihydroxyphenyl)propionic acids have been described as early metabolites that can be further metabolized to 3-(3-′ o 4′-hydroxyphenyl)propionic, 3-phenylpropionic, protocatechuic, 3-(3′-hydroxy)benzoic, benzoic, and vanillic acids (Koistinen et al., 2017; Pereira-Caro et al., 2015; Phan et al., 2020). The presence of 2-(3,4-dihydroxyphenyl) and 2-(3-hydroxyphenyl)acetic acids, phenyllactic acids, and 4-methylcatechol during colonic fermentation of ferulic acid-rich foods has been attributed to the diferulates metabolism (Koistinen et al., 2017). Hydroxyhippuric acid derivatives, together with other microbial metabolites like dihydroferulic acid, previously described in vitro colonic fermentation, represent an important percentage of total circulating and excreted phenolic fractions detected after intake of whole-grain foods (Bresciani et al., 2016) (Table 4).

Caffeic acid

Caffeic acid and its esterified forms with quinic acid (chlorogenic acids) are important PCs in coffee, vegetables, and fruits present in the free and bound fractions (Juániz et al., 2017). When chlorogenic acid reaches the colon, it can be reduced to dihydrocaffeoyl quinic acid and/or hydrolyzed into caffeic and quinic acids by microbial enzymes. As observed in Table 4, the gut metabolism of quinic acid can take an oxidative or reductive pathway to produce benzoic or cyclohexane carboxylic acid-related compounds, respectively (Pinta et al., 2018). 3-(3′,4′-Dihydroxyphenyl)propionic acid and 3-(3′-hydroxyphenyl)propionic acid were described as predominant microbial metabolites of caffeic acid and dihydrocaffeoyl quinic acid (Juániz et al., 2017; Tomas-Barberán et al., 2013). Minor derivatives include benzoic, phenylpropionic, and phenylacetic acids and dihydroxybenzene (Gómez-Juaristic et al., 2018). After acute intake of coffee, free and phase II microbial metabolites of chlorogenic acid were detected in blood and urine to a greater extent than those resulted from small intestine absorption (Gómez-Juaristi et al., 2018; Mills et al., 2017) (Table 4).

Gallic acid

It is found in a wide range of plant products as such, forming polymers (gallotannins) or linked to other PCs (epigallocatechin gallate, theaflavins) (Mosele, Macià, Motilva, et al., 2016; Mosele, Macià, Romero, et al., 2016). Under in vitro conditions, it was deduced that after hydrolysis of gallotannins and release from the food matrix, gallic acid is initially transformed to protocatechuic acid, which is further degraded to catechol and *p*-hydroxyphenylbenzoic acid (Mosele, Macià, Romero, et al., 2016). After acute intake of *Arbutus unedo* rich in gallotannins, an increase in plasma and urine levels of colonic metabolites of

TABLE 4 Microbial metabolites of phenolic acids and lignans identified after in vitro fermentation and dietary interventions studies

Phenolic compounds	Source	Study	Main phenolic content	Detected microbial metabolites	Reference
Ferulic acid and derivatives	Bread enriched with native rye bran (NB) and bioprocessed rye bran (BB)	In vitro digestion and in vitro colonic fermentation. Human feces	Diferulic acid, ferulic acid, sinapic acid, *p*-coumaric acid	Dihydroferulic acid, caffeic acid, 3-(3′- and 4′-hydroxyphenyl)propionic acid, 3-(3′-hydroxy)benzoic acid. From diferulic acid: 3-phenyllactic acid, 3-(4-hydroxyphenyl)lactic and phenylacetic acids	Koistinen et al. (2017)
	Ferulic acid	In vitro colonic fermentation. Human feces	Pure compound	Dihydroferulic acid, 3-(4′-hydroxyphenyl) propionic acid	Pereira Caro et al. (2015)
	Fiber from apple cell wall (ACW) and pure bacterial cellulose (BC). Ferulic acid	In vitro digestion and in vitro colonic fermentation of ACW and BC with pure ferulic acid. Pig feces	Pure compound	Dihydroferulic acid, 3-(3′,4′-dihydroxyphenyl)propionic acid, 4′-hydroxyphenylacetic acid	Phan et al. (2020)
	Bread prepared with whole or aleurone grain	Healthy volunteers. Acute intake. Urine 48 h and blood 24 h	Whole grain bread 87 mg FA/dose; Aleurone bread 43 mg FA/dose; Whole grain bread 87 mg FA/dose	Dihydroferulic acid, dihydroxyphenylpropionic acid, hydroxybenzoic acid.	Bresciani et al. (2016)
Caffeic acid and derivatives	Raw and cooked cardoon	In vitro digestion and in vitro colonic fermentation. Human feces	More than 50% of content corresponds to chlorogenic acid	Caffeic acid, protocatechuic acid, dihydrocaffeoyl quinic acid, dihydroxyphenylpropionic acid, 3-(3′-hydroxyphenyl)propionic acid	Juániz et al. (2017)

