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REVIEW



Dietary polyphenol impact on gut health and microbiota

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ABSTRACT

Polyphenols are naturally occurring compounds in plants and they are the most abundant antioxidants in the human diet. Due to their considerable structural diversity, this largely influences their bioavailability. Since a large proportion of polyphenols remains unabsorbed along the gastrointestinal tract, they may accumulate in the large intestine, where most of them are extensively metabolized by the intestinal microbiota. The formation of bioactive polyphenol-derived metabolites may also benefit the health status of the subjects, although the mechanisms have not been delineated. This review aims to highlight the impact of polyphenols on gut health and the modes of action could be through modulation of intestinal barrier function, innate and adaptive immune response, signaling pathways, as well as the ability to modify gut microbiota composition. The review will conclude by presenting future perspective and challenges of polyphenols application in food products to be used for preventing or treating diseases.

KEYWORDS

Bioavailability; biotransformation; gut health; gut microbiota; metabolism; polyphenols



Introduction

Polyphenols are the most common plant-derived bioactive components in our diet. They are widely present in a variety of foods such as fruits, vegetables, cereals, tea, coffee and wine. More than 8000 polyphenols have been identified so far and they are categorized according to the nature of their carbon skeleton: phenolic acids, flavonoids, stilbenes and lignans (Guo, Kong, and Meydani 2009). Intake of polyphenols varies by geography, possibly due to the different diet habits, as demonstrated in a number of studies (Taguchi et al. 2017; Zamora-Ros et al. 2016). The average dietary intake of polyphenols is speculated to be about 1 g/day (Scalbert and Williamson 2000). It has been estimated that most of the total polyphenol intake remained unabsorbed in the small intestine. Unabsorbed polyphenols (90–95% of total polyphenol intake) may accumulate in the large intestine up to the millimolar range, where most of them are extensively metabolized by the intestinal microbiota (Cardona et al. 2013; Clifford 2004). The colonic microbiota therefore play an important role in the extensive breakdown of the original polyphenolic structures into a series of low-molecular-weight polyphenolic metabolites that can be readily absorbed and confer health benefits (Cardona et al. 2013). Apart from inter-individual variation in daily intake of polyphenols, inter-individual variation in gut microbiota may lead to differences in bioavailability and bioefficacy of polyphenols and their metabolites. During the last decade, there is a growing body of in vitro and in vivo evidence supporting the health-promoting effects of polyphenols, including anti-inflammatory, antioxidant,

anti-microbial, anti-carcinogenic, anti-adipogenic, anti-diabetic, cardio- and neuro-protective activities (Coates et al. 2007; Mandel and Youdim 2004; Middleton, Kandaswami, and Theoharides 2000; Pandey and Rizvi 2009; Sabu, Smitha, and Kuttan 2002; Tipoe et al. 2007; Umeno et al. 2016). The formation of bioactive polyphenol-derived metabolites and the modulation of colonic microbiota may both contribute to host health benefits, although the mechanisms have not been delineated. This review aims to highlight the impact of polyphenols on gut health, and the modes of action could be through modulation of intestinal barrier function, innate and adaptive immune response, signaling pathways, as well as the ability to modify gut microbiota composition (Figure 1).

Polyphenols on intestinal barrier function

Intestinal epithelial barriers are important for normal physiological functions; compromised barriers allow the entry of antigens (bacteria or toxins) and can induce inflammatory diseases. This barrier is maintained by tight junctions, adhering junction and desmosomes, which form a continuous permeability barrier surrounding the apical region of intestinal epithelial cells (IECs) (Gumbiner 1993). The trans-epithelial electrical resistance (TEER) of cell monolayers can be considered as a convenient and sensitive method to check for confluence and barrier integrity of an epithelial cell monolayer. TEER reflects the degree to which small charged particles (mainly ions) passively traverse the cell monolayer, either by transcellular or paracellular routes

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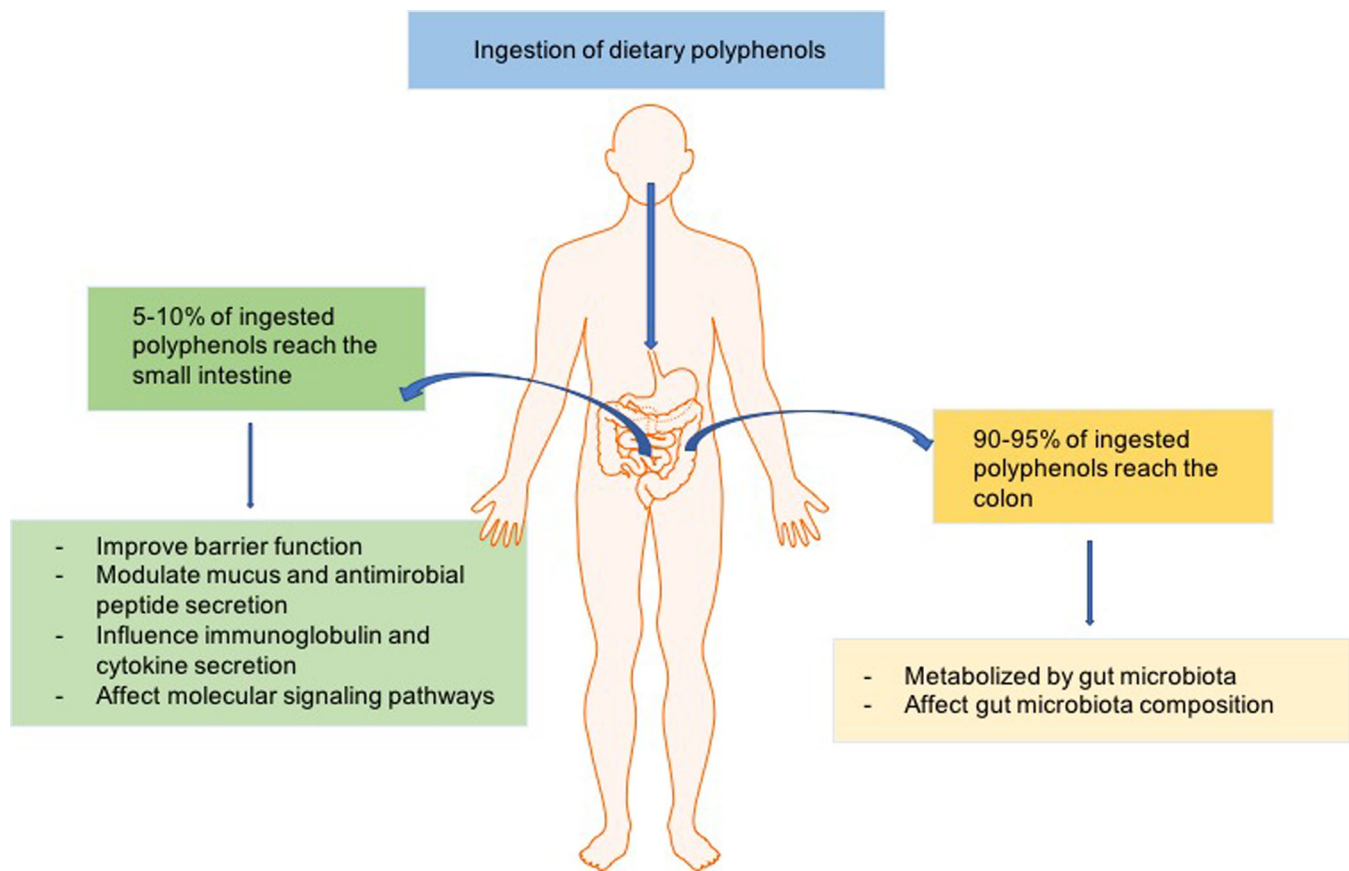


Figure 1. The impact of polyphenols on gut health and the possible modes of action.

(Madara and Trier 1994). However, the TEER measurement indeed reflects mainly the resistance across tight junctions (paracellular) instead of cell membrane (transcellular) (Madara 1983). A review article published in 2011 documented that only four flavonoids had been assessed for the protective effects on intestinal tight junctions (Suzuki and Hara 2011). On top of that, there are several other studies that have reported the effects of polyphenols on intestinal tight junctions and have been summarized previously (for review, refer to (Wan, Ling, and El-Nezami 2018)). Some of these common polyphenols, including quercetin, epigallocatechin gallate (EGCG), genistein, resveratrol, exhibit protective effects on intestinal tight junction barrier functions by increasing TEER through modulation of tight junction protein expression and/or distribution (Amasheh et al. 2012; Amasheh et al. 2008; Cao et al. 2013; Carrasco-Pozo, Morales, and Gotteland 2013; Gu et al. 2011; Ling et al. 2016; Suzuki and Hara 2009). This can prevent subsequent translocation of luminal antigens via the mucosa to the whole body, which can destroy the gut mucosal homeostasis accompanied by an increase in susceptibility to systemic infection, chronic inflammation and malabsorption (Awad, Hess, and Hess 2017).

Polyphenols on innate and adaptive immune responses

Modulation of mucus layer

The luminal surface of the gastrointestinal tract is covered by a mucus gel layer that acts to protect gut epithelial cells

from the harsh luminal environment. Mucin glycoproteins (mucins) are major macromolecular components of epithelial mucus layer overlying the intestinal epithelium. Mucin forms a physiochemical barrier, which protects epithelial cells from chemical, enzymatic, mechanical and microbial damage, and limits microbial adherence and subsequent invasion (Linden et al. 2008). In the gastrointestinal tract, there are two distinctive types of mucins: secreted gel forming mucins and cell-surface mucins (Lindén, Florin, and McGuckin 2008). The gel forming mucins, mainly MUC2 secreted by the goblet cells, are the main components forming the highly viscous mucus layer; while the cell-surface mucins, such as MUC1, MUC3A/B, MUC4 and MUC12, are produced by and present on the apical membranes of all IECs. Cell-surface mucins are dominating constituents of the glycocalyx, limiting harmful molecules from accessing the cell surface (Kim and Ho 2010; Linden et al. 2008). It is expected that polyphenols can modulate the barrier properties of mucus, nutrient absorption through mucus and the viscoelastic microenvironments of intestinal bacteria (Georgiades et al. 2014). There are only two studies regarding the effects of polyphenols on intestinal mucus production. Martin et al. (2004) and Rosillo et al. (2011) reported that ellagic acid (EA) and resveratrol increased mucus production in goblet cells in colon mucosa of a rat model of Crohn's disease. Furthermore, there are also a limited number of studies related to the interaction of polyphenols with the mucus layer. Georgiades et al. (2014) have demonstrated that both naturally derived purified polyphenols, and green

Table 1. Interaction of polyphenols with the mucus gel layer, in vitro, ex vivo & in vivo.

