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Synergic Interactions between Polyphenols and Gut Microbiota in Mitigating Inflammatory Bowel Diseases

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List of abbreviations:

ATG16L1	Autophagy related 16 like 1
CD	Crohn's disease
C_{max}	Maximum serum concentration
DSS	Dextran sulfate sodium
EGCG	Epigallocatechin gallate
IBD	Inflammatory bowel diseases
IFN-γ	Interferon-γ
IL	Interleukin
IRGM	Immunity-related GTPase family M protein
LPS	Lipopolysaccharide
Mdr1a	Multidrug resistance protein 1a
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NOD2	Nucleotide-binding oligomerization domain containing 2
Nrf2	Nuclear factor erythroid 2-related factor 2
SCFA	Short chain fatty acids
TL1A	TNF-like ligand 1A
TLR-4	Toll-like receptor 4
TNBS	2, 4, 6-Trinitrobenzenesulfonic acid
TNF	Tumor necrosis factor
UC	Ulcerative colitis
ZO	Zonula occludens

Abstract

Inflammatory bowel diseases (IBD) are a group of chronic and recurring inflammatory conditions in the colon and intestine. Their etiology is not fully understood but involves the combination of gut dysbiosis, genetics, immune functions, and environmental factors including diet. Polyphenols from plant-based food synergistically interact with gut microbiota to suppress inflammation and alleviate symptoms of IBD. Polyphenols increase the diversity of gut microbiota, improve the relative abundance of beneficial bacteria, and inhibit the pathogenic species. Polyphenols not absorbed in the small intestine are catabolized in the colon by microbiota into microbial metabolites, many of which have higher anti-inflammatory activity and bioavailability than their precursors. The polyphenols and their microbial metabolites alleviate IBD through reduction of oxidative stress, inhibition of inflammatory cytokines secretion (TNF-α, IL-6, IL-8, and IL-1β), suppression of NF-κB, upregulation of Nrf2, gut barrier protection, and modulation of immune function. Future studies are needed to discover unknown microbial metabolites of polyphenols and correlate specific gut microbes with microbial metabolites and IBD mitigating activity. A better knowledge of the synergistic interactions between polyphenols and gut microbiota will help to devise more effective prevention strategies for IBD. This review focuses on the role of polyphenols, gut microbiota and their synergistic interactions on the alleviation of IBD as well as current trends and future directions of IBD management.

Key words: polyphenols, gut microbiota, inflammatory bowel disease, inflammation

1. Introduction

IBD are a group of chronic and recurring inflammatory conditions in the colon and intestine. These diseases have no medical cure and require life-long management of symptoms.[1] IBD have the highest incidence in Europe and North America, and their incidence is rising throughout the world.[2] Common symptoms of IBD include diarrhea, abdominal pain, fever, fatigue, and blood in the stool. Diagnosis of IBD in patients younger than 30 increases their risk of developing colorectal cancers by 8.2 folds as indicated by the standardized incidence ratio.[3] In addition, IBD patients have higher risk of depression and anxiety, which further decrease their quality of life.[4]

The etiology of IBD is not fully understood. The pathogenesis of IBD is the result of numerous factors including environments, genetic predisposition, gut dysbiosis, and immune dysregulation.[5] Environmental factors associated with higher risk of IBD include urban living, smoking, tonsillectomy, appendectomy, the usage of antibiotics, oral contraceptives, vitamin D deficiency, poor diets, and non–*Helicobacter* pylori–like enterohepatic *Helicobacter* species.[6, 7] Studies suggested a positive correlation between high fat, high proteins, high sugar and low fiber diet and IBD incidence. Food additives such as carrageenan and surfactants may increase the risk for IBD. The amount of soft drinks, saturated fats, red meat, and gluten in diets also contribute to the development of IBD.[7]

The genome-wide association studies associated 230 gene loci with IBD. NOD2, ATG16L1, IRGM, IL-23R, and TL1A are IBD susceptible genes.[5, 8, 9] NOD2 is a CD susceptible gene. This gene encodes a protein that functions as an intracellular receptor and identifies molecules consisting of muramyl dipeptide, which originates from

peptidoglycan and is a vital structure for NOD2 recognition.[10] ATG16L1 and IRGM genes play an important role in the autophagy of immune responses in IBD. Autophagy is associated with intracellular homeostasis, degrading and recycling intracellular contents, fighting against infection, and cleaning out intracellular microorganisms. ATG16L1 is indispensable for autophagy of any form and the Thr^{300}-to-Ala mutation for increasing CD risk. IRGM is a member of immune p47 GTPase family. Certain IRGM gene polymorphisms are associated with CD.[11, 12] The IL-23R gene provides guidance for the receptor of pro-inflammatory cytokine IL-23, a protein related to Th17 cells.[13] TL1A, also known as TNFSF15, is a cytokine that belongs to the TNF ligand family. TL1A and its functional receptor death receptor 3 are members of the TNF/TNFR protein family. TL1A and death receptor 3 are upregulated in inflammatory sites of intestine in human and mice with IBD.[8]

The dysfunction of the innate and adaptive immunity contributes to the abnormal response of intestinal inflammation in IBD patients. Early studies on adaptive immunity identified two major forms of IBD: CD associated with a Th1 response and UC related to a non-conventional Th2 response.[14, 15] Recent studies on immunity have found that increased intestinal permeability, defective epithelial barrier, abnormal expression of antimicrobial peptides, and the significant alteration of innate immunity and function, including the expression of NOD and TLRs proteins, increased the risk for IBD.[5]

Gut dysbiosis, any alteration in microbial composition or bowel eubiosis, is a factor for the development of IBD.[16] In healthy individuals, microbiota maintains the homeostasis of the gut by fermenting the indigestible polysaccharides, producing SCFA, synthesizing specific vitamins, providing energy, protecting intestinal mucosa, and

suppressing pathogenic microorganisms. Above 90% of healthy human gut bacteria are classified into 4 major phyla: *Firmicutes*, *Bacteroidetes*, *Proteobacteria,* and *Actinobacteri*a.[17] There are three types of gut dysbiosis, including a decrease of diversity, a loss of beneficial bacteria, and an increase of pathogens. In most cases, these three types of dysbiosis co-exist.[18] Gut dysbiosis has been associated with the development of obesity,[19] atherosclerosis,[20] and type-2 diabetes.[21] In most cases, there is a lower diversity of gut microbiota in IBD patients.[22] A decrease of *Firmicutes* and *Bacteroidetes* and an increase of *Proteobacteria* are the most consistent observations of gut dysbiosis in IBD patients.[23, 24]