(Continues)

TABLE 4 (Continued)

Phenolic compounds	Source	Study	Main phenolic content	Detected microbial metabolites	Reference
	Isotopically labelled and non labelled quinic acid	In vitro colonic fermentation. Human feces	Pure compound	Oxidative path: tri-, di-, and mono-hydroxycyclohexane carboxylic acid Reductive path: hydroxybenzoic acid, benzoic acid Intermediate metabolites: dehydroquinic acid, shikimic acid, dehydroshikimic acid	Pinta et al. (2018)
	Chlorogenic acid	In vitro colonic fermentation. Human feces	Pure compound	Caffeic acid, 3-(3′,4′-dihydroxyphenyl)propionic acid, hydroxyphenylpropionic acid, phenylpropionic acid, dihydrocaffeoyl quinic acid, 3-*O*-(3-hydroxycinnamoyl) quinic acid, caffeoyl glycerol, dihydrocaffeoyl glycerol, 2-(3-hydroxyphenyl)-ethanol.	Tomas-Barberán et al. (2013)
	Instant green/roasted (35/65) coffee blend	Healthy volunteers. Acute intakeBlood and urine	Cup of coffee contained 269.5 mg chlorogenic acid	Dihydroferulic acid, dihydroisoferulic acid, dihydroxyphenylpropionic acid, feruloyl glycine, dihydroferuloylquinic acid, dihydrocoumaroyl quinic acid, dihydrocaffeoyl quinic acid	Gomez-Juaristi et al. (2018)
	Coffee	Healthy man. Acute intake 50 ml. Blood	Low polyphenol: 89 mg chlorogenic acid/50 ml. High polyphenol: 310 mg chlorogenic acid/50 ml	Caffeic acid, methyl ferulic acid, ferulic acid	Mills et al. (2017)

(Continues)

TABLE 4 (Continued)

Phenolic compounds	Source	Study	Main phenolic content	Detected microbial metabolites	Reference
Gallic acid and derivatives	Arbutus unedo fruit	In vitro digestion and in vitro colonic fermentation	Gallic acid and gallotannins	Gallic acid, protocatechuic acid, catechol, *p*-hydroxybenzoic acid	Mosele, Macià, Romero, et al. (2016)
	Arbutus unedo fruit	Healthy adults. Acute intake 50 g lyophilized fruit. Blood and urine	Gallic acid and gallotannins/50 g	Gallic acid, pyrogallol, catechol, hydroxybenzoic acid, and hippuric acid	Mosele, Macià, Motilva, et al. (2016)
Ellagic acid and derivatives	Pomegranate juice (PJ), pulp (PP), and extract (PE)	In digestion and in vitro fermentation	Ellagitannins: 3.2 μmol/g PJ, 2 μmol/g PP, 282 μmol/g PE	Urolithin A, urolithin B, urolithin C, urolithin D, pentahydroxyurolithin	Mosele, Macià, et al. (2015)
	Raspberries	Healthy subjects. Acute intake 300 g raspberries. Urine and blood	300 g: 251 μmol ellagitannins	Dimethyl ellagic acid, urolithin A, urolithin B, isourolithin A	Ludwig et al. (2015)
	Pomegranate juice	Sustained intake 200 ml pomegranate juice. 3 weeks. Feces	200 ml juice: 878.9 mg ellagic acid and ellagitannins	Urolithin A, urolithin B, urolithin C, urolithin D, isourolithin A	Mosele, Gosalbes, et al. (2015)

gallic acid, mainly phase II species of pyrogallol, catechol, hydroxybenzoic acid, and hippuric acid, was observed (Mosele, Macià, Motilva, et al., 2016) (Table 4).

