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Dietary Polyphenols and Human Gut Microbiota: a Review

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Dietary polyphenols are substrates for colonic microbiota. They and their metabolites contribute to the maintenance of gastrointestinal health by interacting with epithelial cells, and largely by modulating the gut microbial composition. Polyphenols may act as promoting factors of growth, proliferation, or survival for beneficial gut bacteria—mainly Lactobacillus strains—and thus, exerting prebiotic actions and inhibiting the proliferation of some pathogenic bacteria such as Salmonella and Helicobacter pylori species. To date the interactions affecting metabolic pathways and numerous metabolites of dietary polyphenols have been widely documented. However, the effects of dietary polyphenols on the modulation of the intestinal ecology and on the growth of gut microbial species are still poorly understood. This paper summarizes data on the influence of dietary polyphenols on gut microbiota and the main interactions between dietary polyphenols and beneficial and pathogenic intestinal bacteria.

Keywords polyphenols, gut microbiota, gastrointestinal health, Lactobacillus, Bifidobacterium, antimicrobial properties

Introduction

The gut microbiota supports a large variety of physiological functions and possesses enzymatic and metabolic activities which impact on host nutrition and health.[1] Intestinal microbial ecology can be modulated by living microorganisms and non-digestible dietary compounds, including plant secondary phytochemicals.[2] Certain bioactive phytochemicals of nutritional importance can be associated with dietary fiber, mainly polyphenols, the most abundant phytochemicals in our diet.[3] Polyphenols are chemical and biologically active plant secondary metabolites derived from phenylalanine and tyrosine with the basic structure of phenol (hydroxybenezene). Polyphenols occur in association with food matrices in plant food products such as cereals, fruits, vegetables, and beverages (coffee, tea, wine and beer).[2] Health benefits of polyphenols have been widely described, especially the prevention of diseases associated with oxidative stress such as cancer, cardiovascular, inflammatory, and neurodegenerative diseases.[4–7] Furthermore, recent evidence suggests that health benefits attributed to polyphenols may be also related to the modulation of gene expression and the gut microbiota balance.[8,9] Evidence from epidemiological studies highlights that populations with diets rich in fruits and vegetables have lower incidences

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of certain types of cancer, including the gastric variety.[13,14] Fruits and vegetables are the major contributors to polyphenol intake. Case-control studies in Spain and Greece reported a significant inverse association between the intake of total flavonols, flavanones, and luteolin, and the risk of gastrointestinal cancer.[15,16] In Mexico, a recent population-based case-control study showed a reduced risk of gastric cancer associated with higher consumption of various polyphenols, including cinnamic acids, secoisolariciresinol, and coumestrol, irrespective of vitamins C and E, and fruit and vegetable consumption.[17] Moreover, consistent evidence from epidemiological studies indicates an inverse relationship between green tea (rich in flavanols) consumption and the risk of digestive tract cancers such as oral, esophageal, stomach or colorectal cancer, and the incidence of chronic active gastritis.[18] Polyphenols possess well-known antioxidant properties and they are associated with numerous physiological effects, exerting a protective effect on the gastrointestinal system. The mechanisms involved are complex and include: the reduction of mutagen formation[19]; stimulation of healing of mucosal damage[20]; reduction of colonic mucosa DNA oxidation; protection of the colonic mucosa architecture; suppression of expression and activities of cyclooxygenases and inducible nitric oxide synthases in colonic tissues; reduction of mucosal apoptosis in the rat colonic mucosa via a modulation of the cellular redox environment[21]; inhibition of chemical colon carcinogenesis; modification of colon microbial ecology; down-regulation of inflammatory response and steroid metabolism in the colon mucosa; reduction of systemic inflammation markers; and regulation of many genes modulating cell surface antigens, metabolic enzymes, and cellular response to oxidative stress.[8,9]

