Received: 22 March 2020 | Revised: 18 May 2020 | Accepted: 18 May 2020

DOI: 10.1002/fft2.25

FOOD FRONTIERS Open Access

REVIEW ARTICLE

Interaction of dietary polyphenols and gut microbiota: Microbial metabolism of polyphenols, influence on the gut microbiota, and implications on host health

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Abstract

The human gastrointestinal tract is inhabited by a vast number of microorganisms that are called as the microbiota. Each individual harbors a unique gut microbial composition, this composition evolves throughout the host's lifetime and it is easily affected by internal or external changes. It has been shown that gut microbiota plays a crucial role in host's health and as this complex community has the ability to interact with each other and with the host's immune system, the presence or absence of some major species can affect the homeostasis. Diet can be considered as one of the pivotal factors in modulating the functionality, integrity, and composition of the gut microbiota as the gastrointestinal tract is the first organ exposed to components of the diet. In this review, we have focused on the effects of polyphenols, key compounds of a healthy diet with several biological activities, on the gut microbial composition, their biotransformation by the gut microbiota, and the effect of their reciprocal interactions in human health and disease.

KEYWORDS
biotransformation, gut microbiota, host health, polyphenols

1 | INTRODUCTION

There is a tremendous research output related to the importance of gut microbiota in host health. Besides being a simple digestive organ, the distal gut is considered as a "microbial organ" or a "bioreactor" due to the vast amount of microorganisms residing in the gut, which are collectively termed as microbiota (Aguirre & Venema, 2015; Fernandes, Faria, Calhau, de Freitas, & Mateus, 2014). Although not being completely described, the human gut harbors a bacterial ecosystem of around 10^{13}–10^{14} bacterial cells. It is estimated that the microorganisms living inside humans are 1.3 times higher than human cells (Sender, Fuchs, & Milo, 2016), and the microbial gene repertoire outnumbers by about two orders of magnitude the amount of human genome (Cani & Delzenne, 2009). The four main phyla reside in the human gastrointestinal tract are Firmicutes (49–76%), Bacteroidetes (16–23%), and at lower percentages, Proteobacteria and Actinobacteria (Serra, Almeida, & Dinis, 2018). Not surprisingly, the composition and quantity of microorganisms change along the gastrointestinal tract and are affected by several factors including host genetics and external environment (such as diets and medication) that provides a unique gut microbial composition for each individual (Sekirov, Russell, Antunes, & Finlay, 2010).

Because the gastrointestinal tract is the first organ exposed to components of the diet, local and systemic health could be affected significantly depending on the diet's ability to influence the integrity, functionality, and composition of the complex gut microbial ecosystem. As reviewed in detail elsewhere, modulation of gut microbiota (composition or functionality) can either induce or prevent inflammatory processes, cancer, Type 2 diabetes, and metabolic processes, and so on (Belkaid & Hand, 2014; Gowd, Karim, Shishir, Xie, & Chen, 2019). Therefore, diet modification is one of the strategies to promote gut health via modulation of the gut microbiota. Phenolic compounds and their metabolites have been shown to have a positive impact on maintaining gut health through encouraging the growth of beneficial microbiota and limiting the proliferation of pathogen bacteria (Cardona, Andrés-Lacueva, Tulipani, Tinahones, & Queipo-Ortuño, 2013). Polyphenols are a large and heterogeneous group of phytochemicals containing one or more aromatic rings with one or more hydroxyl groups. They present as secondary plant metabolites in the majority of fruits and vegetables (H. Zhang & Tsao, 2016) as well as herbs and spices (Guldiken et al., 2018). Polyphenols are of great interest due to their anticancer, antioxidant, antimicrobial, anti-inflammatory effects, as well as preventing chronic diseases such as diabetes, obesity, neurodegenerative diseases, and cardiovascular diseases (Chiva-Blanch & Visioli, 2012; Ozdal et al., 2016). However, despite the health-promoting properties of polyphenols, their bioavailability is the limiting factor for their efficacy in preventing different types of diseases. Especially, polyphenols with higher molecular weights escape the absorption in the small intestine due to their chemical complexity. It has been demonstrated that only 5-10% of the total ingested polyphenols can be absorbed in the small intestine (Gowd et al., 2019), greatly depending on their structures and conjugation to sugar moieties. Due to the fact of their low bioavailability, it should be taken into account how the health-promoting effects of polyphenols occur, because they are poorly absorbed and generally detected in the systemic circulation at trace levels. Recent evidence based on ileostomy patients suggests that a substantial proportion of the consumed polyphenols reaches the colon and is broken down by the colonic microbiota into their low molecular weight (phenolic) metabolites (González-Barrio, Borges, Mullen, & Crozier, 2010). They may also affect the gut microbiota composition. Hence, it has been speculated that health-promoting effects of phenolic compounds, such as polyphenols, may be related to modulation of composition and activity of the gut microbiota, or vice versa, through the production of the bioactive microbial metabolites by the microbiota.

In this regard, the objective of this review is to provide an assessment of the reciprocal interactions of gut microbiota and dietary polyphenols and their implications on human health.

2 | OVERVIEW OF THE HUMAN GUT MICROBIOTA

Under normal circumstances, the gastrointestinal tract of the fetus is considered to be sterile, and its first colonization begins during the passage through the birth canal by the microorganisms present in that environment. During cesarean section births, this does not occur, and babies are exposed to the microbiota of the skin of parents and caretakers and microbes in the hospital environment. Therefore, the infant microbiota varies depending on the delivery method. For instance, *Lactobacillus*, *Prevotella*, and *Atopobium* dominate the vaginally delivered babies' microbiota, whereas in the case of cesarean section, the infant microbiota is mostly composed of maternal skin microorganisms in which *Staphylococcus* and *Propionibacterium* spp. prevail in the microbiota (Nicholson et al., 2012).

Colonization of the infant gut microbiota in its early stages can be called chaotic since the diversity increases over time. Due to these dynamic changes, interpersonal variability in microbial composition and functional gene content was found to be higher in infants compared to adult microbiota (Koenig et al., 2011). Breast-fed neonates build up a gut microbiota that draws attention by its elevated concentration of bifidobacteria where this dominancy prevents the colonization of pathogen microorganisms via competitive exclusion and provides a substantial health benefit to the infants (Sela et al., 2008). The gut microbiota composition in infants shifts to an adult-like composition by the end of 12 months likely due to the introduction of formula foods and other table foods, which leads to a microbiota codominated by the Bacteroidetes and Firmicutes and enriched in functional genes characteristic to that of an adult gut microbiome. Finally, it becomes entirely similar to the adult microbiota by 2.5–4 years of age (Koenig et al., 2011; Palmer, Bik, DiGiulio, Relman, & Brown, 2007). After reaching a mature stage, the microbiota keeps its stability until the old ages.

Studies employing conventional culture-based techniques suggest that most of the same gut bacterial species are common in all healthy adults, such as *Escherichia coli* can be isolated from most people.

Nevertheless, since most of the microorganisms present in the gut are anaerobic, only 10–25% of the microbiota could be analyzed by using culture-based techniques (Jandhyala et al., 2015). However, thanks to the culture-independent high throughput gene sequencing technologies, the description of the complete repertoire of human gut microbiota and highlighting the precedence of bacteria became possible. Our guts shelter more than a thousand "species-level" phylotypes, which are mostly bacteria belonging to just a few phyla (Lozupone, Stombaugh, Gordon, Jansson, & Knight, 2012). In adults, five bacterial phyla, namely, Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, and Verrucomicrobia, and one Archaea (Euryarchaeota) dominate the gut microbiota. The Firmicutes phylum comprises relevant genera, including *Lactobacillus*, *Clostridium*, *Ruminococcus*, and the butyrate-producing bacteria *Faecalibacterium*, *Roseburia*, and *Eubacterium*, whereas the Bacteroidetes phylum involves *Xylanibacter*, *Prevotella*, and *Bacteroides* that are responsible for degrading several complex glycans. The Actinobacteria phylum contains *Collinsella* and *Bifidobacterium*, while *Escherichia* and *Desulfovibrio* fall under the Proteobacteria phylum. The recently explored Verrucomicrobia includes the mucus degrading *Akkermansia*, and finally, *Methanobrevibacter*, which plays a role in the continuation of intestinal methanogenesis, is included in Euryarchaeota (Tremaroli & Bäckhed, 2012). However, when the gut microbial composition is analyzed in species or genus levels, a substantial variation between the fecal samples from human individuals was observed. Therefore, a considerable amount of the identified species-level phylotypes is specific to each person due to this high variability in lower taxonomic levels among the individuals (Alonso & Guarner, 2013). Furthermore, it has been found that elderly people demonstrate a different microbial composition than the young adults, especially in the proportions of *Bacteroides* spp. and *Clostridium* groups that may be linked to the increased incidence of diseases with age and correspondingly the use of medications for their treatment (Claesson et al., 2011; Clemente, Ursell, Parfrey, & Knight, 2012).

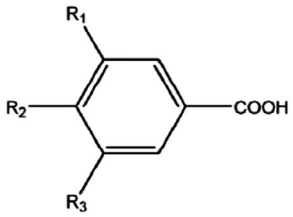
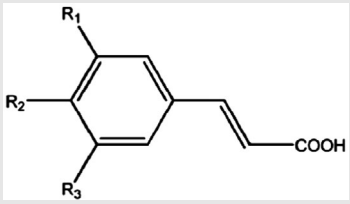
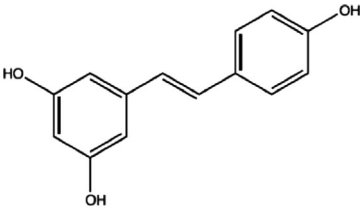
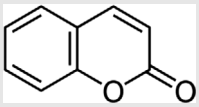
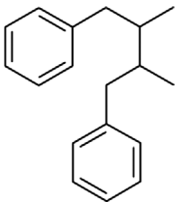
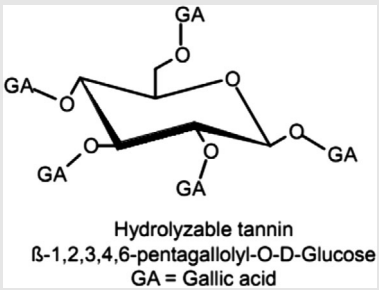
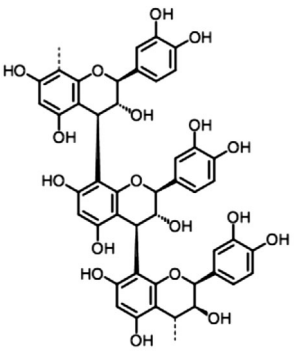
The gut microbiota plays a significant role in health and disease in humans. Thanks to the improvements in sequencing technologies and bioinformatics, studying these diverse microorganisms and their functions, as well as their reciprocal interactions with the host, is now enabled in a detailed way in health and disease. It has been shown that the healthy gut microbiota exhibits several specific functions in (a) nutrient metabolism (e.g., fermentation of indigestible carbohydrates, production of short-chain fatty acids (SCFAs), providing energy source for the host (den Besten et al., 2013)), (b) xenobiotic and drug metabolism (e.g., metabolism of polyphenols (Koppel, Rekdal, & Balskus, 2017)), (c) antimicrobial protection (e.g., lactic acid produced by *Lactobacillus* sp. enhances antimicrobial activity of lysozyme by the cell wall disruption), (d) immunomodulation (e.g., interacting with toll-like receptors (TLR), which are responsible of the detection of invading pathogens (Brown, Wang, Hajishengallis, & Martin, 2011)), and (e) providing the integrity of the gut barrier and structure of the gastrointestinal tract (e.g., germ-free mice have impaired nutrient digestion and absorption due to lower intestinal surface area, thin villi and impaired intestinal peristalsis (Jandhyala et al., 2015)).