Ellagic acid

Ellagitannins are PCs of different degrees of polymerization formed by ellagic acid and are present in substantial amounts in pomegranate and some nuts and berries (Ludwig et al., 2015; Mosele, Gosalbes, et al., 2015; Mosele, Macià, et al., 2015; Mosele, Macià, Motilva, et al., 2016; Mosele, Macià, Romero, et al., 2016). The polymerized forms can be partially degraded during gastrointestinal digestion. Still, most of them are closely associated with the food matrix and reach the colon where ellagic acid is released and subsequently transformed to pentahydroxy-urolithins and then as the time of contact with gut microbiota increases, dehydroxylation occurs to form tetra-, tri-, di-, and monohydroxylated compounds. Urolithin A (dihydroxy-urolithin) and urolithin B (hydroxy-urolithin) have been described as main microbial metabolites also detected under in vivo conditions (Ludwig et al., 2015; Mosele, Gosalbes, et al., 2015; Mosele, Macià, et al., 2015; Mosele, Macià, Motilva, et al., 2016). Microbiota composition seems to play an important role in the bioaccessibility of ellagic acid first because urolithins are more bioavailable than the parent compound and second because it was observed that some individuals are unable to produce them (Ludwig et al., 2015; Mosele, Gosalbes, et al., 2015; Mosele, Macià, Motilva, et al., 2016) (Table 4).

3.2.2 | Flavonoids

Anthocyanins

Commonly present as *O*-glycosides in colored plant products, they contribute to the bound phenolic fraction when interacting to cell walls of fruits, vegetables, cereals, and pulses (Ludwig et al., 2015; Mosele, Macià, et al., 2015; Mosele, Macià, Romero, et al., 2016; Rocchetti, Bhumireddy, et al., 2019). Interaction with dietary fiber tends to protect anthocyanins for degradation during the digestion in the small intestine, carrying them to the colon (Rocchetti, Bhumireddy, et al., 2019). Glycosides of anthocyanins are first deglycosylated to release the aglycone that undergoes C-ring fission and subsequent phase I metabolism to generate mainly phenolic acids (Chen et al., 2017; López de las Hazas et al., 2016; Phan et al., 2020). In vitro microbial metabolism of malvidin-rich products increased the production of pyrogallol and syringic, vanillic, benzoic, and phenylpropionic acids and those rich in pelargonidin produced mainly tyrosol and p-hydroxybenzoic acid (López de las Hazas et al., 2016). Cyanidin can be metabolized to pelargonidin and other metabolites such as protocatechuic, caffeic, vanillic, *p*-coumaric, and *p*-hydroxybenzoic acids, 2,4,6-trihydroxybenzaldehide, and catechol (Chen et al., 2017; Phan et al., 2020). Gallic and syringic acids, 2,4,6-trihydroxybenzaldehide, and pyrogallol were described in fermentation batches inoculated with delphinidin, and the appearance of 3-*O*-methylgallic acid was associated with petunidin catabolism (Chen et al., 2017). Also, microbial metabolites (protocatechuic, vanillic, isovanillic, ferulic, caffeic, hippuric, benzoic, phenylacetic, and phenylpropionic acids) account for the most abundant phenolic species in biofluids after the intake of radiolabeled cyanidin-3-*O*-glucoside and raspberries, thus highlighting the importance of colonic metabolites in the bioaccessibility and bioavailability of dietary anthocyanins (Ludwig et al., 2015) (Table 5).

Flavan-3-ols

Catechin, epicatechin, and their oligomeric and polymeric forms (procyanidins) are among the most studied compounds probably because they are present in foods of high-frequency consumption in several dietary patterns. It is well documented that phase I metabolism, procyanidins are hydrolyzed into their constitutive monomers that undergo C-ring cleavage to produce the mediated formation of 1-(3′,4′-dihydroxyphenyl)–3-(2′′,4′′,6′-trihydroxyphenyl)propan-2-ol and 1-(hydroxyphenyl)–3-(2′′,4′′,6′′-trihydroxyphenyl)propan-2-ol, different hydroxylation patterns of y-valerolactones, and valeric acid, which have been proposed as main microbial derivatives (Le Bourvellec et al., 2019; Phan et al., 2020). The subsequent modifications of valeric acids promote the appearance of dihydroxy, hydroxy, and phenylpropionic acids, which can be metabolized to simpler phenolic acids such as phenylacetic and benzoic acids with different hydroxylation patterns (Le Bourvellec et al., 2019). It was described that procyanidins with a high degree of polymerization could be less affected by the action of gut microbiota (Le Bourvellec et al., 2019) (Table 5).