One issue that needs be addressed is that a major part of dietary polyphenols is not absorbed in the small intestine; they exert biological activity through the intestinal tract and can interact with colonic microbiota when they reach the colon.[4] There are two main reciprocal interactions between the gut microbiota and polyphenols. On the one hand, dietary polyphenols undergo a complex metabolism after ingestion and interact with human and microbial enzymes, leading to the production of a large number of circulating and excreted polyphenol metabolites and catabolic products. Also, polyphenols and their metabolites can influence and induce a modulation of the gut microbiota composition by means of several interactions. To date the interactions affecting metabolic pathways and numerous metabolites of dietary polyphenols have been widely documented,[10,11] however, the effects of dietary polyphenols on the modulation of the intestinal ecology and on the growth of gut microbial species are still poorly understood. It is clear that polyphenols may confer health benefits through interactions with and hence modulation of the gut microbiota. In this regard, polyphenols may exert a doubly positive effect, on the one hand inhibiting pathogenic bacteria, and on the other hand stimulating beneficial bacteria. Some authors therefore suggest that polyphenols can act as a metabolic prebiotic.[12] In this work, our objective was to provide an overview of recent reports on the influence of dietary polyphenols on gut microbiota and to summarize the main interactions between dietary polyphenols and beneficial and pathogenic intestinal bacteria.

Gut Microbiota and Modulation by Dietary Components

Gut microbial ecology is composed of a broad spectrum of highly metabolically active species. About 10^{14} bacteria cells are present throughout the gastrointestinal tract but are predominantly located in the large intestine. *Bifidobacterium, Eubacterium, Clostridium, Peptococcus, Peptostreptococcus* and *Ruminococcus* are the predominant species of colonic microbiota while the subdominant group is composed of *Escherichia,*

Enterobacter, Enterococcus, Klebsiella, Lactobacillus, and *Proteus*.[12] They support a large variety of physiological functions through a wide range of enzymatic and metabolic activities, which impact on host nutrition and health.[12]

Intestinal bacteria can hydrolyze glycosides, glucuronides, sulfates, amides, esters, and lactones through the action of enzymes such as α-rhamnosidase, β-glucuronidase, β-glucosidase, sulfatase, and esterases. Other reactions catalyzed by gut microbial enzymes are aromatic ring-cleavage, reductions (reductases, hydrogenases), decarboxylation (descarboxylase), demethylation (demethylase), isomerization (isomerase), and dehydroxylation (dehydroxylase).[23,24] This large and diverse enzymatic capacity has both beneficial and detrimental effects, which may be substantially modified by diet.

The gut microbiota constitutes a physical and immunologic barrier between the host and the environment.[25] Major important functions of gut microbiota for human hosts are protection against gastrointestinal disorders and pathogens, nutrient processing and modulation of intestinal immune response.[26] A gut microbial composition profile in which beneficial bacteria are predominant over detrimental is desirable in that it provides further health benefits to the host and promotes a beneficial immune function.[25] However, certain endogenous and environmental factors, together with age, diet, genetics and immunological status, can disrupt gut microbiota balance, and consequently gastrointestinal disorders such as irritable bowel syndrome, inflammatory bowel disease and antibiotic-associated diarrhea can arise.[27] Some commensal gut microorganisms, such as some species of *Bacteroides*, *Clostridium* and *Eubacterium*, have been found to increase as a proportion of total bacteria in colorectal and gastrointestinal disorders and are therefore considered detrimental. These bacteria differ from beneficial microorganisms in possessing enzymatic activities related to the generation of carcinogens.[28] The major enzymatic activities of intestinal bacteria associated with the potential formation of carcinogenic metabolites in colon are β-glucuronidase, β-glucosidase, nitrate reductase, nitro-reductase, and 2-amino-3-methyl-3H-imidazo[4,5-f]quinoline (IQ) reductase.[1] Conversely, certain species belonging to the genera *Lactobacillus* and *Bifidobacterium* are considered beneficial microorganisms and are commonly used as probiotics in the manufacture of functional food products. The health properties attributed to beneficial bacteria include modulation of colonic microbiota by inhibiting a wide range of pathogens, improvement of lactose digestion, reduction of serum cholesterol, stimulation of the immune system through cytokine stimulus, reinforcement of intestinal epithelial cell tight junctions and increased mucus secretion.[26,29,30]

