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Digestive Diseases and Sciences (2021) 66:3270–3289
https://doi.org/10.1007/s10620-020-06676-7

REVIEW

Phenolic Compounds Promote Diversity of Gut Microbiota and Maintain Colonic Health

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Received: 4 August 2020 / Accepted: 13 October 2020 / Published online: 28 October 2020

Abstract

The role of non-energy-yielding nutrients on health has been meticulously studied, and the evidence shows that a compound can exert significant effects on health even if not strictly required by the organism. Phenolic compounds are among the most widely studied molecules that fit this description; they are found in plants as secondary metabolites and are not required by humans for growth or development, but they can influence a wide array of processes that modulate health across multiple organs and systems. The lower gastrointestinal tract is a prime site of action of phenolic compounds, namely, by their effects on gut microbiota and colonic health. As with humans, phenolic compounds are not required by most bacteria but can be substrates of others; in fact, some phenolic compounds exert antibacterial actions. A diet rich in phenolic compounds can lead to qualitative and quantitative effects on gut microbiota, thereby inducing indirect health effects in mammals through the action of these microorganisms. Moreover, phenolic compounds may be fermented by the gut microbiota, thereby modulating the compounds bioactivity. In the colon, phenolic compounds promote anti-inflammatory, anti-oxidant and antiproliferative actions. The aim of the present review is to highlight the role of phenolic compounds on maintaining or restoring a healthy microbiota and overall colonic health. Mechanisms of action that substantiate the reported evidence will also be discussed.

Keywords Flavonoids (D005419) · Gastrointestinal tract (D041981) · Inflammation (D007249) · Microbiota (D064307) · Phytochemicals (D064209)

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What Factors Shape the Composition of Gut Microbiota?

We are born sterile, and subsequently colonized by microorganisms, with the highest density in the colon. At about 4 years of age, the microbiota of children is already adult-like and will continue to evolve depending on environmental exposures over a lifetime, including level of sanitation, antibiotics and other drugs, and diet [1]. Microbiota is defined as the group of microorganisms that populate the digestive tract of an animal, including humans, and whose actions can have local and systemic health effects on the host [2]. Before discussing the role of phenolic compounds on gut microbiota, it is crucial to establish which factors have been shown to exert significant changes on it. This section will briefly state some of the most common modulators of gut microbial communities, both negative and positive, including antibiotics, stress, inflammation, diet, exercise, and fecal microbial transplants (FMTs).

Factors That Negatively Alter Gut Microbiota

While antibiotics remain important for treating bacterial pathogens, their non-specific actions cause general disruption of the resident gut microbiota. Studies in mice and humans showed that microbial dysbiosis in early life may have long-term health consequences via epigenetic alterations [3]. For example, Cox et al. [4] transferred the microbiota of mice treated with low-dose penicillin after birth to germ-free mice, observing that antibiotic-altered microbiota made the mice obese (increased adipose fat and total mass) through increased expression of adipogenic genes, an effect that was absent when the microbiota was from an untreated control. The authors concluded that early life antibiotic exposure negatively alters gut microbiota, which was enough to induce obesity later in life, thus suggesting that its role on health is highly significant.

Azad et al. [5] analyzed the use of maternal prophylactic intrapartum antibiotics on full-term infants' microbiota. Bacterial diversity in general was negatively affected by antibiotic exposure, and, specifically, the genera *Bacteroides* and *Parabacteroides* decreased, while *Enterococcus* and *Clostridium* increased significantly at 3 and 12 months. Similar to what Cox et al. [4] reported, this study strengthens the case for the role of early life exposure to microorganisms, which has long-term effects that can potentially alter health later in life. Reijnders et al. [6] studied the effect of a placebo-controlled, 7-day, 1500-mg/day amoxicillin and vancomycin treatment on obese pre-diabetic men ($n = 57$, 35–70 years old). They reported that vancomycin exerted a significant decrease in bacterial diversity, in particular for *Firmicutes*, and, meanwhile, *Proteobacteria*, *Enterococcus*, and others increased. These alterations persisted 8 weeks after vancomycin treatment ceased. Amoxicillin, in contrast, exerted no significant changes after the 7-day treatment or the 8-week follow-up. No changes were found on numerous physiological markers like insulin sensitivity, energy metabolism, inflammation, adiposity, and others. Reijnders et al. [6] therefore concluded that, in contrast to rodents, humans respond differently to antibiotic-mediated alterations to their microbiota. They also caution that their subjects were older metabolically-challenged men (in contrast to the early life exposure discussed above), and that changes may be detectable in women or in a healthier population.

Stress is a prevalent condition that affects the majority of adults, and it has been shown that chronic and even acute bouts of stress can severely impact health through changes to the gut microbiota, in addition to numerous other mechanisms [7]. These findings have been replicated in animal models of social stress. For example, Syrian hamsters under an acute or repeated social antagonism (where one animal dominates another when placed in close proximity) show changes to their gut microbiota that is not due to normal handling [8]. Microbiota is not merely a passive target of stress, it can also influence the animal's response to it; this has been demonstrated in mice whose microbiota is depleted during adolescence (30 days old) and in germ-free rats, where microbiota modulates stress-related cognitive, behavioral, and endocrine responses [9, 10]. In humans, maternal prenatal stress also correlates with an altered infant microbiota [11], changes which can also persist well into adulthood [12]. Furthermore, depression has also been associated with altered bacterial composition in humans [13] and in rats [14], while prebiotics can exert antidepressant-like effects in mice [15].

Inflammation is linked with or is a hallmark of a wide number of diseases, both acute and chronic. The evidence suggests that a healthy gut microbiota may exert anti-inflammatory effects on inflammation-linked conditions like psoriatic arthritis [16], metabolic syndrome [17], Crohn's disease-like ileitis [18], osteoarthritis [19], and nonalcoholic liver disease [20] among others. Furthermore, microbiota is sensitive to sleep deprivation [21], gender, and menopausal status [22].

Factors That Can Maintain or Restore a Healthy Gut Microbiota

Maintenance and restoration of a diverse bacterial population can be achieved through diverse mechanisms. Microbiota composition is shaped by dietary components, particularly bioactives in plant foods such as fruits, vegetables, and cereals. Authors have analyzed the effects of dietary

components on gut microbiota from various perspectives. For example, Kopf et al. [23] showed that fruits and vegetables exert microbiota-mediated health effects in overweight or obese adults. In children [24], and in cirrhosis patients [25], higher fruit, vegetable, and cereal consumption has been linked to greater microbial diversity, which is often associated with positive health outcomes. The Mediterranean diet has been associated with a diverse microbiota [26], while the opposite is true for the Western diet [27]. Microbiota-accessible carbohydrates or fibers, phenolic compounds in general [28], and flavonoids in particular [29] are phytochemicals associated with health benefits, and it has been proposed that phenolic-rich foods be tailored to promote microbiota diversity and health [30].

Exercise has been shown to counter high-fat diet (HFD)-induced decreases in bacterial diversity in healthy and diabetic mice [31–33], as well as in obese, non-obese, and hypertensive rats [34]. Similar findings have been corroborated in lean and obese adult males and females [35]. Nieman et al. [36] studied the effect of a flavonoid supplementation on volunteers with different physical activities, and determined that bouts of vigorous exercise and walking significantly increased plasma concentration of flavonoids, as compared to sedentary subjects. This study provides evidence that the pharmacokinetic profile of phenolic compounds correlates with physical activity. Evidence suggests that physical activity is a strong modulator of bacterial composition, which may override the deleterious effects of dietary habits, weight, adiposity, blood pressure, and other parameters. While exercise influences microbiota, the microbiota may improve physical condition by increasing cardiorespiratory fitness and minimizing fatigue in healthy adults and breast cancer survivors [37, 38]. Altogether, there appears to be an intricate phenolics–exercise–microbiota interdependence.