Polyphenols are natural compounds in plant-based foods including fruits, vegetables, and cereals. Major polyphenols in the diet include hydroxycinnamic acids (e.g. chlorogenic acids), flavonoids, stilbenes (e.g. resveratrol), and tannins. Flavonoids are further classified into flavonols (e.g. quercetin), flavones, flavan-3-ols, isoflavones, flavanones, and anthocyanins. Human interventions in IBD patients, *in vivo*, and *in vitro* studies have shown that polyphenols are effective at preventing and alleviating the symptoms of IBD.[25-27] In IBD patients, polyphenols were shown to improve the diversity of gut microbiota,[28] increase the beneficial bacteria, decrease the harmful bacteria, and reduce the level of pro-inflammatory cytokines.[29] *In vivo* studies use DSS, TNBS, or acetic acid to induce IBD in rodents.[30-32] Other studies have used Mdr1a knock-out or IL-10 knock-out mice, which spontaneously develop IBD.[33, 34] IL-7 transgenic mice and HLA-B27 transgenic rats are two types of commonly used transgenic colitis models.[35, 36] Studies in rodents found that polyphenols mitigated the colitis, prevented the colon shortening, preserved the integrity of the gut barrier, and decreased the expression and

secretion of inflammatory cytokines.[37] The most common *in vitro* models for IBD research used Caco-2, HT-29, and CCD18-Co cells derived from the human colon.[26, 38, 39] I*n vitro* studies showed that polyphenols decreased cytokine expression but enhanced the tight junction proteins in intestinal epithelial cells or monolayers.[38] Anaerobic fermentation experiments demonstrated the degradation of polyphenols by gut microbiota,[40] and the enhancement of beneficial bacteria and inhibition of pathogenic bacteria by polyphenols.[41]

Polyphenols were the sole focus of early studies, but research in the last few years started to investigate the complex interactions between polyphenols and gut microbiota and how they synergistically mitigate IBD.[30, 42, 43] This review will discuss current trends and future research directions on the role of gut microbiota, polyphenols, and their reciprocal interactions in IBD prevention and management.

2. Gut microbiota and IBD

The human gut microbiota contains more than 1000 species and has a symbiotic relationship with the human host.[17] Alternations of gut microbiota and dysbiosis are hallmarks in IBD patients. UC and CD patients have a decreased percentage of *Firmicutes* and *Bacteroidetes* but an increased proportion of *Proteobacteria*.[24, 44] Within the *Firmicutes* phylum, the *Faecalibacterium* and *Roseburia* genera are reduced, whereas *Ruminococcus gnavus* is increased in CD patients.[45-47] *Deltaproteobacteria* from *Proteobacteria* may contribute to the development of colitis because they reduce sulfates to toxic hydrogen sulfide in the colon. Their abundance was increased in UC patients.[48] It has been demonstrated that there was a significant reduction in beneficial bacteria, including *Bacteriodes*, *Lactobacillus*, and *Eubacterium* in IBD patients.[49]

Species such as *Lactococcus lactis* reduce oxidative stress in the colon. The decrease of these species in IBD causes overproduction of reactive oxygen species, which further exacerbates gut dysbiosis.[43] SCFA are the major source of energy for the epithelial cells in the colon. There was a reduction of SCFA-producing microbial strains in IBD patients and most of them belonged to *Firmicutes*, including *Ruminococcaceae*, *Leuconostocaceae*, *Phascolarctobacterium,* and *Roseburia,* as well as *Odoribacter* from the phylum of *Bacteroidetes*.[50, 51]

The diversity of the gut microbiome is significantly lower in IBD patients compared to healthy individuals. Some studies have demonstrated a reduction in the overall species and diversity in the intestinal microbiome of IBD patients.[52] A study using metagenomics sequencing indicated that colon in IBD patients contained 25% fewer genes of mucosal microbes than healthy individuals.[22] It was found that the prevalence of adherent-invasive *Escherichia coli* in CD and UC patients were 75% and 69% higher than those in healthy people, respectively.[53] A multicenter study showed a significantly lower abundance of *Clostridia* in CD patients.[52] *Faecalibacterium prausnitzii* from *Firmicutes* was considered to have anti-inflammatory effects. Several studies found that *F. prausnitzii* was significantly decreased in CD patients.[46, 47] In a metagenomic study, there was a decreased microbial diversity in CD patients (54 ribotypes) compared to healthy individuals (88 ribotypes). The decreased diversity was mainly from *Firmicutes* because there were only 13 *Firmicutes* operational taxonomic units in CD patients compared to 43 in healthy subjects. [22]

Restoring gut dysbiosis is an effective treatment for IBD because fecal microbiota transplantation from healthy individuals restored gut microbiota in IBD patients to a

normal state and reduced inflammation.[54] By contrast, treating IBD using antibiotics is associated with remission and relapse because they may disrupt gut microbiota.[55] An increasing amount of research suggests that polyphenols have prebiotics-like activities to promote the growth of beneficial bacteria in the host and restore gut dysbiosis.[56]

3. Polyphenols and IBD

Anti-inflammatory activities have been reported for polyphenols of different sources and structures. Polyphenols may alleviate IBD through multiple mechanisms, including antioxidant effects to reduce oxidative stress, regulating Nrf2 and NF-κB pathways, gut barrier protection, and immune modulation.[57-59]

In an open-label human intervention, UC patients with mild to moderate symptoms were given anthocyanin-rich bilberries at a dose of 160 g/day (840 mg anthocyanins per day) for six weeks. There was a significant decrease in the clinical disease activity index after 1-week of bilberry intake and a significant decrease in the fecal calprotectin (an IBD biomarker) level after two weeks. After six weeks, IFN-γ and IFN-γ R2 expression in colon biopsy specimens was decreased in UC patients, and an increase of anti-inflammatory cytokine IL-10 was observed in about 50% of patients.[27, 60] Feeding HLA-B27 transgenic rats with a diet containing 7.6% of lyophilized Marie Me´nard apple pulp for 12 weeks alleviated the colon inflammation by decreasing myeloperoxidase activity and down-regulating gene expression of cyclooxygenase-2, IFN-γ, and inducible nitric oxide synthase in the colon.[35] However, these activities were not observed in red delicious apples due to their much lower polyphenol content. This study highlighted the critical role of polyphenols in fruits to mitigate IBD.[35] In another study, male CF-1 mice were treated with 1.5% DSS in drinking water for 7 days and

then EGCG (3.2 mg/mL) in drinking water for 3 days. It was found that EGCG prevented the colon shortening and decreased the protein levels of inflammatory cytokines IL-1β, IL-6, TNF-α, and monocyte chemotactic protein-1 in the colon of DSS-treated mice.[61] Female C57BL/6 mice were gavaged with polyphenols extracted from muscadine grapes or wine at 500 mg/kg for 14 days. DSS (3%) was added in drinking water to induce acute colitis in the last 7 days. Muscadine polyphenols were shown to preserve the structure of gut mucosa and decrease the level of myeloperoxidase activity, IL-1β, IL-6, and TNF-α in the colon.[62] In Caco-2 cells, muscadine polyphenols at 100 μg/mL blunted TNF-α-induced NF-κB activation by reducing IκB phosphorylation and degradation.[62]