The gut microbiota is closely influenced by both endogenous (intestinal mucines, enzymes, gut hormones, mucosa cells) and exogenous substrates.[1] Diet directly influences gut microbial composition and metabolic activity by making substrates available in the form of undigested dietary residues that are resistant to digestive enzymes and the digestion process.[1] A considerable amount of non digestible food components reaches the colon and may interact with microbiota and epithelial cells, feeding the resident colonic bacteria and stimulating their metabolism.[1,32] These colonic dietary substrates can be defined as *food indigestible fraction* and consist of all plant food constituents that are resistant to digestion and absorption in the human small intestine, with complete or partial fermentation in the large intestine.[31] It comprises non-digestible carbohydrates such as non-starch polysaccharides, resistant starch and oligosaccharides, and also other non carbohydrate compounds such as lignin, resistant protein, and other associated compounds of nutritional importance such as the phytochemicals polyphenols and carotenoids, some of them with antioxidant properties.[31] The major components of the food indigestible fraction are carbohydrates, and their bacterial degradation is well-known since their fermentation metabolites such as butyrate are known to promote proliferation of beneficial

bacterial species.[32] Of the minor non digestible components, proteins may also be substrates for colonic microbiota, but their fermentation is usually associated with the growth of potential pathogens and the production of undesirable substances such as amines, whereas fermentation of lipids is associated with the antimicrobial activity of fatty acids and their derivatives.[33] The non digestible food fraction is also carrier of a significant amount of phytochemicals linked to the complex food matrix, mainly polyphenols.[34] Consequently, phenolic compounds are the most important minor constituents associated with the non digestible food fraction.

The non-digestible food fraction and antioxidants are generally addressed separately as groups of food constituents in both chemical and nutritional studies. It is, however, a little known fact that a substantial proportion of the antioxidant polyphenols and carotenoids contained in fruit and vegetables are bound to the non digestible food fraction.[3] In fact, some of the postulated benefits of fiber intake can be attributed to these associated compounds. They are not bioaccessible in the human small intestine but they may exert significant health effects when they reach the colon. Of these substances, resistant starch is a major constituent in cereals, while phytochemicals are the most important ones in fruit and vegetables.[34] Polyphenols bound to food indigestible fraction can account for a substantial part of total phenolic compounds in foods and beverages.[34] While a small proportion of some dietary polyphenols can be absorbed through the small intestine, the majority are either not absorbed, or are excreted and become fermentable substrates for bacterial microflora in the colon along with the non digestible food fraction.[3] The colonic substrates are then broken down to intermediate products (organic acids such as lactate, succinate, pyruvate, butyrate, fumarate), and finally short chain fatty acids (acetate, propionate, butyrate, isobutyrate, isovalerate, malate) and hydrogen and carbon dioxide gases.[33] These are the main fermentation products of undigested carbohydrates; however, other colonic substrates such as polyphenols do not lead to short chain fatty acids.

Certain non-digestible components such as recognized prebiotics may affect the growth and survival of the beneficial bacteria by influencing their growth and metabolites. Consequently, the composition of the diet can influence the profile and metabolic activity of the gut microbial ecology. It has been estimated that up to 60 g of substrates would have to reach the colon to maintain the daily bacterial cell turnover.[31] However, dietary fiber intake in European countries only contributes about 20 g of carbohydrates/day, leaving what is known as a 'carbohydrate gap' of 40 g/day.[35]

To assess the significance of polyphenols in human health it is important to estimate the dietary intake and consider their bioavailability. In this regard, it is particularly important to evaluate the nutritional contribution of whole diets rather than single foods. However, few studies adopt this approach. The mean daily intake of polyphenols in the Spanish diet ranges from 2590 to 3016 mg/day, of which 48% are bioaccessible in the small intestine, while 42% become bioaccessible in the large intestine.[3] A substantial amount of dietary polyphenols (10%) is inaccessible and remains in the food matrix after the digestion process is complete. This is important in that it confirms that a large amount of indigestible polyphenols from the diet remains unabsorbed and can interact with the complex gut microbiota. As a result, fermentation of polyphenols in the colon may improve antioxidant status and yield various metabolites with potential systemic effects.[1]

Interaction of Polyphenols and Gut Microbiota

There are two main reciprocal interactions between the gut microbiota and polyphenols. On the one hand, dietary polyphenols undergo a complex metabolism after ingestion

and interact with human and microbial enzymes, leading to the production of a large number of circulating and excreted polyphenol metabolites and catabolic products. On the other hand, polyphenols and their metabolites can influence and induce a modulation of gut microbiota composition by means of several interactions. The interactions affecting metabolic pathways and numerous metabolites of dietary polyphenols have been widely documented. Recently published reviews discuss extensively, the current information on the subject,[10,11] however, the effects of dietary polyphenols on modulation of the intestinal ecology and on growth of gut microbial species is still poorly understood.