3 | DIETARY POLYPHENOLS AND THEIR BENEFICIAL EFFECTS

Dietary polyphenols are a group of bioactive phytochemicals largely found in a wide variety of fruit, vegetables, seeds, herbs, and beverages (beer, wine, fruit juice, coffee, tea, and chocolate), and to a lesser extent dry legumes and cereal (Vinson, Su, Zubik, & Bose, 2001). They are generally involved in defenses against plant pathogens and atmospheric agents and currently represent a topic of great scientific attention due to interest in their health benefits for humans. They are secondary metabolites and, with over 8,000 structural variants, encompass a wide variety of molecules with polyphenol structures. They are subdivided into different chemical groups according to the number of phenolic rings and moieties linked to these rings (Kabera, Semana, Mussa, & He, 2014). They are divided into flavonoids and nonflavonoids, as shown in Table 1 (Johnsson, 2004; Lamy et al., 2011; Shahidi & Ambigaipalan, 2015). Flavonoids involve a common carbon skeleton of diphenyl propane in which two benzene rings connect by a linear three-carbon chain.

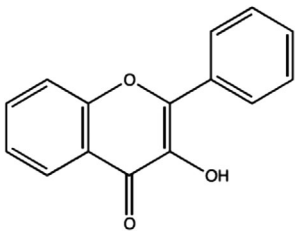
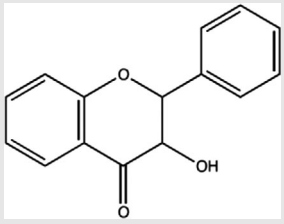
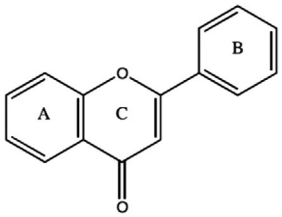
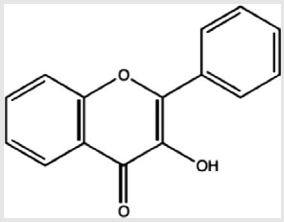
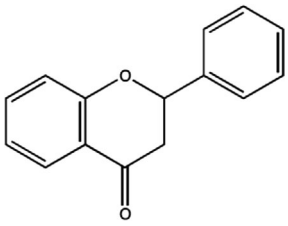
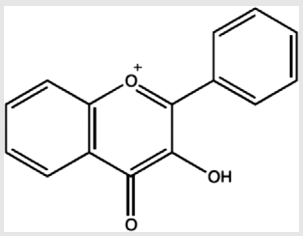
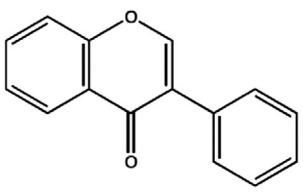
The central three-carbon chain forms a closed pyran ring with the A benzene ring. Flavonoids are then subdivided into several subclasses based on the central pyran ring's oxidation state: flavanols, flavones, anthocyanidins, flavanones, flavonols, and isoflavones. The main groups of nonflavonoids are phenolic acids, which can be subdivided into benzoic acid derivatives, such as gallic acid and protocatechuic acid, and cinnamic acid derivatives including coumaric, caffeic, and ferulic acids. The second major group consists mainly of stilbenes, resveratrol being the main representative, which exists in both cis and trans isomeric forms. Another important nonflavonoid group is the lignans that are produced by oxidative dimerization of two phenylpropane units (Daglia, 2012; Quideau, Deffieux, Douat-Casassus, & Pouységu, 2011). Flavanols are the most ubiquitous form of flavonoid in foods, and their richest sources are onions, broccoli, tea, apples, red wine, and blueberries (Hollman & Katan, 1999). Foods particularly rich in flavanones include citrus fruit such as lemon, grapefruit, and orange (Tomás-Barberán & Clifford, 2000). On the other hand, flavanols are found in tea, blackberries, apples, almonds, and pistachios (Bhagwat, Haytowitz, & Holden, 2014). Anthocyanins are water-soluble flavonoids present in red fruits and vegetables (e.g., raspberry, elderberry, strawberry, pomegranate, cabbage, red onion) (Prasain, Grubbs, & Barnes, 2020; Weber & Larsen, 2017). Examples of flavone sources are acerola, apricot, olive oil, honey, apple, papaya, and mango (Bataglion, da Silva, Eberlin, & Koolen, 2015; Siriamornpun & Kaeweejan, 2017). Isoflavones are bioactive compounds present mainly in the leguminous family with minor quantities (concentrations less than 0.1 mg/kg) in apricot, dried dates, currant, mango, plums, fresh coconuts, and sesame seeds (Bustamante-Rangel, Delgado-Zamarreño, Pérez-Martín, Rodríguez-Gonzalo, & Domínguez-Álvarez, 2018; Liggins et al., 2000), whereas stilbenes are shown to be present in grapes, red wine, and berries (Tomé-Carneiro et al., 2013). Red fruits and vegetables, such as strawberries and blackberries, black radish, onions, and tea, are sources of phenolic acids (Tomas-Barberan & Clifford, 2000).

TABLE 1 Classification of natural polyphenols, their basic structures, and example compounds

Natural polyphenols	**Nonflavonoids**	Phenolic acids		*Hydroxybenzoic acid derivatives* Gallic acid Vanillic acid Syringic acid Ellagic acid
				*Hydroxycinnamic acid derivatives* Caffeic acid Ferulic acid Chlorogenic acid *p*-Coumaric acid
		Stilbenes	 *trans*-resveratrol	Resveratrol
		Coumarins		6-methoxymellein6-hydroxymellein
		Lignans		Pinoresinol
		Tannins	 Hydrolyzable tannin ß-1,2,3,4,6-pentagallolyl-O-D-Glucose GA = Gallic acid	*Hydrolyzable tannins* Ellagitannins Gallotannins
			 Procyanidin (condensed tannin) Epicatechin-(4→8)-epicatechin-(4→8)-catechin	*Condensed tannins (Proanthocyanidins)* Mono-, Di-, Trimers 4-6mers, 7-10 mers, Polymers

(Continues)

TABLE 1 (Continued)

Natural polyphenols	**Flavonoids**	Flavonols		Kaempferol, Quercetin Isorhamnetin
		Flavononols		Genistein, Astilbin Engeletin
		Flavones		Luteolin, Apigenin Rutin
		Flavanols		(−)-Epicatechin (+)-Gallocatechin (+)-Catechin
		Flavanones		Naringenin, Naringin Hesperidin
		Anthocyanidins		Delphinidin, Pelargonidin Cyanidin
		Isoflavonoids		Daidzein, Glycitein Genistein

Many studies have highlighted the potential role of polyphenols in the prevention of a number of diseases such as diabetes, cardiovascular diseases, obesity, and neurodegenerative diseases (Khurana, Venkataraman, Hollingsworth, Piche, & Tai, 2013; Kuriyama et al., 2006; A.-N. Li et al., 2014; Meydani & Hasan, 2010; Mursu et al., 2008; Scalbert, Manach, Morand, Rémésy, & Jiménez, 2005). Polyphenols are potent antioxidant compounds able to counteract oxidative stress and chronic inflammation (Afshari et al., 2019). In light of this, many studies have been focused on their beneficial anti-inflammatory (Beara et al., 2012; Zimmer et al., 2012), analgesic activities (Dos Santos, Almeida, Lopes, & De Souza, 2006), and antimicrobial (Daglia, 2012; Xia, Wu, Shi, Yang, & Zhang, 2011), vasodilatory (Protić et al., 2015), antiallergenic (Gambini et al., 2015), and anticarcinogenic effects (Niedzwiecki, Roomi, Kalinovsky, & Rath, 2016). Polyphenols are metabolized by the gut microbiota to achieve these health benefits. However, it is also important to consider the absorption of polyphenols by the human body. Although there are several attempts to increase the bioavailability of polyphenols including micro- and nanoencapsulation (spray drying, coacervation, liposomes, etc.) methods (Cvejić, Krstonošić, Bursać, & Miljić, 2017; Kumar Vivekanandhan, Ranjan Prasad Verma, & Kumar Singh, 2016), absorption of the most of the polyphenols in the small intestine is relatively low (5–10%) with regard to other macro- or micronutrients (unless they are encapsulated) (Selma, Espin, & Tomas-Barberan, 2009). Then passing to the liver where they are absorbed by the blood, the remaining 90–95% of polyphenols go to the large intestinal lumen and are exposed to the enzymatic activities of gut microbiota to be transformed into low molecular weight bioactive metabolites (Selma et al., 2009). Therefore, the gut microbiota metabolizes the polyphenols into metabolites that may have higher bioavailability than their precursor structures (Faria, Fernandes, Norberto, Mateus, & Calhau, 2014).

4 | IMPACT OF GUT MICROBIOTA ON BIOAVAILABILITY OF DIETARY POLYPHENOLS

4.1 | Intake, bioaccessibility, and stability of polyphenols

It is well known that measuring dietary intake is difficult, and a single method cannot perfectly estimate dietary exposure (Shim, Oh, & Kim, 2014), especially when focusing on micronutrients and bioactive compounds (such as polyphenols). In this regard, in a recent research (Del Bo et al., 2019), the total polyphenol intake for the overall population (including North and South America, Europe, Asia, and Australia) was estimated to be around 900 mg/day; as expected, this value varied depending on the differences in target groups of subjects. Furthermore, the main sources of dietary polyphenols were found to be fruits and vegetables, coffee, tea, and red wine (Del Bo et al., 2019).

Under the term polyphenols, a wide diversity of chemicals is listed. As a consequence, one of the most critical points for a comprehensive assessment of the polyphenol intake is the choice of the database. To date, most of the available studies are based on USDA and Phenol-Explorer databases. However, USDA database focuses mainly on flavonoids as aglycones (Del Bo et al., 2019), while Phenol-Explorer provides information also on other phenolic subclasses such as dihydroflavonols, dihydrochalcones, and chalcones as well as total polyphenols measured through spectrophotometric assays such as Folin-Ciocalteu (Rothwell et al., 2013). Therefore, it becomes clear that the choice regarding the reference database might impact the data on true polyphenol intake severely.

Polyphenol intake can be affected by several other factors, such as dietary habits, characteristics of the population (e.g., gender, age, and cultural factors), and geographical area (Del Bo et al., 2019). Overall, data reported in scientific literature highlight a higher intake in females compared to males, first and foremost when considering the standardization for energy (Karam, del Mar Bibiloni, & Tur, 2018). In this regard, females are the strong consumers of fruit and vegetables compared to males, whereas the latter are higher consumers of beverages and coffee (Del Bo et al., 2019).

Polyphenol intake is strictly related to the concepts of bioaccessibility and bioavailability. In this regard, the release of the polyphenols from food matrix during gastrointestinal digestion, namely bioaccessibility, will have a significant impact on the bioavailability, that is the potential absorption of phenolic compounds to be available for subsequent metabolic pathways. In fact, in plant foods, bioactive compounds such as polyphenols, are entrapped in a complex macromolecular network created by dietary fiber and are commonly released during the different stages of digestion in the gastrointestinal tract (Rocchetti et al., 2020; Tomas et al., 2020). In this way, they can be absorbed in the small and/or large intestine, thus exploiting their real biological effects. Bioaccessibility and bioavailability of polyphenols can be enhanced or attenuated depending on the molecular interactions that occur with other food matrix components. Consequently, in order to assess the bioavailability of polyphenols, several research papers deepened the study on the possible interactions between fiber and these phytochemicals (Jakobek & Matić, 2019). Therefore, dietary fibers might act as a "control mechanism" for monitoring the fraction of polyphenols that are bioaccessible in different parts (lower or higher) of the digestive tract.