A more targeted approach to normalizing gut microbiota can be achieved through FMTs, which achieve a desired effect in the recipient with minimal side effects when properly performed. An FMT was performed using a single-donor Lachnospiraceae/Ruminococcaceae-enriched sample on cirrhosis patients with low antibiotic-associated microbial diversity. Bacterial diversity was successfully restored after a single FMT, as determined by increased production of short-chain fatty acids [39]. Others report that an FMT can be successfully used to treat *Clostridium difficile* infections [40], and that, furthermore, the consequent immunomodulatory effects also resulted in partial reversion of alopecia areata, an autoimmune condition that results in varying degrees of hair loss [41]. Diet-induced steatohepatitis [42], antibiotic and chemotherapy-induced dysbiosis [43], insulin resistance [44], autism spectrum disorder [45], and other conditions have also been reported to respond positively to an FMT. This evidence suggests that the role of gut microbiota extends well beyond gastrointestinal health to immunomodulation that can reverse other chronic diseases or conditions. The use of FMTs is therefore a worthwhile alternative to treat diseases where dysbiosis is a sign, although further analysis is still required. Furthermore, the effects of an FMT are not self-sustained, since an adequate diet is required to maintain bacterial diversity.

According to the evidence, the role of gut microbiota on health is significant. Its composition and influence begin to take shape prenatally, and are influenced thereafter by diet, exercise, pharmacological treatments, and stress. It also affects mood, immunocompetence, physical fitness, and endocrine status. Figure 1 summarizes some of the most common factors that influence and are influenced by gut microbiota.

Effects of Phenolic Compounds on Gut Microbiota

The beneficial health effects of phenolic compounds on gut microbiota depend on numerous factors, such as their chemical structure, glycation pattern, and number of hydroxyl groups. A current report estimates more than 8000 known phenolic compounds [46], although only a fraction of these are present in a given plant food. Furthermore, there is substantial variation among plant tissues, such as leaves, bark, flowers, pulp, peel, seed, stem, or root [47]. This section describes the effect of selected phenolic-rich items on microbiota in different models.

Phenolic Compounds Found in Coffee

Many phenolic compounds are ingested in routinely-consumed beverages. For example, coffee is extremely popular worldwide, with an estimated 2 billion cups brewed and consumed daily [48]. Denmark, Norway, and Finland are the most avid coffee drinkers, reaching a yearly *per capita* consumption of 8.0, 8.7, and 11.4 kg, respectively [49]. Coffee contains a high concentration of bioactive compounds, and, while caffeine is arguably the most popular, it is also a rich source of phenolic compounds, particularly chlorogenic acid, which includes the esters formed between caffeic acid, ferulic acid, or *p*-coumaric acid with quinic acid. Their concentration depends on factors like genetics, environment, and processing. Beans are roasted to enhance the sensorial properties of coffee, which can deplete the concentration of chlorogenic acids by up to 90% [49]; however, coffee is a significant source of chlorogenic acid in the Western diet.

Absorption of chlorogenic acid begins in the stomach and continues in the small intestine. Lafay et al. [50] demonstrated that, in rats, certain chlorogenic acids were detected unchanged in the gastric vein and in the aorta. Nevertheless,

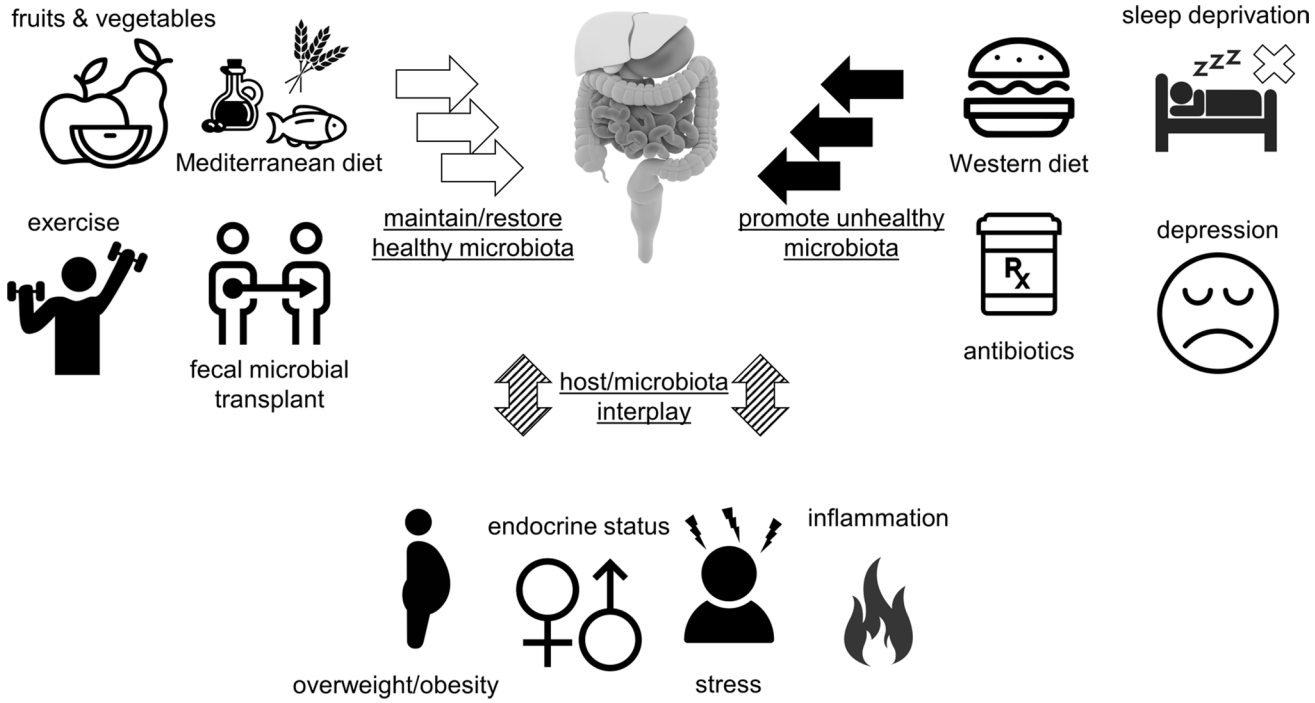

Fig. 1 Overview of different factors that alter microbiota

only a small amount is absorbed, and thus most of the chlorogenic acids ingested (approximately 70%) reaches the colon intact, and are subjected to bacterial esterases, yielding simpler compounds that are readily absorbed and distributed throughout the body. Mills et al. [51] showed that chlorogenic acids were metabolized within 10 h in vitro, when commercial coffee was fermented for 24 h in the presence of human fecal microbiota. They also found that the coffee with the highest concentration of chlorogenic acid increased growth of *Bifidobacterium* spp., *Bacteroides* spp., and the *Clostridium coccoides–Eubacterium rectale* group. Growth of *Lactobacillus* and *Enterococcus* spp. was not affected. In addition, similar results were observed when microbiota was exposed to 5-caffeoyl quinic acid (the most abundant isomer of chlorogenic acid in coffee), but growth of *Bacteroides* spp. was stimulated, while the growth of *Clostridium histolyticum* was inhibited. This suggests that each phenolic compound or a particular combination, such as in different types of coffee, exert variable effects on the microbiota.

Regular coffee consumption has been shown to exert significant microbial population changes. Specifically, González et al. [52] report that avid coffee drinkers (45–500 mL/day) have increased populations of *Bacteroides*, *Prevotella*, and *Porphyromonas*, as compared to those who drink less than 45 mL/day. However, since coffee is subjected to multiple processing steps during its production, its effects are likely to vary according to specific processing conditions. For example, an in vitro fermentation was performed with either green or roasted coffee, showing that the *Bacteroides* population was significantly higher in samples treated with green coffee as compared to roasted, which suggests that food processing may alter a product's phenolic profile, and their subsequent effects on bacterial communities [53]. Since coffee is a major phenolic source across cultures, the effects of its phenolic compounds on gut bacteria and other health-related parameters have been reviewed elsewhere [54].