Most biological properties of polyphenols depend on their bioavailability; the latter is largely influenced by chemical and physical properties and plant-derived conjugation. Dietary polyphenols generally occur in a conjugated form (glycosylated, acylated, esterified, polymerized). The rate and extent of intestinal absorption of polyphenols is strongly influenced by their conjugated form. After the release of the corresponding aglycone, polyphenols undergo conjugation reactions with methyl, sulfate, or glucuronide groups.[6] This is important in that some human metabolites may be more biologically active than the original dietary components.

The gut microbiota, in addition to processing dietary derived material, is capable of performing a range of biotransformations on polyphenols that pass into the colon, thus affecting their absorption and bioavailability.[36] *Clostridium* and *Eubacterium* are the main genera that have been identified as involved in the metabolism of many phenolics such as isoflavone (daidzein), flavonol (quercetin and kaempferol), flavanone (naringenin and isoxanthumol), and flavan-3-ol (catechin and epicatechin).[10] Colonic fermentation of polyphenols yields a broad spectrum of biotransformation products, but the majority can be summarized as derivatives of the following absorbable biotransformation products: phenylacetic, phenylpropionic, phenylbutiric, and valeric acids, valerolactone, phloroglucinol, and the dibenzopyranones urolithin A and urolithin B.[24,37,38]

The composition of the intestinal microbiota can be modulated by phytochemicals such as polyphenols[2], extensive research into the interactions between phenolic compounds and intestinal bacteria has focused on antimicrobial properties against pathogens.[39–42] On the other hand, very few studies have examined the influence of polyphenols on beneficial microorganisms. The most relevant studies on this subject are summarized in Table 1 and discussed below.

Effects of Dietary Polyphenols on Beneficial Microorganisms

Lactobacilli play a crucial role in the production of fermented foods, and they are thought to perform a beneficial role as part of the colonic microbiota. They are found where carbohydrate-rich substances are available and stand out for their beneficial effects in human health.[43] Dietary polyphenols scarcely inhibit the growth of *Lactobacillus* group. Evidence suggests that dietary polyphenols may even help stimulate growth of certain lactobacillus strains.[44] Puupponen-Pimiä et al.[45] reported that berry phenolics selectively inhibited pathogenic bacterial strains, both Gram-positive and Gram-negative, but interestingly the lactic acid bacteria group was hardly affected. A similar trend was reported for a polyphenolic extract from *Mangifera indica* L. seed, rich in tannins and flavones, which inhibited Gram-positive rather than Gram-negative bacteria, but was not active against lactic acid bacteria.[46] In addition, *Lactobacillus acidophilus* CECT 362 was resistant to tea phenolic extracts, containing caffeine; (–)-epicatechin, (–)-epicatechin gallate, (–)-epigallocatechin, (–)-epigallocatechin gallate, and gallic acid, whereas food-borne bacteria were inhibited.[42]

Table 1
Influence of dietary polyphenols on beneficial and pathogenic bacteria

Microorganism	Bioactive compounds	Growth effect	References
Lactobacillus strains	Catechin, epicatechin, epicatechin gallate, epigallocatechin, epigallocatechin gallate, caffeic acid, gallic acid, and phenolic extracts from teas, mango and berries	No inhibition	42, 44–48
Lactobacillus strains	Resveratrol and phenolic extracts from apple juice and red wine	Stimulation	8, 9, 51
Lactobacillus acidophilus	Tannic acid, quercetin and grape extracts	Stimulation	44
Lactobacillus hilgardii	Catechin, acid gallic, quercetin	Stimulation	49, 50
Lactobacillus rhamnosus	Phloridzin and rutin	Stimulation	54
Bifidobacterium spp.	Catechin, resveratrol and phenolic extracts from apple juice and red wine	Stimulation	8, 9, 37, 51
Escherichia coli	Catechin, tannic acid, caffeic and chlorogenic acids, phenolic extracts from fruits, vegetables, tea and coffee	Stimulation	37, 70
Escherichia coli	Gallic, vanillic, protocatechuic, and caffeic acids, rutin, catechin, quercetin, phenolic extracts from cinnamon, olives, teas and infusions, hydroxycinnamic acids, (*E*)-cinnamaldehyde, proanthocyanidins	Inhibition	41, 42, 63, 66, 68
Helicobacter pylori	Phenolic extracts from cranberry, blueberry, grape seed, oregano, green tea, honey, peppers, black currants, raspberry, cinnamon, peppermint, red wine	Inhibition	18, 40, 57–61

(*Continued*)

Table 1
(Continued)

