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REVIEWS: CURRENT TOPICS

Benefits of polyphenols on gut microbiota and implications in human health

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Abstract

The biological properties of dietary polyphenols are greatly dependent on their bioavailability that, in turn, is largely influenced by their degree of polymerization. The gut microbiota play a key role in modulating the production, bioavailability and, thus, the biological activities of phenolic metabolites, particularly after the intake of food containing high-molecular-weight polyphenols. In addition, evidence is emerging on the activity of dietary polyphenols on the modulation of the colonic microbial population composition or activity. However, although the great range of health-promoting activities of dietary polyphenols has been widely investigated, their effect on the modulation of the gut ecology and the two-way relationship "polyphenols ↔ microbiota" are still poorly understood.

Only a few studies have examined the impact of dietary polyphenols on the human gut microbiota, and most were focused on single polyphenol molecules and selected bacterial populations. This review focuses on the reciprocal interactions between the gut microbiota and polyphenols, the mechanisms of action and the consequences of these interactions on human health.

Keywords: Dietary polyphenols; Gut microbiota; Polyphenol bioavailability; Human health; Cancer; Immunity

1. Introduction

Dietary polyphenols are natural compounds occurring in plants, including foods such as fruits, vegetables, cereals, tea, coffee and wine [1]. Chemically, polyphenols are a large heterogeneous group of compounds characterized by hydroxylated phenyl moieties. Based on their chemical structure and complexity (*i.e.*, the number of phenolic rings and substituting groups), polyphenols are generally classified into flavonoids and nonflavonoids [2]. Flavonoids form a major (over 9000 structurally distinct flavonoids have been identified in nature) heterogeneous subgroup comprising a variety of phenolic compounds with a common diphenylpropane skeleton (C6-C3-C6). In turn, flavonoids are also classified into further subclasses according to their structural differences (flavanones, flavones, dihydroflavonols, flavonols, flavan-3-ols or flavanols, anthocyanidins, isoflavones and proanthocyanidins) [3,4]. *In planta*, most polyphenols occur in their glycosylated forms, although modifications such as esterification or polymerization are also commonly found. Once ingested, polyphenols are recognized by the human body as xenobiotics, and their bioavailability is therefore relatively low in comparison to micro and macronutrients. Furthermore, depending on their degree of structural complexity and polymerization, these compounds may be readily absorbed in the small intestine (*i.e.*, low-molecular-weight polyphenols such as monomeric and dimeric structures) [5] or reach the colon almost unchanged (oligomeric and polymeric polyphenols such as condensed or hydrolysable tannins, reaching molecular weight values close to 40,000 Da) [6–10]. It has been estimated that only 5–10% of the total polyphenol intake is absorbed in the small intestine. The remaining polyphenols (90–95% of total polyphenol intake) may accumulate in the large intestinal lumen up to the millimolar range where, together with conjugates excreted into the intestinal lumen through the bile, they are subjected to the enzymatic activities of the gut microbial community [11–26]. The colonic microbiota are therefore responsible for the extensive breakdown of the original polyphenolic structures into a series of low-molecular-weight phenolic metabolites that, being absorbable, may actually be

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responsible for the health effects derived from polyphenol-rich food consumption, rather than the original compounds found in foods.

Currently, it is estimated that 500–1000 different microbial species inhabit the gastrointestinal tract, reaching the highest concentrations in the colon (up to 10^{12} cells per gram of faeces). However, only a few bacterial species (*e.g. Escherichia coli*, *Bifidobacterium* sp., *Lactobacillus* sp., *Bacteroides* sp., *Eubacterium* sp.) catalyzing the metabolism of phenolics have been identified so far, together with the catabolic pathways implicated [26]. However, they do not seem to be ubiquitous but reflect the interpersonal differences in the gut microbial community.