Polyphenols (Dosages)	Cells/Models (Stimulants, if any)	Effects/Key findings	Refs.
Resveratrol (5–10 mg/kg/day)	Rat model of Crohn's disease (induced by TNBS)	• Resveratrol increased mucus production in goblet cells in colon mucosa.	(Martin et al. 2004)
Ellagic acid (EA) (10–20 mg/kg)	Rat model of Crohn's disease (induced by TNBS)	• EA increased mucus production in goblet cells in colon mucosa.	(Rosillo et al. 2011)
Epigallocatechin gallate (EGCG) (400, 4000 μ M) Epicatechin (EC) (400, 4000 μ M)	HT29 and HT29-MTX-E12	• The mucus layer on HT29-MTX-E12 protected the cells against EGCG toxicity. • EC had no effect on HT29 and HT29-MTX-E12 cell viability, which may be attributed to the binding of proteins within the mucus gel layer to the galloyl ring of EGCG.	(D'Agostino et al. 2012)
EC, EGCG, black and green tea extracts and EGCG-rich green tea extract	Isolated porcine gastric and duodenal mucins as model for GI mucus	• EGCG has the highest affinity to interact with mucins, causing precipitation and gelation, whereas EC and non-galloylated ECs do not.	(Georgiades et al. 2014)

and black tea extracts can act as cross-linkers for purified gastrointestinal (GI) mucin derived from the stomach and the duodenum, which could affect the mucus layer's viscoelasticity. This could act as a selective barrier for nutrients and potentially help in defense against pathogens. D'Agostino et al. (2012) revealed that the mucus layer on HT29-MTX-E12 human colonic adenocarcinoma cells probably protected the cells against Epigallocatechin gallate (EGCG) toxicity. Epicatechin (EC) had no effect on HT29 and HT29-MTX-E12 cell viability, which may be attributed to the binding of proteins within the mucus gel layer to the galloyl ring of EGCG. Table 1 summarizes the results and details of the listed references.

Antimicrobial peptide secretion

Another mechanism of mucosal defense is the secretion of antimicrobial peptides, also known as host defense peptides, peptide antibiotics or natural antibiotics. Antimicrobial peptides play a significant role in innate immunity, having both antimicrobial and immunomodulatory activities. Currently, over 400 antimicrobial peptides have been identified in plants and animals. Antimicrobial peptides are produced by cells in the immune system and along the mucosal epithelia (Zhang, Ross, and Blecha 2000). Most antimicrobial peptides act by disrupting the integrity of the microbial cell membranes physically through peptide-lipid interactions, rather than specific receptor-mediated recognition processes, and as a result, they function as a broad-spectrum antimicrobial agent against different pathogens, including bacteria, fungi, yeasts and viruses (Smet and Contreras 2005; Zhang, Ross, and Blecha 2000). In human intestine, two types of antimicrobial peptides are present: defensins (cryptidins) and cathelicidin (Smet and Contreras 2005).

Defensins are further classified into two groups: α -defensins and β -defensins. α -defensins have only been identified in humans, monkeys and rodents, which are expressed in different cell types, including granule-containing granulocytic leukocytes and intestinal paneth cells (Patil, Hughes, and Zhang 2004). β -defensins, on the other hand, are mainly expressed in epithelial cells of organs exposed to the external environment, such as the skin, gastrointestinal tract, and respiratory tract (Veldhuizen et al. 2006). In humans,

there are three enteric β -defensins, human β -defensin-1 (hBD-1), hBD-2 and hBD-3, expressed by different IECs (Smet and Contreras 2005). Studies found that hBD-1 is constitutively expressed, while hBD-2 and hBD-3 are mostly expressed in response to infection and inflammation, particularly in ulcerative colitis and Crohn's disease (Fahlgren et al. 2003; Wehkamp et al. 2002; Wehkamp et al. 2003). Antimicrobial peptides play a pivotal role in modulating the crosstalk between microbe and host cells, thereby maintaining intestinal microbiotic homeostasis (Veldhuizen et al. 2007). They also exhibit immuno-modulatory activities, through modulation of innate and adaptive immunity. These include: enhancement of phagocytosis, promotion of neutrophil recruitment, increased pro-inflammatory cytokine production, inhibition of anti-inflammatory mediators, regulation of complement activation, as well as promotion and antigen uptake of dendritic cell maturation (for review, refer to (Yang et al. 2002; Yang, Chertov, and Oppenheim 2001).

A previous study has demonstrated that the antimicrobial activity of antimicrobial peptides, such as β -defensins, may be associated with bacterial populations in the intestine, which naturally present a barrier limiting undesirable gut mucosal infections and preventing bacterial translocation (Veldhuizen et al. 2008). The effects of polyphenols on antimicrobial peptides have been demonstrated in few studies using non-intestinal models. For example, EGCG induced defensin secretion on gingival epithelial cells (Lombardo Bedran et al. 2014). Black tea extract, theaflavin-3,3'-digallate, as well as EGCG were able to increase the secretion of hBD-1, hBD-2 and hBD-4 on oral epithelial cells in another study (Lombardo Bedran et al. 2015). However, the effect of polyphenols on the secretion of intestinal antimicrobial peptides is poorly documented. Recently, Wan et al. (2016) reported that EGCG reduced bacterial translocation across IPEC-J2 cell monolayers by inducing secretion of antimicrobial peptides, porcine β -defensins 1 and 2 (pBD-1 and 2), which possessed higher antimicrobial activity against *Escherichia coli*. Further mechanistic studies demonstrated that EGCG up-regulated pBD-2 but not pBD-1 via the p38 mitogen-activated protein kinase (MAPK)-dependent pathway. This study suggests the potential of certain polyphenols, such as EGCG in modulating the epithelial

Table 2. Polyphenols regulation of immunoglobulin secretion in vivo.

Polyphenols (Dosages)	Cells/ Models (Stimulants, if any)	Effects/ Key findings	Refs.
Curcumin, rutin, D(+)-catechin, ellagic acid and quercetin (0.5% w/w)	Male Sprague Dawley rats fed high- or low-fat diet	<ul style="list-style-type: none"> Only curcumin elevated fecal IgA in rats fed high-fat diet but not those fed low-fat diet 	(Okazaki et al. 2010)
Cocoa containing a total polyphenol content of 10.62 mg/g	Female Wistar rats	<ul style="list-style-type: none"> A continuous and high cocoa-enriched diet decreased sIgA concentration in intestinal wash and fecal samples. Gene expression data showed that cocoa intake reduced IgA and IL-6 in Peyer's patches and mesenteric lymph nodes, whereas in small intestine, cocoa decreased IgA, CCR9, CCL28, PARα and RARβ. Cocoa dietary intervention resulted in a differential TLR pattern and a decrease in the intestinal IgA secretion and IgA-coating bacteria. 	(Massot-Cladera et al. 2012; Pérez-Berezo et al. 2012)
Cocoa flavonoids (0.2% polyphenols from conventional cocoa, 0.4 and 0.8% polyphenols from non-fermented cocoa)	Male Lewis rats	<ul style="list-style-type: none"> All cocoa polyphenol-enriched diets attenuated age-related increases of both fecal IgA and IgA-coated bacteria. 	(Massot-Cladera et al. 2013)
Cranberry proanthocyanins (PACs) (100 mg/kg bw)	Male ICR mice received elemental enteral nutrition (EEN)	<ul style="list-style-type: none"> Addition to PACs to EEN increased luminal sIgA levels compared with EEN alone. 	(Pierre et al. 2014)
Cocoa flavonoids (0.2% polyphenols from conventional defatted cocoa (PC0.2), 0.4 (PC0.4) and 0.8% (PC0.8) polyphenols from non-fermented cocoa)	Female Wistar and Brown Norway rats	<ul style="list-style-type: none"> Significant decrease in serum IgA were found in Brown Norway rats fed with cocoa polyphenol-enriched diet for 3 weeks. All cocoa polyphenol-enriched diets partially but significantly reduced the age-dependent increase in intestinal IgA concentration in Wistar rats after 14 days of supplementation. Fecal IgA was reduced in Wistar rats fed with PC0.2 and PC0.8 diets at the end of the study. 	(Massot-Cladera et al. 2014)
Aronia polyphenol, haskap polyphenol, bilberry polyphenol (anthocyanin content 0.4%)	Sprague Dawley rats fed high- or low-fat diet	<ul style="list-style-type: none"> Dietary polyphenols from aronia, haskap and bilberry markedly elevated the amount of fecal IgA in rats fed high-fat diet. 	(Taira et al. 2015)

immunological barrier function by induction of defensins expression. Further studies are necessary, to provide a better understanding of how these polyphenols exert their protective actions on intestinal epithelial barrier function against bacterial infection, and to explore if other polyphenols exhibit similar properties.

Immunoglobulin secretion

Secretory immunoglobulin A (sIgA) is the most abundant type of immunoglobulin in human intestinal lumen, sIgA displays an array of properties that are crucial to mucosal immunity and homeostasis (Mantis, Rol, and Corthesy 2011). The secretory component protects the sIgA from degradation, withstanding proteolytic and digestive enzymes present in the gut lumen (Phalipon et al. 2002). Unlike other antibodies, such as IgG, that are present in an almost sterile systemic environment, sIgA resides in intestinal lumen heavily infested with microbes. Therefore, sIgA functions very differently from other antibodies, via steric hindrance, receptor blockade, or immune exclusion, resulting in less inflammatory response (Mantis, Rol, and Corthesy 2011).

There is limited information on the effects of polyphenols on systemic and/or intestinal IgA secretion in vivo (Table 2). Most studies focus on the effects of cocoa polyphenols on IgA levels using different experimental designs involving rats. Cocoa polyphenols were shown to reduce the age-dependent increases in serum, intestinal and fecal IgA levels in two studies by Massot-Cladera et al. (2014; 2013). Pérez-Berezo et al. (2012) demonstrated that a continuous and high cocoa-enriched diet decreased sIgA concentration in intestinal wash and fecal samples. Long-term cocoa intake may affect IgA production by down-regulating the gene expression of cytokines, such as IL-6, which is required for the activation of B cells to become IgA-secreting cells in Peyer's patches (PPs) and mesenteric lymph nodes (MLNs), chemokines and chemokine receptors such as CCR9 and CCL28, together with RAR α and RAR β which are involved in the gut homing of IgA-secreting cells. Cocoa intake was also shown to affect the gut microbiota composition in rats and this was related to an altered toll-like receptor (TLR) pattern that could be responsible for the changes observed in the intestinal immune system (Massot-Cladera et al. 2012; Pérez-Berezo et al. 2012).

Furthermore, it has been documented that certain polyphenols could increase the amount of fecal IgA in rats fed high-fat diets. Okazaki et al. (2010) reported that curcumin elevated fecal IgA in rats fed high-fat diet but not those fed low-fat diet. Whereas in another study by Taira et al. (2015), dietary polyphenols from aronia, haskap and bilberry also markedly elevated the amount of fecal IgA in rats fed high-fat diet. These studies suggest that dietary polyphenols may improve intestinal immune function in high-fat-fed animals through elevation in luminal IgA, by increasing IgA production and/or suppressing IgA degradation. This may be associated with changes in the gut microbiota composition.

Modulation of cytokines and chemokines expression and secretion

Cytokines, and also chemokines, are small proteins, which are important mediators that are involved in regulation of a wide range of biological functions, including innate and adaptive immunity, and inflammatory responses. Cytokines can be produced by a broad range of cells, including immune cells such as dendritic cells, macrophages, lymphocytes, but also cells other than immune cells such as intestinal epithelial cells (IECs). Several cytokines, including transforming growth factor alpha (TGF- α), interleukin (IL)-1, IL-6, IL-10, IL-15, IL-18 and granulocyte-macrophage colony-stimulating factor (GM-CSF) are constitutively expressed by the intestinal epithelium for maintenance of epithelial cell growth and homeostasis (Stadnyk 2002), but some cytokines, such as IL-8, monocyte chemotactic protein-1 (MCP-1), GM-CSF, tumor necrosis factor (TNF)- α are markedly up-regulated in response to bacterial infection (Jung et al. 1995). In the case of intestinal inflammation, several cytokines and chemokines were also produced, which include IL-6, IL-8, IL-1 β , and TNF- α . The secretion of these inflammatory cytokines may be an integral part of the immune response, dysregulation of these cytokines balance plays a key role in the pathogenesis of inflammatory bowel diseases (IBDs), encompassing Crohn's disease and ulcerative colitis. Therefore, it is vital to control the secretion of these cytokines for maintenance of intestinal homeostasis (Son, Satsu, and Shimizu 2005).