Phenolic Compounds Found in Tea

Tea consumption trails that of coffee, making it the second most consumed beverage worldwide [55]. Green, black, and oolong are the main types of tea, all produced from the leaves of the *Camellia sinensis* plant by specific processes. The health benefits of tea consumption are well studied, most of them attributed to its phenolic compound profile [56]. Unprocessed tea leaves are rich in flavan-3-ols, whereas black tea is rich in theaflavins and thearubigins, due to the fermentation process that oxidizes catechins and forms polymers. Oolong tea is rich in epigallocatechin gallate (EGCG), and is a source of the *O*-methylated form of EGCG [epigallocatechin 3-*O*-(3-*O*-methyl)-gallate (EGCG3″Me)] (in addition to Benifuki tea as another major source of this compound [57]), which has been reported to exert anti-obesity actions, inhibit digestive enzymes, and maintain gut microbial eubiosis in obese mice [58, 59].

Cheng et al. [59] showed that the *Bacteroidetes*-to-*Firmicutes* ratio increased significantly when HFD was supplemented with oolong tea-derived phenolics and administered to mice during a 4-week period. The populations of *Faecalibacterium* (which is one of the main butyrate producers), *Ruminocccus*, and *Lachnospira* were also drastically depleted, whereas *Bacteroides* and *Prevotella* increased. In another study, Zhang et al. [60] showed that gallocatechin gallate (GCG), EGCG and EGCG3″Me promoted the gradual growth of *Lactobacillus–Enterococcus* groups and *Bifidobacterium* spp. in an in vitro fermentation for 24 h. They found that short chain fatty acids (SCFAs) were produced, namely, formic, acetic, and propionic. Black tea theaflavins stimulated growth of *Lactobacillus plantarum* 299v and *Bacillus subtilis*, while simultaneously metabolizing it into simpler compounds like gallic acid and pyrogallol [61]. SCFAs, gallic acid, pyrogallol, and other bacterial metabolites are thought to be key mediators of microbiota-related health effects.

The effects of tea consumption on gut microbiota have been shown to extend beyond the gut itself into other tissues and organs. For example, Jung et al. [62] reported that a 7-day green tea extract supplementation exerted significant protection against UV-induced stress in mice. Most notably, populations of *Bifidobacteria* and *Lactobacillus* spp. increased in response to the treatment, which were also associated with skin barrier function-related metabolites. Due to the rich phenolic profile of tea, their main components (catechins) have been extensively studied regarding phenolic–bacteria interactions, that may explain their effects on gut microbiota [63]. Furthermore, the role of processing and metabolism has also been shown to significantly alter their bioactivities [64].

Phenolic Compounds Found in Wine

Red wine is associated with prevention of cardiovascular disease (CVD), obesity-related metabolic disorders, and neurodegenerative diseases [65, 66]. The most striking evidence appears to be the French paradox, which was proposed in the early 1990s and states that the high consumption of red wine in France is associated with its low rate of CVD [67]. The high concentration of phenolic compounds in red wine (900–1400 mg/L [68]) is thought to be at least partially responsible for the health effects related to the French paradox. Main compounds present in red wine are anthocyanins (up to 70% of total phenolics), stilbenes (*cis*- and *trans*-resveratrol), hydroxybenzoic acids (gallic and protocatechuic acids), flavan-3-ols (catechin and epicatechin), and flavonols (quercetin). Intake of alcohol-free red wine is associated with an increase in the genera *Bifidobacterium*, *Enterococcus*, *Prevotella*, *Blautia coccoides–Eubacterium rectale* groups, *Bacteroides uniformis*, and *Eggerthella lenta* without altering *Lactobacillus* growth [69]. Individually administering phenolics found in red wine can exert different effects on microbiota. For example, resveratrol promotes the growth of *Bifidobacterium* and *Lactobacillus*, whereas proanthocyanins promote *Bifidobacterium* growth in humans after a 6-week period [68]. Some anthocyanins like peonidin stimulate growth of *B. bifidum*, *B. adolescentis*, *B. infantis* and *L. acidophilus*, while inhibiting growth of *Salmonella typhimurium* and *Streptococcus aureus* [70]. Anthocyanins also decreased *Clostridium histolyticum* abundance by promoting *Lactobacillus* spp. growth, which compete for substrate and adhesion sites [71].

Sun et al. [72] analyzed how red and white wine affect bacterial populations in an in vitro digestion, and if wine-drinking patterns had significant effects. They showed that red wine had a higher inhibitory effect on *Enterococcus* and Enterobacteriaceae, as compared to white wine. They also proposed that a higher wine intake does not directly translate into a higher phenolic bioaccessibility or microbiota-related improvements, and that drinking after a meal yields better results overall. Others argue that wine phenolics can also have a significant influence on oral bacteria and systemic inflammation [73], which is also associated with changes to the gut–brain axis, according to an antidepressant-like effect exerted by these compounds [74]. According to this information, the complex metabolism of wine phenolics and their interactions with gut bacteria is currently an active area of study [75, 76].

Phenolic Compounds Found in Oranges

Oranges are among the most consumed citrus fruits worldwide, either as is or processed into juice. Flavanones stand out as the most representative phenolics, and can be divided in neohesperidoside flavanones (rhamnosyl-a-1,2 glucose) naringin, neohesperidin, and neoeriocitrin, which are responsible for the bitter taste, and rutinoside flavanones (rhamnosyl-a-1,6 glucose) hesperidin, narirutin, and didymin, which are tasteless. Total content of flavanones in fresh orange fruit is approximately 442 mg/L, with hesperidin as the most abundant molecule (80% of total phenolics) [77]. Pereira-Caro et al. [78] demonstrated that flavanones like hesperidin and naringenin are metabolized by bacterial enzymes into 3-(3′-hydroxy-4′-methoxyphenyl)-propionic acid and 3-(phenyl)-propionic acid, respectively. In addition, the effects of two varieties of orange juice ('Bahia' and 'Cara Cara') on the composition of fecal gut microbiota of healthy human subjects have been studied. 'Cara Cara' juice promoted the growth of members of the Lachnospiraceae family (*Lachnospira* and *Dorea*) and Ruminococcaceae, whereas 'Bahia' juice decreased growth of the Ruminococcacea family and *Faecalibacterium prausnitzii* and increased the Enterococcaceae and Veillonellaceae families after a

7-day treatment [79]. An in vitro study used the SHIME (simulator of the human intestinal ecosystem) reactor to study the effects of fresh orange juice (105 mL) on different bacterial populations. Results showed a positive effect on the growth of *Lactobacillus* spp., *Enterococcus* spp., *Bifidobacterium* spp., and *Clostridium* spp., while a negative effect was apparent on members of *Enterobacteria* after a 2-week period. On the other hand, pasteurized orange juice specifically stimulated the growth of *Lactobacillus* and reduced the *Enterobacteria* population during the same experimental period [80].

Daily orange juice consumption (300 mL) has shown significant effects on gut bacteria in healthy adult female volunteers, according to Lima et al. [81]. They showed that *Lactobacillus* spp., *Bifidobacterium* spp., and total fecal anaerobe populations increased in response to the treatment, an effect that persisted during the washout period. Since oranges are often consumed as juice, processing has been studied as an important variable that can alter the bioavailability and metabolism of phenolic compounds present in oranges (mainly hesperidin, naringin, and narirutin), and associated effects on gut bacteria [82].

Phenolic Compounds Found in Mango

Mango is a popular tropical fruit whose phenolic profile is made up of hydroxybenzoic acids like gallic, protocatechuic, ferulic, vanillic, and chlorogenic acids, whereas the peel is rich in mangiferin, gallotannins, and quercetin [83]. These compounds make mango pulp and peel potential microbiota modulators. An in vitro fermentation (with fecal inoculum) of mango pulp with previous in vivo mastication showed that phenolics were metabolized by bacteria in the first 10 h, generating 3-(4-hydrohyphenyl)-propanoic and 4-hydroxyphenylacetic acid as main metabolites detected, derived from catechin and feruloylquinic acid, respectively [84]. Sáyago-Ayerdi et al. [85] evaluated the effect of predigested mango peel on microbiota composition using the validated TIM-2 simulator of the colon. They reported an increase in butyrate, which could be related to increases in *Bifidobacterium* (the most abundant genus after 24 h) and *Lactobacillus*, *Dorea*, and *Lactococcus* (after 72 h), all of which are consider health-promoting bacteria. From these reports, it can be argued that fruit peels, in addition to pulp, can exert important actions, possibly due to a higher concentration of phenolic compounds present therein [86, 87].