Microorganism	Bioactive compounds	Growth effect	References
Listeria monocytogenes	Phenolic extracts from cranberry, green tea, and cinnamon, hydroxycinnamic acids, (*E*)-cinnamaldehyde, proanthocyanidins	Inhibition	45, 63, 67, 68
Salmonella strains	Phenolic extracts from berries, green tea, olives and cinnamon extract, hydroxycinnamic acids, (*E*)-cinnamaldehyde, proanthocyanidins, catechin, epicatechin, phloridzin, rutin, naringenin, daidzen, genistein, quercetin	Inhibition	45, 54, 63, 66, 68
Staphylococcus aureus	Phenolic extracts from berries, green tea, olives and cinnamon, hydroxycinnamic acids, (*E*)-cinnamaldehyde, proanthocyanidins	Inhibition	45, 63, 66, 68
Bacillus cereus	Phenolic extracts from cinnamon, teas and infusions, hydroxycinnamic acids, (*E*)-cinnamaldehyde, proanthocyanidins	Inhibition	42, 63, 68
Pseudomonas aeruginosa	Phenolic extracts from olives, teas and infusions	Inhibition	42, 66
Proteus mirabilis	Phenolic extracts from teas and infusions, gallic, vanillic, protocatechuic, and caffeic acids, rutin, catechin, quercetin, resveratrol	Inhibition	41, 64
Serratia marcescens	Phenolic extracts from teas and infusions, gallic, vanillic, protocatechuic, and caffeic acids, rutin, catechin, quercetin	Inhibition	41
Klebsiella pneumoniae	Gallic, vanillic, protocatechuic, and caffeic acids, rutin, catechin, quercetin	Inhibition	41

(*Continued*)

Table 1
(Continued)

Microorganism	Bioactive compounds	Growth effect	References
Flavobacterium sp.	Gallic, vanillic, protocatechuic, and caffeic acids, rutin, catechin, quercetin	No inhibition	41
Micrococcus luteus and *Candida albicans*	Phenolic extracts from teas and infusions	Inhibition	41

Gallic acid (500 μg/mL) did not inhibit *L. acidophilus* ATCC 4356.[47] A similar result was observed with *Lactobacillus hilgardii* in the presence of catechin and gallic acid.[48] This is corroborated by a report that at concentrations normally present in wines, phenolic compounds (gallic acid and (+)-catechin) induced a biomass increase of *L. hilgardii* 5w. [49] Also, Figueiredo et al. [50] determined an increased final cell density of *L. hilgardii* in presence of quercetin (40 mg/L) compared to the control. When phenolic extracts from grape seed and grape pomace, and various dietary polyphenols (caffeic acid, gallic acid, tannic acid, catechin, epicatechin, and quercetin) were tested on probiotic *L. acidophilus* CECT 903, no inhibition was observed. [44] The same study reported that both grape extracts and tannic acid, and in lower extent for quercetin, tended to stimulate *L. acidophilus* growth. Grape pomace extract was found to induce a significant increase of *L. acidophilus* biomass.[44]

Tzounis et al.[37] found that the common dietary polyphenols (–)epicatechin and (+)-catechin can be metabolized by fecal bacteria even in the presence of favorable carbon sources such as sucrose and fructo-oligosaccharides. Both phenolic compounds led to production of the same metabolites: 5-(3',4'-dihydroxyphenyl)-γ-valerolactone, 5-phenyl-γ-valerolactone, and phenylpropionic acid.[46] Incubation in the presence of (+)-catechin (150 mg/L) significantly increased growth of the beneficial *Bifidobacterium* spp., *Clostridium Eubacterium* rectale group and *Escherichia coli*, whereas *Clostridium histolyticum* was significantly inhibited.

These effects have been confirmed in some animal studies. Administration of extraction juices from apples, rich in polyphenols, increased rat fecal counts of *Lactobacillus* and *Bifidobacterium*.[51] In red wine polyphenol-treated rats, the main bacterial strains in the feces were *Bacteroides*, *Lactobacillus* and *Bifidobacterium* spp., while the microorganisms predominantly identified in control-fed rats were *Bacteroides*, *Clostridium* and *Propionibacterium* spp.[8] Similarly, resveratrol, a compound commonly found in grape, promoted fecal cell counts of *Bifidobacterium* spp. and *Lactobacillus* spp. in a rat model.[9]