Flavonols

Quercetin and kaempferol can be found as free or bound PCs in a wide range of plant products. The colonic fermentation of rutin (quercetin-3-rutinoside) is initiated by its de-glycosylation to release quercetin, which is further metabolized to produce mainly 3,4-dihydroxyphenylacetic acid. However, other metabolites such as 3-hydroxyphenylacetic, 3-(3′- and 4′-hydroxyphenyl)propionic, protocatechuic, and

TABLE 5 Microbial metabolites of the flavonoids subgroups identified after in vitro fermentation and dietary interventions studies

	Phenolic compounds	Source	Phenolic content	Study	Microbial metabolites	Reference
Anthocyanidins	CyanidinDelphinidin	Mulberries	Isolated (>95% purity) cyanidin-3-*O*-glucoside, cyanidin 3-*O*-rutinoside, delphinidin-3-*O*-rutinoside	In vitro fermentation. Rat feces	Initial appearance of chalcone pseudobase Cyanidins: 2,4,6-trihydroxybenzaldehide, protocatechuic acid, vanillic acid, *p*-coumaric acid, *p*-hydroxybenzoic acid, catechol Delphinidin: 2,4,6-trihydroxybenzaldehide, gallic acid, pyrogallol, syringic acid	Chen et al. (2017)
	MalvidinPelargo	Red grape and strawberry	Grape extract rich in malvidin Strawberry extract rich in pelargonidin	In vitro fermentation. Human feces	Malvidin: syringic acid, vanillic acid, hydroxyphenylpropionic acid Pelargonidin: *p*-hydroxybenzoic acid, tyrosol, hydroxyphenylacetic acid	López de las Hazas et al. (2016)
	Cyanidin	Pure standard	Cyanidin-3-*O*-glucoside incubated with apple cell wall (ACW) and pure bacterial cellulose (BC).	In vitro gastrointestinal digestion and in vitro fermentation. Pig feces	Cyanidin and pelargonidin aglycones, protocatechuic acid, hydroxybenzoic acid, caffeic acid	Phan et al. (2020)
	Cyanidin	Raspberries	53% of total phenolic content corresponds to anthocyanins, mainly cyanidin glycosides	Healthy subjects. Acute intake 300 g. Blood and urine	4-hydroxybenzoic acid, protocatechuic acid, hippuric acid, caffeic acid, ferulic acid, 3′,4′-dihydroxyphenylacetic acid, 3′-methoxy-4′-hydroxyphenylacetic acid, 4-hydroxyhippuric acid, dihydroxyphenylpropionic acid	Ludwig et al. (2015)

(Continues)

TABLE 5 (Continued)