Although many polyphenols were found effective at alleviating IBD, it is unknown whether a subclass of polyphenols has higher bioactivity than others. The safe and effective dose of polyphenols remains unknown in IBD patients.

4. The catabolism of polyphenols by gut microbiota

Polyphenols have a low absorption rate in their intact form. The unabsorbed polyphenols are metabolized by the microbiota in the colon. Microbial catabolism of dietary polyphenols, phase II metabolism, and transport of absorbed microbial metabolites in humans are depicted in **Figure 1**. **Figure 2** shows microbial catabolism of dietary polyphenols by microbiota in the colon using malvidin-3-glucoside, epicatechin gallate, and ellagic acid as examples.

Fermenting polyphenols with human fecal bacteria under an anaerobic condition provides direct knowledge on the microbial degradation of polyphenols. Incubating a

grape extract with fecal microbiota led to the hydrolysis of anthocyanins to their aglycones. Malvidin-3-glucoside was completely degraded into syringic acid after incubated with a human fecal slurry for 24 hours (Figure 2A). Gallic acid, *p*-coumaric, and syringic acid were formed after a mixture of anthocyanins were incubated with healthy human fecal bacteria.[40] *Bifidobacterium spp*. in microbiota contain enzymes that catalyze *O*-deglycosylation and *C*-ring-cleavage of flavonoids, including anthocyanins.[63] Microbial degradation of flavan-3-ols and proanthocyanidins follow a similar pathway to generate a unique product of 5-(3',4'-dihydroxyphenyl)-Y-valerolactone, which undergoes dihydroxylation and oxidation to produce phenolic acids (Figure 2B).[64] Ellagitannins and ellagic acid are found in many nuts and fruits. Ingested ellagitannins were hydrolyzed to release ellagic acid in the jejunum of animals and humans. Ellagic acid undergoes ring fission, decarboxylation, and dihydroxylation by microbes in the colon to produce urolithin D, C, A, B, and isourolithin A (Figure 2C).[65, 66]

Microbial catabolism of polyphenols often results in metabolites with higher bioavailability and bioactivity than their precursors. After a single dose of 500 mg of cyanidin-3-glucoside was given to healthy men, sixteen microbial metabolites were detected in serum. The C_{max} of cyanidin-3-glucoside was 141 nM, whereas the C_{max} of its microbial metabolites, including protocatechuic acid and vanillic acid, were 382 nM and 1845 nM respectively, indicating a higher bioavailability of the metabolites.[67] After human subjects were given a single dose of pomegranate ellagitannin extract (1 g), peak plasma concentration of urolithin A glucuronide reached 2.47 μM which was over 80 fold of the C_{max} of ellagic acid (0.02-0.061 μM), also indicative of much higher bioavailability of urolithins.[68] The 4-hydroxybenzoic acid is a microbial metabolite of

multiple flavonoids including quercetin, epicatechin, hesperetin, and cyanidin-3-glucoside. In human THP-1 monocytes, 1 μM of 4-hydroxybenzoic acid significantly decreased the LPS-induced IL-1β secretion while none of its precursor flavonoids were effective at the same concentration, suggesting that anti-inflammatory activity of these flavonoids was largely due to their microbial metabolites.[69]

The inflammation in macrophages is related to the etiology of intestinal inflammation since it is a necessary process to protect the host from pathogenic bacteria and to promote healing. Inflammation in murine macrophage cell line RAW 264.7 was stimulated by LPS (250 ng/mL) before they were incubated with different urolithins for 24 h. It was found that urolithin A, B, and C at the concentration of 40 μM decreased the LPS-induced NO production, iNOS production, and the mRNA expression of inflammatory cytokines IL-1β, TNF-α, and IL-6. Urolithin A showed the highest inhibition activity followed by urolithin B and C because their minimum effective concentrations to inhibit the production of NO were 2.5, 20 and 40 μM, respectively.[70] Pretreatment of HT-29 and Caco-2 monolayers cells with 50 μM of urolithin A for 24 h preserved gut barrier function impaired by 50 ng/mL of LPS. Such activities were associated with increased mRNA levels of claudin 4, occludin, and ZO-1. Upregulation of tight junction protein expression by urolithin A was mediated by activation of aryl hydrocarbon receptor and Nrf2 dependent pathways.[71]

The higher absorption rate and anti-inflammatory activity of polyphenol microbial metabolites suggest they play a bigger role than precursors in mitigating IBD. Microbial catabolism of polyphenols produces numerous metabolites and most of them are

unknown. Discovering new microbial metabolites with possibly new bioactivity remains a challenge for current and future research.

5. The modulation of gut microbiota by polyphenols

Animal and human studies showed that polyphenols have prebiotic activities to alter the composition and diversity of gut microbiota. Polyphenols have been consistently observed to increase the diversity of gut microbiota, enhance beneficial bacteria, and inhibit pathogenic ones.[28] The modulation of gut microbiota by polyphenols in human and rodents is summarized in **Table 1**.