It is clear that endogenous factors such as microbiota and digestive enzymes, together with characteristics of the food matrix, can considerably affect bioaccessibility, uptake, and further metabolism of phenolic compounds. In addition, some polyphenols, such as anthocyanins, might be degraded before absorption, thus resulting in bioaccessibility levels <10% (Bouayed, Hoffmann, & Bohn, 2011). Therefore, in order to comprehend and determine the actual bioaccessibility of the polyphenols in the gut, it is very important to have an extensive understanding of the reactions that take place during gastrointestinal digestion. In the last years, several studies evaluated the bioaccessibility of phenolic compounds following *in vitro* large intestinal fermentation of different food matrices, such as pomegranate by-products (Fellah et al., 2020), nonconventional rice cookies (Rocchetti, Senizza, et al., 2019), pigmented gluten-free flours (Rocchetti, Lucini, Giuberti, et al., 2019), blackberry puree (Tomas et al., 2020), edible nuts (Rocchetti, Bhumireddy, et al., 2019), gluten-free

pasta (Rocchetti et al., 2017), mulberry (Yu et al., 2019), and Goji berries (Rocchetti, Chiodelli, et al., 2018). Overall, these authors underlined the potential of targeted/untargeted metabolomics-based platforms (such as high-resolution chromatography coupled with mass spectrometry) to study the phenolic bioaccessibility into the gut (Rocchetti, Giuberti, & Lucini, 2018).

The gut microbiota impacts the stability of dietary polyphenols via multienzymatic reactions, including deglycosylation, sulfation, glucuronidation, C ring cleavage of the benzo-γ-pyrone system, dehydroxylation, decarboxylation, and hydrogenation. First, most *O*-glycosides are transferred to aglycones, which are further conjugated to *O*-glucuronide and/or *O*-sulfate forms. Then gut microbes carry out the catabolic transformations such as carbon–carbon separation of aromatic rings, decarboxylation, hydrogenation, and dehydroxylation of alkene moieties. For example, quercetin 3-*O*-glucoside is converted to phloroglucinol, 2,4,6-trihydroxybenzoic acid, and protocatechuic acid by the intestinal bacteria (Hein, Rose, van't Slot, Friedrich, & Humpf, 2008; Hirooka & Fujita, 2010; Schneider, Simmering, Hartmann, Pforte, & Blaut, 2000). The proanthocyanidins are transferred to 3,4-dihydroxyphenylacetic acid, 3-(3-hydroxyphenyl)propionic acid, 3-hydroxyphenylacetic acid and 5-(3′-hydroxyphenyl)-γ-valerolactone in the large intestine (Appeldoorn, Vincken, Aura, Hollman, & Gruppen, 2009). Anthocyanidins are frequently metabolized by the gut microbiota to form 2,4,6-trihydroxyphenylacetic acid and protocatechuic acid (Aura et al., 2005). Curcumin is catabolized to its hydrogenated, *O*-glucuronide, desmethyl, and *O*-sulfate forms (Ireson et al., 2002). Gut microbiota converted ellagic acid to urolithins via dehydroxylation and intramolecular condensation (González-Sarrías et al., 2010). Cyanidin glucosides are primarily transformed into 3,4-dihydroxybenzoic acid in the human colon (Vitaglione et al., 2007).

4.2 | Metabolism and biotransformation

As stated above, the gut microbiota contributes to the metabolism of dietary polyphenols, thus impacting the bioavailability of both parent polyphenols and their (potentially also bioactive) metabolites. Overall, mammalian metabolic transformations of polyphenols are included in phase I and phase II metabolism and characterized by the conjugation, O-methylation and O-demethylation of hydroxy groups, and hydroxylation of aromatic rings to generate sulfates and glucuronides (Cassidy & Minihane, 2017). However, the gut microbiota is able to influence polyphenol bioaccessibility/bioavailability by the hydrolytic release of aglycones from hepatic O-glucuronides and O-glycosides. Besides the enzymatic glycoside cleavage ability, gut microbes can perform carbon–carbon separation of aromatic and heterocyclic rings in flavonoids, together with dehydroxylation, decarboxylation, and/or hydrogenation of alkene moieties (Stevens & Maier, 2016). Therefore, the released aglycones are exposed to ensuing microbial transformations, such as α- or β-oxidation, ring fission, dehydroxylation, dehydrogenation, and demethylation, thus resulting in the generation of lower molecular weight, more simple phenolic compounds (Mosele, Macià, & Motilva, 2015). Such metabolic transformations have been described not randomly to occur, but rather follow specific reactions. In this regard, the catabolic routes allowing the generation of phenolic metabolites have been widely described in the literature, considering both flavonoids and nonflavonoid compounds. For example, Mosele et al. (2015) reported the metabolic and microbial processes in the large intestine ecosystem as related by not-absorbed polyphenols.

Among flavonoids, the flavan-3-ols (such as epigallocatechin, epigallocatechin gallate, epicatechin, and catechin) can be subjected to C-ring fission reactions, followed by several dehydroxylations, thus leading to the production of phenyl-γ-valerolactones and phenylvaleric acids, which have been proposed as exclusive gut metabolites of flavan-3-ols (Mena et al., 2019). Their subsequent microbial transformation is able to generate different hydroxylated forms of phenyl and benzoic acids, depending on the specific metabolic capacity of each individual microbiota and the composition/structure of flavan-3-ols in the substrate. Other phenolic classes, such as flavonols, flavanones, and flavones, share some transformation products (Mosele et al., 2015). In fact, hydroxyphenylpropionic acid has been described as a major fermentation product of naringenin and kaempferol (Mosele et al., 2015; W. Zou et al., 2015), while dihydroxyphenylpropionic acid can be considered the final catabolic product of eriodictyol and quercetin (Mosele et al., 2015). Another interesting class widely processed by gut microbiota during large intestine fermentation is that of anthocyanins. After microbial deglycosylation, the ring fission of aglycones produces two portions, one from the A-ring and the second one from the B-ring, both undergoing further catabolism (Mosele et al., 2015; Rocchetti, Giuberti, et al., 2019). Regarding the fission of the B-ring, several metabolites (such as protocatechuic acid and dihydrocaffeic acid) have been proposed as the markers of the consumption of cyanidin glucoside-rich foods (Mosele et al., 2015; Rocchetti, Giuberti, et al., 2019). In addition, hydroxybenzoic acid has been reported as the microbial metabolite of pelargonidin glucoside, vanillic acid of peonidin glucoside, syringic acid of malvidin glucoside, methyl gallic acid of petunidin glucoside, and gallic acid of delphinidin glucoside. Regarding the fission of A-ring, the most important metabolites reported are phloroglucinol and resorcinol (Mosele et al., 2015). Metabolic fate of dietary anthocyanins has been shown in Figure 1 (adapted from Fang, 2014, and McGhie & Walton, 2007). Briefly, after ingestion anthocyanin glycosides can be absorbed promptly through the stomach wall and they enter to the systemic circulation after being metabolized by methylation, glucuronidation, and sulfation reactions in the liver. The remaining unabsorbed portion of the anthocyanins is transported to the small intestine. Here, they are converted into hemiketal, chalcone, and quinonoidal forms due to higher pH value in the intestines and then their absorption seems to occur in the jejunum. After absorption from the intestines, they reach the liver, may be metabolized and enter the systemic circulation. The part that remained unabsorbed in the gastrointestinal tract moves to the colon and is exposed to an intense metabolization by the enzymes of gut microbial community. In this fermentation process, they may be degraded into sugars and simpler phenolic components. By further metabolization of these degradation products, C-ring form can be disrupted and yield phenolic acids and aldehydes.

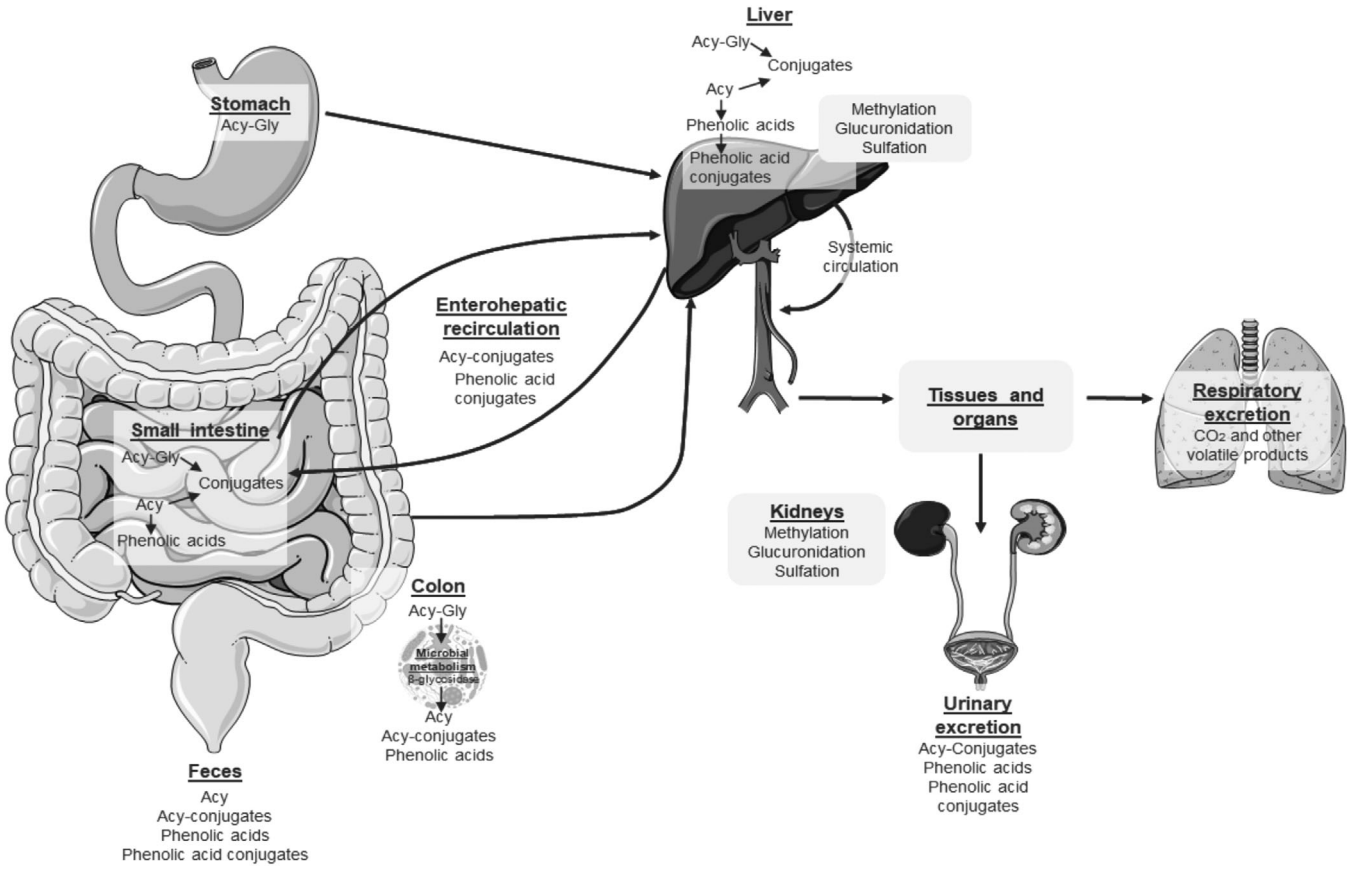


FIGURE 1 Possible metabolic fate of anthocyanins (Acy: Anthocyanin, Acy-Gly: Anthocyanin glycosides)

A portion of the produced products are absorbed from the colon, while the remaining part is excreted with feces. On the other hand, the portion entered to the systemic circulation is distributed to the tissues and organs such as eyes, brain, and lungs. At the end, they can be excreted in urine and bile as intact or metabolized forms. Interestingly, high amounts of volatile metabolites produced from [^{13}C]-Cy-3-glucoside have been determined in breath (Fang, 2014; McGhie & Walton, 2007).