	Phenolic compounds	Source	Phenolic content	Study	Microbial metabolites	Reference
	Catechin	Pure standard	Catechin incubated with ACW and pure BC.	In vitro gastrointestinal digestion and in vitro fermentation. Pig feces	5-(3′,4′-dihydroxyphenyl)valerolactone, 5-(3′,4′-dihydroxyphenyl)valeric acid	Phan et al. (2020)
	MonomersProcy	Apples	Apple matrix with covalent and noncovalent bond procyanidins with similar content of EC, Cat y procyanidins	In vitro fermentation. Human feces	5-(3,4-dihydroxyphenyl)-ɣ-valerolactone, 5-(3-hydroxyphenyl)-ɣ-valerolactone, 5-(3-hydroxyphenyl)valeric acid, 3-(3′,4′-dihydroxyphenyl)propionic, 3-(3′- and 4′-hydroxyphenyl)propionic acid, 3-phenylpropionic acid, 3,4-dihhydroxyphenylacetic acid, 3-hydroxyphenylacetic acid	Le Bourvellec et al. (2019)
	Quercetin	Pure standard	Rutin	In vitro fermentation. Human feces	3,4-dihydroxyphenylacetic acid, 3- and 4-hydroxyphenylacetic acid, Phenyl acetic acid, 3-(3′- and 4′-hydroxyphenyl)propionic acid, *p*-hydroxybenzoic acid	Mansoorian et al. (2019)
	Kaempferol	Pure compounds	Kaempferol	In vitro fermentation. Human feces	3-(4′-hydroxyphenyl)propionic acid, phenylacetic acid	Vollmer et al. (2018)
Flavonones	NaringeninHesperetin	Pure compounds	NaringeninHesperetin	In vitro fermentation. Human feces	Hesperetin: dihydroferulic acid, 3-(3′,4′-dihydroxyphenyl)propionic acid, 3-(3′-hydroxyphenyl)propionic acid Naringenin: 3-phenylpropionic acid	Pereira Caro et al. (2015)
	NaringeninHesp	Orange juiceFresh oranges	Fresh orange 1774 μmol and orange juice 751 μmol of flavanones mainly hesperidin and narirutin	Healthy subjects. Acute intake. Urine	3-(3′-hydroxy-4′-methoxyphenyl)propionic acid,3-(3′-hydroxyphenyl)hydracrylic acid, 4-hydroxyhippuric acid, and hippuric acid	Aschoff et al. (2016)
	NaringeninHesperetin	Pulp enriched orange juice	250 ml: 114 μmol naringenin-7-*O*-rutinoside, 329 μmol hesperetin-7-*O*-rutinoside as major compounds	Healthy subjects. Acute intake of 250 ml. Urine	3-(3′hydroxy-4′-methoxyphenyl)hydracrylic acid, 3-(3′hydroxyphenyl)hydracrylic acid, dihydroferulic acid, 3′-methoxy-4′-hydroxyphenylacetic acid, 4′-hydroxyphenyl acetic acid, hippuric acid, 3-hydroxyhippuric acid	Pereira Caro et al. (2015)

(Continues)

TABLE 5 (Continued)

Phenolic compounds	Source	Phenolic content	Study	Microbial metabolites	Reference
Apigenin	Pure compounds	Apigenin	In vitro fermentation. Human feces	3-(4′-hydroxyphenyl)propionic acid, 3-phenylpropionic acid, phenylacetic acid	Vollmer et al. (2018)
Luteolin	Raw and cooked cardoon	Luteolin glucoside and acetylglucoside	In vitro fermentation. Human feces	3-(3′,4′-dihydroxyphenyl)propionic acid, 3-(3′-hydroxyphenyl)propionic acid	Juániz et al. (2017)

p-hydroxybenzoic acids were also detected (Mansoorian et al., 2019). On the other hand, degradation products of kaempferol under in vitro conditions were 4-hydroxyphenylpropionic and phenylacetic acids (Vollmer et al., 2018). The role of carbohydrates interacting with flavonols in the gut is not completely clear because under in vitro conditions, the inhibition of microbial phenolic acids' production was observed (Mansoorian et al., 2019), but the presence of soy fiber enhances the bioavailability of quercetin glycoside after long-term feeding of rats (Trakooncharoenvit et al., 2019) (Table 5).

Flavanones

Naringenin, hesperetin, and its glycosylated forms interact with macromolecules of citric fruit pulp (Aschoff et al., 2016). Primary microbial metabolites detected under in vitro experiments and dietary interventions were quite similar. Hesperetin generates important amounts of 3-(3′-hydroxy-4′-methoxyphenyl)propionic (dihydroferulic acid), 3-(3′,4′-dihydroxyphenyl)propionic, and 3-(3′-hydroxyphenyl)propionic acids, whereas phenylpropionic acid was the major metabolite of naringenin (Pereira-Caro et al., 2015). Identification of the later metabolites was made together with 3-(3′hydroxy-4′-methoxyphenyl)hydracrylic acid, 3-(3′hydroxyphenyl) hydracrylic acid, and 3′-methoxy-4′-hydroxyphenylacetic acid in a complex urinary and plasma phenolic profile after acute intake of orange juice and whole fruit (Aschoff et al., 2016) (Table 2).