In a human study, healthy volunteers consumed 250 mL/day red wine for 28 days. A significant increase in the diversity of gut microbiota was observed among intervention groups after the wine consumption compared to baseline.[28] A randomized, controlled, double-blind, crossover human intervention found that the addition of cocoa flavanol at 494 mg/d for four weeks increased the relative abundance of *Lactobacillus spp*. and *Bifidobacterium spp*. This study associated these changes in gut bacteria with a significant reduction of C-reactive protein in blood.[72] In a randomized, crossover, controlled human study, overweight-obese participants consumed 0.45 g/day of placebo or 1.8/day g of pomegranate extract daily for 3 weeks. Treatments were separated by 3-week washout periods. A significant decrease of plasma lipopolysaccharide-binding protein was observed after intake of 1.8 g pomegranate extract, but not after the low dose. Such change was associated with increases of *Faecalibacterium* and *Odoribacter* and decreases of *Parvimonas* in the gut microbiota. The high dose of extract decreased pro-inflammatory microorganisms including *Parvimonas*, *Methanobrevibacter*, and *Methanosphaera*.[56]

In a rodent study using Wistar rats, supplementation of quercetin at a dose of 30 mg/kg/day for six weeks reduced the abundance of *Bacillus* and *Erysipelotrichaceae*. Both species were elevated by a high-fat-diet, which induced inflammation in the intestine.[73] In C57BL/6J mice, after oral gavage of cranberry polyphenol extracts with a daily dose of 200 mg/kg for 8 weeks, intestinal inflammation and oxidative stress were alleviated in mice fed a high fat/high sucrose diet.[74] A high-fat diet decreased the abundance of mucin-degrading bacterium *Akkermansia* in C57BL/6 mice, and such decreases were partially corrected by a cranberry extract and grape polyphenols.[74, 75] Dealcoholized muscadine wine containing anthocyanins and flavonols decreased *Clostridium* from *Firmicutes,* but increased *Roseburia*, *Anaerotruncus*, and *Coprococcus* in *Firmicutes* phylum in DSS-treated colitis mice.[76] In a fermentation study, apple matrices were incubated with fecal slurries from healthy volunteers for 48 h under anaerobic conditions. About 70% of the total phenolics in apple matrices were procyanidins and hydroxycinnamic acids. It was found that fermentation with apple matrices significantly increased β-diversity of the microbiota compared to baseline. Apple matrices increased seven bacterial groups belonging to *Firmicutes* but decreased three, including *Clostridium*, *Eisenbergiella, and Lachnospiraceae* ND3007 group.[77] Cranberry extracts or whole cranberry powder was added into a human gut simulator inoculated with human stool sample at a dose of 1 mg/mL every 24 hours five times. Cranberries decreased the abundance of *Enterobacteriaceae* from *Proteobacteria* but increased *Bacteroidaceae* from *Bacteroidetes.* Salicylate, a phenolic acid, isolated from cranberries inhibited the growth of pathogenic *E. coli*.[41]

The effects of polyphenols on gut bacteria depend on the bacterial species, the structure of the polyphenols, and the dosage tested. It was reported that EGCG and its acetate, EGCG octaacetate, had a wide inhibitory effect on both gram-positive and gram-negative food-borne pathogens. The minimum inhibitory concentration of EGCG and EGCG octaacetate was 130 μg/mL and 100 μg/mL, respectively, on gram-positive bacteria *Bacillus subtilis,* and 580 μg/mL and 250 μg/mL on gram-negative bacteria *E. Coli*, respectively. Both EGCG and EGCG octaacetate altered the bacterial membrane permeability of *E. coli* to induce its death. EGCG octaacetate was more effective than EGCG due to its higher lipophilicity.[78] EGCG increased the sensitivity of *S. aureus* to β-lactam antibiotics. EGCG also upregulated autolysins associated with the cell wall, increased lipoteichoic acid released from the cytoplasmic membrane, and enhanced lysostaphin resistance, leading to the alteration of structure in cell wall teichoic acid. Thus, the properties of cell-surface were modulated to keep the β-lactam-resistant phenotype. This phenotype was able to inhibit *S. aureus*.[79] An additional study demonstrated that EGCG inhibited the primary functions of porin proteins, such as the passive transport of small molecules (glucose), which prevented the growth of *E. Coli*.[80] Grape seed extract reduced the level of autoinducer-2, a signal molecule for quorum sensing, in non-O157 Shiga toxin-producing *E. coli* effectively even at the concentration of 0.5 mg/mL. The main polyphenols in the grape seed extract are flavonols and proanthocyanidins.[81]

All previous research relied on 16S sequencing to investigate microbiome composition in the gut because it is more cost-effective than metagenomics sequencing. However, 16S sequencing identifies only bacteria, not viruses or fungi, which also

contribute to IBD development. Shotgun metagenomics sequencing is needed to overcome the drawbacks of 16S sequencing and provide information about the functions of an organism in the microbiome.

6. Polyphenols and gut barrier

Studies found that polyphenols have beneficial effects on the gut barrier, which is formed by epithelial cells lining the gut lumen. These cells are held together by tight junction assembles consisting of ZO, occludin, and claudins. Gut barrier junction is affected by protein expression of tight junction proteins and distribution of these proteins between cell membrane and cytoplasm. IL-10 deficient mice spontaneously develop colitis, which is associated with gut barrier dysfunction. Grape seed extract at a proportion of 1% in the diet increased barrier-forming claudin-1 protein expression in the ileum but reduced pore-forming claudin-2 protein expression.[34] Adding 0.1%(w/v) of grape seed extracts in drinking water for 12 weeks was also found to protect gut barrier function in IL-10 deficient mice and their bioactivity was possibly obtained *via* inhibiting Wnt/β-catenin pathway.[82] Male Sprague-Dawley rats were gavaged with grape seed extracts containing 89% proanthocyanidins (100 mg/kg daily) for seven days before colon hyperpermeability and inflammation was induced by water avoidance stress in the next three days. Grape seed extract significantly reduced colonic permeability, colonic levels of IL-6 and IL-1β, and TLR4 expression compared with the vehicle. These were accompanied by decreased relative expression of claudin-2 and increased expression of claudin-7, which are key proteins in the colon tight junction complex. IL-6 and IL-1β (10 ng/mL) increased permeability and induced inflammation in Caco-2 monolayers. Treating monolayers with 3 μg/mL grape seed extract for 72 hours preserved

permeability and increased claudin-2 expression but reduced the expression of claudin-3 and claudin-7.[83]