Consequently, apart from the interindividual variation in daily intake of polyphenols, interindividual differences in the composition of the gut microbiota may lead to differences in bioavailability and bioefficacy of polyphenols and their metabolites [27,28]. The scenario appears even more complex when considering the two-way relationship "polyphenols ↔ microbiota". Recent studies have in fact suggested that both the phenolic substrates supplied to the gut bacteria through different patterns of dietary intake and the aromatic metabolites produced may in turn modulate and cause fluctuations in the composition of the microflora populations through selective prebiotic effects and antimicrobial activities against gut pathogenic bacteria [29–38]. The formation of bioactive polyphenol-derived metabolites and the modulation of colonic microbiota may both contribute to host health benefits, although the mechanisms have not been delineated. The health properties attributed to beneficial bacteria for human hosts include protection against gastrointestinal disorders and pathogens, nutrient processing, reduction of serum cholesterol, reinforcement of intestinal epithelial cell-tight junctions and increased mucus secretion and modulation of the intestinal immune response through cytokine stimulus [39–41]. Likewise, in the last decade, a growing body of *in vivo* interventional and epidemiological studies has furnished new evidence on the wide range of health promoting activities of dietary polyphenols, already documented by *in vitro* data, including their antiinflammatory, antioxidant, anticarcinogenic, antiadipogenic, antidiabetic and neuroprotective potentials, suggesting an association between the consumption of polyphenol-rich foods and a reduced risk of several chronic diseases [42–48]. However, the effect of dietary polyphenols on the modulation of the gut ecology, including the underlying mechanisms and the actual benefits of such bioactive agents, is still poorly understood.

The aim of this review is to provide an overview of recent reports on the dual nature of polyphenol–microbiota interactions and its relevance to human health.

2. Polyphenols and their biotransformation in the gut

Fig. 1 schematically illustrates the metabolic fate of dietary polyphenols in humans. Briefly, a small percentage of dietary polyphenols (5–10% of the total intake, mainly those with monomeric and dimeric structures) may be directly absorbed in the small intestine, generally after deconjugation reactions such as deglycosylation [7]. After absorption into the small intestine, these less complex polyphenolic compounds may be subjected to extensive Phase I (oxidation, reduction and hydrolysis) and particularly Phase II (conjugation) biotransformations in the enterocytes and then the hepatocytes, resulting in a series of water-soluble conjugate metabolites (methyl, glucuronide and sulfate derivatives) rapidly liberated to the systemic circulation for further distribution to organs and excretion in urine. In the large intestine, colonic bacteria are known to act enzymatically on the polyphenolic backbone of the remaining unabsorbed polyphenols (90–95% of the total polyphenol intake), sequentially producing metabolites with different physiological significance [49]. The metabolism of polyphenols by microbiota involves the cleavage of glycosidic linkages and the breakdown of the heterocyclic backbone [50]. As an example, the microbial catabolism of proanthocyanidins (oligomers and polymers of flavan-3-ols) has been extensively described in recent years. It results in the sequential production of lactones and aromatic and phenolic acids with different hydroxylation patterns and side-chain lengths, depending on the precursor structures (phenylvalerolactones, phenylvaleric acids, phenylpropionic acids, phenylacetic acids, hippuric and benzoic acids) [11,22]. The metabolism by gut microflora of these polyphenols abundant in wine, tea, chocolate and many fruits may also influence tissue exposure to high-molecular-weight polyphenols, including proanthocyanidins or oxidized polymeric polyphenols, which are poorly absorbed in the proximal part of the gastrointestinal tract [51]. In addition, the microbial transformation of nonflavonoid polymeric molecules called ellagitannins (or hydrolysable tannins) has also been investigated in the last decade [23,24]. After the consumption of ellagitannin-rich food such as strawberries, raspberries, walnuts, oak-aged wines and pomegranates, these tannin structures are subjected to hydrolysis in the intestinal lumen, releasing free ellagic acid. Once in the large intestine, ellagic acid is metabolized by human colonic microflora to produce a series of derivative compounds called urolithins, characterized by a common 6H-dibenzo[b,d]pyran-6-one nucleus and a decreasing number of phenolic hydroxyl groups (urolithin D→C→A→B). All these microbial-derived phenolic metabolites may be absorbed or excreted by faeces. When absorbed, they reach the liver through the portal vein where they may be further subjected to extensive first-pass Phase II metabolism (including glucuronidation, methylation, sulfation or a combination of these) until they finally enter the systemic circulation and are distributed to the organs or eliminated in urine. Microbial glucuronidase and sulphatase activity may also deconjugate the Phase II metabolites extruded *via* the bile throughout the enterohepatic circulation, enabling their reuptake and effective bioavailability. *Clostridium* and *Eubacterium* are the main genera involved in the metabolism of many phenolics such as isoflavones (daidzein), flavonols (quercetin and kaempferol), flavones (naringenin and ixoxanthumol) and flavan-3-ols (catechin and epicatechin) [32]. As *Firmicutes* possess a disproportionately smaller number of glycan-degrading enzymes than *Bacteroidetes* [52], it might be hypothesized that intake of different polyphenols could reshape the gut microbiota differently.