This evidence strongly suggests that polyphenols may act as promoting factors of growth, proliferation or survival for beneficial members of the gut microbiota. A number of mechanisms may account for the stimulatory effect of phenolic compounds. The first possibility is the ability of some microorganisms to use polyphenols as substrates. Lactic acid bacteria are able to degrade tannic acid and obtain energy.[52] Certain lactobacilli, such as *Lactobacillus plantarum* strains, are able to degrade complex esters of gallic acid and glucose, containing galloyl groups esterified directly to the glucose molecule. The proposed

mechanism is that tannic acid is hydrolyzed to gallic acid and glucose, and the gallic acid formed is further decarboxylated to pyrogallol through the action of tannase and decarboxylase gallate enzymes.[52] In addition, some microorganisms are able to tolerate and even metabolize hydroxycinnamic acids through the reduction of the carbon-carbon double bond to produce the corresponding hydroxyphenylpropionic acids, which can be further decarboxylated to *p*-ethylphenols.[53] In fact, some lactobacilli metabolize phenolic compounds during their growth phase to obtain energy. Phenolic compounds, besides positively affecting bacteria metabolism, can enhance consumption of nutrients[48,49,53] such as sugars. The antioxidant properties of flavon-3-ols have also been associated with stimulation of *L. hilgardii* growth in their presence. In addition, the chelating activity of polyphenols may mainly affect aerobic microorganisms, but in the case of lactobacilli, iron is not considered a growth factor because they lack heme enzymes, and the most important iron-containing ribonucleotide reductase has been replaced by an enzyme using adenosylcobalamine.[47]

The positive influence of dietary polyphenols on expression of phenotypic characteristics, such as bacterial adhesion behavior, may be also related. The adhesion of probiotic *Lactobacillus rhamnosus* to Caco-2 cells in the presence of several dietary polyphenols was hardly affected, unlike pathogenic bacteria.[54] In fact, phloridzin and rutin have been shown to significantly enhance the proliferation and adhesion of probiotic *L. rhamnosus*. A possible explanation for this is that catechin and epigallocatechin gallate, abundant in grape pomace, can mimic acetylated homoserine lactones, compounds that act as regulating factors of biofilm formation involved in bacterial adhesion.[55]

An alternative synergistic mechanism involved in the modulation of the gut microbiota is that certain lactobacilli can strongly inhibit gastrointestinal pathogens such as *Salmonella typhimurium* SL1344.[30] *Lactobacillus johnsonni* La1 is able to modulate the gut microbiota by acting against several pathogens including *H. pylori*.[30]. This inhibitory activity of most *Lactobacillus* strains is due to the production of lactic acid alone, influencing the pathogen invasion of human epithelial cells. However, in the case of some strains, such as *L. johnsonii* La1 and *L. plantarum* ACA-DC 287, a combination of lactic acid and bacteriocin-like compounds production was also detected.[56]

Antimicrobial Properties of Dietary Polyphenols

The antimicrobial properties of polyphenols against both spoilage and pathogenic bacteria have been extensively investigated.[39–42] Of particular interest are studies on modulation of *Helicobacter pylori* by dietary polyphenols due to its widespread incidence.

Related problems with peptic ulcers linked to *H. pylori* are a major problem in many parts of the world. *H. pylori* is a spiral, Gram-negative, acid tolerant, microaerophilic bacterium that lives in the stomach and duodenum.[40,57] The first step in *H. pylori* infection is colonization of the human gastric mucosa, and for that purpose *H. pylori* must first survive in an acidic environment. To counteract stomach acidity, *H. pylori* releases a protein with urease activity, which converts urea into bicarbonate and ammonia, creating an acid-neutralizing environment for protection.[40] Once *H. pylori* has colonized the human gastric mucosa, it causes inflammation that leads to various gastric-related diseases such as atrophic gastritis, peptic ulcer, mucosa-associated lymphoid tissue lymphoma, and gastric cancer.[58] The vacuolating cytotoxin VacA is a major virulence factor of the *H. pylori* bacterium. It causes cell vacuolation and tissue damage by forming anion-selective, urea-permeable channels in plasma and endosomal membranes. [58] Allowing the bacteria to access urea from stomach cells is probably the key function of this toxin since bacterium

survival depends on hydrolysis of the urea provided by the epithelium in order to buffer the pH in and around the bacterium cell.