Flavones

Apigenin-7-glucoside is first deglycosylated by gut microbiota and then metabolized to naringenin (transient) and 3-(4′-hydroxyphenyl)propionic and 3-phenylpropionic acids (Vollmer et al., 2018). Additional metabolites, including phloretin, 3-(3′,4′-dihydroxyphenyl)propionic acid, and 4-hydroxycinnamic acid, can be detected in urine following apigenin-7-glucoside administration. Similarly, after the release of the aglycone, the microbial degradation of luteolin generates 3-(3′,4′-dihydroxyphenyl)propionic acid, 3-(3′-dihydroxyphenyl)propionic acid, 3,4-dihydroxyphenylacetic acid, and 3,4-dihydroxyphenylbenzoic acid (Juániz et al., 2017) (Table 5).

Isoflavones

Genistein, daidzein, and their glycosides are particularly abundant in soy and soy derivatives, gaining relevance in modern diets as animal-based products substitute. Daidzein is converted to equol, *O*-desmethylangolensin (ODMA), or dihydrodaidzein, and genistein is transformed into dihydroxygenistein and 6′-hydroxy-ODMA (Giuberti et al., 2020). Overall, the microbial metabolism of these

isoflavones can be stimulated by dietary fiber in the food matrix.

3.2.3 | Lignans

Seed oils are the richest lignan products but, considering the frequency of intake, whole grains-based products (especially rye), cruciferous vegetables, nuts, and fruits such as berries are significant contributors to the daily intake of lignans in Western diets (Rocchetti, Bhumireddy, et al., 2019). Among the most studied compounds of this group are secoisolariciresinol, matairesinol, lariciresinol, syringaresinol, pinoresinol, and isolariciresinol. In the large intestine, plant lignans are converted to the mammalian lignans enterodiol and enterolactone, that mediate the catabolic action of the gut microbiota. Regarding the colonic pathways of parent compounds, secoisolariciresinol can be converted to enterodiol, which is subsequently transformed into enterolactone or well converted to matairesinol that generates enterolactone. The metabolic pathway of pinoresinol includes its transformation into lariciresinol, which is subsequently converted to secoisolariciresinol that follows the fate described above. Isolariciresinol is transformed into lariciresinol and then to enterodiol and enterolactone. The amount of mammalian lignans produced by gut microbiota could be affected by the food matrix characteristics; for example, significant detection of enterodiol and enterolactone was observed after the fermentation of flaxseed flour compared with whole flaxseed, both rich in secoisolariciresinol diglucoside (Fuentealba et al., 2014). The in vitro fermentation of alfalfa seed flour-enriched, gluten-free cookies evidenced an increase of pinoresinol bioaccessibility due to the appearance of cyclolariciresinol, isomeric forms of hydroxyenterodiol, 7-hydroxymatairesinol, and secoisolariciresinol (Rocchetti, Senizza, Gallo, et al., 2019).

Overall, it is true that intestinal microbiota catabolism modifies the chemical structure of parent compounds, which can alter the bioactivity of the original compounds. Nevertheless, consistent evidence that microbial metabolites of PCs also participate as protective factors against chronic diseases also exists. BPs could be proposed as a kind of reservoir that delivers PCs into the large intestine, where they are released and eventually transformed by microbiota. On the other hand, the bioaccessibility and bioavailability of phenolic metabolites produced in the gut are, on many occasions, increased with respect to the original compounds.

3.3 | Modulation of gut microbiota by phenolics

The diet has a significant impact on the structure and activity of the gut microbiota; in this regard, PCs have received increasing attention in the latest years as a food-based intervention to modulate gut microbial ecology and improve overall health. The influence of dietary fiber on the catabolism of PCs by gut microbiota has been thoroughly reviewed elsewhere (Loo et al., 2020). Noteworthy, these authors highlighted the need to consider the interaction between phenolics and dietary fiber, as they are co-occurring in plant-based foods. Recent work has highlighted the synergistic effect of polyphenols and fiber on the antiobesity molecular mechanisms in rats, linking this to gut microbiota shaping (Li et al., 2019). A number of in vitro and animal studies and, to a lesser extent, human clinical trials have provided evidence that the intake of PCs can influence the intestinal microbiome, and this effect has been ascribed to both single compounds and/or plant extracts. The vast majority of studies addressing PCs' impact on gut microbiota are focused on soluble FPs, thus overlooking the putative biological function of insoluble BP extracts. Nevertheless, the association between dietary fiber and PCs may prevent the latter from being metabolized and absorbed in the small intestine, thus allowing PCs to reach undisturbed the distal part of the gut as widely suggested by in vitro models. Here, both PCs and fiber undergo microbial bioconversion, leading to the production of phenolic acids and short-chain fatty acids, respectively. Indeed, the interaction between these two biologically active substances may produce combined effects in the colon resulting in specific and/or synergistic modulation of gut microbiota.