A major fraction of the polyphenols present in the plasma and excreted in urine of rats fed with red wine polyphenols comprises aromatic acid metabolites formed in the gut [53]. Incubating an anthocyanin extract from Cabernet Sauvignon grapes with the contents of the large intestine of pigs for 6 h results in a loss of the parent compound but the generation of three identifiable metabolites [54]. It is possible that these metabolites offer a protective effect against colon cancer, such as decreased carcinogen-induced aberrant crypt formation, colonic cell proliferation and oxidative DNA damage, which have been attributed to anthocyanin consumption [55].

3. Effects of dietary polyphenols on modulation of intestinal ecology

Previous human intervention trials have shown that apart from interindividual variation in the daily intake of polyphenols, interindividual differences in the composition of the human microbiota may lead to differences in bioavailability and bioefficacy of polyphenols and their metabolites [56,57]. In addition, polyphenols may be converted by the colonic microbiota to bioactive compounds that can affect the intestinal ecology and influence host health. There is evidence from *in vitro* animal and human studies that certain doses of selected polyphenols may modify the gut microbial composition, and while certain bacterial groups can be inhibited, others can thrive in the available niche of the ecosystem. Phenolic compounds alter gut

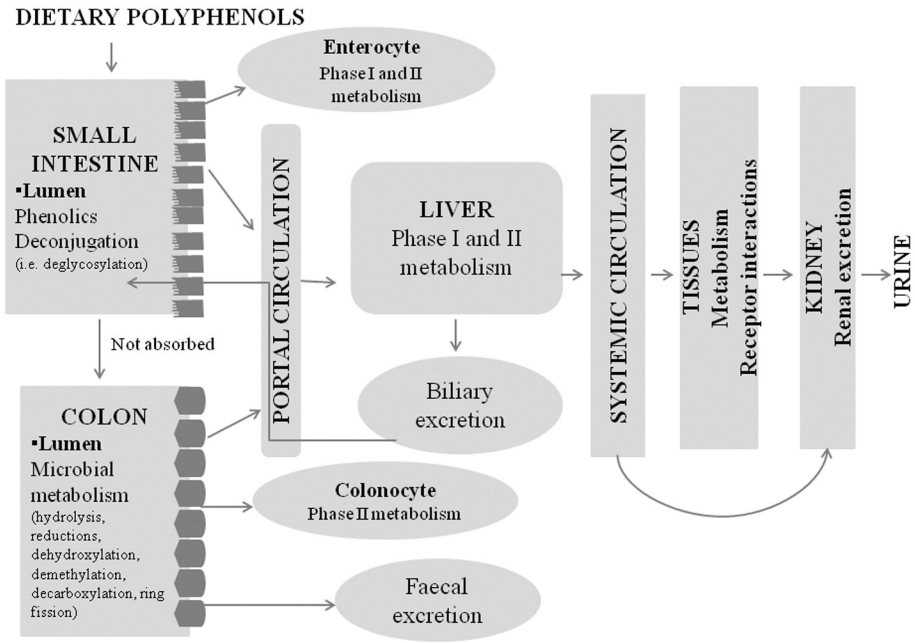

Fig. 1. Routes for dietary polyphenols and their metabolites in humans. Within the host, dietary polyphenols and their microbial metabolites successively undergo intestinal and liver Phase I and II metabolism, biliary secretion, absorption in the systemic circulation, interaction with organs and excretion in the urine.

microbiota and, consequently, alter the *Bacteroides*/*Firmicutes* balance [19,29,58]. For example, Tzounis *et al.*, in an *in vitro* study using a batch-culture model reflective of the distal region of the human large intestine, suggested that flavan-3-ol monomers such as (−)epicatechin and (+)catechin may be capable of influencing the large intestinal bacterial population even in the presence of other nutrients, such as carbohydrates and proteins. These authors found that (+)catechin significantly inhibited growth of *Clostridium histolyticum* and enhanced growth of *E. coli* and members of the *Clostridium coccoides–Eubacterium rectale* group, while growth of *Bifidobacterium* and *Lactobacillus* spp. remained relatively unaffected [59].