It is well known that polyphenols have significant anti-inflammatory activity and therefore it is proposed that polyphenols could be used as an alternative natural approach to prevent or treat chronic inflammatory diseases, particularly gastrointestinal diseases. Indeed, numerous studies have shown the effects of polyphenols on intestinal inflammation (Table 3). To mimic intestinal inflammation in vivo, IECs were treated with a cocktail of pro-inflammatory substances, including IL-1 β , TNF- α , IFN- γ and lipopolysaccharides (LPS), which were reported as prominent and synergistic contributors in the development of IBDs (Puleston et al. 2005). The inflammatory state was characterized by an over-expression of mRNA and/or protein levels for pro-inflammatory markers such as IL-6, IL-8, MCP-1, etc. Treatment with polyphenols, for example genistein, ellagic acid, green

tea polyphenols, EGCG, quercetin, cyanidin-3-O-glucoside (C3G), pinoresinol can provoke a decrease in the expression of these cytokines (During et al. 2012; Ferrari et al. 2016; Oz and Ebersole 2010; Romier et al. 2008; Ruiz and Haller 2006; Sergent et al. 2010).

Dextran sulfate sodium (DSS) and 2, 4, 6-trinitrobenzene sulfonic acid (TNBS) have commonly been used to chemically induce colitis in animal models, which displays symptoms similar to those observed in human ulcerative colitis (Okayasu et al. 1990) and Crohn's disease (Antoniou et al. 2016). There are numerous studies reported on the effects of polyphenols against DSS- or TNBS-induced colitis (Table 3). For example, piceatannol (Kim et al. 2008), resveratrol (Martin et al., 2004; Sánchez-Fidalgo et al. 2010; Singh et al. 2010), curcumin (Isabel, Susana, and Alarcón 2011), naringenin (Azuma et al. 2013), ellagic acid (Marín et al. 2013), gallic acid (Pandurangan et al. 2015), thearubigin (Maity et al. 2003) have been shown to alleviate or prevent DSS- or TNBS-induced colitis by suppressing pro-inflammatory cytokines such as IL-1 β , IL-6, IL-8, TNF- α , IFN- γ and sometimes IL-12 p40. These results showed that polyphenols might present an alternative way to improve intestinal inflammation, such as IBD. However, so far, there is no definite mechanism that could explain all polyphenols effects and it is reported that the anti-inflammatory response of polyphenols is dependent on the cell type and is signal specific (Romier et al. 2009; Tunon et al. 2009). Therefore, further investigations are necessary to validate the potential beneficial role of polyphenols and also to understand the underlying mechanisms responsible for modulation of intestinal inflammation.

Polyphenols on molecular signaling

Studies from the last decade have demonstrated that polyphenols are able to confer their anti-oxidative, anti-inflammatory, anti-cancer through modulation of cellular molecular signaling pathways. A notable property of polyphenols is their ability to regulate the redox status in cells (Ramos 2008). Reactive oxidative species (ROS) are by-products of normal cellular metabolism or environmental triggers that are useful for signaling. However, at high levels, ROS can cause oxidative stress and damage DNA, lipids and proteins. Oxidative stress occurs when there is an imbalance between reactive ROS and antioxidants, and it is found in chronic gastrointestinal disorders such as IBD (Liu et al. 2017). Oxidative stress markers are also elevated in various kinds of cancers, including colorectal cancer (CRC) (Liou and Storz 2010). For example, nitric oxide, lipid peroxides, catalase (CAT), glutathione peroxidase (GPx) levels are increased in CRC cells (Haklar et al. 2001; Perše 2013; Rainis et al. 2007). It is suggested that the anti-oxidative properties of polyphenols, which are attributed to their free radical scavenging ability and antioxidant enzyme modulation, could counter oxidative stress to achieve chemoprevention (Link, Balaguer, and Goel 2010; Ross and Kasum 2002). Several dietary polyphenols, including resveratrol, EGCG and curcumin, are found to upregulate NF-E2-related

Table 3. Polyphenols regulation of intestinal cytokine expression and secretion in vitro, in vivo and ex vivo.

Polyphenols (Dosages)	Cells/ Models (Stimulants, if any)	Effects/ Key findings	Refs.
Red wine polyphenol	Zinc-deficient male Sprague-Dawley rats	<ul style="list-style-type: none"> Treatment with red wine polyphenol decreased the expression of zinc deficiency induced pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, cytokine-induced neutrophil chemoattractant (CINC), whereas that of the anti-inflammatory interleukin (IL)-10 in jejunum. 	(Canali et al. 2000)
Green tea polyphenol (5 g/L in water)	IL-2 ^{-/-} C57BL/6J mice	<ul style="list-style-type: none"> Green tea polyphenol-treated mice demonstrated a significant reduction in the spontaneous release of IFN-γ and TNF-α from colon explants and lamina propria lymphocytes. 	(Varilek et al. 2001)
Thearubigin (10–100 mg/kg/day)	Female Balb/c mice with trinitrobenzene sulfonic acid (TNBS)-induced colitis	<ul style="list-style-type: none"> Thearubigin reduced T-helper 1 cytokines (e.g. IFN-γ and IL-12 p40) and induced T-helper 2 cytokine (IL-4) mRNA in colon tissue samples of TNBS-treated mice. 	(Maity et al. 2003)
Resveratrol (5–10 mg/kg/day)	TNBS-induced male Wistar rats	<ul style="list-style-type: none"> Resveratrol reduced mucosal level of IL-1β in colitic rats. 	(Martin et al. 2004)
Green tea extract	Rats with dinitrobenzene sulfonic acid (DNBS) induced colitis	<ul style="list-style-type: none"> Green tea extract attenuated colitis induced by DNBS by a remarkable amelioration of the disruption of the colonic architecture, significant reduction of colonic myeloperoxidase and TNF-α. 	(Mazzon et al. 2005)
Genistein (100 μ mol/L)	TNF and IL-1 β treated Mode-K cells	<ul style="list-style-type: none"> Genistein inhibited TNF and IL-1β induced IL-6 production in cell supernatants. 	(Ruiz and Haller 2006)
Ellagic acid, genistein, EGCG, resveratrol (50 μ mol/L)	IL-1 β -treated Caco-2 cells	<ul style="list-style-type: none"> Ellagic acid, genistein and EGCG decreased IL-1β induced IL-8 secretion Resveratrol increased significantly IL-8 secretion. 	(Romier et al. 2008)
Piceatannol (1, 2.5, 5 or 10 mg/kg bw)	Dextran sulfate sodium (DSS)-induced female Balb/c mice	<ul style="list-style-type: none"> Piceatannol prevented significant increases in IL-1β, IL-6 and TNF-α in colon of DSS-induced mice. 	(Kim et al. 2008)
Apple procyanidins (ACT) (0.0013, 0.0025, 0.005%)	Phorbol 12-myristate 13-acetate (PMA)-induced Caco-2 cells	<ul style="list-style-type: none"> ACT inhibited PMA-induced secretion of IL-8 in cell supernatants. 	(Yoshioka et al. 2008)
Grape seed, cocoa, sugar cane, oak, mangosteen and pomegranate polyphenolic extract (50 μ M of gallic acid equivalent/l)	IL-1 β induced Caco-2 cells	<ul style="list-style-type: none"> Grape seed, sugar cane, oak and pomegranate polyphenolic extract reduced IL-1β induced IL-8 secretion. 	(Romier-Crouzet et al. 2009)
Green tea polyphenols (0.1, 0.25, 0.5 and 1%)	DSS-induced male ICR mice	<ul style="list-style-type: none"> DSS-induced increase in IL-1β and MIF production in colonic mucosa were attenuated by 0.1% green tea polyphenols. The levels of IL-1β were increased by 0.5% and 1% green tea polyphenols treatment groups with DSS-induced colitis. 	(Mihye et al. 2010)
Grifola frondosa water extract (1 g/kg)	Sprague-Dawley rats with TNBS-induced colitis	<ul style="list-style-type: none"> The polyphenol-enriched extract inhibited the TNBS-induced TNF-α expression in the colon tissue. 	(Lee et al. 2010)
Grifola frondosa water extract (10, 50 and 100 μ g/ml)	TNF- α induced HT29 cells	<ul style="list-style-type: none"> The polyphenol-enriched extract inhibited TNF-α induced MCP-1 and IL-8 mRNA and protein levels. 	(Lee et al. 2010)
EGCG and genistein (50 μ M)	Caco-2 cells exposed to a cocktail of IL-1 β , IFN- γ , TNF- α and LPS	<ul style="list-style-type: none"> EGCG reduced significantly the secretion of IL-6 and IL-8, whereas genistein lowered significantly the levels of IL-6 and MCP-1. 	(Sergent et al. 2010)
Resveratrol (10, 50, 100 mg/kg bw)	DSS-induced C57BL/6 mice	<ul style="list-style-type: none"> Resveratrol decreased IFN-γ, TNF-α, IL-6 and IL-1β in serum of mice with acute colitis. 	(Singh et al. 2010)
Resveratrol (3 mg/kg bw)	DSS-induced female C57BL/6 mice	<ul style="list-style-type: none"> Resveratrol reduced DSS-induced increase in TNF-α and IL-1β, and caused a reduction in IL-10 in colon tissues. 	(Sánchez-Fidalgo et al. 2010)
Ellagic acid (60 mg/kg bw)	1,2-Dimethylhydrazine-induced male Wistar albino rats	<ul style="list-style-type: none"> Ellagic acid reduced the expression of TNF-α and IL-6 in rat colon tissues as confirmed by immunohistochemical, immunoblot and immunofluorescence analysis. 	(Syed and Ganapasam 2010)
Green tea polyphenols (50, 200 and 400 μ g/ml)	TNF- α stimulated IEC-6 cells	<ul style="list-style-type: none"> Green tea polyphenols prevented TNF-α induced IL-8 release in a dose-dependent manner. 	(Oz and Ebersole 2010)

(continued)

Table 3. Continued.