In vitro studies found that mycotoxin deoxynivalenol at 4 μM impaired barrier function of Caco-2 monolayers and caused the translocation of *E. coli* through the monolayers. Treating monolayers with 50 μM resveratrol for 12 hours decreased paracellular permeability of the monolayers and prevented the translocation of *E. coli*. This was associated with the upregulation of protein expression of claudin-4 in the tight junction.[84] Treating Caco-2 monolayers with 7.5% ethanol for 1 hour caused the redistribution of ZO-1, claudin-4, and occludin proteins from cell membrane to cytoplasm. Pretreatment of monolayers by citrus peel flavanols prevented such redistribution as indicated by immunostaining.[85] The ZO-1 proteins in the Caco-2 monolayers were redistributed from membrane to cytoplasm after incubation with 0.2 mM deoxycholic for 6 h. Pretreating the monolayers with 10 μM of procyanidin hexamers for 30 min retained ZO-1 protein on the cell membrane.[86] Another *in vitro* study showed that red wine extracts at 600 μg/mL enhanced the expression of tight junction proteins including occludin, claudin-5, and ZO-1, and decreased the intestinal permeability in HT-29 intestinal epithelial cells treated by a mixture of pro-inflammatory cytokines (20 ng/mL TNF-α, 10 ng/mL IL-1 and 50 ng/mL INF-γ).[38]

Although polyphenols, their microbial metabolites, and butyrate co-exist in the colon, it is unknown if there are syngenetic interactions among them for reducing inflammation and protecting the gut barrier.

7. The interaction of polyphenols and gut microbiota in IBD

Increasing number of studies have demonstrated that alleviation of IBD symptoms by polyphenols was associated with modulation of gut microbiota. **Table 1** summarizes the functions and changes of gut microbiota and their interactions with dietary polyphenols in the alleviation of IBD.

In a rodent study, male Sprague-Dawley rats were treated with 3% DSS water for 48 h every two weeks for three times. The rat diets contained 6% fiber from cellulose, or 6% fiber from different types of sorghum bran, Black (containing 3-deoxyanthocyanins), Sumac (containing condensed tannins), or Hi Tannin black (containing both 3-deoxyanthocyanins and condensed tannins). The results indicated that rats fed the diets containing 3-deoxyanthocyanins or condensed tannins increased the abundance and diversity of *Bacteroides* and *Lactobacillus*. Rats fed diets containing sorghum bran had a reduced abundance of *Proteobacteria,* a phylum that mainly consists of pathogenic bacteria such as *Salmonella* and *Escherichia*.[87] In another study, 5 groups of male Sprague-Dawley rats were given 2% DSS in drinking water for 5 days, and four groups of the DSS-treated rats were gavaged with sugars (19.2 g/kg BW), honey (25 g/kg), honey polyphenols (10.5 mg/kg), and sulfasalazine respectively twice a day for 7 days. It has been found that honey polyphenols downregulated the expression of genes related to inflammation, IL-6, TNF-α, and IL-1β in male rats with DSS-induced colitis. ACE (abundance-based coverage estimator), diversity index of gut microbiota, was significantly increased in honey treated groups compared to the only DSS-treated rats. Honey polyphenols inhibited the growth of *Corynebacterium*, *Bacteroides*, and *Proteus*. There was a positive correlation between the decreased inflammatory gene expressions and supplementation of honey polyphenols as well as the key strains of gut flora,

including *Treponema* and *Bacteroides*.[88] The anthocyanin-rich jaboticaba extract was found to perform better than mesalazine, a medicine for IBD treatment, to enhance the growth of *Lactobacillus* and *Bifidobacterium* and the synthesis of SFCA in TNBS-treated rats.[32] In another rodent study, mice were fed a diet containing 1% freeze-dried tomato powder for 14 days and then provided with drinking water containing 1% DSS for 14 days. It was found that the tomato powder contained anthocyanins, stilbenoids or flavonols. The supplementation of bronze tomatoes prevented the weight loss and the increase of disease activity index induced by DSS. Moreover, regarding the gut microbiome, mice fed a diet containing bronze tomato had a significantly higher abundance of *Lactobacillus* from *Firmicutes* phylum and *Parabacteroides* from *Bacteroidetes* phylum, and a decreased abundance of *Blautia* and *Oscillospira* from *Firmicutes* phylum compared to DSS-treated mice with control diet.[89]

Most polyphenols have low absorption rates in small intestine and are degraded by microbiota in the colon to microbial metabolites which often have much higher bioavailability than their precursors. Some polyphenol microbial metabolites have been shown to be effective in treating IBD. Male Fischer 344 rats were treated with 4% DSS water for 4 days to induce colitis before they were given a diet supplemented with hydrocaffeic acid with a dose of 50 mg/kg/day for 18 days. Hydrocaffeic acid is a major gut microbial metabolite of caffeic acid and chlorogenic acid in colon. Results indicated that hydrocaffeic acid attenuated the colitis by reducing the expression of inflammatory cytokines including TNF-α and IL-8.[90] In another study, urolithin A, a gut microbial metabolite of ellagic acid, upregulated tight junction proteins in HT-29 cells.[71] The 3, 4-dihydroxyphenylpropionic acid and 3, 4-dihydroxyphenylacetic acid are microbial

metabolites of many polyphenols. At a concentration of 1 μM, these metabolites significantly decreased the secretion of pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 in LPS-stimulated peripheral blood mononuclear cells obtained from healthy people, suggesting their usefulness to alleviate IBD.[91] These studies provided valuable information on the bioactivities of polyphenol microbial metabolites for the treatment of IBD. Within the *Firmicutes* phylum, *Eubacterium* and *Clostridium* are the main genera with capacities to catabolize flavonols, flavanones, and flavan-3-ols. A series of genera are responsible for the metabolism of isoflavone, such as *Bacteroide*, *Lactobacillus*, *Enterococcus* and etc.[92]

Fecal microbial transplant has drawn much attention in recent years for the treatment of IBD. In one study, nine CD patients with different degrees of colitis symptoms received fecal microbial transplants *via* nasogastric tube. This transplant led to alleviation of symptoms in most of the colitis patients.[93] However, a different trial found that there was no significant improvement after fecal microbial transplant for UC patients.[94] Alrafas et. al. conducted a study combining resveratrol and fecal transplantation on BALB/c mice with TNBS-induced colitis. They found that resveratrol (100 mg/kg by gavage for 5 days) decreased the T-cell subsets related to inflammation and improved anti-inflammatory Tregs.[42] Resveratrol was reported to decrease the production of reactive oxygen species, inhibit NF-κB pathway, and preserve gut barrier function.[43] Moreover, colitis mice that received feces from resveratrol-treated mice had lower levels of inflammatory cytokines including serum amyloid A, lipocalin-2, and myeloid peroxidase. H&E staining results showed that the mice that received fecal transplant had no symptoms of tissue damage or cellular infiltration, indicating that the

gut microbiota from resveratrol treated mice had a protective effect in mice with TNBS-induced colitis. This study also demonstrated that resveratrol increased the abundance of a bacterium classified as *Ruminococcus* from *Firmicutes,* which was considered to have anti-inflammatory properties by maintaining the integrity and function of the gut.[42]

8. Conclusions and future research directions

Gut microbiota metabolize dietary polyphenols into microbial metabolites, which often have increased absorption rate and bioactivity than their precursor polyphenols. Reciprocally, polyphenols increase the diversity of gut microbiota, stimulate the beneficial microbiota, and retard the pathogenic strains in most cases. Such interactions between polyphenols and gut microbiota collectively and synergistically contribute to the alleviation and mitigation of IBDs. The benefits of polyphenols for IBD alleviation result from combined activities of precursor compounds, microbial metabolites, and improvements of the gut microbiome.