Dietary administration of proanthocyanidin-rich extracts also appears to have a similar effect. The faecal bacteria composition of rats whose diet was supplemented for 16 weeks with a dealcoholized, proanthocyanidin-rich red wine extract shifted from a predominance of *Bacteroides*, *Clostridium* and *Propionibacterium* spp. to a predominance of *Bacteroides*, *Lactobacillus* and *Bifidobacterium* spp. [60].

Yamakoshi *et al.* documented that a proanthocyanidin-rich extract from grape seeds given to healthy adults for 2 weeks was able to significantly increase the number of bifidobacteria [61]. Nevertheless, recent studies indicate that monomeric flavan-3-ols and flavan-3-ol-rich sources such as chocolate, green tea and blackcurrant or grape seed extracts may modulate the intestinal microbiota *in vivo*, producing changes in beneficial bacteria such as *Lactobacillus* spp. but inhibiting other groups such *Clostridium* spp. in both *in vivo* and *in vitro* studies [30,59,62,63]. More recently, a cocoa dietary intervention in a rat model showed a significant decrease in the proportion of *Bacteroides*, *Clostridium* and *Staphylococcus* genera in the faeces of cocoa-fed animals [64].

Other rat studies carried out by Smith *et al.* found that when rats were given a tannin-rich diet, the *Bacteroides* group increased significantly while the *Clostridium leptum* cluster decreased significantly [65]. Dolara *et al.* reported that, when rats were treated with red-wine polyphenols, they had significantly lower levels of *Clostridium* spp. and higher levels of *Bacteroides*, *Bifidobacterium* and *Lactobacillus* spp. [60]. Similarly, the resveratrol commonly found in grape promoted faecal cell counts of *Bifidobacterium* spp. and *Lactobacillus* in a rat model [66].

A human intervention study indicated that consumption of red wine polyphenols significantly increased the number of *Enterococcus*, *Prevotella*, *Bacteroides*, *Bifidobacterium*, *Bacteroides uniformis*, *Eggerthella lenta*, and *Blautia coccoides-E. rectale* group while the quantity of *Lactobacillus* spp. was unaltered [31]. On the other hand, when bacteria were cultured with various tea phenolics, the growth of pathogenic bacteria such as *Clostridium perfringens*, *Clostridium difficile* and *Bacteroides* spp. was significantly repressed, while commensal anaerobes like *Bifidobacterium* and *Lactobacillus* were affected less [29]. Vendrame *et al.* found a significant increase in the amount of *Bifidobacterium* after the consumption of a wild blueberry drink, suggesting an important role of the polyphenol present in wild blueberries on the intestinal microbiota composition modulation [67].

Cueva *et al.* analyzed the potential of flavan-3-ols from grape seed to influence the growth of intestinal bacterial groups using *in vitro* fermentation models. They found that the flavan-3-ol profile of a particular food source could affect the microbiota composition (promoting the growth of *Lactobacillus*/*Enterococcus* and decreasing the *C. histolyticum* group) and its catabolic activity, inducing changes that could in turn affect the bioavailability and potential bioactivity of these compounds [68].

Finally, important prebiotic effects and selective antimicrobial activities against gut pathogenic bacteria have also been attributed to the polyphenolic fraction contained in the skin covering the kernel of several nuts, mostly composed of nonflavonoid tannin structures (ellagitannins), flavan-3-ols and proanthocyanidins [36–38].