A study in humans with inflammatory bowel disease show that, after an 8-week mango intake, the concentration of different inflammatory markers decreased, an effect which was accompanied by increases in different *Lactobacillus* populations [88]. Others have focused their attention on mango byproducts, such as peel, which also contain bioactive phenolic compounds, dietary fiber, and other molecules. For example, Sayago-Ayerdi et al. [89] performed an in vitro colonic digestion (TIM-2) of mango peel, and determined that it was able to increase *Bifidobacterium* and *Lactobacillus* populations (and others), in addition to associated positive effects. Similar subsequent experiments showed that adding mango peel to a bar (snack) also increased the *Bacteroidetes* population and the *Firmicutes–Bacteroidetes* ratio, an indicator of its ability to promote a healthy and diverse bacterial population. This allowed the authors to propose that mango peel exerts a prebiotic-like effect, similary to other evidence reported for its pulp [90].

Phenolic Compounds Found in Pomegranate

Pomegranate is commercially grown in Mediterranean countries and consumed worldwide, and its intake has increased due to numerous reported health benefits such as anti-oxidant, anti-inflammatory, and chemo-preventive effects [91]. There is evidence that pomegranate juice may exert higher anti-oxidant activity than wine and green tea [92]. The main phenolics present are ellagitannins (punicalin, punicalagin, and pedunculagin), which are responsible for 90% of the anti-oxidant activity, in addition to anthocyanins (delphinidin, cyaniding, and pelargonidin) [93]. Due to their high molecular weight and chemical complexity, ellagitannins and ellagic acid cannot be absorbed in the upper gastrointestinal tract, thus reaching the large intestine, where they are transformed by the native microbiota to numerous simple compounds like urolithins. In contrast to their parent compounds, urolithins are readily absorbed into systemic circulation, where they can exert health benefits on peripheral tissues, in addition to effects on bacterial composition of the colon. In vitro studies suggest that pomegranate could exert a prebiotic-like effect, due to an increase in *Lactobacillus* and *Bifidobacterium* and a decreased number of *Bacteroides*, *Clostridium*, and *Enterobacteria* [94]. However, when a pomegranate extract was consumed for 3 weeks by healthy overweight–obese individuals, there were no significant changes in the populations of the aforementioned genera, only an increase in *Gordonibacter*, which has been shown to be responsible for the production of urolithins [95]. Zhang et al. [96] supplemented high-fat/high-sucrose diets with pomegranate, which, when administered to C57BL/6 mice, led to an increase in Turicibateraceae and Ruminococcaceae. Among the different bioactivities documented for pomegranate and pomegranate juice, the prebiotic effect has been recognized, most notably, because of the ability to favorably modulate bacterial populations in the gut [97]. This and other effects are mainly attributed to its phenolic profile in general, and to ellagitannins in particular, as well as some complementary interactions with dietary fiber [98].

Urolithins are major metabolites of phenolic compounds present in pomegranate and other ellagitannin-rich

products, and are the main metabolites considered in the present work. However, there are numerous others types of metabolites whose bioactivities on colon (and overall) health have been documented, for example, benzoic acids, simple phenols, phenolic acids, phenylacetic acids, valerolactones, valeric acids, hydroxybenzaldehyes, hydroycinnamic acids, hydroxycoumarins, hydroxyphenylpropanoic acids, and various others. They have been detected and quantified in serum, organs, urine, and feces of animals and humans after consuming different phenolic-rich products [99, 100], and their effects on health have been reviewed elsewhere [101]. Only some of the reactions that lead to their synthesis are precisely known, while others have been proposed [102]. Furthermore, their effects are also influenced by multiple interactions with the host and the various microbial populations [103].

Phenolic Compounds Found in Berries

Berries are very popular fruits due to attractive colors and culinary versatility. Their high anti-oxidant capacity can be attributed to anthocyanin pigments, flavan-3-ols, and flavonols. Blueberries, blackberries, black/red raspberries, cranberries, elderberries, and strawberries are among the most consumed. Among them, elderberries contain the highest anthocyanin concentration (791 mg/g fresh weight), followed by blueberries (495 mg/g fresh weight) [104]. A blueberry extract was administered to high-fat diet-induced obese C57BL/6 mice for 12 weeks, which increased *Bifidobacterium*, *Desulfovibrio*, *Helicobacter*, and *Flexispira*, without changes in *Lactobacillus* and a with decrease in *Adlercreutzia* and *Prevotella*. This may be related to the antibacterial activity of berries on some pathogens [104]. Tian et al. [71] suggested that each type of berry will have a specific effect on gut microbiota, which may be related to the precise phenolic profile of each fruit. For example, anthocyanins may stimulate *Lactobacillus*, while punicalagins may stimulate *Gordonibacter*. Furthermore, specific phenolic compounds are metabolized in different sections of the colon (ascending, transversal or distal) [105], while exposure time also affects the phenolic–bacterial interaction, resulting in unique effects on microbiota composition.

Some specific phenolic compounds have been identified that may be responsible for the bacteria-modulating effect of some berries. In the case of wild raspberries, pelargonidin-3-*O*-glucoside has been shown to increase *Prevotella* and the *Bacteroidetes–Firmicutes* ratio, as evidenced in male *db*/*db* mice that were orally administered 150 mg/kg [106]. However as with compounds present in other fruits, their metabolism is key in determining what effects will be exerted on the gut microbiota and health overall, as discussed by Lavefve et al. [107].

Table 1 shows additional studies that describe modulatory effects of phenolic compounds on microbiota in different models, as well as some related health effects.

Effects of Phenolic Compounds on Gastrointestinal Health

Polyphenols are poorly absorbed or metabolized by human enzymes during their passage through the upper gastrointestinal tract; thus, most of the ingested amount reaches the colon. Once there, bacterial enzymes may depolymerize complex compounds into simpler ones, while some microorganisms can exert a more intricate metabolism that yields bacterial metabolites, which exert direct actions on colonocytes that can favor this organ's wellbeing. A low percentage of these compounds are absorbed and reach systemic circulation, which allows them to influence distant organs. This section focuses on reported effects of phenolics on the gastrointestinal tract, with particular emphasis on colonic health.

Effects of Phenolic Compounds Against Colitis

Colitis is a common inflammatory condition that can progress to colon cancer if it remains untreated for long periods of time. The potential anti-inflammatory effect of some phenolic compounds has been used as a preventive or corrective measure. For example, Silva et al. [120] analyzed the effect of flaxseed phenolics on 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis [single 100 µL intrarectal (IR) dose of 1.0 mg/mL TNBS] in female BALB/c mice. Lignan-rich flaxseed extracts were administered (200 mg/kg) to the animals as therapeutic or prophylactic (7 days prior to induction) treatments. Compared to untreated mice, the lignan extracts prevented weight loss and mitigated tissue damage and leukocyte infiltration. While no single treatment (therapeutic of prophylactic) was able to exert all of the aforementioned effects, evidence suggested that phenolic compounds were highly bioactive in the TNBS-induced colitis model and beneficial effects were reportedly due to anti-inflammatory and anti-oxidant effects of the lignan extract.