Ellagitannins (a class of tannins containing gallic acid) are another class of phenolic compounds extensively underwent transformations by the metabolic activity of gut microbiota (Piwowarski, Granica, Stefańska, & Kiss, 2016). Indeed, ellagitannins can be processed to be converted into different types of urolithins, such as A-B-C-D. However, a strong individual variability has been observed in the type and amounts of urolithins detected, with urolithin A (dihydroxy-urolithin) and urolithin B (hydroxy-urolithin) being produced by the majority of individuals (Selma et al., 2017). Nonetheless, a group of people has been reported to be incapable of producing any class of urolithins (likely due to the absence of some bacteria belonging to the *Gordonibacter* genus).

Phenolic acids represent another abundant class of plant phenolics that includes hydroxycinnamic and hydroxybenzoic acids. These compounds are characteristic of coffee, cereal, spices, wine, and other food matrices (Kumar & Goel, 2019). Chlorogenic acid (one of the most studied hydroxycinnamic acid) was reported to undergo an initial hydrolysis into caffeic acid, followed by a further degradation leading to di- and monohydroxylated phenylpropanoic acids as the main metabolites detected (Mosele et al., 2015). Other metabolites, such as hippuric acid and derivates, have been detected in urine samples after the administration of chlorogenic acids (Ogawa, Suzuki, Endo, Kawamoto, & Kayama, 2011; Rothwell et al., 2018). In fact, hippuric acid is the most common and most abundant phenolic metabolite detected in plasma and urine after the intake of several phenolic-rich sources. This metabolite arises from the hepatic metabolism of benzoic acids or conversion of the quinic acid moiety by the gut microbes.

Finally, stilbenes, lignans, and phenolic alcohols are characterized by specific catabolic pathways (Mosele et al., 2015). Lignans are widely studied considering their potential phytoestrogen activity (Rocchetti, Lucini, Ahmed, & Saber, 2019), exerted by enterodiol and its oxidized product (enterolactone), while oleuropein (belonging to the phenolic alcohol pathway) has been subjected to several studies considering that one of its main microbial products, that is, hydroxytyrosol is the only phenolic compound regulated by the European Food Safety Agency and possessing a health claim as follows "protection of LDL particles from oxidative damage, maintenance of normal blood HDL-cholesterol concentrations, maintenance of normal blood pressure, anti-inflammatory properties, contributes to the upper respiratory tract health, can help to maintain a normal function of the gastrointestinal tract, and contributes to body defenses against external agents" (EFSA Panel on Dietetic Products & Allergies, 2011).

To date, there are few studies focusing on the actual metabolic pathways and underlying enzymatic reactions for the generation of these metabolites (Stevens & Maier, 2016). In fact, according to the literature, comprehensive information related to the type of phenolic metabolite and the type of a specific microorganism responsible for certain metabolic actions could allow, in the next future, to estimate microbial metabolite patterns based on the composition of the gut microbiota and to better establish an enterotype. Nevertheless, some information is being provided by the literature (Rowland et al., 2018; Stevens & Maier, 2016). *Bacillus subtilis* strain 168 has been reported to possess carbon–carbon cleavage capacity toward both quercetin (flavonol) and cyanidin (anthocyanins) derivatives, as exerted by the enzyme quercetin 2,3-dioxygenase. In addition, a dehydroxylation ability of polyphenols (such as hydroxybenzoic acids) has previously been studied for *Gordonibacter urolithinfaciens* and *Clostridium coccoides*. According to the literature (Stevens & Maier, 2016), most of the gut bacteria are able to promote the hydrogenations of alkene, enone, and keto moieties, by acting on different polyphenol classes, such as stilbenes (mainly resveratrol) and isoflavones (such as daidzein, dihydrodaidzein, and tetrahydrodaidzein). Notably, the biotransformation of daidzein into the phytoestrogens equol is strictly dependent on the gut microbiota composition (Iino et al., 2019). In fact, to date, *Eggerthella* species (Maruo, Sakamoto, Ito, Toda, & Benno, 2008) and some bacteria isolated from human fecal material and belonging to the genus *Slackia* have been reported within the genetically characterized equol-producing bacteria (Rafii, 2015).

5 | MODULATION OF HOST GUT MICROBIOTA BY DIETARY POLYPHENOLS

5.1 | Change in microbial composition

In general, the absorption of orally administered polyphenols in the upper gastrointestinal tract is relatively low; a significant portion of polyphenols accumulate in the colon, where they may alter the composition of gut microbiota. An important reason for this situation is that the bioavailability of polyphenols in their native form is very low, andthey undergo enzymatic catabolism in the small intestines. However, depending on their glycosylation feature and polymerization degree, a significant fraction of dietary polyphenols still moves to the colon (Van Duynhoven et al., 2011). Intake of polyphenols may benefit the host through the modulation of gut microbiota by favoring the growth of beneficial bacteria and/or inhibiting the growth of harmful bacteria (Pistollato et al., 2016). A randomized, double-blind, placebo-controlled human trial showed that oral intake of epigallocatechin-3-gallate and resveratrol (282 and 80 mg/day, respectively) for 12 weeks significantly decreased fecal abundance of Bacteroidetes and tended to decrease *Faecalibacterium prausnitzii* in overweight men compared with those taking placebo (Most, Penders, Lucchesi, Goossens, & Blaak, 2017). Consumption of resveratrol (0.025% w/w in diet) inhibited the microbiota dysbiosis induced by dextran sodium sulfate (DSS) in colitic mice by significantly elevating the fecal abundance of *Bifidobacterium* and lowering the abundance of *Dorea*, *Sutterella*, and *Bilophila* (F. Li et al., 2020). Dietary administration of quercetin (30 mg/kg body weight/day) in rats prevented gut microbiota dysbiosis induced bya high-fat diet by lowering the Firmicute/Bacteroidetes ratio and decreasing the abundance of obesity-associate bacteria, such as *Erysipelotrichaceae*, *Bacillus*, and *Eubacterium cylindroides* (Etxeberria et al., 2015). Apart from the pure polyphenols, administration of polyphenol-rich foods/extracts also altered the composition of gut microbiota. Intake of green tea polyphenol extracts for 18 weeks in canines inhibited the abundance of Bacteroidetes and Fusobacteria, and increased the Firmicutes (Y. Li et al., 2020). Dietary anthocyanins (3.5 and 7.0 μmol/g in diet, equivalent to anthocyanins content in 5% and 10% freeze-dried black raspberry powder in diet) from black raspberry in mice treated with azoxymethane/DSS for 12 weeks increased the fecal abundance of beneficial bacteria, such as *Faecalibacterium prausnitzii*, *Lactobacillus*, and *Eubacterium rectale*, and reduced the abundance of pathogens, such as *Desulfovibrio* sp. and *Enterococcus* spp. (L. Chen et al., 2018). Similarly, in a recent study, administration of wild blueberry polyphenolic extract and a fraction isolated from the blueberries (including oligomeric proanthocyanidins with a degree of polymerization less than four phenolic acids and favonols) to high-fat high-sucrose diet-induced obese mice favored the growth of polyphenol degrading bacteria *Adlercreutzia equolifaciens*, suggesting that inclusion of these bacteria in the metabolism of polyphenols may contribute to the amelioration of metabolic disturbances in obesity and diabetes by producing bioactive molecules involved in these processes (Rodríguez-Daza et al., 2020).

5.2 | Short-chain fatty acids

Gut microbiota can utilize the undigested food to produce SCFAs, such as acetate, propionate, and butyrate, and these SCFAs play important roles in maintaining human health (J. M. Wong, De Souza, Kendall, Emam, & Jenkins, 2006). The administration of polyphenols may modify the production of SCFAs by changing the composition and thus the function of gut microbiota. *In vitro* fermentation of chlorogenic acid, caffeic acid, rutin, and quercetin significantly increased the production of propionate and butyrate, and caffeic acid fermentation showed that the highest increase in butyrate and production of propionate was the highest with rutin (Parkar, Trower, & Stevenson, 2013). Mango beverage (475.9 mg gallic acid equivalent/L) remarkably increased the production of butyrate and valerate in DSS-treated colitic mice (H. Kim et al., 2018). Importantly, mango beverage treatment significantly increased the abundance of butyrate-producing bacteria *Clostridium butyrium*, as well as other beneficial bacteria, such as *Lactobacillus plantarum* and *Lactococcus lactis* (H. Kim et al., 2018). On the contrary, administration of boysenberry beverage in humans (Wallace et al., 2015) and trans-resveratrol in high-fat diet-treated rats (Etxeberria et al., 2015) did not cause significant difference in the production of SCFAs. The different types of polyphenols, experimental models, and the complexity of gut microbiota may be the potential reason for the discrepancy. In another study, hesperidin (1% in the diet) and its

aglycone hesperetin (0.5% in the diet) were assessed for their effect on the production of SCFAs by gut microbiota of Wistar rats. It has been found that intake of hesperetin significantly enhanced the cecal levels of total SCFAs (acetic, propionic, and butyric acids), while hesperidin showed no significant effect compared to the control diet that was attributed to their possible different effects on the production and activity of microbial enzymes (Unno, Hisada, & Takahashi, 2015). SCFA production was affected by proanthocyanidins of different freeze-dried apple preparations (fruits, enzymatically digested fruits, isolated cell walls, isolated proanthocyanidins, or apple ciders) from two apple varieties (Marie Ménard and Avrolles varieties). The undigested freeze-dried apples showed higher SCFA production compared to the other preparations. Also, the presence of long-chain proanthocyanidins was found to be able to suppress the SCFA production most likely depending on the inhibition of the cell wall degrading microbial enzymes (Bazzocco, Mattila, Guyot, Renard, & Aura, 2008). Unno and Osakabe (2018) investigated the extent of SCFA production inWistar rats fed decaffeinated green tea or black tea extract. The levels of SCFA in cecum have been shown to be affected by both extracts in different manners. Administration of 10 g/kg of green tea extract restricted the SCFA production compared to the control diet, whereas feeding of 10 g/kg of black tea extract did not significantly affect the SCFA level in cecal digesta. It is noteworthy that the diet including green tea extract resulted in a substantial portion of undigested starch excreted in feces, showing that the black tea extract may have an inhibitory effect on pancreatic α-amylase resulting in higher amounts of starch in cecum available for the production of SCFAs.

5.3 | Mucus production and luminal oxygen levels

Colonic mucus acts as the first barrier against enteric pathogens, which may be ascribed to the gel-forming property of mucin glycoprotein (Desai et al., 2016; Rosillo, Sanchez-Hidalgo, Cárdeno, & de La Lastra, 2011). The depletion ofthe mucus barrier in mice resulted in a large amount of pathogen erosion in the large intestine, leading to the colonic inflammation (Desai et al., 2016), thus the integrity of mucus barrier is critical for colon health. Polyphenols were found to be able to promote the secretion of mucus. Cranberry proanthocyanidins promoted the secretion of mucus by increasing interleukin (IL)-4 and IL-13, stimulating goblet cell proliferation and MUC2 production (Pierre et al., 2013). It is worthy of noting that polyphenols treatment can promote the growth of specific bacteria, such as *Akkermansia* (Pierre et al., 2013), these mucin-degrading bacteria stimulated the mucin production (Everard et al., 2013). Furthermore, polyphenols may prevent mucus from eroding by inhibiting the growth of mucus-eroding bacteria. For example, pomegranate peel extract inhibited the overgrowth of *Citrobacter rodentium*, a kind of pathogen that can degrade mucus (Desai et al., 2016), leading to less colonic damage in *Citobacter rodentium*-infected mouse (George et al., 2019). It is critical to note that polyphenols may promote the entire balance of gut microbiota composition to maintain the integrity of mucus, although specific mucin-degrading bacteria may not be inhibited by polyphenols. For example, administration of quercetin changed the balance of gut microbiota composition and maintained the integrity of mucus in colitic mice, although quercetin did not significantly inhibit the growth of *Citobacter rodentium*, a potential mucin-degrading bacterium (R. Lin, Piao, & Song, 2019; Rodríguez-Piñeiro & Johansson, 2015). Collectively, these findings suggested that polyphenols can maintain the integrity of mucus by stimulating the secretion of mucin, inhibiting the growth of mucus-degrading bacteria, and improving the balance of gut microbiota composition thus the less damage of mucus.