4. Mechanisms of action of polyphenols on bacterial cell membrane

The influence of polyphenols on bacterial growth and metabolism depends on the polyphenol structure, the dosage assayed and the microorganism strain [34]. For instance, Gram-negative bacteria are more resistant to polyphenols than Gram-positive bacteria, possibly due to the differences found in their wall composition [69]. Recent findings suggest a variety of potential mechanisms of action of polyphenols on bacterial cells. For example, polyphenols can bind to bacterial cell membranes in a dose-dependent manner, thus

disturbing membrane function and therefore inhibiting cell growth [70]. Polyphenols, such as catechins, act on different bacterial species (*E. coli*, *Bordetella bronchiseptica*, *Serratia marcescens*, *Klebsiella pneumonie*, *Salmonella choleraesis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Bacillus subtilis*) by generating hydrogen peroxide [71] and by altering the permeability of the microbial membrane [72]. Sirk *et al.* also reported that the mechanism of antimicrobial, anticancer and other beneficial health effects of catechins and theaflavins may be governed by hydrogen bonding of their hydroxyl groups to lipid bilayers of cell membranes. The molecular structure and aggregated condition of the catechins significantly influences their absorption, as well as their ability to form hydrogen bonds with the lipid head groups. The molecular structure of the catechins and theaflavins influences their configuration when binding to the bilayer surface, as well as their ability to form hydrogen bonds with the lipid head groups [73,74].

Another component of green tea, the (−)-epicatechin gallate (ECg), sensitizes methicillin-resistant *S. aureus* to beta-lactam antibiotics, promotes staphylococcal cell aggregation and increases cell-wall thickness. ECg-mediated alterations of the physical nature of the bilayer can elicit structural changes to wall teichoic acid that result in modulation of the cell-surface properties necessary to maintain the beta-lactam-resistant phenotype [75].

Microbes stressed by exposure to polyphenols up-regulate proteins related to defensive mechanisms, which protect cells while simultaneously down-regulating various metabolic and biosynthetic proteins involved, for example, in amino acid and protein synthesis as well as phospholipid, carbon and energy metabolism [76]. Most bacteria are able to regulate phenotypic characteristics, including virulence factors, as a function of cell density under the control of chemical signal molecules. Polyphenolic compounds can also interfere with bacterial quorum sensing, which is achieved by producing, releasing and detecting small signal molecules identified as autoinducers (acylated homoserine lactones in Gram-negative bacteria and oligopeptides in Gram-positive bacteria) [77,78]. For example, polyphenols have been reported to interfere with the production of small signal molecules by bacterial cells of *E. coli*, *Pseudomonas putida* and *Burkholderia cepacia* that trigger the exponential growth of a bacterial population [79]. Studies performed with synthesized or isolated Phase II-conjugated metabolites of flavan-3-ols have revealed that they could have an effect beyond their antioxidant properties, by interacting with signalling pathways implicated in important processes involved in the development of diseases [10].

On the other hand, red wine and green tea polyphenols strongly inhibit the VacA toxin, a major virulence factor of *Helicobacter pylori* [80]. The inhibitory mechanisms of dietary polyphenols against *H. pylori* may include suppression of urease activity, affecting bacterial proliferation and damaging bacterial membranes, thus 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 [81].

Moreover, the B ring of the flavonoids may play a role in intercalation or hydrogen bonding with the stacking of nucleic acid bases, and this may explain the inhibitory action on DNA and RNA synthesis [82]. Plaper *et al.* reported that quercetin binds to the GyrB subunit of *E. coli* DNA gyrase and inhibits the enzyme's ATPase activity [83]. In agreement with these earlier findings, more recently, Gradisar *et al.* determined that the catechins inhibit bacterial DNA gyrase by binding to the ATP (adenosine triphosphate) binding site of the gyrase B subunit [84].

In both *in vivo* and in animal studies, the phenolic substances were suggested to be responsible for the observed anticaries effect of cocoa powder [85], possibly due to their inhibition of the synthesis of water-insoluble glucans [86]. On the other hand, a rich source of flavonoids such as onion extracts has been reported to act on *Streptococcus mutans* and *Streptococcus sobrinus* as well as on *Porphyromonas gingivalis* and *Prevotella intermedia*, which are considered to be the main causal bacteria of adult periodontitis [87].

Another hypothesis leans toward the formation of polyphenol–metal ion complexes, which in turn would lead to iron deficiency in the gut and could, therefore, affect sensitive bacterial populations, mainly aerobic microorganisms [65]. Aerobic microorganisms need iron for several functions, such as reduction of the ribonucleotide precursor of DNA and to form heme groups. In contrast, it has been demonstrated that dietary catechols may promote the growth of enteropathogenic bacteria by providing iron under iron-restrictive conditions and can enable gut bacterial growth [88]. Several mechanisms of action of polyphenols on specific intestinal bacterial functions are still unknown, and further research is needed for a better understanding.