Other authors reported similar effects against TNBS-induced colitis when using other sources of phenolic compounds. For example, Direito et al. [121] used persimmon (*Dyospiros khaki*) phenolics in CD-1 mice, and showed that they alleviated some signs of colitis (decreased loss of colon length, ulcers, inflammation, and others), which the authors partly attributed to decreased expression of inflammatory genes [cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS)]. Valcheva-Kuzmanova et al. [122] administered a daily oral dose of black chokeberry (*Aronia melanocarpa*) juice (2.5, 5.0, and 10.0 mL/kg) to

Table 1 Effects of different sources of phenolic compounds on microbiota and related health effects

Phenolic source	Dose	Conditions	Effects on microbiota	Related health effects	Reference
In vitro models					
Punicalagin-rich pomegranate extract	1.8 g/day	TWIN-SHIME with fecal inoculum from healthy donors, 3 weeks	↑ *Akkermansi*a and *Gordonibacter*	↑ Urolithin and propionate	[108]
Açaí pulp	60 g	In vitro digestion simulating the large intestine	↓ *Bacteroides, Prevotella* and *Clostridium*	↑ Acetate and propionate after 24 h	[109]
Gallic acid- and catechin-rich grape seed extract		In vitro fermentation with fecal inoculum from healthy donors, 36 h	↑ *Bifidobacterium Lactobacillus–Enterococcus.* ↓ *Clostridium histolyticum* and *Bacteroides–Prevotella*	Altered short chain fatty acid profile	[110]
Grape pomace extract	Acute single dose of 700 mg and chronic intake of 700 mg/day	Dynamic gastrointestinal digestion simulator with fecal inoculum from healthy donors, 14 days	↑ *Lactobacillus* and *Bacteroides* (chronic intake)	↑ Short chain fatty acids after chronic intake	[111]
In vivo models					
Cranberry extract	200 mg/kg	High-fat, high-sucrose diet fed to C57BL/6J mice, 8 weeks	↑ *Akkermansia*	↓ Liver weight and triacylglycerol accumulation	[112]
Green and black tea phenolics	0.25 g/100 g diet	High-fat high-sucrose diet fed to C57BL/6J mice, 4 weeks	↑ *Parabacteroides, Bacteroides, Oscillibacter* and *Prevotella.* ↓ *Lactobacillus, Roseburia, Blautia, Anaerostipes, Bryantella, Lactococcus* and *Acetitomaculum*	↓ Body weight, subcutaneous, mesenteric, and epidermal fat. ↑ Intestinal short chain fatty acids	[113]
Green coffee extract	220 mg/kg of chlorogenic acids	High-fat diets fed to ApoE$^{-/-}$ mice, 14 weeks	↑ Mogibacteriaceae, *Coprococcus*, *Dorea*, *Ruminocccus*, *Desulfovibrio* and *Firmicutes*	Improved markers of carbohydrate and lipid metabolism	[114]
Grape proanthocyanidins	360 mg/kg	High-fat diets fed to C57BL/6J mice, 14 days	↑ *Akkermansia muciniphila*	Improved oral glucose tolerance	[115]
Camu camu extract	200 mg/kg	High-fat, high-sucrose diets fed to C57BL/6J mice, 8 weeks	↑ *Barnesiella* spp, *Turicibacter* spp and *Akkermansia muciniphila*	↑ Energy expenditure and glucose homeostasis	[116]
Studies on humans					
Red wine phenolics	272 mL	Obese and non-obese healthy human subjects, 30 days	↑ *Bifidobacteria, Lactobacillus*, *Faecalibacterium prausnitzii* and *Roseburia*	↓ Glucose, triacylglycerols, coleserol, C-reactive protein	[66]
Blueberry extract	200 mg/kg	High-fat, high-sucrose diet fed to C57BL/6J mice, 12 weeks	↑ *Proteobacteria* and *Deferribacteres.* ↓ *Actinobacteria*	Prevented body weight gain and normalized serum lipids	[117]
EGCG and resveratrol	282 mg/day of EGCG, 80 mg/day resveratrol	Randomized double-blind placebo-controlled study, 18 obese men and 19 obese women, 12 weeks	↓ *Bacteroides* and *Faecalibacterium prausnitzii* in men	Modulated in lipid oxidation in men	[118]

Table 1 (continued)

Phenolic source	Dose	Conditions	Effects on microbiota	Related health effects	Reference
Tart cherry juice rich in cyanidin-glucosyl rutinoside, quercetin-rutinoside, chlorogenic and neochlorogenic acids	8 oz (c.225 g)/day	Healthy individuals, 5 days	↓ *Bacteroides* and *Bifidobacterium* ↑ Lachnospiraceae, *Ruminococcus* and *Collinsella*	↑ 4-hydroxyphenylpropionic acid and epicatechin by gut microbiota	[119]

male Wistar rats, and compared its effect to a pharmacological agent (sulfasalazine). Treatments mitigated weight loss, loss of colon length, necrotized area, and other signs, with a similar or superior effectiveness to the pharmacological compound. The authors suggested that the anti-oxidant and anti-inflammatory actions of the phenolic compounds were responsible for the observed effects; the main compounds present were cyanidin glycosides and chlorogenic acid isomers. Altogether, Silva et al. [120], Direito et al. [121] and Valcheva-Kuzmanova et al. [122] provided evidence of the protective effect that various phenolic compounds exert on the colon of rats with TNBS-induced colitis, which is apparently based on separate, but complementary, actions on this organ.

In addition to TNBS, colitis can be induced with dextran sodium sulfate (DSS), each resulting in a disease that resembles either ulcerative colitis (TNBS) or Crohn's disease (DSS) [123]. Thus, testing phenolic compounds against different etiologies of the inflammatory bowel disease makes the evidence more robust. To that end, there is substantial evidence that DSS-induced colitis can be mitigated in laboratory rodents when treated with phenolic compounds from walnuts (gallic acid, chlorogenic acid, catechin, ellagic acid) [124], black chokeberries (anthocyanins, phenolic acids, flavonols) [125] and cranberries (cyanidins) [126]. These studies report similar effects of the treatments, such as less inflammation, weight loss, and histological damage. Furthermore, the mechanism of action of these samples is closely related to their ability to inhibit secretion of tumor necrosis factor (TNF)-α and inflammatory interleukins.

Others provide complementary information, for example, Monk et al. [127] suggested that the effects of cranberries are mediated by positively altering mice microbiota, while Kim et al. [128] proposed that mango fiber promotes bacterial synthesis of butyrate and valerate; both results in DSS-treated mice and rats. Pure compounds like quercetin and its derivatives have shown to lessen pro-inflammatory cytokine production in mice models of DSS-induced colitis (in addition to induce recovery of the histological pattern of the transverse colon after loperamide-induced constipation in rats [129]), while strawberry administration, by oral or rectal routes, diminished the inflammatory process and lessened epithelial necrosis and lesions in acetic acid-induced colitis in a rat model [130].

This indicates that phenolic compounds exert their effect independently of the way they reach the colon.

Effects of Phenolic Compounds Against Colon Cancer

Colon cancer is one of the leading causes of death worldwide, being the second most prevalent cause of cancer deaths for both genders after lung cancer, and the third

most commonly diagnosed cancer worldwide. Colonocytes are directly exposed to reactive oxygen species (ROS) and mutagens consumed in the diet (e.g., aflatoxins produced by fungi associated with corn, peanuts, and tree nuts); hence, mitigating oxidative stress has important implications for the prevention and treatment of colonic diseases. Grape polyphenols and β-carotene were demonstrated to reduce HFD-induced ROS in murine gut [131]. Of note, the biology and clinical aspects of rectal cancer is different from colon cancer, perhaps due to their distinct embryological origin, anatomy; and function [132]. Nonetheless, metastasized rectal and colon cancer are nowadays treated alike.

Hashemzaei et al. [133] tested quercetin (10–120 μM) against murine colon carcinoma (CT-26) and other malignant cells, showing an antiproliferative effect at all concentrations and an enhanced effect with longer incubation periods. Sensitivity to quercetin also correlated with higher apoptotic rate. Further experiments demonstrated that intraperitoneally-administered quercetin (50–200 mg/kg) reduced tumor volumes in mice implanted with CT-26 cells.

Cancer cells reprogram their glycolytic pathways to anaerobic glycolysis (Warburg effect), rather than oxidative phosphorylation. This is further promoted by signaling pathways mediated by pro-inflammatory cytokines, glycolytic enzymes; and wingless-related integration site signaling (Wnt) [134]. In this sense, Guven et al. [135] tested the anti-inflammatory properties of hesperidin and quercetin on irradiated colon in rats. They found a reduced inflammatory response of the irradiated tissue, probably due to effective scavenging of ROS that can damage DNA. This was suggested because quercetin showed anti-apoptotic activity via caspases 3, 8, and 9.

The study of naturally-occurring chemo-preventive substances in food is important to develop new approaches to treat human diseases like colon cancer. Because many compounds can target multiple biochemical pathways, it is also important to identify intracellular targets that may be responsible for their health effects.