Redox homeostasis is important to maintain the normal cellular metabolism and functions (G. Yang, Bibi, Du, Suzuki, & Zhu, 2017). The overproduction of reactive oxygen species (ROS) leads to the oxidative stress, which is associated with inflammation (Gessner, Ringseis, & Eder, 2017). The inhibition of overproduction of ROS in the large intestine takes an important part in the colon health. Importantly, the redox status can alter the gut microbiota composition. A more oxidative redox state associated with a higher ROS production in the small intestine in mice showed a lower Shannon diversity, an increase in the abundance of Bacteroidetes *S24-7*, and reduction in the abundance of Firmicutes, *Clostridiales*, *Ruminococcaceae*, and *Oscillospira* (Yardeni et al., 2019). In an aging model, the older the mice, the higher production of ROS, with a decreased Shannon diversity, as well as the decrease in *Clostridiales* and the increase of *S24-7* (Yardeni et al., 2019). The abolish of ROS by *N*-acetylcysteine in mice increased the Shannon diversity associated with the reduction in *S24-7* and the increase in Firmicutes (Yardeni et al., 2019). Polyphenols may directly react with ROS and scavenge ROS (Hussain et al., 2016), maintaining the systemic redox homeostasis, eventually improving the balance of gut microbiota. For example, persimmon vinegar polyphenols inhibited the overproduction of ROS in HepG2 cells (B. Zou et al., 2018), β-carotene and grape polyphenol extract decreased ROS level in the gut (Kuhn et al., 2018), and green tea polyphenols decreased Pb-induced ROS generation (H. Wang et al., 2016). Furthermore, the interaction between commensal bacterial and intestinal epithelial cells can trigger the generation of ROS (Jones & Neish, 2017). *Lactobacillus rhamnosus* stimulated the production of local ROS in intestinal epithelia, resulting in the oxidation of key enzymes such as Ubc12, which can lead to the inhibition of NF-κB activation and subsequent reduction of inflammatory responses (P. W. Lin et al., 2009). Thus, the enrichment of lactobacilli or its increased adhesion capacity on epithelia by polyphenols, such as *Sesbania grandiflora* flower extracts (China et al., 2012) and apple peel extract (Volstatova, Marsik, Rada, Geigerova, & Havlik, 2017), is of potential to modulate the ROS generation and the inflammatory responses.

5.4 | Intestinal immune system and inflammation

The intestinal immune system has a wide variety of cell types. Intestinal immunity can be schematically (Figure 2) separated into an innate component consisting of epithelial cells and antigen-presenting cells (APCs), and an adaptive component consisting of lymphocytes. The adaptive component can itself be separated into inducing and effector sites of the response. The inducing sites are essentially Peyer patches,

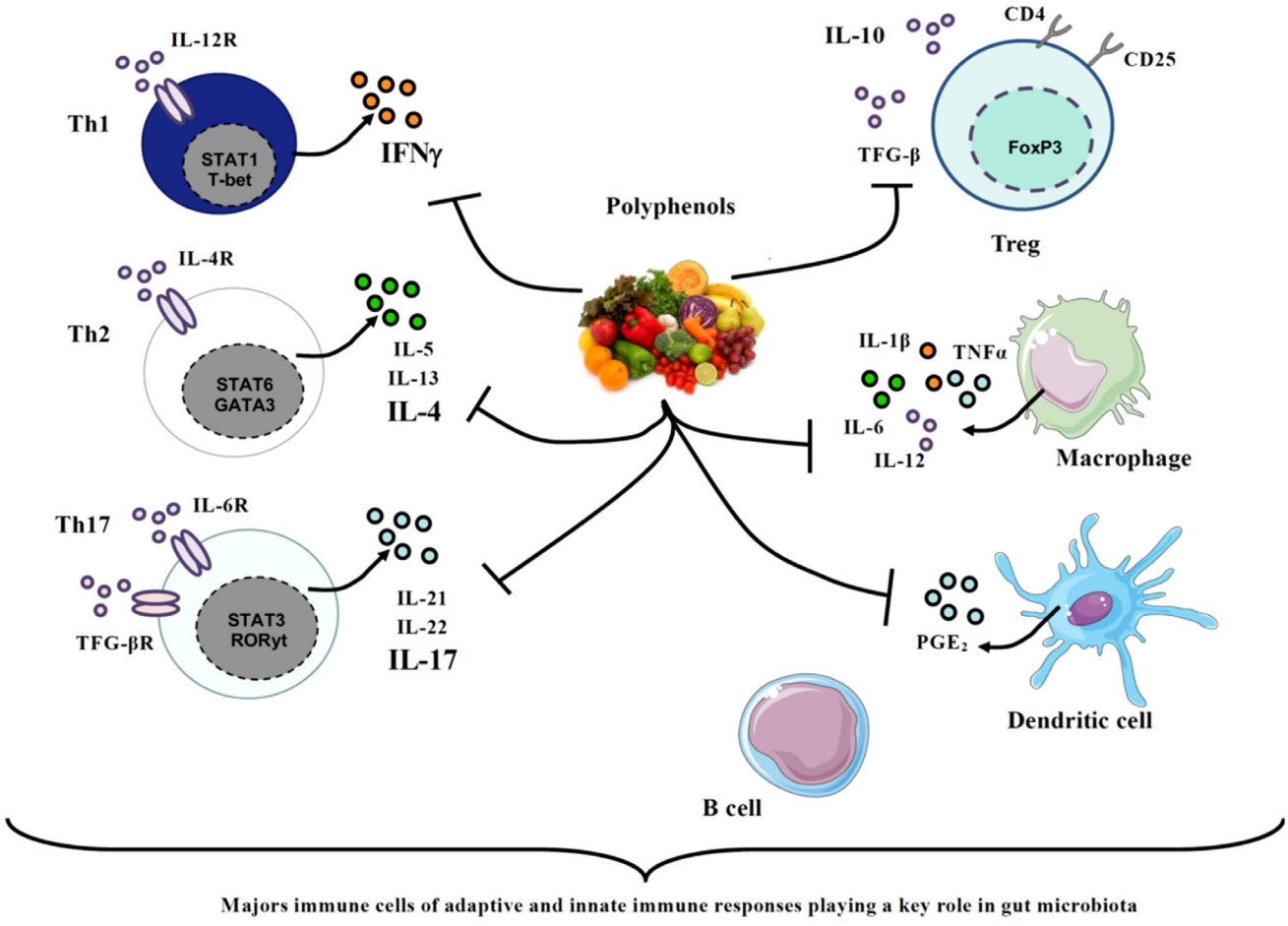


FIGURE 2 Innate and adaptive components of intestinal immunity

isolated lymphoid follicles. The effector sites are the immune cells that populate the entire height of the mucosa.

5.4.1 | Adaptive immune system and microbiota

The adaptive immune system consists of highly specialized systemic cells and processes that eliminate or inhibit pathogenic growth. Adaptive immune cells are initially stimulated through cross-priming by dendritic cells (DCs). The cells of the adaptive immune system involve various cell types such as lymphocytes T cells and B cells that are the primary types of lymphocytes. B cells are lymphocytes that take an essential part in the humoral immune response and produce antibodies against antigens (Taher et al., 2017). Lymphocytes B cells produced in an isolated lymphoid node, a Peyer patches, or a mesenteric ganglion leave these structures by the effective lymphatic system that drains them, and then reach lymphatic circulation and finally flow through the thoracic duct into the systemic circulation. These activated B-lymphocytes then colonize all mucosal territories by blood, leaving the peripheral circulation at the level of the post-capillary veins that irrigate these tissues. B lymphocytes activated into few hours in response to the antigen end their differentiation into plasmocytes and produce specific A-immunoglobulin (IgA) of the antigen. After the presentation of the antigens by the APCs to the resident T lymphocytes (mainly $CD4^+$) of the lamina propria, T lymphocytes are activated. Depending on the inflammatory environment (especially the presence of cytokines), naïve T lymphocytes will take on a pro-inflammatory (or effector) or anti-inflammatory (or regulatory) phenotype. Depending on this environment, the T-response will either be effective or regulatory. T helpers (Th cells), also called $CD4^+$ T cells since CD4 protein is expressed on their surface, are usually considered to play a predefined role as helper T cells in the immune system. When major histocompatibility complex (MHC) class II molecules that are expressed on the surface of APCs present Th cells with peptide antigens, they become activated. After activation, they are immediately separated and secrete cytokines that are small proteins regulating or assisting the active immune response. Th cells can differentiate into one of the various subtypes such as Th1, Th2, Th3, and Th17 that secrete cytokines to enable another sort of immune response (Luckheeram, Zhou, Verma, & Xia, 2012). The mechanism by which T cells are directed into a particular subtype is not well understood, although signaling patterns from the APC are considered to play an important role. More specifically, microbiota induces the maturation of naïve T cells into Th17 that release IL-17, which stimulates the production of antimicrobial peptides by the intestinal epithelium. Moreover, microbiota contributes to stimulation of the synthesis of

regulatory T cells (Treg cells) with the role to restrain autoreactive T cells that escaped the process of negative selection in the thymus and to shut down T-cell-mediated immunity toward the end of an immune reaction. The adaptive and the naturally occurring Treg cells have been characterized as the two primary classes of $CD4^+$ regulatory T cells (L. Wang, Zhu, & Qin, 2019). In the intestine, there is an activation of T lymphocytes at a basal level, even in the absence of infection. This activation is largely dependent on bacteria from the gut microbiota and is believed to play a role in maintaining gut homeostasis. In particular, there is a fine balance between the Th17 and Treg populations (L. Wang et al., 2019). When this balance is upset, it can result in uncontrolled intestinal inflammation, as is the case, for example, in Crohn's disease.