Similarities in chemical structures have been found between potent VacA inhibitors such as 4,4′-diisothiocyanatostilbene-2,2′-disulphonic acid (NPPB) and various polyphenols.[58] As a result, several food polyphenols have been tested for ability to inhibit *H. pylori* growth. Cranberry juice extract with added blueberry, grape seed, and oregano extract is reported to act in this manner.[40] Various polyphenol extracts from green tea, honey, peppers, black-currants, raspberry, cinnamon, and peppermint exhibit inhibitory activity against *H. pylori*.[18,57,59,60] Red wine and green tea, particularly concentrated sources of polyphenols, strongly inhibit the VacA toxin.[58] A recent study showed that polyphenols present in olive oil can diffuse into the gastric juice and exert a potent bactericidal effect against eight strains of *H. pylori* at very low concentrations (1.3 μg/mL).[61]

Inhibitory mechanisms of dietary polyphenols against *H. pylori* may include suppression of urease activity directly affecting bacterium proliferation and damage to bacterial membranes, thereby making cells more sensitive to external compounds such as antibiotics and leading to a disruption of proton motive force through the loss of H^+-ATPase and membrane-associated functions.[57] Moreover proanthocyanidins extracted from cranberry act by inhibiting adhesion of *H. pylory* to the human gastric mucosa.[59] Although many polyphenols have been associated with anti-*H. pylori* activity, only cranberry polyphenols have been definitively linked to this activity.[30,62]

Polyphenols from various sources (food and plant extracts and pure phenolic compounds) have been extensively tested at a wide range of concentrations and on a great variety of pathogenic and spoilage bacteria. Of dietary polyphenols, the beneficial properties of green tea and other related polyphenol-rich infusions have been widely examined, including their antimicrobial properties. Green tea is commonly consumed in Eastern Asia, whereas black tea is preferred in European countries and India.[18] Extracts from several catechin-rich teas and infusions have been found to act against the pathogens *S. marcescens*, *E. coli*, *P. mirabilis*[41], *B. cereus*, *Micrococcus luteus*, *Pseudomonas aeruginosa,* and *Candida albicans*.[42] In addition, a green tea extract has been found to inhibit the pathogens *E. coli O157:H7*, *Salmonella typhimurium DT104*, *L. monocytogenes*, *S. aureus*, and *B. cereus*.[63] It is worth noting that the antimicrobial activity of nonfermented tea is greater than that of semi-fermented or fermented tea.[42] The highest antimicrobial activity positively correlates with the highest values of total polyphenol concentration and antioxidant activity.[43] Additionally, grape stilbenoids, such as resveratrol suppressed ochratoxigenic fungi and the expression of virulence factors in *P. mirabilis*.[64,65] Olive extracts exhibited antimicrobial and fungicidal activities against Gram-positive *S. aureus, B. subtilis*, Gram-negative *P. aeruginosa, E. coli, Salmonella enteric*, and the fungi *Candida albicans* and *Aspergillus niger*.[66]

Focusing on the pathogens of main interest, the dietary polyphenols gallic, vanillic, protocatechuic, and caffeic acids, and the flavanoids rutin, catechin, and quercetin, have been found to inhibit *S. marcescens*, *P. mirabilis*, *E. coli* and *Klebsiella pneumoniae. E. coli* is the most sensitive to polyphenols whereas *Flavobacterium sp*. is resistant to all phenolic compounds.[41] With regard to *L. monocytogenes*, several berry fruits (bilberry, lingonberry, red raspberry, cloudberry, strawberry, blackcurrant and cranberry) have been tested as inhibitors of *L. monocytogenes* E991205, but only cranberry showed antimicrobial activity.[45] Similar antimicrobial activity against several strains of pathogenic *L. monocytogenes* has been reported for hydroxycinnamic acids.[67] Cinnamon stick and its major components (*E*)-cinnamaldehyde and proanthocyanidins also possess antibacterial

properties against *L. monocytogenes* and other common foodborne pathogens: *B. cereus*, *S. aureus*, *E. coli*, and *Salmonella anatum*.[68]