Molecular Pathways and Plausible Mechanisms of Action of Phenolic Compounds Against Colitis, Colon Cancer and Overall Health

Phenolic compounds have been thoroughly studied during the preceding decades, and yet there are numerous knowledge gaps that have not allowed us to generate a complete and detailed picture of how specific molecules exert some health effects. For example, after a compound is ingested as part of a meal, it is processed and metabolized along the gastrointestinal tract; a small fraction is absorbed in the small intestine and systemically transported to specific tissues or cells, while the majority traverses intact throughout the upper digestive tract. In the colon, bacteria cleave the sugar moiety to yield the corresponding aglycone, which may be further metabolized (by the microbiota), undergo phase II metabolism (by the host), and contribute to produce physiological effects in situ or be excreted in feces.

Colon inflammation is commonly triggered by different internal and external stimuli that aim to protect the cells; when this process is signaled by cancer cell growth, a consortium of cells (e.g., immune cells) is activated to orchestrate a cytoplasmic protein complex (inflammasome) to activate a protease caspase-1 system. This caspase-1 activation leads to proteolytic cleavage and release of pro-inflammatory cytokines IL-1β and IL-18 to initiate pyroptosis [136]. In particular, colorectal cancer has been associated with inflammasome complexes of leucine-rich repeat-containing proteins 3 (NLRP3) and absent in melanoma 2 (AIM2). For example, mice lacking NLPR3 given azoxymethane and DSS, both colitogens, are more susceptible to colitis and colitis-associated colorectal cancer [136]. Indeed, mice lacking IL-18 show susceptibility to DSS-induced intestinal inflammation and tumorigenesis, but conditioned isoforms of IL-18 showed resistance to DSS-induced colitis. In mice with similar microbial profiles, IL-18 responses commanded by inflammasome-regulated caspase-1 activation may be dysfunctional in colorectal cancer cells, where flavonoids such as quercetin might contribute to suppress inflammation via suppression of the IFN/JAK2/STAT1 signaling pathway [137]. Another example was shown on HCT116 and HT29 cells, both human colorectal cancer cell lines, that were tested with dihydroquercetin (taxifolin) to determine cytotoxicity in a dose- and time-dependent manner, via cell growth arrest, where Razak et al. [138] showed that these effects were associated to Wnt/β-catenin signaling. Quercetin and three synthetic analogues have also been shown to exert antiproliferative effects by modifying histone-mediated epigenetic changes, specifically by inhibiting the activity of histone deacetylase 8 (HDAC8) [139].

The potential health benefits of flavonoids are quite dependent on their absorption and concentration reaching target cells. There are a number of factors that have significant impact on this variable. For instance, quercetin-4′-glucoside must be deglycosylated by small intestine luminal lactase phlorizin hydrolase or inside enterocytes by cytosolic β-glucosidase [140, 141]. Free quercetin may also be sulfated by phase II enzymes, which is then distributed in this form throughout the circulatory system and delivered to target tissues. In this scenario, it is known to be partially absorbed in the colon rather than in the small intestine. This can be inferred by studies where rutin (quercetin-3-*O*-rutinoside) plasma metabolites are detected 2–24 h after ingestion of this compound [141]. In addition, their concentration varied between subjects, which suggests that, in humans,

anti-oxidant-related health benefits depend on the composition of the colonic microbiota, intestinal transit times, and other (some yet to be identified) variables. Moreover, when flavonoids were given to patients with or without colons, it was found that rutin derivatives were deglycosylated by microbial enzymes (such as α-L-rhamnosides and β-glucosidases), after which quercetin then reached the bloodstream [141]. In contrast to rutin, it has been reported that apple juice phenolics (e.g., hydroxycinnamic acids, flavan-3-ols, procyanidins, flavonols, dihydrochalcones, and anthocyanins) are assimilated almost entirely in the small intestine, but a small proportion can reach the colon [142].

Attri and Goel [143] showed that phenolic compounds increased bacterial ability to biotransform phenolic compounds in the colonic stage of a simulated digestion system, which may also influence their bioavailability. This suggests a potential interplay between phenolics modulating the microbiota and microbiota regulating the metabolism of phenolic compounds. This points to a fine and multivariate system, since, in humans, the colon harbors over 1000 species of bacteria that possess catalytic and hydrolytic ability to metabolize phenolics to the corresponding aglycone. The aglycone can then be absorbed by colonocytes into systemic circulation [144], while also generating metabolites that can also modulate bacterial profile and phenolic metabolism.

Numerous questions arise once specific foods, compounds, and bacterial populations are considered, for example, what mechanisms of action promote growth of certain bacterial species while limiting that of others? To what extent should phenolic compounds or food that contain them be consumed to positively influence the microbiota? What phenolic–phenolic and phenolic–nutrient interactions are relevant to these effects? These and other questions are currently under debate and experimental validation. In order to offer plausible answers, the positive effects of phenolic compounds can be classified and described on three main fronts: (1) modulation of microbiota ecology, (2) attenuation of inflammation, and (3) maintenance of gut barrier function. These are discussed in the following sections.

Phenolic Compounds and Microbiota

Many studies have associated the gut microbiota with multiple conditions including obesity, chronic inflammatory diseases, cardiovascular disease, cancers, stress, and neurodegenerative disorders [145]. Major attention has been given to the effects of dietary compounds, including phenolic compounds, on microbiota modulation. Pre-clinical studies have shown that phenolic compounds can reshape the microbiota ecology [146], and the bloom in *Akkermansia muciniphila* has become a signature after phenolic intervention [112, 115, 147, 148], although this is dependent on which phenolic compounds are used, as not all phenolic compounds have the same effect. For example, the effects of grape phenolics administered to rats fed high-fat diets have been shown to depend on inducing an *A. muciniphila* bloom, according to two similar but independent models [115, 147]. Bofutsushosan (a Japanese herbal medicine made up of at least 11 individual components) was also able to induce it on high-fat diet fed mice, but the effect could not be replicated when the individual components were administered, suggesting that some synergy was required between different compounds [149]. Because of this, some have attempted to pinpoint which specific compounds or type of compounds are responsible for such effects. In the case of blueberries, an oligomeric proanthocyanidin-rich fraction was among the most notable for its bioactivity in this regard, as compared to fractions rich in anthocyanins/phenolic acids and polymeric proanthocyanidins in mice fed high-fat high-sucrose diets [150]. This highlights the varying ability of different phenolic sources and particular compounds within those sources to alter a host's microbiota.

A. muciniphila has been extensively studied in the context of insulin resistance and type 2 diabetes, and a direct link has been established between this bacterium and intestinal permeability through Amuc_1100, an extracellular membrane protein of *A. muciniphila*. The administration of Amuc_1100 to HFD-fed mice activated Toll-like receptor 2, which correlated with an increased expression of the junctional proteins claudin 3 and occludin compared to the control group [151]. This effect partially corrected the metabolic phenotype observed in the HFD group, including lower body weight, hypercholesterolemia, hypertriglyceridemia, insulin resistance, and plasma lipopolysaccharide (LPS) levels. Likewise, extracellular vesicles isolated from *A. muciniphila* increased occludin expression and decreased gut permeability of LPS-treated Caco-2 cells and in the colon of type 2 diabetic mice [152]. Although molecular mechanisms were not investigated, it is possible that Amuc_1100 was involved.

The antibacterial activity of phenolic compounds has been widely addressed, and this might be one of the mechanisms behind the modulatory effects of gut microbiota. For instance, phenolic compounds may selectively promote the growth of certain bacteria (e.g., *A. muciniphila*) by suppressing competitor microbes. Moreover, a large portion of dietary phenolics, particularly oligomeric and polymeric (condensed and hydrolyzable tannins), bypass the small intestine and reach the colon where they are metabolized by the microbiota (see above). Thus, it is believed that phenolic compounds can conduct a prebiotic-like effect modulating microbial composition and function [153]. However, a recent report has shed some light on the potential of phenolic compounds to regulate gut microbiota ecology via activation of host signaling pathways (Fig. 2).