Polyphenols (Dosages)	Cells/ Models (Stimulants, if any)	Effects/ Key findings	Refs.
Kiwifruit extracts	Intestinal epithelial cells isolated from the large intestine of C57BL/6J and IL10 ^{-/-} mice, stimulated by LPS	<ul style="list-style-type: none"> Kiwifruit extracts inhibited LPS-induced IL-6, TNF-α and IFN-γ secretion in culture supernatants. 	(Edmunds et al. 2011)
Curcumin (0.6% diet)	DSS-induced C57BL/6 mice	<ul style="list-style-type: none"> Curcumin resulted in down-regulation of colonic IFN-γ and TNF-α levels. 	(Isabel et al., 2011)
Apple polyphenols	DSS-induced female C57BL/6 mice	<ul style="list-style-type: none"> Apple polyphenols dampened the mRNA expression of IFN-γ, TNF-α, IL-1β, IL-6, IL-17, IL-22, and macrophage inflammatory protein (MIP)-1α in colon tissues. 	(Skyberg et al. 2011)
Apple polyphenol extract	Rats with TNBS-induced colitis	<ul style="list-style-type: none"> Apple extract reduced the TNBS-induced increase in TNF-α mRNA and protein in colon mucosa. 	(D'Argenio et al. 2012)
Quercetin and pinoresinol (50 μ mol/L)	IL-1 β stimulated Caco-2 cells	<ul style="list-style-type: none"> Quercetin decreased IL-1β induced IL-6 and IL-8 levels. Pinoresinol had a significant inhibitory effect on IL-6 secretion. 	(During et al. 2012)
Aqueous cinnamon extract	Freshly isolated intestinal enterocytes	<ul style="list-style-type: none"> Cinnamon extract inhibited the mRNA expression of IL-1β, IL-6 and TNF-α. 	(Qin et al. 2012)
Cocoa polyphenolic extract (10 μ g/ml)	TNF- α stimulated Caco-2 cells	<ul style="list-style-type: none"> Cocoa polyphenolic extract treatment protected TNF-α induced IL-8 secretion. 	(Rodríguez-Ramiro et al. 2013)
Apple peel polyphenols (phenolic acids, flavonol glycosides, flavan-3-ols, procyanidins)	Caco-2/15 cells induced by iron-ascorbate and lipopolysaccharide (LPS)	<ul style="list-style-type: none"> Apple peel polyphenols abolished the increase in TNF-α and IL-6 protein expression induced by iron-ascorbate and LPS. 	(Denis et al. 2013)
Naringenin (0.3% diet)	DSS-induced male Balb/c mice	<ul style="list-style-type: none"> Gene expression of IFN-γ, IL-6, MIP-2 and IL-17A in colons of DSS-induced mice were attenuated by feeding naringenin. 	(Azuma et al. 2013)
Sardinian wine extracts (30 and 60 μ M)	Oxysterol induced Caco-2 cells	<ul style="list-style-type: none"> Sardinian wine extracts reduced oxysterol induced IL-6 and IL-8 protein levels. 	(Biasi et al. 2013)
Ellagic acid (2%)	DSS-induced female Balb/c and C57BL/6 mice	<ul style="list-style-type: none"> Ellagic acid inhibited DSS-induced TNF-α, IL6 and IFN-γ protein levels in the colon. 	(Marín et al. 2013)
Red wine extract (100, 200, 400 and 600 μ g/ml)	HT29 cells stimulated with TNF- α , IL-1 and IFN- γ	<ul style="list-style-type: none"> Red wine extract partially suppressed cytokines-induced IL-8 production. 	(Nunes et al. 2013)
Cyanidin-3-glucoside (25 μ M)	HT29 cells	<ul style="list-style-type: none"> Cyanidin-3-glucoside inhibited IL-8 production by cells induced by cytokines (IL-1α, TNF-α and IFN-γ). 	(Serra et al. 2013)
Grape marc meal extract (GSGME) or spent hops (SH) (Total polyphenol content 8.5% and ~5% for GSGME and SH, respectively)	Weaned pigs	<ul style="list-style-type: none"> GSGME reduced mRNA of intercellular adhesion molecule (ICAM-1) and IL-8 in duodenum, ICAM-1, IL-1β, IL-8 and TNF-α in both ileum and colon. SH lowered mRNA of IL-1β and IL-8 in duodenum and ileum, and of IL-1β and TNF-α in colon. 	(Fiesel et al. 2014)
Chlorogenic acid (20 and 50 mg/kg)	LPS challenged Sprague-Dawley rats	<ul style="list-style-type: none"> Chlorogenic acid significantly reduced concentrations of TNF-α and IFN-γ in jejunum and colon of weaned rats. Only chlorogenic acid at 50 mg/kg affected the concentration of IL-10 in the jejunum. 	(Ruan et al. 2014)
Green tea, cocoa and red wine polyphenols (50 μ M total polyphenols, calculated as GA equivalents)	LPS induced Caco-2 cells	<ul style="list-style-type: none"> Wine and green tea polyphenols reduced basolateral IL-6 secretion from Caco-2 monolayers grown on Transwells and challenged with LPS. 	(Nicod et al. 2014)
Cranberry phenolic compounds (250 μ g/ml)	Caco-2/15 cells induced by iron-ascorbate and LPS	<ul style="list-style-type: none"> Cranberry phenolic compounds were able to significantly decrease TNF-α and IL-6 production. 	(Denis et al. 2015)
Chlorogenic acid (CHA), caffeic acid (CA) and quinic acid (QA) (0.5–2 mmol/L)	TNF- α and H ₂ O ₂ -induced Caco-2 cells	<ul style="list-style-type: none"> CHA and CA significantly inhibited TNF-α and H₂O₂-induced IL-8 secretion, but not for QA. 	(Shin et al. 2015)
Chlorogenic acid (CHA) and caffeic acid (CA) (354 mg/kg for CHA, 180 mg/kg for CA)	DSS-induced female C57BL/6 mice	<ul style="list-style-type: none"> CHA significantly reduced colonic mRNA levels of macrophage inflammatory protein (MIP)–2 and IL-1β. CA inhibited only IL-1β mRNA expression induced by DSS. 	(Shin et al. 2015)
Gallic acid (10 mg/kg bw)	DSS-induced male Balb/c mice	<ul style="list-style-type: none"> Gallic acid attenuated mRNA expression levels of TNF-α, IL-1β, IFN-γ, IL-6, and IL-17 in colon. 	(Pandurangan et al. 2015)
Tea polyphenols (0.03, 0.06 and 0.09 g/kg bw)	Broiler chickens	<ul style="list-style-type: none"> Tea polyphenols reduced intestinal IL-1β, IL-4, IL-6, IL-10 and IFN-γ mRNA expression. 	(Li et al. 2015)

(continued)

Table 3. Continued.

Polyphenols (Dosages)	Cells/ Models (Stimulants, if any)	Effects/ Key findings	Refs.
Red grape pomace extracts (Total phenolic content 1.16 mg/g diet)	DSS-induced male Wistar rats	<ul style="list-style-type: none"> Red grape pomace extracts abolished the colonic increase of IL-1α, IL-6 and IFN-γ and significantly reduced TNF-α levels. 	(Boussenna et al. 2016)
Dried apple peel powder (DAPP) (200 and 400 mg/kg/day)	DSS-induced male C57BL6 mice	<ul style="list-style-type: none"> DAPP significantly suppressed intrinsic TNF-α and IL-6 elevations in DSS-induced mice. 	(Denis et al. 2016)
Cyanidin-3-O-glucoside (C3G) (20 and 40 μ M)	TNF- α induced Caco-2 cells	<ul style="list-style-type: none"> C3G reduced TNF-α induced IL-6 mRNA expression. 	(Ferrari et al. 2016)
Resveratrol (50 μ M)	IPEC-J2 cells stimulated with dexoxynivalenol (DON)	<ul style="list-style-type: none"> Resveratrol reduced DON-induced secretion of IL-6 and IL-8. 	(Ling et al. 2016)
Resveratrol (5 and 20 μ M)	TNF- α stimulated Caco-2 endothelial EA.hy926 coculture	<ul style="list-style-type: none"> Resveratrol significantly reduced the secretion of IL-8 and ICAM-1 in culture media. 	(Toaldo et al. 2016)
Mango polyphenols (include gallic acid and gallotannins)	DSS-induced male Sprague-Dawley rats	<ul style="list-style-type: none"> Mango polyphenols reduced IL-1β and TNF-α mRNA, as well as IL-1β, TNF-α and IL-6 protein levels in the intestinal mucosa. 	(Hyemee et al. 2017)
Pomegranate polyphenols (Ellagic acid as major polyphenol)	DSS-treated Sprague-Dawley rats	<ul style="list-style-type: none"> Pomegranate polyphenols reduced TNF-α and IL-1β mRNA, and TNF-α, IL-1β and IL-6 protein levels in intestinal mucosal samples. 	(Kim et al. 2017)
Black carrot polyphenols	TNF- α stimulated Caco-2 endothelial EA.hy926 coculture	<ul style="list-style-type: none"> Black carrot polyphenols reduced the secretion of IL-8, monocyte chemoattractant protein (MCP)-1 and ICAM-1 under both non-inflammatory and inflammatory conditions. 	(Kamiloglu et al. 2017)

factor-2 (Nrf-2), a transcription factor related to oxidant resistance, and several antioxidant enzymes, to ameliorate oxidative stress (Cheng et al. 2012; Ghanim et al. 2011; González-Reyes et al. 2013; Sahin et al. 2010). Interestingly, the effect of polyphenols on redox modulation can be different depending on cell lines. While they act as anti-oxidants to normal, healthy cells, it can be pro-oxidant to cancerous cells (Amawi et al. 2017). This is also known as “oxidative therapy”, where cancer cells are killed from damage caused by oxidative stress. Khan et al. (2014) suggested the signal/cell-specific aspect of polyphenols may be due to the different amount of copper ions present in normal cells and cancer cells. In their study, EGCG, resveratrol, apigenin and luteolin did not inhibit growth of normal cells, unless they were cultured in copper-supplemented media. Since the anti-cancer effects of polyphenols in colorectal cancer are not the main focus of this review, readers may refer to León-González, Auger, and Schini-Kerth (2015) and Lee, Huang, and Shyur (2013) for more comprehensive view of the relationship between polyphenols and cancer pathways.

As mentioned in Section “*Modulation of cytokines and chemokines expression and secretion*”, polyphenols can regulate the expression and production of various cytokines and chemokines, to attenuate inflammation. This is because polyphenols are inhibitors of NF- κ B, a key transcription factor for inflammatory response. Shakibaei et al. (2007) reported that curcumin reduced inflammatory response by downregulation of cyclo-oxygenase-2 (COX-2) and matrix metalloproteinase-9 (MM-9) via the NF- κ B pathway. Mice fed with grape seed proanthocyanidins experienced less inflammation, because the phenolic compounds inhibited NF- κ B that was activated by the high-fat diet (Liu et al. 2017). There are many more studies displaying the anti-inflammatory

properties of polyphenols, including resveratrol (Ma et al. 2015), tea polyphenols (Tang et al. 2009), and quercetin (Ruiz et al. 2007). Hence, they are proposed to be used for treatments and preventives for several diseases, including inflammatory bowel disease (IBD), colitis and cancer (Amawi et al. 2017; Shapiro et al. 2007).

Reciprocal interaction between polyphenols and gut microbiota

The human intestines house a diverse community of microbial species, which comprises mainly of bacteria (Eckburg et al. 2005). Some consider the gut microbiota to be a “metabolic organ” that can modulate nutrient absorption and interact with the immune system (Guinane and Cotter 2013; Kau et al. 2011; Krajmalnik-Brown et al. 2012). A “healthy composition” of gut microflora can form a physical barrier against infections, whereas disturbance in the balance of gut ecology (dysbiosis) causes higher susceptibility to pathogens. Multiple literature has discussed the linkage between dysbiosis and disease development, including obesity, IBD and cancer (Everard and Cani 2013; Ni et al. 2017; Ridaura et al. 2013; Zitvogel et al. 2015). Therefore, understanding the interactions between polyphenols and gut microbiota is crucial to giving insight on their implications on gut health.