Despite significant progress, several gaps need to be addressed in future research about polyphenols, gut microbiota, and IBD. Current findings suggest that gut microbiome catabolize polyphenols to numerous metabolites with diverse structures. The known metabolites are likely a small subset of all microbial metabolites. Many unknown metabolites remain to be discovered by future studies. Untargeted metabolomics can be a powerful tool to discover new metabolites of polyphenols from either anaerobic fermentation or feeding studies. Dietary polyphenols increase the levels of many microbial metabolites which are associated with complex changes of gut microbiome. It is important to correlate specific gut microbes with a microbial metabolite

in order to elucidate their interactions and mechanisms. This will require an integrated analysis of metabolomics data and microbiome data.

Previous studies using rodents with intact gut microbiota were unable to dissect the role of gut microbiota and polyphenols microbial metabolites in IBD mitigation. A recent study using germ-free mice found that the reduction of colitis severity by some diets are microbiota-dependent whereas others had microbiota-independent activities.[95] The use of germ-free mice in the future will help us to dissect the function of polyphenols and gut microbiota. Future studies are needed to investigate the efficacy of polyphenols on CD because nearly all previous studies have focused on UC. Lastly, the safe and effective dose of polyphenols in IBD patients should be defined in future human intervention studies. A high dose of polyphenols may adversely affect gut microbiota and alter the efficacy of drugs for IBD treatment. A better understanding on the synergistic interactions between polyphenols and gut microbiota will help to devise more effective strategies for IBD intervention in the future.

Conflicts of interest

There are no conflicts of interest to declare.

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Figure Captions

Figure 1 Microbial catabolism of dietary polyphenols, phase II metabolism and tranport of absorbed microbial metabolites in human. A majority of polyhenols are not absorbed in the small intestine. They are hydrolyzed, demethylated, decarboxylated, dehydroxylated, and ring fissioned by microbiota in colon to produce numerous microbial metabolites. These microbial metabolites undergo phase II metabolism in colon and liver. Part of phase II metabolites re-enter small intestine *via* bibliary excretion. Other metabolites enter systemic circulation to exhibit their biological effects in various organs and tissue. Unabsorbed polyphenols and microbial metabolites are excreted in feces whereas absorbed micrbioal metabolites are mostly excreted in the urine.

Figure 2 Microbial catabolism of dietary polyphenols by microbiota in colon using malvidin-3-glucoside, epicatechin gallate, and ellagic acids as examples. (A) Malvidin-3-glucoside is deglycosylated to malvidin. The C-ring fission of malvidin gives rise to syringic acid. Gallic acid is formed after *O*-demethylation of syringic acid. (B) Epicatechin gallate is hydrolyzed to gallic acid and epicatechin. Gallic acid is further decarboxylated to pyrogallol. The C-ring fission of epicatechin yields to diphenylpropan-2-diol which is further degraded to 5-(3',4'-dihydroxyphenyl)-γ-valerolactone. (C) Ring-fission and decarboxylation of ellagic acid yield urolithin D, which loses 1, 2, and 3 hydroxyl groups to form urolinthin C, A, and B, respectively.

