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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