5. Polyphenols, microbiota and cancer

Several studies have linked the microbial metabolism of dietary polyphenols to cancer prevention. These studies have found phylum-level differences among the gut microbiota of patients with and without colorectal cancer. Some phyla are increased, whereas others are decreased, but exactly how these changes affect the cancer process is not clear [89,90]. Studies done *in vitro* and in gnotobiotic rats have shown that plant lignin secoisolariciresinol diglucoside can be converted to enterodiol and enterolactone by a gut microbiota consortia composed of *Clostridium saccharogumia*, *Eggertella lenta*, *Blautia producta* and *Lactonifactor longoviformis* [91,92]. Furthermore, colonization with this lignin-metabolizing microbial community protected germ-free rats from 7,12-dimethylbenz(a)anthracene-induced cancer. Moreover, colonization significantly decreased tumour number, size and cell proliferation but increased tumour cell apoptosis [93].

Some polyphenol dietary components may also influence bacterial metabolizing enzymes and thus influence the overall cancer risk. For example, in a rat model, resveratrol supplementation (8-mg/kg body weight/day, intragastrically) significantly reduced activities of faecal and host colonic mucosal enzymes, such as β-glucoronidase, β-glucosidase, β-galactosidase, mucinase and nitroreductase compared to control animals (21%, 45%, 37%, 41% and 26%, respectively). The reduced bacterial enzyme activity was associated with a significant reduction in colonic tumour incidence in the resveratrol-fed rats compared to control rats, but it is not clear if these changes were a result of modifications of enzymatic activity within a subpopulation of microorganisms or a change in the proportion of specific bacteria [94]. The stilbene resveratrol is important in relation with colon cancer. The antiinflammatory activity of resveratrol includes inhibition of proinflammatory mediators, modification of eicosanoid synthesis and inhibition of enzymes including COX-2, NF-κB, AP-1, TNF-α, IL6 and VEGF (vascular endothelial growth factor) [95]. In cell culture, several phenolic compounds inhibit COX-2 activity, possibly by binding to the enzyme [96].

Ellagic acid has been reported to show a multitude of biological properties including antioxidant and cancer protective activities [97,98]. Interestingly, both urolithins A and B, the most representative microbial metabolites of dietary ellagitannins, have shown oestrogenic activity in a dose-dependent manner, even at high concentrations (40 microM), without antiproliferative or toxic effects towards MCF-7 breast cancer cells [99]. Other authors have analyzed the impact of selected intestinal polyphenol metabolites (with 3,4-dihydroxyphenylacetic acid (ES) and 3-(3,4-dihydroxyphenyl)-propionic acid, metabolites of quercetin and chlorogenic acid/caffeic acid) on modulation of enzymes involved in detoxification and inflammation in LT97 human adenoma cells. They showed an up-regulation of GSTT2 and a down-regulation of COX-2 that could possibly contribute to the chemopreventive potential of polyphenols after degradation in the gut [96]. Recently, Kang *et al.* reported that

coffee and caffeic acid specifically inhibited colon cancer metastasis and neoplastic cell transformation in mice by inhibiting MEK1 and TOPK (T-LAK cell–originated protein kinase) [100]. Several studies using animal and cell culture models have shown that tea-derived catechins, such as epigallocatechin-3-gallate, hold anticancer activity and mediate various cellular events that could be protective against cancer [101,102]. In addition, other nontea flavonoids such as quercetin from apples and vegetables have been found to have anticancer effects, including inhibition of cell proliferation and induction of apoptosis [103]. Whether the concentration of these compounds can be sufficiently achieved in human diets to affect these pathways is not known. Based on these previous studies, multiple mechanisms appear to be involved in the inhibition of carcinogenesis by dietary polyphenols (Fig. 2).