Biotransformation and bioavailability of polyphenols

Due to their complex structures and high molecular weights, up to 95% of the consumed dietary polyphenols cannot be absorbed in the small intestines, but are passed on to the colon and metabolized by the residing bacteria (Cardona

et al. 2013; Marín et al. 2015). Biotransformation of polyphenols in the gut has been demonstrated in a number of in vitro studies by inoculating phenolic compounds with intestinal bacteria. Aura et al. (2005) discovered that gut bacteria deconjugate anthocyanins by cleaving their glycosidic bonds, to form lower molecular weights metabolites. Parkar, Trower, and Stevenson (2013) reported the catabolism of four common polyphenols, including rutin, quercetin, chlorogenic acid and caffeic acid, by a mixture of bacteria representing the gut microbiota, to smaller phenolic acids. Lee et al. (2006) revealed that the content of flavonoids and phenolic acids initially present in tea extracts decreased after 24-hour incubation with fecal bacteria, coupled by an emergence of aromatic metabolites (Lee et al. 2006). Interestingly, the catabolism of polyphenols is associated to the gut microbiota composition, as illustrated by an investigation conducted by Sánchez-Patán et al. (2015, 2012) and Tzounis et al. (2008). In both studies, polyphenols were incubated with fecal samples collected from different volunteers. Flavonoids and anthocyanins in wine were gradually catabolized to simpler phenols and phenolic acids over the course of 48 hours, while (–)-epicatechin (EC) and (+)-catechin (C) were degraded to more polar metabolites (Torres and Rosazza 2001; Tzounis et al. 2008). However, the rates and extent of polyphenol biotransformation in each inoculum were different, implying that dietary intake is not the only factor in the bioavailability of polyphenols and their metabolites. The finding is in line with previous studies that showed varying capacities of different bacteria to metabolize different polyphenols and produce different derivatives (Ozidal et al. 2016; Schoefer et al. 2003). Multiple studies and reviews have demonstrated how phenolic compounds are metabolized in the gut (refer to (Marín et al. 2015; Ozidal et al. 2016; Selma, Espín, and Tomás-Barberán 2009)).

Modulation of gut microbiota by polyphenols

While the bioavailability and bioactivity of polyphenols are largely dependent on bacterial metabolism, it should be noted that polyphenols can shape the composition of the gut bacteria. The most studied aspect in this regard is polyphenols' ability to inhibit growths of specific bacteria. Foods rich in dietary polyphenols have been studied for their antimicrobial activities against common foodborne pathogens and profiled for their phenolic contents. These studies range from simple in vitro studies, where food extracts were incubated with selected microbes, to comprehensive in vivo studies, where fecal bacteria were analyzed before and after exposure to polyphenols. Table 4 summarizes the results and details of the listed references.

In in vitro settings, incubation of phenolic acids and bacteria revealed that pathogenic *E. coli*, *S. aureus* and *C. albicans* were susceptible to most phenolic acids tested (Burdulis et al. 2009). Lee et al. (2006) reported inhibition of most tested bacteria, in particular pathogenic *E. coli*, *S. typhimurium* and *C. perfringens*, by tea polyphenols, and their derivatives. They then examined the antimicrobial capacities of each phenolics and metabolites individually. It

was found that the metabolites, especially the ones with an aromatic ring in their structure, were more adept at bacterial inhibition than their parent polyphenols. This is of no surprise as it is known that the metabolites resulting from gut bacterial transformation of polyphenols often exhibit different, if not enhanced, bioefficacy than their original forms, due to the altered chemical structure and bioavailability (Blaut and Clavel 2007). In another similar study, green tea extracts were also shown to inhibit growths of several strains of bacterial pathogens, including *L. monocytogenes*, *P. aeruginosa*, *S. aureus* and *B. cereus* (Sourabh et al. 2013). Chan et al. (2011) compared the antimicrobial properties and polyphenol concentrations in different types of teas. They found that the teas were only effective against gram-positive bacteria, with green tea being the best antibacterial. However, in other studies, tea extracts were able to inhibit also gram-negative bacteria, albeit to a lesser extent (Chan et al. 2011; Lee et al. 2006; Sourabh et al. 2013). This could be due to the different solvents used during extraction in these studies, which in turn affects the amount of tea polyphenols extracted. Among the tea polyphenols extracted, EGCG showed the highest antibacterial potential, followed by (–)-epicatechin-3-gallate (ECG) and (–)-epigallocatechin (EGC) (Lee et al. 2006). Several studies found that phenolic compounds in blueberries, such as quercetin and chlorogenic acid, can inhibit growth of several pathogens, including *Listeria monocytogenes*, *Salmonella enteritidis*, *H. pylori*, *Bacillus cereus*, etc. (Burdulis et al. 2009; Nohynek et al. 2006; Shen et al. 2014). More recently, Singh et al. (2019) showed that the interesting role of urolithin A, a major microbial metabolite derived from polyphenolics of berries and pomegranate fruits in barrier integrity in addition to anti-inflammatory effects. Since gut microbiota play an important physiological role in catabolizing dietary components into absorbable metabolites, it is speculated that it is the interaction of polyphenol together with the antimicrobial peptides (e.g. bacteriocins) produced by certain gut microbiota, for example lactic acid bacteria, provides greater health benefits. However, there are only a few studies on the synergistic effects of polyphenols and probiotics on antimicrobial effects or gut microbiota modulation (de Souza et al. 2019; Westfall, Lomis, and Prakash 2018). Also, there are only few studies discussing polyphenols' synergy with probiotics to manage inflammation and prevent diseases (Banerjee and Dhar 2019; Rupasinghe, Parmar, and Neir 2019) but these studies do not explain what causes the synergy (i.e. whether it's the bacterial products that interact with polyphenols or the bacteria itself).

Apart from acting as antimicrobial agents against pathogens, polyphenols are also suggested to confer their protective effects as prebiotics. Prebiotic is defined to be a “nonviable food component that confers a health benefit on the host associated with modulation of the microbiota” (Pineiro et al. 2008). Polyphenols may be able to fit into this description because of their specificity against pathogens, while beneficial bacteria remain unaffected, if not stimulated, by polyphenols. Tzounis et al. (2008) demonstrated that epicatechin and catechin not only inhibited foodborne

Table 4. Effect of polyphenols and polyphenol-rich foods on microbial growth, in vitro, ex vivo & in vivo.

Polyphenols (Dosages)	Models	Effects/ Key findings	Refs.
Apple peel polyphenol-rich extract (APPE) (150 or 300 mg/kg/day)	C57BL6/J mice	<ul style="list-style-type: none"> APPE inhibited growth of <i>H. pylori</i> after the mice were infected with the pathogen. 	(Pastene et al. 2010)
Blueberry extract containing chlorogenic acid, quercetin, ellagic acid, quercetin-3-galactoside (112.5–900 mg/mL)	<i>L. monocytogenes</i> and <i>S. enteritidis</i>	<ul style="list-style-type: none"> Blueberry extract inhibited the growth of <i>L. monocytogenes</i> and <i>S. enteritidis</i>. 	(Shen et al. 2014)
Blueberry extract (1% v/v for Fecal Batch Culture Fermentation; or 10–25% v/v for Plate count)	<i>Lactobacillus rhamnosus</i> NZRM 299 and <i>Bifidobacterium breve</i> NZRM 3932	<ul style="list-style-type: none"> Blueberry extract significantly increased number of <i>Lactobacillus rhamnosus</i> and <i>Bifidobacterium breve</i>. 	(Molan et al. 2009)
Blueberry extract (4 mL/kg/d)	Female Sprague Dawley rats	<ul style="list-style-type: none"> Rats gavaged with blueberry extract for 6 days had increased amount of <i>Lactobacillus rhamnosus</i> and <i>Bifidobacterium breve</i> in the cecum. 	
Blueberry drink (25 g blueberry powder/d)	Healthy human individuals	<ul style="list-style-type: none"> 6 weeks consumption of the wild blueberry drink increased the amount of <i>Bifidobacterium spp.</i> in the human intestines. 	(Vendrame et al. 2011)
Bilberry extract and blueberry extract (anthocyanidins are the major polyphenols) (50 µL/well)	<p>Bacteria: <i>Listeria monocytogenes</i> ATCC 19117, <i>Staphylococcus aureus</i> ATCC 25923, <i>Bacillus subtilis</i> ATCC 6633, <i>Enterococcus faecalis</i> ATCC 29212, <i>Escherichia coli</i> ATCC 25922, <i>Pseudomonas aeruginosa</i> ATCC 27853, <i>Citrobacter freundii</i> ATCC 8090, and <i>Salmonella typhimurium</i> ATCC 14028</p> <p>Yeast: <i>Debaryomyces hansenii</i>, <i>Trichosporon cutaneum</i>, <i>Kluyveromyces marxianus</i> var. <i>lactis</i>, <i>Sacharomyces cerevisiae</i>, <i>Candida parapsilosis</i>, <i>Torulasporea delbrueckii</i>, <i>Pichia kluyveri</i>, and <i>Rhodotorula rubra</i></p>	<ul style="list-style-type: none"> Blueberry and bilberry extracts showed similar inhibitory effects against all tested bacteria, but the yeast strains were not affected. 	(Burdulis et al. 2009)
Benzoic acids, including butyl gallate, ethyl 3,5-dihydroxybenzoate, 3,4-dihydroxy-benzoic acid methyl ester, 2,4-dihydroxy-3,6-dimethylbenzoic acid, isopropyl 3,4,5-trihydroxybenzoate, methyl 3,5 dihydroxybenzoate	<i>S. aureus</i> CNRZ3, <i>B. subtilis</i> ATCC6633, <i>L. monocytogenes</i> ATCC 19115, <i>E. coli</i> ATCC 25922, <i>P. aeruginosa</i> ATCC 27853, <i>S. Enteritidis</i> E0220	<ul style="list-style-type: none"> Ethyl 3,5-dihydroxybenzoate inhibited growth of <i>E. coli</i> ATCC 25922, <i>S. Enteritidis</i> E0220 and <i>B. subtilis</i> ATCC6633 3,4-dihydroxy-benzoic acid methyl ester inhibited growth of <i>E. coli</i> ATCC 25922, <i>S. Enteritidis</i> E0220, <i>L. monocytogenes</i> ATCC 19115 and <i>B. subtilis</i> ATCC6633 Methyl 3,5 dihydroxybenzoate inhibited <i>B. subtilis</i> ATCC6633, <i>S. Enteritidis</i> E0220 and <i>E. coli</i> ATCC 25922 Isopropyl 3,4,5-trihydroxybenzoate inhibited <i>E. coli</i> ATCC 25922, <i>S. Enteritidis</i> E0220 and <i>B. subtilis</i> ATCC6633 2,4-dihydroxy-3,6-dimethylbenzoic acid promoted growth of <i>E. coli</i> ATCC 25922 but inhibited <i>S. Enteritidis</i> E0220 Butyl gallate inhibited all tested bacteria except <i>P. aeruginosa</i> ATCC 27853 	(Bouarab-Chibane et al. 2019)
Berry extracts (1 mg/mL, contains >400 mg polyphenols/g dry wt of berries)	<i>B. cereus</i> ATCC 9139, <i>C. jejuni</i> LMG 8841, <i>C. albicans</i> NCPF 3179, <i>C. perfringens</i> ATCC 13124, <i>E. coli</i> ATCC 11775, <i>H. pylori</i> NCTC 11637, <i>L. rhamnosus</i> VTT E-97800, <i>L. rhamnosus</i> GG VTTE-96666, <i>S. enterica</i> sv. <i>Infantis</i> VTT E-97738, <i>S. enterica</i> sv. <i>Typhimurium</i> SH-5014,	<ul style="list-style-type: none"> <i>H. pylori</i> and <i>B. cereus</i> were inhibited by all berry extracts. Cloudberry, raspberry and strawberry extracts were most effective against all bacteria strains. 	(Nohynek et al. 2006)

(continued)

Table 4. Continued.