Radulovic et al. [154] observed that apigenin activates NOD-like receptor family pyrin domain-containing 6

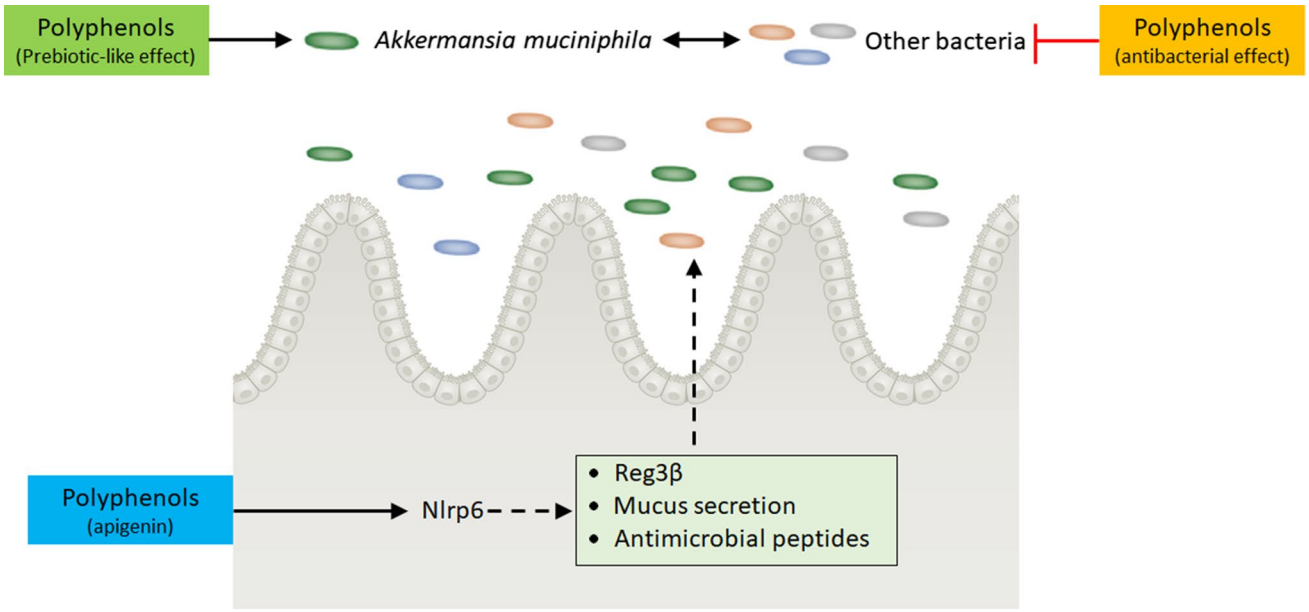

Fig. 2 Effects of phenolic compounds that involve actions on bacteria and on host signaling pathways

(Nlrp6) and thereby reprograms the gut microbiota protecting mice against colitis. Co-housing nontreated and apigenin-treated mice before induction of acute colitis pinpointed that apigenin protects against inflammation by regulating the composition of the gut microbiota, since both groups presented similar histological scores and shortening of the colon. Furthermore, 16S rRNA analysis revealed similar bacterial communities in co-housed nontreated and apigenin-treated groups. However, when apigenin was administered to Nlrp6 knockout mice ($Nlrp6^{-/-}$), global changes in the composition of the gut microbiota were not present, suggesting that the Nlrp6 signaling pathway was involved in microbiota remodeling by apigenin. $Nlrp6^{-/-}$ mice showed a decreased expression of the stress-induced regenerating islet-derived protein 3 β (Reg3β). Importantly, the C-type lectin Reg3β has been shown to possess antibacterial effects and to restrict the number of mucosa-associated intestinal bacteria [155]. However, the authors did not demonstrate a direct causal link between Reg3β expression and microbiota remodeling. Nlrp6 regulates mucus secretion and antimicrobial peptide production [156], which may alternatively explain the effects of apigenin on microbiota changes.

Phenolic compounds have the potential to modulate the gut microbiota; however, the nature of this interaction is still elusive. The work of Radulovic et al. [154] has proven that the reductionist thinking of a direct interaction through an antibacterial and prebiotic-like effect is far from explaining phenolic compound–microbiota interactions. Instead, they have highlighted that phenolic compounds can regulate host metabolic pathways that can indirectly impact microbiota ecology, with important implications in human health.

Phenolic Compounds and Colonic Inflammation

The gut immune system has the key task to preserve tolerance to luminal antigens from food and commensal bacteria and to prevent the invasion of pathogens by averting a chronic pro-inflammatory environment and maintaining the intestinal barrier intact. Some pathological conditions, such as ulcerative colitis and colon cancer, are preceded by a chronic inflammatory state [157, 158], which, to some extent, are related with an obese phenotype [159, 160]. Furthermore, the pro-inflammatory environment in the colon associated with obesity seems to be implicated in the development of metabolic diseases such as type 2 diabetes and cardiovascular disease [161].

During chronic inflammation, there is a deregulated activation of inflammatory signals including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and TNF-α, which triggers the expression of iNOS, COX-2, prostaglandin E2 (PGE2), IL-1β, and IL-6 [161, 162]. Pre-clinical studies have shown that some dietary phenolic compounds are capable of attenuating colonic inflammation by blocking NF-κB activation and downstream effectors.

Phenolic compounds such as naringenin and luteolin can inhibit NF-κB activation, although through a different mechanism. In a mouse model of experimental colitis, naringenin attenuated the expression of Toll-like receptor 4 (TLR4) which is required for NF-κB activation. This was in line with a decreased expression of NF-κB and downstream signals [iNOS, intercellular adhesion molecule 1 (ICAM-1), monocyte chemoattractant protein 1 (MCP-1), COX-2, TNF-α, and IL-6]. Further evidence was obtained by treating

mouse RAW264.7 macrophage cells with LPS, a ligand of TLR4, where naringenin prevented the nuclear translocation of NF-κB p65 [163]. On the other hand, in an in-deep mechanistic study using multicellular models, luteolin was able to block NF-κB signaling by inhibiting IκB kinase (IKK) activity. Luteolin blocked IκB phosphorylation/degradation, NF-κB activation and ICAM-1 gene expression in LPS-treated mouse intestinal cells. Similarly, in bone marrow-derived dendritic cells isolated from mice, luteolin reduced LPS-induced IκB phosphorylation, IL-12, and TNF-α gene expression, suggesting a direct effect of luteolin on IKK activity, since IKK is a common signal transductor for inducing NF-κB activity [164]. Table 2 shows other phenolic compounds that have been reported to attenuate pro-inflammatory signals through the described biochemical pathways.

The nuclear factor erythroid 2-related factor 2 (Nrf2) has been identified as an upstream regulator of cytokine production through redox control, and therefore an interesting target for reducing inflammation [176]. Recently, the aryl hydrocarbon receptor (AhR)-Nrf2 has been underlined as a possible molecular pathway for the effects of phenolic compounds on alleviating inflammation [165]. Specifically, urolithin A, a microbial metabolite derived from the breakdown of ellagitannins [177], decreased LPS-induced IL-6 and TNF-α in mouse bone marrow-derived macrophages in a concentration-dependent manner. This was further confirmed in vivo in a pre-clinical model of experimental colitis, in which treatment with urolithin A reduced myeloperoxidase activity (MPA), IL-6, TNF-α, CXCL1 (CXCL1 chemokine [C-X-C motif] ligand 1), and IL-1β in both preventive and therapeutic applications settings [165]. Furthermore, the authors observed that urolithin A activates the AhR receptor and its translocation to the nucleus in HT29 cells, and Nrf2 was identified as a target of the AhR signaling cascade. Finally, using $AhR^{-/-}$ and $Nrf2^{-/-}$ mice models, it was unambiguously established that urolithin A protects against inflammation in experimental colitis via the AhR-Nrf2 pathway.