6. Modulation of gut microbiota by polyphenols and the impact on human gut health metabolism and immunity

In the following section, we summarize the effects of polyphenols and metabolites from polyphenol microbial metabolism on specific aspects of health and immunity. After a human intervention study, Tzounis *et al.* reported that flavonols induced an increase in the growth of *Lactobacillus* spp. and *Bifidobacterium* spp. and they may have been partly responsible for the observed reductions in the plasma C-reactive protein (CRP) concentrations, which are a blood marker of inflammation and a hallmark of the acute phase response [30]. Similarly, Fogliano *et al.*, in an *in vitro* model, found that the bacterial fermentation of water-insoluble cocoa fractions was associated with an increase in bifidobacteria and lactobacilli as well as butyrate production. These microbial changes were associated with significant reductions in plasma triacylglycerol and CRP, suggesting the potential benefits associated with dietary inclusion of flavonol-rich foods [104]. Recently, Queipo-Ortuño *et al.* [31] carried out a human intervention study and found that the regular intake of red wine polyphenols generated significant decreases in the plasma levels of blood pressure, triglycerides and high-density lipoprotein cholesterol, and these significant reductions may be partly due to the polyphenol-induced increase in the growth of *Bacteroides* genera. Moreover, they also reported a significant decrease in uric acid levels after the consumption of red wine polyphenols that can be explained by the significant increase in *Proteobacteria* observed in this stage, which has previously been reported to degrade uric acid [105]. Finally, they noted a significant reduction in the concentration of CRP after red wine treatment. This could be due to the increase seen in the number of *Bifidobacterium*. CRP is a blood marker of inflammation, and its concentration is a specific predictor of cardiovascular event risk in healthy subjects. Its reduction in this study links polyphenol intake to cardiovascular benefits in the host [106,107].

The weight-lowering property of fruits, green tea and vinegar wine in obese people may be partly related to their polyphenol content, which changes the gut microbiota either through the glycan-degrading capability of *Bacteroides*, which is higher than *Firmicutes*, or through the end products of colonic metabolism of polyphenols [33].

Martin *et al.* performed a clinical trial in a population of human subjects classified as having low or high anxiety traits using validated psychological questionnaires. They found that the daily consumption of dark chocolate (which is rich in flavonoids, mainly flavan-3-ols) resulted in a significant modification in the metabolism in healthy and free living human subjects, with potential long-term term health consequences, as per variation of both host and gut microbial metabolism. Human subjects with higher anxiety traits, however, showed a distinct metabolic profile, indicative of a different energy homeostasis (lactate, citrate, succinate, *trans*-aconitate, urea and proline), hormonal metabolism (adrenaline, DOPA [dihidroxifenilalanina] and 3-methoxy-tyrosine) and gut microbial activity (methylamines, *p*-cresol sulfate and hippurate) [108].

Monagas *et al.* observed that dihydroxylated phenolic acids (3,4-dihydroxyphenylpropionic acid, 3-hydroxyphenylpropionic acid and 3,4-dihydroxyphenylacetic acid) derived from microbial metabolism of proanthocyanidins presented marked *in vitro* antiinflammatory properties, reducing the secretion of TNF-α, IL-1b and IL-6 in