5.4.2 | Role of polyphenols in adaptive immune system/microbiota

The relationship between the intestinal chronic inflammatory syndromes and intestinal microbiota is strongly associated with a dysfunction of the immune system and the production of various pro-inflammatory cytokines (Lobionda, Sittipo, Kwon, & Lee, 2019). Consequently, modulation of immune cells by dietary compounds such as polyphenols alone or in association with probiotics could be a good strategy to counteract these disorders. Liso and colleagues (2018) have recently shown that a diet containing an engineered tomato fruit called "Bronze" that is enriched in several different polyphenols was capable of providing a shift in the gut microbial composition of healthy mice and partly restrict the host inflammatory response to decrease or retard the occurrence of intestinal devastation induced by DSS application. This action requires a decrease in the ratio of IL-17A $CD4^+$ cells in mice and with a decrease in $IFN\gamma^+CD4^-$ cells in a murine model of spontaneous ulcerative colitis (UC) called Winnie (Liso et al., 2018). Very interestingly, the microbial composition of both WT and Winnie mice was altered by 2 weeks of dietary intervention: they have observed an augmentation in *Flavobacterium* and a decline in the relative amount of *Oscillospira* (Liso et al., 2018). Other authors have highlighted a downregulation of mucosal energy metabolism, changes in microbial profiles, and attenuation of intestinal inflammation, these events could account for the smaller adenoma size in cloudberry-fed mice compared to bilberry-fed mice (Päivärinta et al., 2016). More specifically, the cloudberry diet decreased the proportion of intraepithelial to total mucosal $CD3^+$ T lymphocytes, and very interestingly, berry feeding altered the predominant bacterial diversity in cecal contents, where the microbial profiles of the bilberry-fed mice were determined to be more diverse than the other treatments. The authors suggested an increase of Clostridiales order as a member of the Lachnospiraceae family, which is generally considered as a commensal or a beneficial bacterium. Moreover, the microbial profiles of cloudberry-fed mice were associated with smaller adenoma size and clustered together, indicating that the gut microbiota was modulated by cloudberry feeding in a manner where the growth of adenomas slowed down (Päivärinta et al., 2016). Furthermore, other studies have shown that flavan-3-ol monomers such as epicatechin and catechin may be able to influence the gut microbial population even in the presence of other nutrients, such as proteins and carbohydrates. It was observed that catechin significantly hindered the growth of *Clostridium histolyticum* and reinforced the growth of *E. coli* and members of the *Clostridium coccoides–Eubacterium rectale* group, while the growth of *Bifidobacterium* and *Lactobacillus* spp. remained relatively unaffected (Tzounis et al., 2008).

Intestinal microbiota, which produces tolerogenic response influencing gut DCs and inhibiting Th17 cell anti-inflammatory pathway, could be improved by polyphenols that are able to modulate the intestinal microbiota and subsequently attenuating inflammatory pathway (Magrone & Jirillo, 2013). Polyphenols may change $CD4^+$ T cell activation and polarization directly. For instance, an increase in the mucosal CD4+ T cells and B cells and a decrease in adenoma formation have been observed when $Min/^+$ mice treated with curcumin (Churchill, Chadburn, Bilinski, & Bertagnolli, 2000). Moreover, resveratrol and curcumin are able to change the activity of B cells as demonstrated by a substantial inhibition of lymphokine secretion, antibody production, and proliferation (Sharma, Chopra, Kulkarni, & Agrewala, 2007). The molecular mechanism appears to comprise several transcription factors such as members of the signal transducers and activators of transcription (STAT) and the nuclear factor-κB (NFκB) as well as modulation of receptor expression at the cell surface (e.g., CD28/CTLA-4). Indeed, the expression of CD28 and CD80 can be decreased by resveratrol and curcumin, while the production of CTLA-4 and the IL-10 is increased (Sharma et al., 2007). This modulation is significant since the T cell receptor signaling can be reduced or enhanced by the modification of the expression of CD28/CTLA-4 and IL-10 is known to limit the immune response (Akdis & Blaser, 2001; Ansari & Sayegh, 2006; Thomson & Forrester, 1994). Nuclear factors are also included because NF-κB p65 nuclear translocation in activated $CD4^+$ T-cells is restrained in curcumin diets (W. Kim et al., 2009). Curcumin regulates STAT4 activation in human $CD4^+$ T cells and reduces their capacity of differentiating in Th1 cells (Fahey, Adrian Robins, & Constantinescu, 2007). The polarization of Th17 also appears to be modulated by apple polyphenols. They decrease the production of T cell IL-17 regarding a murine sulfate dextran–induced colitis (Skyberg et al., 2011). Additionally, the production of $IL\text{-}17^+/IL\text{-}10^+$/Th17 cells is augmented by resveratrol regarding experimental autoimmune encephalitis (Imler & Petro, 2009). Consequently, it can be deduced from these data, Th1 and Th17 inflammatory processes are lessened by polyphenols possibly by the direct and indirect effects on T cells, while human leukocyte antigen (HLA) class II-mediated immune recognition of malignant B cells could be enhanced (Radwan et al., 2012). Moreover, it was shown in another context that resveratrol can alter the Th17 differentiation process (Limagne et al., 2017). Indeed, resveratrol deacetylates the transcriptional factor STAT3 that is unable to produce retinoic-acid-related orphan receptor-gamma t (RORγt), which is a transcriptional nuclear factor essential to the process of lymphocyte differentiation (Limagne et al., 2017). In this way, resveratrol and other polyphenols can act on various inflammatory diseases by blocking interleukins-associated Th17 and disrupting Th17 polarization. By their action of the state of

the immune response, polyphenols partly determine the therapeutic outcome of patients with various diseases, particularly diseases where the inflammatory component plays a major role.

Another potential role of polyphenol in this adaptive immune response in the gut could be their action on the Treg cells that act a critical part in retaining immune tolerance and suppressing autoimmunity. Treg cells contribute to the evasion of immune surveillance, suppressing cell populations such as $CD4^+$, $CD8^+$ T cells, DCs, osteoblasts, macrophages, B cells, NK cells, and mast cells, thereby avoiding immunopathological, allergic, or autoimmune diseases and helping to develop immunological tolerance to organ grafts (Wan & Flavell, 2007). Biochemistry analysis shows that TGFβ and FoxP3 are present at the polyphenol action, TGFβ production is downregulated by resveratrol (Y. Yang, Paik, Cho, Cho, & Kim, 2008), curcumin (Bhattacharyya et al., 2010), and genistein (T. L. Guo, Chi, Hernandez, Auttachoat, & Zheng, 2007), inducing the inhibition of Treg cells activity. Curcumin downregulates the suppressor function and expression of FoxP3 in $CD4^+CD25^+$ Treg cells (Forward et al., 2011). Interestingly, in the mouse intestine, differentiation of naïve $CD4^+$ T cells into resembling Treg cells including IL-10-producing bacterial antigen-specific Tr1 cells and $CD4^+CD25^+FoxP3^+$ Treg is induced by curcumin-treated DC (Cong, Wang, Konrad, Schoeb, & Elson, 2009). Indeed, in the presence of TGFβ, $CD4^+CD25^-$ T cells could be transformed into $CD25^+$ Treg by T-cell receptor (TCR) stimulation (W. Chen et al., 2003), and in the presence of high dose of IL-10, antigen-specific Tr1 cells could be induced by antigens (Groux et al., 1997). This Treg inhibits antigen-specific T-cell activation *in vitro*and inhibits colitis by virtue of antigen-specific pathogenic T cells *in vivo* (Cong et al., 2009). On the contrary, in the nontumoral context, epigallocatechin-gallate (EGCG) could act as DNA methyltransferase (DNMT) inhibitor and induce FoxP3 expression as well as increase Treg number *in vivo* (C. P. Wong et al., 2011). Moreover, IL-10 is downregulated in the presence of genistein and curcumin, and subsequently, the capability of effector T cells to destroy cancer cells is enhanced and type 2 immune response against tumors is increased (Bhattacharyya et al., 2010; T. L. Guo et al., 2007). For another example, when applied immediately after the onset of middle cerebral artery occlusion (MCAO) in C57BL/6 mice for 3 days, resveratrol provided a balance between Th1 and Th2 toward Th2 polarization and skewed the balance between Treg and Th17 toward Treg in the small intestinal lamina propria, and attenuated small intestinal pro-inflammatory cytokine expression by changing intestinal microflora at 3 days post-ischemia (Dou, Rong, Zhao, Zhang, & Lv, 2019).

5.4.3 | Innate immune system and microbiota

The innate immune system, also known as the nonspecific immune system and secondary line of defense, involves the cells and mechanisms that defend the host from the infections caused by other organisms in a nonspecific way. The innate response includes soluble factors and several cellular effectors, including (a) phagocytes such as macrophages CD11b+CX3CR1hi (C-X3-C motif chemokine receptor 1) that are physiological situation, the most numerous cells in the chorion and initiate T-cell responses by antigen presentation (Bain et al., 2014) and (b) DCs that play a main role as immune sentinels in the initiation of T-cell responses.

The innate immune system sends signals to adapt the host physiology in tissue level when the system perceives information about the metabolic state of the gut microbial community. Also, the composition and function of the gut microbiome might be regulated by the innate immune system. Genetic discoveries based on the human and mice studies show that the innate immune system acts significantly to adjust compositional and interindividual variations in the microbiota. Innate immune pathways such as TLRs, Nod-like receptors, and C-type lectins have been shown to play a significant role in host-microbiota mutualism (Thaiss, Zmora, Levy, & Elinav, 2016). For example, in innate immune-deficient mouse models such as mice without NOD2, NLRP6, or TLR5, alterations in microbial composition, also called dysbiosis, have been reported. Correspondingly, the innate immune system might perform to maintain a stable gut microbial community via contributing to the growth of beneficial microbes (Thaiss, Levy, Suez, & Elinav, 2014).

5.4.4 | Role of polyphenols in innate immune system/microbiota

Although there are plenty of studies on macrophages and polyphenols concerning different domains such as cancer, autoimmune diseases, inflammation, and coronary heart damage, there are very few studies focusing on the effects of polyphenols on macrophages in relation to the intestinal microbiota. For example, *Camellia sinensis* (oolong, white, yellow, green, dark, and black tea) and *Litsea coreana* (hawk tea) significantly reduce the production of pro-inflammatory cytokines (tumor necrosis factor-α, IL-6, and IL-12) and increase the anti-inflammatory cytokines (IL-10) in LPS-stimulated RAW 264.7 macrophages and a DSS-induced colitis mouse model (Liu et al., 2020). Very interestingly, these tea extracts act as prebiotics on the gut microbiota because they augment the quantity of potentially beneficial bacteria (e.g., *Bifidobacterium* and *Faecalibaculum*), and reduce the amount of potentially harmful bacteria (e.g., *Mucispirillum* and *Bacteroids*) (Liu et al., 2020). Chlorogenic acid significantly suppresses the secretion of IFNγ, tumor-necrosis factor alpha (TNFα), and IL-6 and the colonic infiltration of $CD177^+$ neutrophils, $CD3^+$ T cells, and $F4/80^+$ macrophages by means of inhibition of the active NF-κB signaling pathway (Zhang et al., 2017). In similarly, Aloe metabolites derivatives, a polyphenolic anthranoid-containing Aloe vera leaves, reduce the production of nitric oxide (NO), TNFα, and IL-12 by murine peritoneal macrophages. Furthermore, administration of Aloe significantly lowered the NO level produced by macrophages and exhibited protective effects against sepsis-related death in LPS-induced septic mice (C.-Y. Li et al., 2017).

Other immune cells playing an essential role in innate response are the DCs. A recent study has shown that treatment with curcumin nanoparticles increased the fecal butyrate levels and abundance of butyrate-producing bacteria (Ohno et al., 2017). This was allied with increased expansion of $CD4^+$ $Foxp3^+$ regulatory T cells and CD103+ CD8α-regulatory DCs in the colonic mucosa, and thus, could constitute

a promising therapeutic option for the treatment of inflammatory disorders (Ohno et al., 2017). This is an important point because the plasticity of the DCs probably allows them to adapt their function to the signals received in the intestinal microenvironment, in particular via the microbiota (Bekiaris, Persson, & Agace, 2014). The biochemical analysis discloses a common mechanism involving the transcription factors STAT and NF-κB, kinases, the cyclo-oxygenase (COX). Indeed, polyphenols hinder the COX-2 expression, the prostaglandin E2 (PGE2) production (Jeong et al., 2007), the activation, and DNA binding of STAT1 to the interferon regulatory factor 1 (IRF-1) promoter in response to IFNγ (Jeong et al., 2007, 2009). The action of polyphenols could be provided by different factors such as kinases because polyphenol-pretreated DC restrains LPS-induced MAPKs such as p38, (JNK), ERK1/2, and NF-κB p65 translocation (Ahn et al., 2004; G.-Y. Kim et al., 2005).