Polyphenols (Dosages)	Models	Effects/ Key findings	Refs.
Berry extracts (containing 230–470 mg/g extract depending on the berries) (1 mg/mL)	<i>S. enterica</i> sv. <i>Typhimurium</i> VTT E-981151, <i>S. aureus</i> ATCC 6538, <i>S. aureus</i> ATCC 25923, <i>S. aureus</i> ATCC 12600 and <i>S. epidermis</i> DSM 20044 <i>Bifidobacterium lactis</i> VTT-E-94508 (Bb-12), <i>Enterococcus faecalis</i> VTT E-93203T (DSM 20478), <i>E. coli</i> 50 VTT E-94564T (ATCC 11775), <i>E. coli</i> CM 871, <i>Lactobacillus crispatus</i> VTT E-96725 (M247), <i>Lactobacillus johnsonii</i> VTT E-97797 (LJ1), <i>Lactobacillus paracasei</i> F19 VTT E-94510 (LMG P-17806), <i>Lactobacillus plantarum</i> VTT E-78076, <i>Lactobacillus reuteri</i> VTT E-97849 (ATCC 55730), <i>Lactobacillus rhamnosus</i> VTT E-97800, <i>Lactobacillus rhamnosus</i> GG VTT E-96666 (ATCC 53103) and <i>Salmonella enterica</i> ser. <i>Typhimurium</i> SH5014	<ul style="list-style-type: none"> • In liquid culture, <i>E. coli</i> CM 871 and <i>E. coli</i> 50 were inhibited by all the berry extracts, except for black currant extract. • <i>Salmonella enterica</i> ser. <i>Typhimurium</i> SH5014 was inhibited by all berry extracts except for blueberry extract. • <i>Lactobacillus</i> group remained unaffected by berries in liquid culture. 	(Puupponen-Pimiä et al. 2001)
Berry extracts (50 µL/disc)	<i>Clostridium perfringens</i> ATCC 19404, <i>Bacillus subtilis</i> ATCC 6633, <i>Listeria innocua</i> ATCC 33090, <i>Staphylococcus aureus</i> ATCC 6538, <i>Sarcina lutea</i> ATCC 934, <i>Micrococcus flavus</i> ATCC 40240, <i>Escherichia coli</i> ATCC 25922, <i>Pseudomonas aeruginosa</i> ATCC 9027, <i>Salmonella enteritidis</i> ATCC 13076, <i>Shigella sonnei</i> ATCC 25931, <i>Klebsiella pneumoniae</i> ATCC 10031 and <i>Proteus vulgaris</i> ATCC 8427	<ul style="list-style-type: none"> • Blackthorn, European cornel and wild blackberry extracts inhibited all the tested gram-positive bacteria, including <i>C. perfringens</i>, <i>B. subtilis</i>, <i>L. innocua</i>, <i>S. aureus</i>, <i>S. lutea</i>, and <i>M. flavus</i>. • For gram-negative, <i>E. coli</i>, <i>P. aeruginosa</i>, <i>S. enteritidis</i> and <i>S. sonnei</i> were susceptible to all berry extracts, but <i>P. vulgaris</i> was only inhibited by blackthorn and European cornel extracts. 	(Radovanović et al. 2013)
Cinnamic acid, including, caffeic acid, caffeic acid 1,1-dimethylallyl ester, chicoric acid, cinnamyl-3,4-dihydroxy- α -cyanocinnamate, 2,4-dihydroxycinnamic acid, ethyl 3,4-dihydroxycinnamate, chlorogenic acid, CU-CPT22 acid	<i>S. aureus</i> CNR23, <i>B. subtilis</i> ATCC6633, <i>L. monocytogenes</i> ATCC 19115, <i>E. coli</i> ATCC 25922, <i>P. aeruginosa</i> ATCC 27853, <i>S. Enteritidis</i> E0220	<ul style="list-style-type: none"> • Chlorogenic acid promoted growth of <i>B. subtilis</i> ATCC6633 but inhibited <i>L. monocytogenes</i> ATCC 19115 • Caffeic acid inhibited <i>S. aureus</i> CNR23, <i>L. monocytogenes</i> ATCC 19115, <i>S. Enteritidis</i> E0220 and <i>E. coli</i> ATCC 25922 • Caffeic acid 1,1-dimethylallyl ester inhibited <i>S. aureus</i> CNR23, <i>B. subtilis</i> ATCC6633, <i>L. monocytogenes</i> ATCC 19115 and <i>S. Enteritidis</i> E0220 • CU-CPT22 acid inhibited <i>S. aureus</i> CNR23, <i>B. subtilis</i> ATCC6633 and <i>E. coli</i> ATCC 25922 • Chicoric acid inhibited , <i>L. monocytogenes</i> ATCC 19115 and <i>S. Enteritidis</i> E0220 • Ethyl 3,4-dihydroxycinnamate inhibited <i>B. subtilis</i> ATCC6633, <i>L. monocytogenes</i> ATCC 19115 and <i>S. Enteritidis</i> E0220 • Cinnamyl-3,4-dihydroxy-α-cyanocinnamate inhibited all tested bacteria 	(Bouarab-Chibane et al. 2019)
Cocoa powder (10 or 20 g/d)	Male pigs	<ul style="list-style-type: none"> • Pigs fed with flavanol-enriched cocoa powder had more <i>Lactobacillus</i> and <i>Bifidobacterium</i> species in the colon. 	(Jang et al. 2016)
Cocoa flavanols (23 or 494 mg/d)	Healthy human volunteers	<ul style="list-style-type: none"> • Consumption of cocoa flavanols for 4 weeks changed the abundance of <i>Bifidobacterium</i> spp., <i>C. histolyticum</i> group, <i>E. rectale</i>-<i>C. coccoides</i> group and <i>Lactobacillus</i> and <i>Enterococcus</i> spp. compared to control. 	(Tzounis et al. 2011)

(continued)

Table 4. Continued.

Polyphenols (Dosages)	Models	Effects/ Key findings	Refs.
Coumarins, including baicalein, 3',5'-dihydroxyflavone, 5,7-dihydroxy-4-phenylcoumarin, 5,7-dihydroxy-4-propylcoumarin, 5,7-dihydroxy-4-methylcoumarin	<i>S. aureus</i> CNRZ3, <i>B. subtilis</i> ATCC6633, <i>L. monocytogenes</i> ATCC 19115, <i>E. coli</i> ATCC 25922, <i>P. aeruginosa</i> ATCC 27853, <i>S. Enteritidis</i> E0220	<ul style="list-style-type: none"> The group that consumed 494 mg cocoa flavanols per day had a more significant increase in <i>Lactobacillus</i>, <i>Enterococcus</i> and <i>Bifidobacterium</i> spp., and decreased the amount of <i>C. histolyticum</i> group, compared to the group who consumed less cocoa flavanols. Baicalein inhibited <i>L. monocytogenes</i> ATCC 19115 5,7-dihydroxy-4-propylcoumarin inhibited <i>S. aureus</i> CNRZ3 and <i>L. monocytogenes</i> ATCC 19115 5,7-dihydroxy-4-phenylcoumarin inhibited <i>S. aureus</i> CNRZ3, <i>B. subtilis</i> ATCC6633 and <i>L. monocytogenes</i> ATCC 19115 3',5'-dihydroxyflavone inhibited all bacteria except <i>B. subtilis</i> ATCC6633 5,7-dihydroxy-4-methylcoumarin inhibited <i>L. monocytogenes</i> ATCC 19115 	(Bouarab-Chibane et al. 2019)
Cranberry extract	<i>Staphylococcus aureus</i> ACTT 25923	<ul style="list-style-type: none"> Cranberry extract inhibited the growth of <i>S. aureus</i>. 	(Lian et al. 2012)
(-)-epicatechin (EC) and (+)-catechin (C) (150 or 1000 mg/L)	Human fecal samples	<ul style="list-style-type: none"> 24-hour incubation with EC increased the growth of <i>C. coccoides</i>-<i>E. rectale</i> group in fecal samples significantly. C increased the amount of <i>C. coccoides</i>-<i>E. rectale</i> group, <i>Bifidobacterium</i> spp., and <i>E. coli</i>, but inhibited <i>C. histolyticum</i>. 	(Tzounis et al. 2008)
Flavonoids, including cardamonin, dihydromyricetin, diosmin, epigallocatechin gallate, myricetin, myricitrin, quercetin 3- β -D-glucoside, rutin, silibinin, taxifolin, wedelolactone	<i>S. aureus</i> CNRZ3, <i>B. subtilis</i> ATCC6633, <i>L. monocytogenes</i> ATCC 19115, <i>E. coli</i> ATCC 25922, <i>P. aeruginosa</i> ATCC 27853, <i>S. Enteritidis</i> E0220	<ul style="list-style-type: none"> Taxifolin inhibited <i>S. aureus</i> CNRZ3 and <i>L. monocytogenes</i> ATCC 19115 Myricitrin dihydrate promoted growth of <i>B. subtilis</i> ATCC6633 but inhibited <i>L. monocytogenes</i> ATCC 19115 Diosmin inhibited <i>S. Enteritidis</i> E0220, <i>S. aureus</i> CNRZ3 and <i>L. monocytogenes</i> ATCC 19115 Rutin hydrate inhibited <i>B. subtilis</i> ATCC6633, <i>E. coli</i> ATCC 25922 and <i>P. aeruginosa</i> ATCC 27853 Myrecitin inhibited <i>E. coli</i> ATCC 25922, <i>S. Enteritidis</i> E0220 and <i>S. aureus</i> CNRZ3 Dihydromyricetin inhibited <i>S. aureus</i> CNRZ3 and <i>L. monocytogenes</i> ATCC 19115 Cardamonin inhibited <i>S. aureus</i> CNRZ3, <i>B. subtilis</i> ATCC6633, <i>L. monocytogenes</i> ATCC 19115, <i>E. coli</i> ATCC 25922 Quercetin 3-β-D-glucoside inhibited <i>S. aureus</i> CNRZ3 and <i>L. monocytogenes</i> ATCC 19115 Silibinin promoted growth of <i>S. Enteritidis</i> E0220 Epigallocatechin gallate inhibited all tested bacteria except <i>E. coli</i> ATCC 25922 Wedelolactone promoted growth of <i>S. Enteritidis</i> E0220 	(Bouarab-Chibane et al. 2019)
Flavonoids, including naringenin, hesperidin, quercetin and rutin (2, 20 or 100 μ g/mL)	<i>B. bifidum</i> , <i>B. adolescentis</i>	<ul style="list-style-type: none"> For <i>B. bifidum</i>, naringenin only inhibited its growth at 2 μg/mL at 2 hours incubation, while other concentrations and incubation time did not affect bacterial growth. Hesperidin, quercetin and rutin all inhibited bacterial growth first at 0.5 incubation hour, then promoted bacterial growth at 2 hour 	(Gwiazdowska et al. 2015)

(continued)

Table 4. Continued.