It is known that phenolic compounds such as epicatechin, epicatechin-3-gallate and quercetin [178, 179] activate Nrf2, and the work of Singh et al. [165] showed evidence that this might be downstream of AhR activation. However, the role of phenolic compounds, and specifically urolithin A in AhR-regulating inflammation, deserves further investigation since

Table 2 Recent studies showing the anti-inflammatory properties of phenolic compounds and phenolic-rich extracts

Extract/phenolic compound	Dose	Disease model	Animal/cell model	Biomarkers	Reference
Urolithin A	0.1–50 µM	Ulcerative colitis	Mouse	↓ MPO activity, IL-6, TNF-α, CXCL1 and IL-1β	[165]
Apple peel (glycosylated quercetin and dihydrochalcone. Catechin, epicatechin and proanthocyanidin)	200 and 400 mg/kg/d	Ulcerative colitis	Mouse	↓ NF-Kβ, TNFα, COX-2, iNOS, MDA, H_2O_2 ↑ Nrf2, SOD, GPx	[166]
Cranberry	1.5% (w/w)	Colon cancer	Mouse	↓ TNF-α, IL-6, IL-1β, COX-2, HO-1, NQO1, Caspase-3, P53, P21, P27	[167]
Proanthocyanidins (Type B2)	0.0125–0.1 mg/mL	Intestinal inflammation	Caco-2	↓ NF-κB, TNF-α, IL-6, IL-1β ↑ SOD, CAT, GPx, HO-1	[168]
Urolithin A	10 µM	Intestinal inflammation	Caco-2	↓ AhR, IL-6 and PTGS	[169]
Apple peel extract (coumaric acids, caffeoylquinic acids, phloretin, phlorizin, (+)-catechin, (−)-epicatechin, (+)-catechin gallate and quercetin)	200 and 400 mg/kg/d	Ulcerative colitis	Mouse	↓ MPO activity, MDA levels, NF-Kβ, TNF-α, IL-6, COX-2, PGE2 ↑ Nrf2, SOD, GPx	[170]
Resveratrol	50 µM	Intestinal inflammation	SW480	↓ NF-κB and AKT signaling	[171]
Luteolin	50 and 100 µM	Intestinal inflammation	HT-29	↓ JAK/STAT pathway, COX-2, iNOS, NO radical	[172]
Pomegranate (ellagic acid, ellagitannins)	2504.74 mg GAE	Ulcerative colitis	Rat	↓ NF-κB, TNF-α, IL-6, IL-1β, iNOS, COX-2	[173]
Mangiferin	10–30 mg/kg/d	Ulcerative colitis	Rat	↓ TNF-α, IL-17, SOD, MDA	[174]
Cocoa (Epicatechin, catechin, Proanthocyanidin B1 and B2)	12% (w/w)	Ulcerative colitis	Rat	↓ TNF-α, iNOS, COX-2	[175]
Cocoa (Epicatechin, catechin, Proanthocyanidin B1 and B2)	0.020 mg/mL	Intestinal inflammation	Caco-2	↓ NF-κB, TNF-α, IL-8, COX-2, iNOS	[175]

it has been reported that inhibition of AhR-transcriptional activity by urolithin A was necessary for attenuating IL-6 and prostaglandin-endoperoxide synthase 2 (PGES2) production [169].

Phenolic Compounds and Intestinal Barrier

The intestinal epithelium must balance the opposing tasks of facilitating selective transport, while also forming a barrier that restricts free flux across the paracellular space where the apical junctional complex plays a crucial to both properties (for a detailed review, see Buckley and Turner [180]). The loss of epithelial barrier function has been shown to be a key component in the dysregulation of metabolic- and immune-related diseases like type 1 and 2 diabetes, colon cancer, and celiac disease, among others [181, 182].

Studies conducted in Caco-2 cells have shown that certain phenolic compounds enhance intestinal barrier function via distribution of junctional proteins and upregulating their expression. For instance, quercetin decreased cell permeability in a time- (0–72 h) and dose- (0–200 μM) dependent manner via transcriptional expression of the junctional protein claudin-4 [183]. Similar results were observed in an independent subsequent study where the assembly of ZO-2, occludin, and claudin-1 were involved in the regulatory pathway [184]. Kaempferol promoted the actin cytoskeletal association of the tight junction proteins, ZO-1, ZO-2, occludin, claudin-1, claudin-3, and claudin-4 in the cholesterol-rich lipid microdomain fraction, which caused an enhanced tight junction integrity of 40% [185]. Similarly, in the Caco-2/15 cell line, a cranberry extract offset LPS-mediated downregulation of occludin protein expression and permeability [170]. Chronic inflammation has been associated with the loss of intestinal barrier; thus, the effect of phenolic compounds on intestinal barrier homeostasis has been often related with their anti-inflammatory properties, as discussed in the previous sections.

Recent studies indicate that AMP-activated protein kinase (AMPK) activity controls epithelial permeability and inflammatory signals [167, 186, 187]. Interestingly, some phenolic compounds are known activators of AMPK [188, 189], suggesting they may maintain intestinal barrier homeostasis through the activation of this master regulator. Indeed, a phenolic-rich extract from purple potato increased expression of caudal type homeobox 2 (CDX2), a key transcriptional factor regulating intestinal epithelial differentiation in Caco-2 cells and ex vivo guts, which translated to an increased expression of ZO-1 and decreased paracellular flux of FITC-dextran [190]. In a loss and gain of function models, knocking out AMPK with CRISPR/Cas9 system averted the positive effects of phenolic compounds on intestinal epithelial differentiation and barrier function, along with the reduced expression of CDX2 [190]. In contrast, a phenolic-rich extract from propolis enhanced intestinal barrier integrity independent of epithelial differentiation in Caco-2 cells [191]. Mechanistically, treatment with the phenolic extract increased the phosphorylation of AMPK and ERK1/2, whereas the use of dorsomorphin (a selective inhibitor of AMPK signaling) and PD98059 (a selective inhibitor of ERK1/2 signaling) reduced epithelial integrity as assessed by transepithelial electrical resistance and gene and protein expression of ZO-1 and occludin [191].

The data presented above suggest that phenolic compounds may maintain intestinal barrier function through the activation of AMPK activity which could be associated with downstream effects on inflammatory signals. The activation of AhR receptor and glucagon-like peptide 1 secretion (GLP-1) have been shown to modulate the expression of junctional proteins and intestinal permeability [165, 192]. Noteworthy, phenolic compounds may activate AhR [165, 193] and induce GLP-1 secretion [193, 194]; thus, they may represent additional molecular pathways underlining their regulatory effects on intestinal permeability, which deserves further investigation.

Conclusion

Phenolic compounds ingested as part of a regular diet and traverse the gastrointestinal tract to finally reach the large intestine, where they may exert health-promoting effects. First, they favor a diverse bacterial profile of the resident microbiota and promote colonic health. For instance, colonic microbiota has been shown to prevent obesity, inflammation, and related disorders, thereby improving health and wellbeing in studied subjects. Microbiota is extremely sensitive to dietary habits, exercise, sleep, stress, and other factors; hence, diets rich in phenolic compounds might be a valuable tool to maintain or restore it. Preserving colonic health is also important, since it is continuously exposed to a plethora of aggressors, which can result in life-threatening diseases like colon cancer, or pathologies such as colitis, that severely decrease an individual's quality of life. The mechanisms of action of phenolic compounds when exerting these effects are varied, but they include prebiotic-like actions, gene expression regulation associated with inflammatory processes, and preserving an adequate intestinal barrier. Overall, the evidence suggests that phenolic compounds contribute to improving health. Further studies are needed to better understand their roles as potential candidates to prevent and treat gastrointestinal pathologies.

Funding This work was supported by Instituto de Bebidas de la Industria Mexicana de Coca-Cola through project "Inducción de saciedad y modulación de la digestión intestinal de lípidos ejercidos por los

compuestos fenólicos de aguacate Hass" (Premio Nacional en Ciencia y Tecnología de Alimentos 2019); Consejo Nacional de Ciencia y Tecnología (CONACYT) (265216) through project "Satiety-inducing actions and modulation of lipid digestion exerted by phenolic compounds from avocado byproducts. An enteroendocrine and behavioral study"; and by CIAD.

Compliance with Ethical Standards

Conflicts of interest The authors declare that there are no conflicts of interest.

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