Figure 1

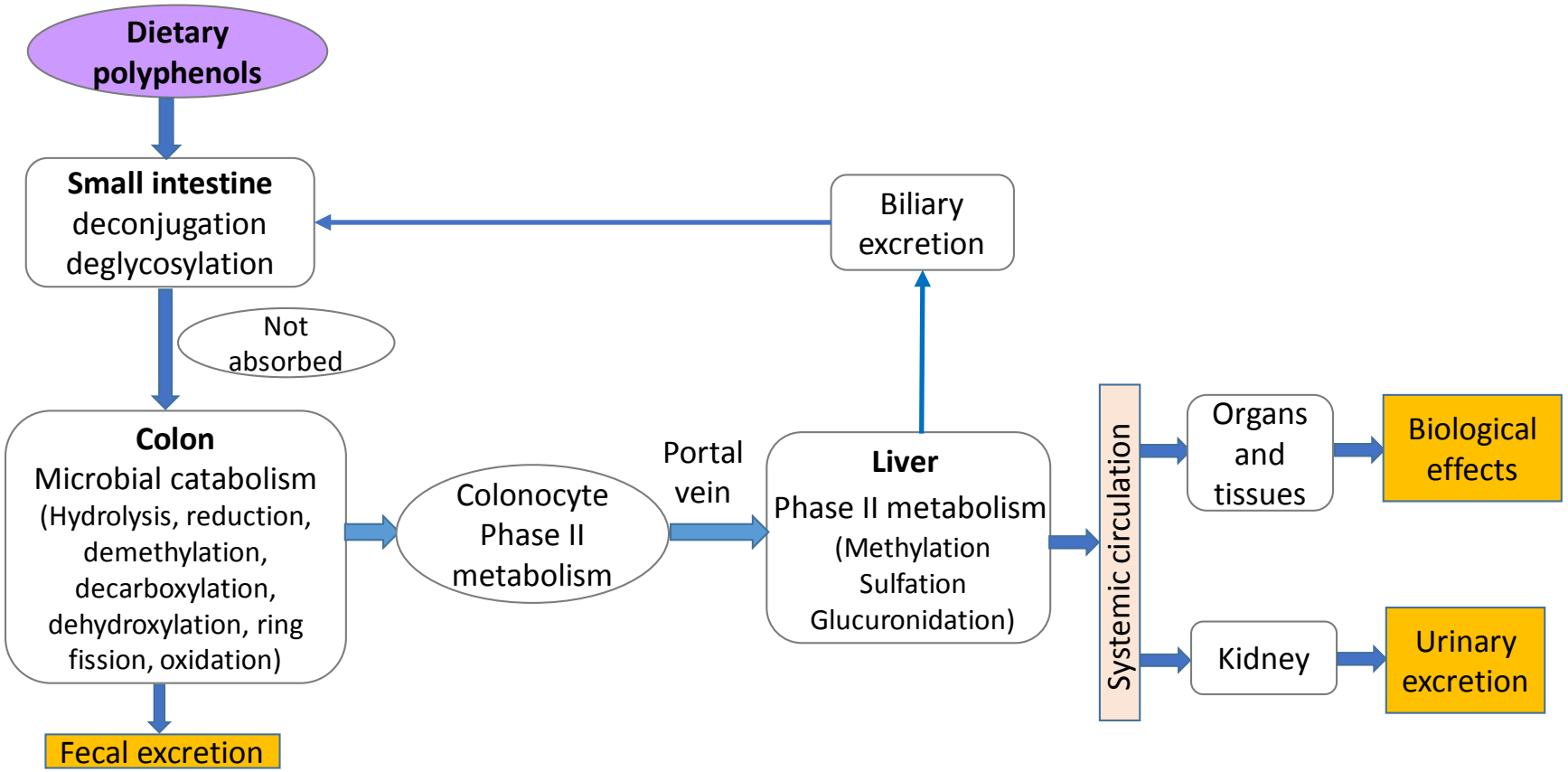

Dietary polyphenols
Small intestine
deconjugation
deglycosylation
Biliary excretion
Not absorbed
Colon
Microbial catabolism
(Hydrolysis, reduction, demethylation, decarboxylation, dehydroxylation, ring fission, oxidation)
Fecal excretion
Colonocyte Phase II metabolism
Portal vein
Liver
Phase II metabolism
(Methylation
Sulfation
Glucuronidation)
Systemic circulation
Organs and tissues
Biological effects
Kidney
Urinary excretion

Figure 2

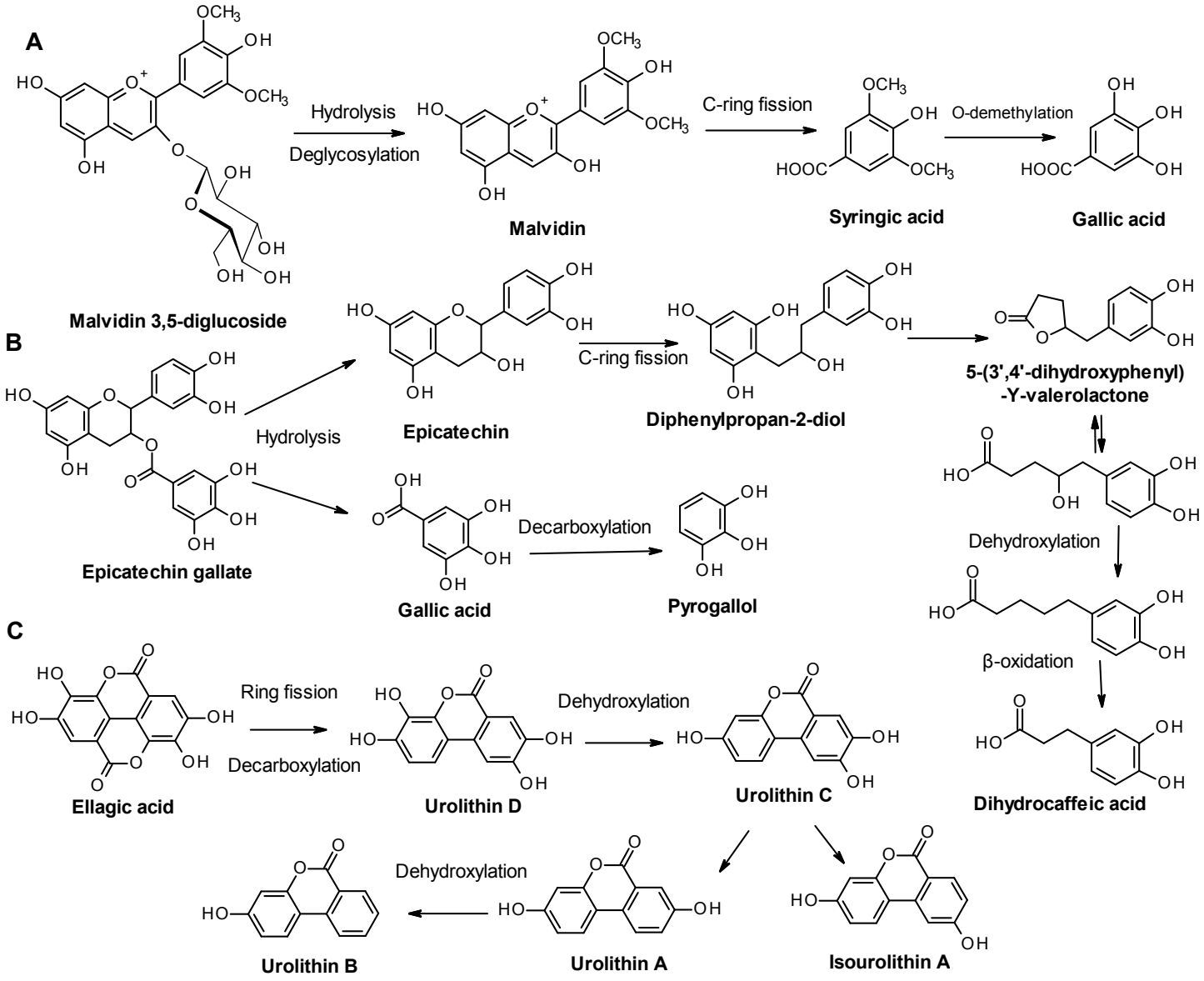
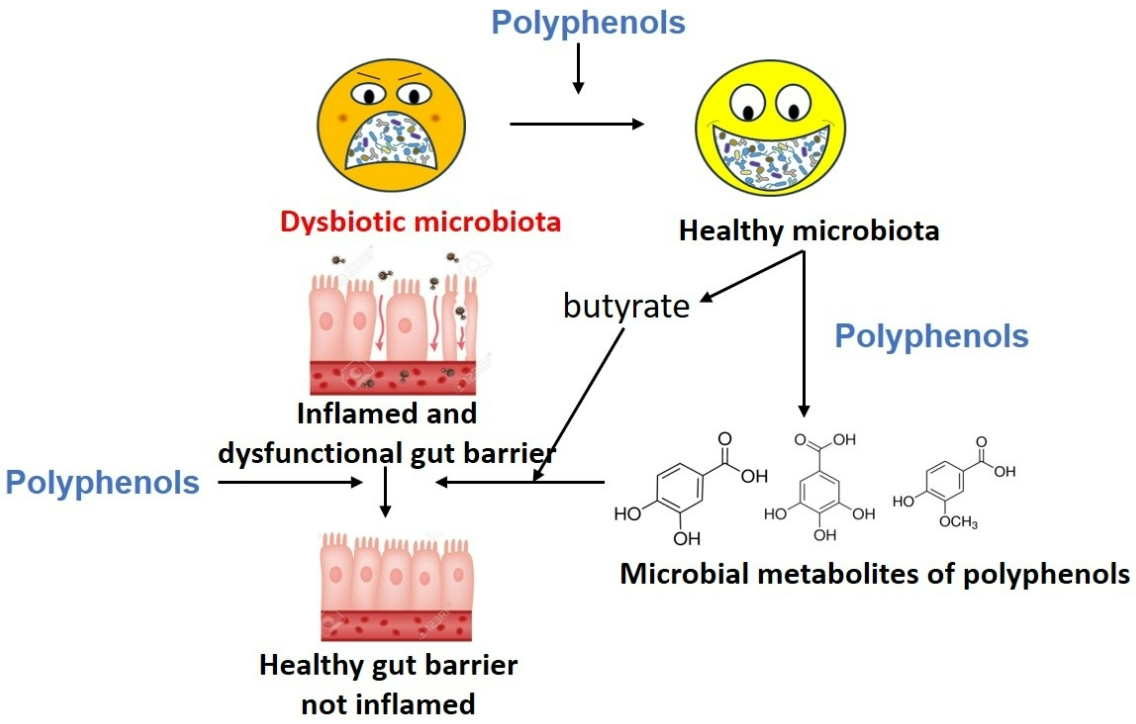