Polyphenols (Dosages)	Models	Effects/ Key findings	Refs.
		incubation which then returned to comparable rates as control at longer incubation time points.	
Grape pomace concentrate (GPC) and grape seed extract (GSE) (60 g GPC/kg; 7.2 g GSE/kg)	Broiler chicks	<ul style="list-style-type: none"> At 100µg/mL, <i>B. adolescentis</i> growth was inhibited by naringenin, hesperidin, and quercetin after 2 hours incubation. But as incubation time increased, the growth inhibition effect became diminished. Rutin only inhibited its growth in the first 0.5 hour. GPC and GSE increased the number of <i>Enterococcus</i>, but decreased the amount of <i>Clostridium</i> in the ileum after 21 days. In the cecum, GPC and GSE increased the number of <i>Escherichia coli</i>, <i>Lactobacillus</i>, <i>Enterococcus</i>, and <i>Clostridium</i>. GPC and GSE increased the population of phenol-degrading bacteria in the chicks. GPC and GSE increased the biodiversity of the gut microbiota of the birds. 	(Viveros et al. 2011)
Grape seed extract (GSE) (1% w/w in 2 kg diet)	Crossbred female pigs	<ul style="list-style-type: none"> 6-day GSE diet increased the amount of <i>Lachnospiraceae</i>, <i>Clostridiales</i>, <i>Lactobacillus</i> and <i>Ruminococcaceae</i> in feces. 	(Choy et al. 2014)
Grape seed extract (GSE) (flavan-3-ol fraction) (600 mg/L)	Human fecal samples	<ul style="list-style-type: none"> GSE increased the population of <i>Lactobacillus</i> and <i>Enterococcus</i> but reduced the number of <i>C. histolyticum</i> group. 	(Cueva et al. 2013)
Grape seed proanthocyanidin extract (GSPE) and gallic acid (500 mg/kg)	Female Wistar rats	<ul style="list-style-type: none"> 8-day treatment with GSPE increased the abundance of <i>Bacteroides</i>, <i>Parabacteroides</i>, <i>Sutterella</i>, <i>Phascolarctobacterium</i>, and <i>Bilophila</i> in the cecum. Amount of <i>Ruminococcus</i>, <i>Oscillospira</i>, <i>Coproccoccus</i> and <i>Dehalobacterium</i> were reduced by GSPE. 	(Casanova-Martín et al. 2018)
Grape seed proanthocyanidins (GSPs) (250 mg/kg)	Crossbred weaned piglets	<ul style="list-style-type: none"> GSPs increased the diversity and abundance of gut microbiota in the piglets significantly. GSPs decreased the amount of <i>Lactobacillaceae</i>, but increased the abundance of <i>Clostridiaceae</i> in the piglets. 	(Han et al. 2016)
Hydroxycinnamic phenolic acids, including <i>p</i> -cumaric acid, ferulic acid, sinapic acid, caffeic acid, and chlorogenic acid (2, 20 or 100µg/mL)	<i>B. bifidum</i> , <i>B. adolescentis</i>	<ul style="list-style-type: none"> <i>p</i>-cumaric acid and caffeic acid promoted growth of <i>B. bifidum</i> at 2-hour incubation, but not at longer incubation periods Ferulic acid, at 100µg/mL, inhibited <i>B. bifidum</i> growth for 2 hours. The phenolic acids used did not affect <i>B. adolescentis</i> growth significantly. 	(Gwiazdowska et al. 2015.)
Napthoquinones, including 5,8-dihydroxy-1,4-naphthoquinone, 2,3-dichloro-5,8-dihydroxy-1,4-naphthoquinone	<i>S. aureus</i> CNRZ3, <i>B. subtilis</i> ATCC6633, <i>L. monocytogenes</i> ATCC 19115, <i>E. coli</i> ATCC 25922, <i>P. aeruginosa</i> ATCC 27853, <i>S. Enteritidis</i> E0220	<ul style="list-style-type: none"> 5,8-dihydroxy-1,4-naphthoquinone inhibited all tested bacteria except <i>P. aeruginosa</i> ATCC 27853 2,3-dichloro-5,8-dihydroxy-1,4-naphthoquinone inhibited <i>S. Enteritidis</i> E0220, <i>S. aureus</i> CNRZ3, <i>B. subtilis</i> ATCC6633, and <i>L. monocytogenes</i> ATCC 19115 	
Phenolic acids, including benzoic acids, phenylacetic acids and phenylpropionic acids (62.5, 125, 250, 500 and 1000 µg/mL)	<i>E. coli</i> ATCC 25922, <i>E. coli</i> O157:H7, <i>E. coli</i> lpxC/tolC, <i>Lactobacillus paraplantarum</i> LCH7, <i>Lactobacillus plantarum</i> LCH17, <i>Lactobacillus fermentum</i> LPH1, <i>L. fermentum</i> CECT 5716,	<ul style="list-style-type: none"> The nonpathogenic strain of <i>E. coli</i> ATCC 25922 was only inhibited by 4 out of 13 phenolic acids tested, whereas the pathogenic <i>E. coli</i> O157:H7 was inhibited by most phenolic acids 	(Cueva et al. 2010)

(continued)

Table 4. Continued.

Polyphenols (Dosages)	Models	Effects/ Key findings	Refs.
	<i>Lactobacillus brevis</i> LCH23, <i>Lactobacillus coryniformis</i> CECT 5711, <i>C. albicans</i> MY1055, <i>S. aureus</i> EP167 and <i>P. aeruginosa</i> PAO1	<ul style="list-style-type: none"> <i>Lactobacillus paraplantarum</i> LCH7 and <i>Lactobacillus coryniformis</i> CECT 5711 were inhibited by most phenolic acids but the rest of the <i>Lactobacillus</i> group was not affected. Pathogen <i>S. aureus</i> EP167 was inhibited by the phenolic acids. 	
Purple sweet potato (PSP) polyphenols (0.16% (w/v))	Fresh pig feces	<ul style="list-style-type: none"> PSP polyphenols increased the relative abundance of <i>Bifidobacterium</i> in the presence of cellulose, but lowered relative abundance of <i>Bifidobacterium</i> in the presence of inulin PSP polyphenols lowered the relative abundance of <i>Proteobacterium</i>, with or without dietary fiber PSP polyphenols, mixed with cellulose, increased the relative abundance of <i>Actinobacteria</i> 	(Kilua et al. 2019)
Red wine polyphenols	Human fecal samples	<ul style="list-style-type: none"> Red wine extract inhibited the growth of <i>C. histolyticum</i> group in human fecal inoculum. 	(Sánchez-Patán et al. 2012)
Red wine polyphenols (272 mL/d)	Healthy human males	<ul style="list-style-type: none"> 4-week consumption of red wine polyphenols increased the number of <i>Enterococcus</i>, <i>Prevotella</i>, <i>Bacteroides</i>, <i>Bifidobacterium</i>, <i>Bacteroides uniformis</i>, <i>Eggerthella lenta</i>, and <i>Blautia coccoides</i>–<i>Eubacterium rectale</i> groups 	(Queipo-Ortuño et al. 2012)
Stilbenes, including hapontin, resveratrol and pinosylvin	<i>S. aureus</i> CNRZ3, <i>B. subtilis</i> ATCC6633, <i>L. monocytogenes</i> ATCC 19115, <i>E. coli</i> ATCC 25922, <i>P. aeruginosa</i> ATCC 27853, <i>S. enteritidis</i> E0220	<ul style="list-style-type: none"> Resveratrol inhibited all tested bacteria Pinosylvin inhibited all tested bacteria except for <i>P. aeruginosa</i> ATCC 27853 	(Bouarab-Chibane et al. 2019)
Tea extracts	<i>M. luteus</i> , <i>S. aureus</i> and <i>B. cereus</i>	<ul style="list-style-type: none"> Green tea extract inhibited all 3 bacteria while black tea and white tea only inhibited <i>M. luteus</i> and <i>B. cereus</i>. 	(Chan et al. 2011)
Tea polyphenols (0.1% w/v)	Human fecal bacteria, and 28 strains of bacteria (refer to (Lee et al. 2006))	<ul style="list-style-type: none"> Tea polyphenols strongly inhibited growth of pathogenic <i>C. perfringens</i>, <i>C. difficile</i>, and <i>Bacteroides</i> spp. Commensal bacteria and probiotics were less affected by the tea polyphenols. 	(Lee et al. 2006)
Tea polyphenols (1.2 g/d)	Healthy human individuals	<ul style="list-style-type: none"> 4-week consumption of tea polyphenols lowered the number of <i>C. perfringens</i> and other <i>Clostridium</i> spp. in the volunteers' feces, while number of <i>Bifidobacterium</i> spp. increased. 	(Okubo et al. 1992)

pathogens, but also increased the count of probiotics like *Lactobacillus*, and *Bifidobacterium* spp. and *Eubacterium rectale*–*C. coccoides*. A follow-up study by Tzounis et al. (2011) supplied volunteers with high or low amounts of cocoa flavanols. After 4 weeks, even the total count of fecal bacteria remained unchanged, the number of *Lactobacillus* and *Bifidobacterium* spp. was increased. The increase was also dose-dependent to concentrations of consumed flavanols. Similar findings were produced in pigs that were fed cocoa flavanols, which saw an increase in *Lactobacillus* and *Bifidobacterium* spp. in the feces (Jang et al. 2016). Another in vivo experiment showed that 4-week consumption of red wine polyphenols resulted in a significant increase in *Enterococcus*, *Prevotella*, *Bacteroides*, *Bifidobacterium* spp., and *Blautia coccoides*–*Eubacterium rectale* groups (Queipo-

Ortuño et al. 2012). Broiler chicks fed with grape extracts had more *Lactobacillus* spp. in their intestines, and a more diverse gut microbiota, which is associated with gut health (Guinane and Cotter 2013; Viveros et al. 2011). Meanwhile, the count of *Clostridium* spp., which are linked to Irritable Bowel Syndrome (IBS) and IBD, was lowered (Ghoshal et al. 2012; Morgan et al. 2012; Wehkamp et al. 2003). This finding is in line with a recent in vitro study where *Clostridium* spp. was decreased after inoculation with red wine extracts (Sánchez-Patán et al. 2012). Grape seed and wine polyphenols were found to lower amount of *Firmicutes* in the intestines, which are associated with metabolic disorders (Queipo-Ortuño et al. 2012). An interesting human study performed by Mayta-Apaza et al. (2018) demonstrated that the polyphenol-induced change in gut microbiota

composition is also dependent on the preexisting gut microbes. Ten healthy individuals consumed tart cherry juice for 5 days, and their stool was examined before and after the intervention. Mayta-Apaza et al. (2018) discovered that, before the intervention, there was already significant difference in gut microbiota among the individuals, marked by the abundance of *Bacteroides*. The group with fewer *Bacteroides* had a different response to the cherry polyphenols than the group with more *Bacteroides*. The former had an increase in *Bacteroides* and *Bifidobacterium* after the intervention, while the latter experienced a decrease in those bacterial groups. However, the authors acknowledged that the differential response may be due to different dietary habits in each individual. Similar to this study, a major drawback in most human studies for the effects of polyphenols is the lack of a control diet. In the human studies mentioned above, polyphenols were often consumed by volunteers in the form of juice or powder supplements. The studies did not take into account of the amount of polyphenols in study participants' normal diet. The effects observed may not be entirely due to the polyphenols that were tested in the studies, but a combined effect of various polyphenols found in the supplements and diet. Therefore, more well-devised clinical trials may be required for us to fully understand the effects of polyphenols in humans.

A recurring theme in these studies is that the bioactivity of polyphenols against bacteria is structure-dependent, and the bacterial susceptibility to polyphenols is strain-dependent. For example, tea polyphenols are more effective against gram-positive bacteria, whereas berry polyphenols are more effective against gram-negative bacteria. The authors attributed the selective actions of phenolic compounds to the different structures of gram-positive and gram-negative bacteria. In the case of tea polyphenols, the presence of negatively-charged lipopolysaccharides (LPS) on the cell membrane in gram-negative bacteria may repulse and reduce cell uptake of tea phenolics, making them more resistant. Taguri, Tanaka, and Kouno (2004) observed that the most effective antibacterial polyphenols, such as ECG and EGC, all contained a galloyl group in their chemical structure (Taguri, Tanaka, and Kouno 2004). Bouarab-Chibane et al. (2019) studied the effects of 35 polyphenols on 6 bacterial strains, where they also noted the strain-specific nature of polyphenols' antibacterial properties. Rarely was any of the tested polyphenols effective against all gram-positive or gram-negative bacteria. They concluded that the antibacterial effects of polyphenols cannot be categorized according to the polyphenol class. Even within the same phylum, bacteria may respond differently to the same polyphenolic compound. Gwiazdowska et al. (2015) observed the effects of flavonoids and phenolic acids on the in vitro growth of different strains of *bifidobacterium* over the span of 48 h. Bacterial growths were either inhibited or promoted, depending on strain, polyphenolic compound, concentration of polyphenol and incubation time. Also, different flavonoids or phenolic acids exerted different effects on the same bacterial strain, compared with other polyphenolic compounds of the same class.