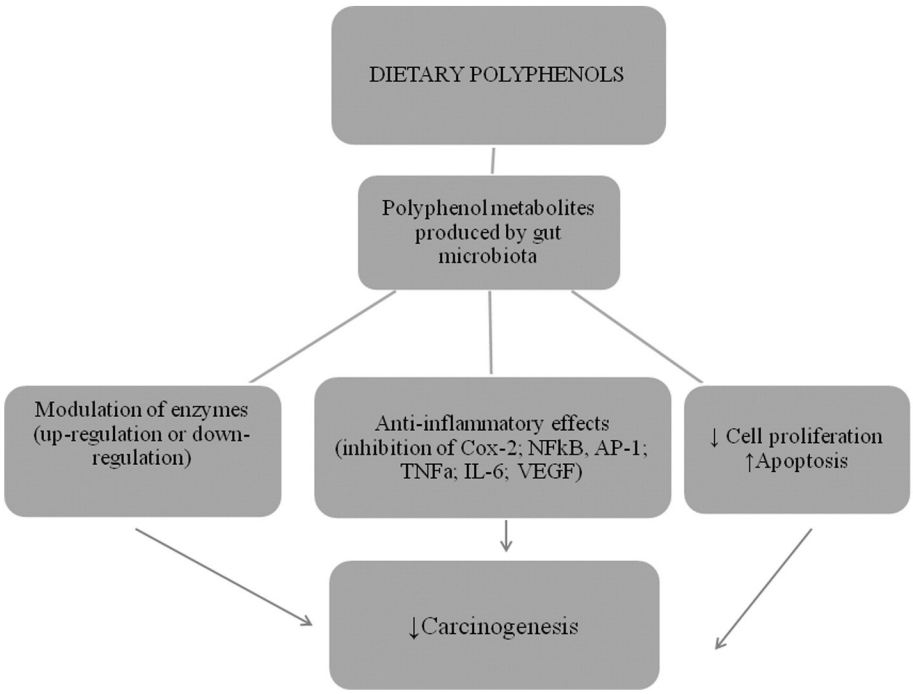

Fig. 2. Possible mechanisms proposed for the prevention of cancer by dietary polyphenols.

lipopolysaccharide-stimulated peripheral blood mononuclear cells from healthy subjects. It has been suggested that these microbial metabolites could be among the new generation of therapeutic agents for the management of immunoinflammatory diseases such as atherosclerosis [109], as well as for dampening the inflammatory response to bacterial antigens, which may have implications for chronic inflammatory or autoimmune diseases such as inflammatory bowel disease [110].

Larrosa *et al.*, after screening different microbial catabolites of polyphenols for their antiinflammatory potential *in vitro*, found that hydrocaffeic, dihydroxyphenylacetic and hydroferulic acid reduced prostaglandin E2 production by at least 50% in CCD-18 colon fibroblast cells stimulated with IL-1β. These results suggest that foods containing significant hydrocaffeic acid precursors (procyanidins, hydroxycinnamic acid derivatives, *etc.*) such as artichoke, cocoa, apples and strawberries could exert antiinflammatory activity and reduce intestinal inflammation in humans [111].

In addition, it has been shown that microbial metabolites of plant polyphenols may also affect disease risk in the metabolic syndrome. Verzelloni *et al.* demonstrated that two microbial metabolites of polyphenols, urolithins and pyrogallol derived from ellagitannin are highly antiglycative compared to parent polyphenolic compounds in an *in vitro* model of protein glycation. Moreover, it is known that protein glycation plays an important pathological role in diabetes and diabetes-associated disorders, including blindness [112].

Tucsek *et al.* [113] induced an inflammatory response by treating macrophages with bacterial endotoxin and found that end products of polyphenol degradation, such as ferulaldehyde, exerted a beneficial antiinflammatory response by diminishing MAP (mitogen-activated protein) kinase activation, thereby inhibiting NF-κB activation, mitochondrial depolarization and reactive oxygen species production. Similar results were found by Chirumbolo using many purified aglycone flavonoids [114]. It is arguable that the antimicrobial activity of polyphenols might be principally due to their well-recognized antiinflammatory potential.

Very recently, Beloborodova *et al.* [115] analyzed the role of phenolic acids of microbial origin as biomarkers in the progress of sepsis. They found that *p*-hydroxyphenylacetic acid showed the capacity to inhibit ROS (reactive oxygen species) production in neutrophils. By affecting neutrophils, they retard the immune response, whereas, while acting on mitochondria, they prevent or reduce the development of multiple organ failure. Thus, during the development of bacteremias and purulent foci of infection associated with *P. aeruginosa* and *Acinetobacter baumanii*, their metabolite *p*-hydroxyphenylacetic acid can directly enter the systemic blood flow and inhibit the phagocytic activity of neutrophils.

Finally, all these results support the hypothesis that not only the food polyphenols but also their microbial metabolites must be taken into account when assessing the impact of polyphenols on host health.

7. Conclusion

The bioavailability and effects of polyphenols greatly depend on their transformation by components of the gut microbiota. Different studies have been carried out to understand the gut microbiota transformation of particular polyphenol types and identify the microorganisms responsible. The modulation of the gut microbial population by phenolics was also reviewed in order to understand the two-way phenolic-microbiota interaction. It is clear that dietary polyphenols and their metabolites contribute to the maintenance of gut health by the modulation of the gut microbial balance through the stimulation of the growth of beneficial bacteria and the inhibition of pathogen bacteria, exerting prebiotic-like effects. However, data on the impact of polyphenols on the gut microbiota and their mechanisms of action in humans are scarce. In addition, a better understanding of the dietary phenolic and gut microbiota relationship by the combination of metagenomic and metabolomic studies provides more insight into the health effects of polyphenols.

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