So far, most of the evidence available comes from in vitro studies. Different fruit by-product water extracts (FWE) were used as sources of BPs in the study by Albuquerque et al. (2018); their findings demonstrated that FWE were able to boost the growth of the probiotic strain *Lactobacillus rhamnosus* GG and enhance its adhesion to the human colon cell line Caco-2. On the other hand, BPs from Peruvian purple corn (mainly phenolic acids) were not able to either stimulate the growth of *Lactobacillus helveticus* and *Bifidobacterium longum* or inhibit the pathogenic *Helicobacter pylori* (Gálvez Ranilla et al., 2017). Unfortunately, in vitro models relying on single strains in culture medium provide limited information on the impact of dietary factors on gut microbes. In fact, they fail to mimic the intestine's physiological conditions and to represent the actual behavior of microorganisms within a mixed microbial population.

Collins et al. (2016) used a rodent model to investigate the potential of an extractable (EP) or nonextractable (NEP) fraction of table grapes to counteract the detrimental metabolic consequences of a high-fat diet (HFD), with the NEP fraction consisting of insoluble PCs bound to fiber. As a result, they found that both EP and NEP were able to improve a number of biochemical markers associated with hosting metabolic status and with inducing specific changes in several gut bacterial populations. Compared with HFD-fed mice, mice given the NEP fraction showed higher levels of genus *Coprococcus* and unclassified family RF39 (class *Mollicutes*). Ou and co-workers (2016) explored the ability of feruloylated oligosaccharides (FOs) from maize bran to modulate the rat gut microbiota in vivo. Although no differences were observed in rats fed FOs regarding growth features, FOs significantly increased bacterial diversity, decreased the ratio of *Firmicutes* to *Bacteroidetes*, and increased *Lactobacillus* and *Ruminococcus* while decreasing *Clostridium* in rat feces. Notably, a high gut microbiota diversity is generally considered beneficial for health as many inflammatory diseases display a reduction of bacterial diversity, whereas an increased Firmicutes/Bacteroidetes ratio has been directly related to obesity.

Given the considerable amount of BPs in whole-grain dietary fiber, Zhang et al. (2019) assessed the activity of BPs released after in vitro gastrointestinal digestion and colonic fermentation of rice bran dietary fiber (RBDF). RBDF stimulated the growth of *Lactobacillus* spp., *A. muciniphila*, and *F. prausnitzii* populations stronger than phenolics-removed RBDF. In their later study, the same group investigated the effects of BPs in RBDF on regulating glucose metabolism in diabetic mice (Zhang et al., 2020). Compared with phenolics-removed RBDF, RBDF reduced the relative abundance of potentially pathogenic *Enterobacteriaceae* while increasing the proportions of several butyrate-producing genera, including *Lachnospiraceae_NK4B4_group*, *Ruminococcus_1*, and *Roseburia*. Remarkably, the abundance of these specific bacterial groups correlated negatively with the fasting blood glucose levels that were reduced after RBDF administration. Taken together, these findings suggest that BPs might be the critical determinant of the health benefits ascribed to grain dietary fiber.

Despite a scarcity of studies in this area, the data available in the literature appear to support the conclusion that PCs associated with dietary fiber may have significant effects on gut microbes. Further investigation is undoubtedly required to gain insight into the interplay between BPs present in plant food and gut microorganisms and its potential consequences for human health.

4 | CONCLUSIONS

Undoubtedly, the scientific community recognizes both PCs and dietary fiber as functional components of foods. However, some information about the processes underlying their health-promoting effects is likely to be unraveled. Within this concept, the amount and type of bound PCs may contribute to understanding their functional role in foods. The actual amount of BPs depends on several factors, including the specific phenolic class considered, the plant species and cultivar, and the food processing conditions. Nonetheless, BPs can reach the large intestine and undergo an intense transformation by the microbial community to produce lower molecular weight PCs. In the last years, PCs therein have been receiving increasing attention and may represent a promising food-based intervention to modulate gut microbial ecology and improve overall health. More in-depth knowledge of the functional implications related to BPs in human health is advisable to better elucidate their actual role in terms of nutraceutical potential.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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