There are several mechanisms whereby dietary polyphenols influence the gut bacterial community. The influence of polyphenols on bacterial growth and metabolism depends on microorganism strain, polyphenols structure, and dosage assayed.[42,69] Gram-negative bacteria are more resistant to polyphenols than Gram-positive microorganisms, probably due to the differences observed in their cell wall composition.[45] This may be explained by the fact that polyphenols can be adsorbed to cell wall, alter the cell structure,[11,45] and act on specific cell membrane proteins causing the expulsion of certain compounds from inside the cell. This produces a decrease in the concentrations of substances such as potassium ion, glutamic acid, intracellular RNA, etc, as well as an alteration of fatty acids composition.[45] Alternative mechanisms involving interactions with cell enzymes have also been reported. Certain metabolic enzymes and functional proteins may be implicated in the inhibitory effect of phenolic compounds through a tannin-protein interaction. Inhibition of specific bacterial species may also be explained by the strong iron binding capacity of tannins, mainly affecting aerobic microorganisms.[47] Aerobic microorganisms need iron for several functions such as reduction of the ribonucleotide precursor of DNA and to form heme groups. Conversely, it is interesting that the iron chelating capacity of polyphenols may be also related to growth stimulation, since it has been demonstrated that dietary catechols can promote the growth of enteropathogenic bacteria by providing iron under iron-restrictive conditions and may enable intestinal bacteria growth.[70] The disadvantage of this is that both pathogenic and non-pathogenic bacteria may be stimulated. Finally, there is also the effect of polyphenols on the expression of bacterial virulence factors, since they seem to be crucial for survival, invasion and proliferation. A recent study [54] determined that several polyphenols occurring in foods (hydroxycinnamic acids, catechin, epicatechin, phloridzin, rutin, naringenin, daidzen, genistein, quercetin) exhibited an inhibitory effect on the adhesion of pathogenic bacteria *Salmonella typhimurium* to Caco-2 cells, preventing growth and survival of the pathogenic microorganism. Most bacteria are able to regulate phenotypic characteristics, including virulence factors, as a function of cell density under the control of chemical signal molecules.[71] Quorum sensing (cell-to-cell communication) can occur within a single bacterial species as well as between multiple species. The quorum sensing-coordinated process is achieved by producing, releasing, and detecting small signal molecules known as auto-inducers. These auto-inducer molecules have been identified as oligopeptides in Gram-positive bacteria, and acylated homoserine lactones (AHLs) in Gram-negative bacteria. Microorganisms can use quorum sensing to coordinate their communal behaviors, biofilm formation, swarming, motility, production of extracellular polysaccharides, etc.[72,73] To date there have been few studies to investigate the potential of different phenolic compounds to reduce food spoilage by inhibiting bacteria cell-to-cell communication,[74] however, this is an important area of study.

The influence of polyphenols on specific intestinal bacteria functions is still unknown. One of the main limitations in previous studies is that most phenolic fractions and pure phenolic compounds have been assayed without considering the bioavailability and the chemical nature of phenolic compounds reaching the colon. Another limitation is that the concentrations tested are rarely physiological, then there is also the lack of in vivo studies. Further research into both positive and negative interactions between bioactive food compounds and specific intestinal bacteria is needed.

Originally, modulation of gut microbial ecology induced by phenolic compounds was examined through conventional culture techniques. However, new approaches (molecular, genomics, metagenomics, metabonomics, and trans-genomics) are becoming increasingly

important for providing novel insights into the composition, function and evolution of our gut microbiota.[75] These approaches can reveal the compositional data and the metabolic potential encoded by the combined genomes of the gut microbiota, the metabolic kinetic or flux of metabolites through an ecosystem, the function of the gut microbiota in situ and how it responds to different environmental stimuli, and how changes in metabolite profiles within human biofluids correlate with microbiota compositional metagenomic data.[23] Nowadays it is known that higher organisms such as mammals have a symbiotic relationship with their gut microbiota, which have co-evolved with the human genome and diet.[23] The human gut microbiome is currently recognized as a metabolically versatile biological digester that plays an essential role in regulating the host metabolome.[75]

In conclusion, dietary polyphenols and their metabolites contribute to the maintenance of gastrointestinal health, largely by modulation of gut microbial balance with the simultaneous inhibition of pathogens and stimulation of beneficial bacteria. In the past, the concept of prebiotics was limited to non-digestible carbohydrates, but the recently-accumulated evidence strongly suggests that polyphenols have the ability to exert prebiotic action. Indeed, the prebiotic effect could be enhanced when a substantial amount of polyphenols is associated with dietary fiber. Therefore, the regular consumption of a diet rich in plant foods with high polyphenol contents may beneficially balance the gut microbial ecology, helping to prevent gastrointestinal disorders and thus enhancing the health of the host.

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