Together these data show that polyphenols can act on immune cells through the disruption of T cell differentiation, a limitation of DCs maturation, or inhibition of macrophages, and subsequently, their ability to produce pro-inflammatory cytokines. These incidents may encourage a tolerogenic state and could restrict the inflammatory process in various physiopathological disorders.

6 | LOCAL BENEFICIAL EFFECT OF POLYPHENOL INTAKE

Emerging evidence from *in vitro* and *in vivo* studies, clinical trials, and meta-analyses shows that a regular intake of polyphenols can improve human health and reduce the risk of chronic and inflammatory disease (Fiorentini, Zambonin, Vieceli Dalla Sega, & Hrelia, 2015). The inflammatory process plays a central role in the development and progression of a number of pathological conditions, such as inflammatory bowel disease (IBD). Worldwide incidence and prevalence of IBD have led it to gain the status of a global disease (Burisch et al., 2014; Molodecky et al., 2012). In IBD, chronic inflammation causes mucosal disruption along with a high production of ROS and may contribute to the onset, progression, and metastatic diffusion of cancer. Polyphenols are potent anti-inflammatory compounds that could provide an interesting alternative candidate in IBD management. Studies performed on strawberry anthocyanins have highlighted their anti-IBD effects, mostly attributed to their free-radical scavenging and anti-inflammatory properties (Boyer & Liu, 2004). The protective effects of berry fruits and apple against colon cancer have been shown in murine models, in particular, green tea polyphenols have been found to enhance antioxidant response, reduce inflammatory markers (IL-6, TNF-α, and serum amyloid A), alleviate pathological lesions, and protect colonic microstructure in a similar way to sulfasalazine, the conventional agent used in IBD therapy (Woods & Turchi, 2013) Epidemiological, preclinical and clinical studies have consistently emphasized important relationships between gut microbiota, large bowel inflammation, and colorectal cancer (CRC). Other inflammation-related CRC risk factors include high-fat/low-fiber diets, obesity, and family history of CRC and an abnormal gut microbial composition (Peng, Weigl, Boakye, & Brenner, 2018; Shen et al., 2018). The conventional treatments for CRC include surgery and chemotherapy. Unfortunately, chemotherapy induces cytotoxic effects, drug resistance, and adverse reactions. CRC is the fourth leading cause of malignant tumor-related deaths worldwide (Ferlay et al., 2015). A large amount of scientific evidence has linked the Western dietary model to the increased risk of CRC, while the Mediterranean diet and the vegetarian diet have been associated with a lower risk of CRC. Specific dietary components present in the diet, such as polyphenols (i.e., curcumin, epigallocatechin gallate, resveratrol, and hydroxytyrosol) have been proposed as chemopreventive agents capable of delaying the development of CRC by modulating biological mechanisms that play a key role in the onset of the CRC (Graf, Milbury, & Blumberg, 2005; Henning et al., 2013; Pan et al., 2015). Resveratrol, a polyphenol extracted from Chinese herbal medicine *Polygonum cuspidatum* (Linnaeus, 1828), has been shown to have apoptotic and antiproliferative effects on CRC, affecting MALAT1 (Metastasis Associated Lung Adenocarcinoma Transcript 1) expression inhibiting invasion and metastasis (Ji et al., 2013). Epigallocatechin gallate has been investigated in colon carcinoma cell lines and it induces growth inhibition by suppressing Akt, p38MAPK, cyclin D1, and by downregulating ErbB2, ErbB3, and EGFR (Cerezo-Guisado et al., 2015). Engelbrecht et al. (2007) have reported that grape seed extract induces apoptosis and suppresses viability of CaCo-2 cells. Persimmon (*Diospyros kaki* L.) fruits, characterized by their high proanthocyanidin content, have been benefited in Chinese traditional medicine for a long time for their health-promoting effects, mainly against hypertension, bleeding, body temperature, and general oxidative effects (Gu et al., 2008; Hibino, Nadamoto, Fujisawa, & Fushiki, 2003). Fisetin, a flavonoid present in persimmons, has also been found to lower the severity of colitis by decreasing the expression of COX-2 and iNOS in the colon tissue of experimentally induced colitis (Sahu, Kumar, & Sistla, 2016). Colitis is one of the predisposing factors for CRC and the intake of persimmon as a source of flavonoids is important to prevent it.

7 | TARGETING GUT MICROBIOTA FOR HOST HEALTH BY DIETARY POLYPHENOLS

7.1 | Diabetes

According to Diabetes Atlas published by International Diabetes Federation (2019), diabetes is one of the worldwide health concerns of the 21st century, and it is still growing very fast. In 2019, the number of people with diabetes worldwide was estimated to be 463 million and this number is anticipated to reach 700 million by 2045.

Insulin is the key hormone responsible for blood glucose regulation and in normal conditions, its secretion from the pancreatic β-cells decreases glucose output by the liver and raises glucose uptake by skeletal muscles and adipose tissue. This state is referred to as normoglycaemia—a balanced reciprocation between insulin action and insulin secretion. However, if there is a dysfunction in the pancreatic β-cells and/or insulin resistance in the liver, skeletal muscle, or adipose tissue, systemic glucose concentrations

increase (hyperglycemia) (Stumvoll, Goldstein, & van Haeften, 2005; Zheng, Ley, & Hu, 2018). Recent evidence propounds that there is a difference in the number and composition of gut microbiota between diabetic and nondiabetic individuals. Larsen et al. (2010) identified the composition of fecal microbiota in Chinese adults with type 2 diabetes as compared to non-diabetic controls. Their results suggest that the blood glucose level is positively and significantly correlated with the ratios of Bacteroidetes:Firmicutes as well as the ratio of *Bacteroides-Prevotella*:*Clostridium coccoides-Eubacteria rectale* groups. Likewise, class *Betaproteobacteria* was found to be abundant in diabetic volunteers compared to nondiabetic ones with a positive correlation between plasma glucose levels. Furthermore, proportions of the phylum Firmicutes and class *Clostridia* showed a significant decrease in the diabetic group. Another similar study conducted on European women with type 2 diabetes elucidated that there is an increase in the amount of opportunistic pathogenic *Clostridium clostridioforme*, whereas a decrease in butyrate forming bacteria *Roseburia* was found, which resulted in an improvement of the insulin sensitivity in the individuals with metabolic syndrome (Karlsson et al., 2013). This shows that depending on the population (continent where the study was performed), different effects have been observed.

It has been speculated based on preclinical experiments mostly in rodent models that polyphenols may exhibit antidiabetic activity either directly depending on their absorption rate or indirectly, that is, by modulation of the gut microbiota (Anhê et al., 2013). Oral administration of polyphenol-rich cranberry extract (200 mg/kg/day) for 8 weeks significantly improved the metabolic syndrome-associated indications including insulin sensitivity in high-fat—high-sugar fed mice and the obtained beneficial effects were attributed to the relative increase in the proportion of *Akkermansia* spp. in the gut (Anhê et al., 2015). Polyphenol-rich extract of *Dendrobium loddigesii* ameliorated the symptoms of and complications of diabetes in db/db mice via several possible mechanisms; by decreasing inflammation and oxidative stress, as well as enhancing the intestinal microbiota balance. After the treatment with polyphenol-rich extract, there was an increase in Bacteroidetes:Firmicutes ratio together with the relative abundance of *Prevotella*/*Akkermansia* as well as a decrease in the relative abundance of *S24-7*/*Rikenella*/*E. coli* (X.-W. Li et al., 2018). In another *in vitro* study, metabolism of *Radix scutellariae* extract (a traditional Chinese medicinal herb commonly used to treat diabetes) by intestinal bacteria from healthy and type 2 diabetic mice was investigated. According to the results, the intestinal microbiota from both mouse groups converted baicalin (the main flavone glycoside) to its deglycosylated from (baicalein). Interestingly, metabolites of baicalin, with better absorption rates contributing to the treatment of type 2 diabetes, were higher in the diabetic samples compared to healthy fecal samples, while another flavone aglycone (oroxylin A) was detected in type 2 diabetic samples. Although the microbial composition of the samples was not analyzed, the underlying reason for this difference was attributed to the possibly higher β-D-glucuronidase activity in the microbial community of diabetic mice compared to its nondiabetic counterparts (Xu et al., 2014). Furthermore, human gut microbial metabolites of blackberries were found to have a higher antidiabetic activity due to higher biological activity of the metabolites produced during microbial fermentation. By this means, glucose consumption and glycogen content in HepG2 cells were significantly increased after the addition of blackberries (Gowd et al., 2018).

7.2 | Cancer

The positive effects of polyphenols in cancer have widely been reported. Several molecules, polyphenol-rich foods, and even dietary patterns may be of interest from the point of view of cancer. Curcumin is one of these foods rich in polyphenols. The chemopreventive effect of curcumin on reducing colonic tumor burden has been linked with the retention of high microbial diversity (McFadden et al., 2015). On the other hand, Shakibaei et al. (2014) illustrated the interesting effects of curcumin in enhancing chemosensitization to 5-FU-based chemotherapy by targeting the cancer stem cells subpopulation.

According to the EPIC study, Mediterranean diet has been associated with a lower incidence of colorectal cancer (Orlich et al., 2015). This preventive effect has been associated mainly with being rich in ω-3 polyunsaturated fatty acids and polyphenols (Song et al., 2016). Some of the phenolic compounds widely present in the Mediterranean diet are ferulic acid (from whole grain), catechins (from walnuts and apples), hydroxytyrosol (from olive oil), and naringenin (from tomatoes) (Manach, Scalbert, Morand, Rémésy, & Jiménez, 2004). Recently, Piazzi et al. (2019) have described how a Mediterranean diet pattern is able to counteract colorectal cancer development in a murine model through the regulation of apoptosis and gut microbiota.

Some of the most interesting evidence in cancer come from prostate cancer. Prostate cancer is the second most common cancer in men, with external factors, including nutrition, heavily influencing prostate cancer risk (Haas, Delongchamps, Brawley, Wang, & de la Roza, 2008). It has been demonstrated that consuming high amounts of flavan-3-ol and ellagitannin-rich products such as green tea and pomegranate preparations seems to decrease the risk of prostate cancer (Stanisławska et al., 2019). Oral intake of some of these products has been shown to inhibit the development of prostate cancer in animal studies and also epidemiologic evidence is available (Stanisławska, Piwowarski, Granica, & Kiss, 2018; Stanisławska et al., 2019). Despite that, clinical trials of pomegranate extracts in patients bearing prostate cancer did not provide definitive results (Paller, Pantuck, & Carducci, 2017). The reason for this lack of positive effects may be the lower active concentrations *in vivo* or the interaction of polyphenols with microbiota. In that sense, both ellagitannins and green tea flavan-3-ols are catabolized by the gut microbiota, of which the main bioavailable products are urolithin A (uroA) and (poly) hydroxyphenyl-γ-valerolactone (M4). Stanisławska et al. (2018) have established the effects of these catabolites on LNCaP cells, an androgen-dependent prostate cancer *in vitro* model. M4 showed antiproliferative activity in LNCaP cells. UroA decreased proliferation and induced apoptosis of LNCaP cells. M4 potentiated inhibition of prostate-specific antigen secretion and increased retention of androgen receptor in cytoplasm caused by uroA. Also, uroA increased the pSer473 Akt level in LNCaP cells. These results

indicate that chemoprevention of prostate cancer might be achieved by the colonic metabolites of polyphenols.