A
Malvidin 3,5-diglucoside
Hydrolysis
Deglycosylation
Malvidin
C-ring fission
Syringic acid
O-demethylation
Gallic acid
B
Epicatechin gallate
Hydrolysis
Epicatechin
C-ring fission
Diphenylpropan-2-diol
5-(3',4'-dihydroxyphenyl)
-Y-valerolactone
Gallic acid
Decarboxylation
Pyrogallol
Dehydroxylation
β-oxidation
Dihydrocaffeic acid
C
Ellagic acid
Ring fission
Decarboxylation
Urolithin D
Dehydroxylation
Urolithin C
Dehydroxylation
Urolithin B
Urolithin A
Isourolithin A

Table 1. The changes of IBD-related gut microbes by dietary polyphenols or polyphenol-rich foods in human and animals**.**

Altered gut microbes	Main functions	Change of relative abundance	Type of study, subjects, and length of study	Polyphenols or foods, and dose	References
Human interventions					
Bifidobacteria, Lactobacillus, Faecalibacterium prausnitzii	Produce SCFA, protect intestinal barrier	Increase	Randomized cross-over human intervention, obesity people, 30 days	Red wine polyphenols, 272 mL/day	96
Enterobacter cloacae	Produce lipopolysaccharides	Decrease	Randomized cross-over human intervention, obesity people, 30 days	Red wine polyphenols, 272 mL/day	96
Butyricicoccus, Odoribacter, Butyricimonas	Protect intestinal barrier	Increase	Randomized cross-over human intervention, obesity people, 3 weeks	Pomegranate extract, 450 mg/day or 1.8 g/day	56
Parvimonas, Methanobrevibacter, Methanosphaera	Pro-inflammatory	Decrease	Randomized cross-over human intervention, obesity people, 3 weeks	Pomegranate extract, 450 mg/day or 1.8 g/day	56
Faecalibacterium prausnitzii	Butyrate production, anti-inflammatory, block NF-kB activation	Increase	Randomized cross-over human intervention, healthy and constipated participants, 4 weeks	Kiwifruits, 2400 mg or 600 mg/day	97
Roseburia intestinalis	Butyrate production, inhibit interleukin-17 excretion	Increase	Randomized, crossover human intervention, 3 weeks, healthy people	Walnuts, 45 g/day	98
Animal studies					
Lactobacillus	Produce SCFA, protect intestinal barrier	Increase	IL-10 (-/-) mice, 16 weeks	grape seed extracts, 1% (w/w)	34
Bacteroides	Interact with T regulatory cells and macrophages,	Increase	IL-10 (-/-) mice, 16 weeks	grape seed extracts, 1% (w/w)	34

	stimulate anti-inflammatory IL-10 production				
Clostridium perfringens	Release enterotoxin, associate with diarrhea	Decease	Mdr1a (-/-) mice, 21 weeks	Dry blueberries, 10% (w/w)	33
Enterococcus faecalis	Associated with increased Crohn disease activity index and fecal calprotectin level	Decease	Mdr1a (-/-) mice, 21 weeks	Dry blueberries, 10% (w/w)	33
Escherichia coli	Colonize the mucosa, produce toxin	Decease	Mdr1a (-/-) mice, 21 weeks	Dry blueberries, 10% (w/w)	33
Akkermansia municiphila	Degrade mucin	Decreased by diet, increased by polyphenol	High fat/sucrose diet-fed mice, 8 weeks	Polyphenol-rich cranberry extract, 200 mg/kg/day	74
Akkermansia	Facilitate mucin turn over in gut mucosa	Increased by DSS, decreased by wine	DSS-treated mice, 28 days	Dealcoholized muscadine wine, 5.5% (v/w)	76
Coprococcus	Produce butyric and acetic acids	Decreased by DSS, increased by wine	DSS-treated mice, 28 days	Dealcoholized muscadine wine, 5.5% (v/w)	76
Bifidobacterium	Butyrate production, protect intestinal barrier, decrease C-reactive protein	Increase	TNBS-treated rats, 2 weeks, or 6 weeks	Brazilian Berry extract, 50 g/L in water	32


Polyphenols
Dysbiotic microbiota
Healthy microbiota
butyrate
Polyphenols
Inflamed and
dysfunctional gut barrier
Polyphenols
Microbial metabolites of polyphenols
Healthy gut barrier
not inflamed