Colorectal cancer has been recorded as one of the common cancer types, which is the second most frequently diagnosed cancer in women and the third in men (Agudelo, Ceballos, Gómez-García, & Maldonado-Celis, 2018). The effect of black raspberry intervention (10% black raspberry in diet) on the intestinal tumor-bearing mice has been investigated by May, McDermott, Marchesi, and Parry (2020). It has been shown that black raspberry administration altered the gut microbial composition in both healthy and tumor-bearing mice that may have a protective effect on the onset and progression of colorectal cancer (Afrin et al., 2018; May et al., 2020).

7.3 | Obesity

Being overweight or obese, in other words, having a body mass index (BMI) equal to or greater than 30 kg/m^2, is getting more and more prevalent particularly in the developed countries due to adoption of a modern lifestyle where people move less and eat unhealthily (Guida & Venema, 2015; Mokdad et al., 2001). Consuming energy-dense foods and having a sedentary lifestyle cause an imbalance between the gained and spent energy in the body, and thus, excessive body fat storage occurs due to the redundant energy. However, it is important that obesity should not be considered as a cosmetic problem that affects certain individuals because there is an association between obesity and several health problems such as type 2 diabetes, coronary heart disease, some types of cancer, and sleep-breathing (Kopelman, 2000). The occurrence of obesity is determined by the interaction of environmental, genetic, and physiological factors that affect energy intake and expenditure (Kopelman, 2000).

Gut microbiota is accepted as one of these environmental factors involved in the development of obesity. Previous reports suggested that the gut microbiota plays a significant role in the formation of fat mass and the changed energy homeostasis. Several studies conducted on gnotobiotic mice (germ-free mice that were grown in the absence of any microorganisms) revealed that germ-free mice are leaner than those that harbor microbial communities in their gut. Additionally, the obese microbiome was found to have a higher ability to harvest energy from the diet and the most important, when the gut microbiota from obese mice was transplanted to germ-free mice, this leads to higher fat deposition than upon a lean microbiota transplant (Turnbaugh, Bäckhed, Fulton, & Gordon, 2008; Turnbaugh et al., 2006). Human studies also indicated changes in gut microbial composition depending on obesity. Ley, Turnbaugh, Klein, and Gordon (2006) showed that Firmicutes:Bacteroidetes ratio is increased in obese people compared with the lean people and that this ratio decreases as the individuals lose weight with two types of a low-calorie diet. However, this has not been observed in other studies (Guida & Venema, 2015).

The modulation of the obese gut microbiota by phenolic compounds was investigated by several research groups in order to interpret the reciprocal interaction between phenolic compounds and gut microbiota (X. Guo et al., 2017; Jiao et al., 2019; Moreno-Indias et al., 2016; X. Zhang et al., 2018). It is evident that dietary polyphenols and their metabolites have a positive effect on promoting gut health by shifting the gut microbial composition via stimulating the growth of beneficial bacteria, while inhibiting pathogen bacteria. Polyphenols from oolong, black, and green teas have been shown to affect the microbial composition significantly by increasing *Bifidobacterium* spp., *Lactobacillus* spp. and *Enterococcus* spp. while increasing the production of SCFAs and decreasing the generation of *Prevotella*, *Bacteroides*, and *Clostridium hystolyticum* (Sun et al., 2018). Phenolic compounds from plum were shown to limit weight gain in conjunction with modulation of the gut microbiota (e.g., increase in *Faecalibacterium* spp., *Lactobacillus* spp., and *Bacteroidetes* spp.) and decreased fecal SCFAs in obese rats (Noratto et al., 2014). Similarly, the administration of quercetin to the high-fat sucrose diet-induced obese mice inhibited the body weight gain and decreased the Firmicutes:Bacteroidetes ratio by hampering the growth of *Eubacterium cylindroides*, *Bacillus*, and *Erysipelotrichaceae*, which are associated with the diet-induced obesity (Etxeberria et al., 2015). On the other hand, obesity is commonly regarded as a condition of chronic, low-grade inflammation (Guida and Venema 2015). This situation involves the accumulation of inflammatory cytokines such as TNF-α, IL-1β, and CCL2 in adipose tissue, as well as an increase in macrophages, mast cells, and natural killer T cells (Gregor & Hotamisligil, 2011; Saltiel & Olefsky, 2017). Inflammation in obese mice was found to be downregulated via the production of glucagon-like peptide-2, which reduces intestinal permeability and thus reduces the translocation of lipopolysaccharides in association with changing the gut microbiota in favor of the *Bifidobacterium* spp. (Cani et al., 2009). Accordingly, inflammatory markers of obesity may be suppressed by colonic fermentation of polyphenols that have been shown to enhance the growth of *Bifidobacterium* spp. (Espley et al., 2013; Tzounis et al., 2008).

7.4 | Cardiovascular diseases

The World Health Organization (WHO) recommends an increased consumption of fruit, vegetables, and fiber as a key lifestyle change to reduce the risk of noncommunicable diseases such as cardiovascular diseases. Cardiovascular diseases, including stroke, heart failure, and hypertension, are the most common cause of mortality in developed countries. Current studies have highlighted the emerging role of polyphenols in preventing such disease as part of the human diet and correlating the intake of foods with high polyphenol contents (i.e., cocoa, tea, wine, fruit, and vegetables) with decreased cardiovascular diseases. It has been reported that high polyphenol intake, especially of stilbenes and lignans, correlated with reduced risk of mortality (Tresserra-Rimbau et al., 2014). Consumption of food sources of hydroxycinnamic acids and flavonoids reduces high blood pressure, one of the major risk factors for cardiovascular diseases (Fuentes & Palomo, 2014). Similarly, an analysis on the consumption of coffee in the Brazilian population showed an inverse correlation with hypertension. Coffee is the primary food item contributing to the phenolic acid intake (Miranda et al., 2016).

Recent studies have reported that the intake of food with a high content of flavan-3-ol (such as tea, nuts, cocoa, grapes, and legumes) has a positive effect on blood pressure and cholesterol levels (Fraga, Croft, Kennedy, & Tomás-Barberán, 2019). A study was performed from 1975 to 2010 on 953 participants on the cardiovascular benefits derived from dark chocolate and cocoa consumption. Chocolate intake was inversely associated with type 2 diabetes reducing the probability of developing stroke or ischemic heart disease (Crichton, Elias, Dearborn, & Robbins, 2017). One of the factors correlated with the risk of cardiovascular diseases is trimethylamine N-oxide (TMAO), an amine oxide deriving from the metabolization of L-carnitine and choline by the colonic microbiota, such as Proteus, Aerobacter, Clostridia, and Shigella (Subramaniam & Fletcher, 2018). Several foods having substantial L-carnitine, lecithin, and choline content, such as red meat, eggs, and salt-water fish, have been considered dietary sources of TMAO (Cho & Caudill, 2017). Modification of the gut microbiota with a regular intake of antioxidant and antimicrobial food, such as polyphenols, is one of the goals in reducing the risk of cardiovascular diseases. For instance, resveratrol inhibits the expression of Proteus virulence factors (Bostanghadiri et al., 2017). Ellagitannins, the main phenolic compounds in *Rubus* and *Fragaria* genus fruits, show very interesting properties on the growth of selected Gram-negative intestinal bacteria such as *Clostridium* (Puupponen-Pimiä et al., 2001) involved in TMAO metabolism. An *in vivo* study on a mice model demonstrated the ability of resveratrol in the reduction of TMAO levels, modifying microbiota composition with an increase in *Lactobacillus* and *Bifidobacterium* growth (M.-l. Chen et al., 2016). A pilot study carried out by Annunziata et al. (2019) demonstrated that Taurisolo®, a novel nutraceutical formulation containing grape pomace rich in polyphenols (particularly in resveratrol), was able to remodel the microbiota and reduce TMAO levels in healthy subjects as well as the risk of cardiovascular diseases.

7.5 | Aging

Aging is a physiological process that represents a great challenge for society as long as the population ages and lives longer. Therefore, keeping that population as far away as possible from the pathologies associated with age will lead to less dependence and economic cost. Nutrition is closely related to aging so that a good dietary pattern can make the aging process healthier. The outstanding point in this context is that the composition of the intestinal microbiota substantially changes with aging and related disease outcomes (Lakshminarayanan, Stanton, O'Toole, & Ross, 2014). The age-related changes in the gut microbiota composition lead to lower microbiota diversity, an increase in the abundance of subdominant species, certain Proteobacteria, and proteolytic bacteria, while a decrease in saccharolytic bacteria, the abundance of dominant species, the ratio of Firmicutes to Bacteroides, and bifidobacterial counts (Vaiserman, Koliada, & Marotta, 2017). The role of phenolic compounds in aging has widely been documented. Thus, it is known as the administration of foods rich in phenolic compounds or extracts enriched with these compounds improves some typical aging patterns. These naturally occurring compounds are considered potential antiaging agents because of their ability to modulate oxidative damage, inflammation, cell senescence, and autophagy (Russo et al., 2019). Although the intake of polyphenols exerts a significant effect on the gut resident community, the effect of dietary polyphenols on the gut microbiota within age remains poorly defined. Chacar et al. (2018) have investigated the effect of long-term intake of grape pomace, rich in phenolic components, on rat gut microbiota. These authors treated male Wistar rats on different concentrations of phenolic compounds from grape pomace for 14 months. Authors found that this long-term treatment modulated rat gut microbiome selectively to a healthier phenotype, with a higher presence of probiotic bacteria and a lower abundance of Clostridium. In another study, Alkhaldy, Edwards, and Combet (2019) investigated how urinary phenolic acid profile changes between older and younger adults after consuming a polyphenol-rich meal. Healthy participants, younger (23–43 years) and older (51-76 years), followed a 3-day low-polyphenol and a 3-day high-polyphenol diet. Total urinary phenolic acids were higher in the older group after the high-polyphenol diet compared to the younger group. The authors also observed that urinary phenolic acids were less diverse in older participants despite the limited differences in the functional capacity of *in vitro* fecal fermentation. So, until now, evidence on the interaction between microbiota and polyphenols in aging is very limited, which promises further research in this field. These investigations should be extended to study the effects of these compounds on pathologies associated with aging, such as hypertension, diabetes, neurodegenerative diseases, and others.

8 | CONCLUDING REMARKS

The intake and the bioavailability of polyphenols determine their health effects. Despite the high abundance of polyphenols in our diet, the plasma concentration of these individual polyphenolic molecules seldomly exceeds the micromolar level. However, studies on the determination of plasma antioxidant capacity suggest that there is still a high amount of phenolic compounds present in the plasma, mostly in the form of metabolites that might be produced in the tissues or by the action of gut microbiota. To date, several studies have been conducted in order to understand the biotransformation of polyphenols by the colonic microflora and identify the responsible microorganisms. On the other hand, the modulation of the gut microbiota composition by the phenolic compounds has also been assessed to render the reciprocal interactions between phenolics and gut microbiota. Based on these studies, it is evident that dietary polyphenols and their metabolites promote gut health by acting like a prebiotic and modulating the gut microbial composition in a positive manner, in which the growth of beneficial microbes are stimulated, whereas the pathogens are inhibited. However, data on the two-way interactions between polyphenols on the gut microbiota and their resultant effects in humans still need to be elaborated. In conclusion, employing the emerging advances in high-throughput metagenomic, transcriptomic, and proteomic approaches to obtain a better understanding about the interplay between dietary polyphenols and gut microbiota would be

crucial in order to describe the genes and microorganisms taking part in the metabolism of polyphenols, and thus, to elucidate the implications of the relations between polyphenol intake, their metabolism, and change in gut microbial composition for providing health benefits.

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How to cite this article: Catalkaya G, Venema K, Lucini L, et al. Interaction of dietary polyphenols and gut microbiota: Microbial metabolism of polyphenols, influence on the gut microbiota and implications on host health. *Food Frontiers*. 2020;1–25. https://doi.org/10.1002/fft2.25