Current studies provide us some insight on how a single polyphenolic compound affects the growth of selected few bacteria in vitro, or composition of the gut microbiota in vivo. And most in vivo studies only demonstrate the general effects of polyphenols on certain bacterial phylum, for example cocoa flavanols and grape anthocyanidins increase the abundance of *Bifidobacterium*. However, much still remains unknown, when polyphenols of the same category, such as flavonoids, flavanols, anthocyanins, etcetera, can have varying effects on the same bacterial strain in in vitro settings. And in vivo, there are large variations in gut microbiota among individuals, which may result in a different response to the same polyphenol, due to the different polyphenolic metabolites and bacterial metabolites. Also, there are many things to consider when assessing the in vivo effects of polyphenols, including the interaction of polyphenols and other components in diets, which could interfere with polyphenol-bacterial interactions. For example, a recent study (Kilua et al. 2019), demonstrated that the same purple sweet potatoes polyphenols modulates swine gut microbiota, but the extent to which the polyphenols promote or inhibit bacterial growth depended on the type of dietary fiber in the mix. And Mansoorian et al. (2019) showed that fermentable fibers changed the way rutin was metabolized by fecal bacteria. Therefore, it is difficult to conclude how polyphenols in a whole changes bacterial growth or affects the gut microbiota or vice versa with studies at hand.

Future perspective and challenges for the use of polyphenol

Because of the anti-oxidative, anti-inflammatory, and anti-carcinogenic properties of polyphenols, they have been proposed to be promising candidates in preventing and combating various gastrointestinal diseases. However, much is still unknown about polyphenols. A crucial challenge in the use of polyphenols is determining the dosage. Given how polyphenol concentrations vary in different food source, and can be altered by food preparation methods (Manach et al. 2004), or the fact that polyphenols can interact with other food substances and the gut microbiota, we should consider how much is needed to achieve the desired effect while avoiding side-effects from overconsumption. Although there is a general consensus that polyphenols are anti-oxidants, some evidence showed that they can be pro-oxidant in excess (Halliwell 2008). In a study done by Jones and Hughes (1982), there was a far more detrimental effect than oxidative stress induced by high amounts of polyphenols. Mice fed with too much quercetin in a long term experienced premature death. Moreover, there is a lack of clinical trials to tackle the optimal dose of polyphenols, or to observe potential side-effects of long term exposure in humans (Balentine et al. 2015). Without them, it would be difficult to develop polyphenol-based treatments, even though animal models demonstrate promising results. The same challenge goes with using polyphenols as prebiotics, as the concentration of polyphenols to allow them to act as

prebiotics vary from different probiotic strains (de Souza et al. 2019).

Conclusion

There is increasing evidence in literature to show and emphasize the positive effects of polyphenol-rich plants, their extracts, and also individual compounds, on gut health, which may be used as alternative approach for prevention or treatment of different diseases related to oxidative stress and inflammation, such as IBD. The impact of polyphenols on gut health and the modes of action could be through modulation of intestinal barrier function, innate and adaptive immune response, signaling pathways, as well as the ability to modify gut microbiota composition. A clear understanding of these mechanisms is necessitated, which will allow for appropriate polyphenol(s) to be selected for certain applications, and may lead to discovery of new therapeutic targets that could be modulated through more conventional pharmacological approaches. Extensive human clinical trials are also indispensable to confirm that polyphenols could in fact constitute a preventive or therapeutic approach for specific types of diseases. Although polyphenols exist abundantly in most dietary sources such as fruits, vegetables, tea and wine, more detailed studies are still needed to determine their absorption and bioavailability. Provided that polyphenols may undergo considerable degree of modifications during digestion and absorption and that the modified forms may have different biological properties and potencies, future work should also consider the activity of their metabolites, which may affect the health outcomes.

References

- Amasheh, M., J. Luettig, S. Amasheh, M. Zeitz, M. Fromm, and J. D. Schulzke. 2012. Effects of quercetin studied in colonic HT-29/B6 cells and rat intestine *in vitro*. *Annals of the New York Academy of Sciences* 1258 (1):100–7. doi: [10.1111/j.1749-6632.2012.06609.x](https://doi.org/10.1111/j.1749-6632.2012.06609.x).
- Amasheh, M., S. Schlichter, S. Amasheh, J. Mankertz, M. Zeitz, M. Fromm, and J. D. Schulzke. 2008. Quercetin enhances epithelial barrier function and increases claudin-4 expression in Caco-2 cells. *The Journal of Nutrition* 138 (6):1067–73. doi: [10.1093/jn/138.6.1067](https://doi.org/10.1093/jn/138.6.1067).
- Amawi, H., C. R. Ashby, T. Samuel, R. Peraman, and A. K. Tiwari. 2017. Polyphenolic nutrients in cancer chemoprevention and metastasis: Role of the epithelial-to-mesenchymal (EMT) pathway. *Nutrients* 9 (8):911. doi: [10.3390/nu9080911](https://doi.org/10.3390/nu9080911).
- Antoniou, E., G. A. Margonis, A. Angelou, A. Pikouli, P. Argiri, I. Karavokyros, A. Papalois, and E. Pikoulis. 2016. The TNBS-induced colitis animal model: An overview. *Annals of Medicine and Surgery* 11:9–15. doi: [10.1016/j.amsu.2016.07.019](https://doi.org/10.1016/j.amsu.2016.07.019).
- Aura, A. M., P. Martin-Lopez, K. A. O'Leary, G. Williamson, K. M. Oksman-Caldentey, K. Poutanen, and C. Santos-Buelga. 2005. *In vitro* metabolism of anthocyanins by human gut microflora. *European Journal of Nutrition* 44 (3):133–42. doi: [10.1007/s00394-004-0502-2](https://doi.org/10.1007/s00394-004-0502-2).
- Awad, W. A., C. Hess, and M. Hess. 2017. Enteric pathogens and their toxin-induced disruption of the intestinal barrier through alteration of tight junctions in chickens. *Toxins* 9 (2):60. doi: [10.3390/toxins9020060](https://doi.org/10.3390/toxins9020060).
- Azuma, T., M. Shigeshiro, M. Kodama, S. Tanabe, and T. Suzuki. 2013. Supplemental naringenin prevents intestinal barrier defects and inflammation in colitic mice. *The Journal of Nutrition* 143 (6): 827–34. doi: [10.3945/jn.113.174508](https://doi.org/10.3945/jn.113.174508).
- Balentine, D. A., J. T. Dwyer, J. W. Erdman, Jr., M. G. Ferruzzi, P. C. Gaine, J. M. Harnly, and C. L. Kwik-Urbe. 2015. Recommendations on reporting requirements for flavonoids in research. *The American Journal of Clinical Nutrition* 101 (6):1113–25. doi: [10.3945/ajcn.113.071274](https://doi.org/10.3945/ajcn.113.071274).
- Banerjee, A., and P. Dhar. 2019. Amalgamation of polyphenols and probiotics induce health promotion. *Critical Reviews in Food Science and Nutrition*. 59 (18):2903–26. doi: [10.1080/10408398.2018.1478795](https://doi.org/10.1080/10408398.2018.1478795).
- Biasi, F., T. Guina, M. Maina, B. Cabboi, M. Deiana, C. I. Tuberioso, S. Calfapietra, E. Chiarpotto, B. Sottero, P. Gamba, et al. 2013. Phenolic compounds present in Sardinian wine extracts protect against the production of inflammatory cytokines induced by oxysterols in CaCo-2 human enterocyte-like cells. *Biochemical Pharmacology* 86 (1):138–45. doi: [10.1016/j.bcp.2013.03.024](https://doi.org/10.1016/j.bcp.2013.03.024).
- Blaut, M., and T. Clavel. 2007. Metabolic diversity of the intestinal microbiota: Implications for health and disease. *Journal of Nutrition* 137 (3 Suppl 2):751S–5S.
- Bouarab-Chibane, L., V. Forquet, P. Lantéri, Y. Clément, L. Léonard-Akkari, N. Oulahal, P. Degraeve, and C. Bordes. 2019. Antibacterial properties of polyphenols: Characterization and QSAR (quantitative structure-activity relationship) models. *Frontiers in Microbiology* 10: 829. doi: [10.3389/fmicb.2019.00829](https://doi.org/10.3389/fmicb.2019.00829).
- Boussenna, A., J. Cholet, N. Goncalves-Mendes, J. Joubert-Zakey, D. Fraisse, M. P. Vasson, O. Texier, and C. Felgines. 2016. Polyphenol-rich grape pomace extracts protect against dextran sulfate sodium-induced colitis in rats. *Journal of the Science of Food and Agriculture* 96 (4):1260–68. doi: [10.1002/jsfa.7214](https://doi.org/10.1002/jsfa.7214).
- Burdulis, D., A. Sarkinas, I. Jasutienė, E. Stackevicėnė, L. Nikolajevs, and V. Janulis. 2009. Comparative study of anthocyanin composition, antimicrobial and antioxidant activity in bilberry (*Vaccinium myrtillus* L.) and blueberry (*Vaccinium corymbosum* L.) fruits. *Acta Poloniae Pharmaceutica* 66 (4):399–408.
- Canali, R., F. Vignolini, F. Nobili, and E. Mengheri. 2000. Reduction of oxidative stress and cytokine-induced neutrophil chemoattractant (CINC) expression by red wine polyphenols in zinc deficiency induced intestinal damage of rat. *Free Radical Biology and Medicine* 28 (11):1661–70. doi: [10.1016/S0891-5849\(00\)00285-9](https://doi.org/10.1016/S0891-5849(00)00285-9).
- Cao, M., P. Wang, C. Sun, W. He, and F. Wang. 2013. Amelioration of IFN- γ and TNF- α -induced intestinal epithelial barrier dysfunction by berberine via suppression of MLCK-MLC phosphorylation signaling pathway. *PLoS One* 8 (5):e61944. doi: [10.1371/journal.pone.0061944](https://doi.org/10.1371/journal.pone.0061944).
- Cardona, F., C. Andrés-Lacueva, S. Tulipani, F. J. Tinahones, and M. I. Queipo-Ortuño. 2013. Benefits of polyphenols on gut microbiota and implications in human health. *Journal of Nutritional Biochemistry* 24 (8):1415–22. doi: [10.1016/j.jnutbio.2013.05.001](https://doi.org/10.1016/j.jnutbio.2013.05.001).
- Carrasco-Pozo, C., P. Morales, and M. Gotteland. 2013. Polyphenols protect the epithelial barrier function of Caco-2 cells exposed to indomethacin through the modulation of occludin and zonula occludens-1 expression. *Journal of Agricultural and Food Chemistry* 61 (22):5291–97. doi: [10.1021/jf400150p](https://doi.org/10.1021/jf400150p).
- Casanova-Martín, Á., J. Serrano, K. J. Portune, Y. Sanz, M. T. Blay, X. Terra, A. Ardévol, and M. Pinent. 2018. Grape seed proanthocyanidins influence gut microbiota and enteroendocrine secretions in female rats. *Food & Function* 9 (3):1672–82. doi: [10.1039/C7FO02028G](https://doi.org/10.1039/C7FO02028G).
- Chan, E. W. C., E. Y. Soh, P. P. Tie, and Y. P. Law. 2011. Antioxidant and antibacterial properties of green, black, and herbal teas of *Camellia sinensis*. *Pharmacognosy Research* 3 (4):266–72. doi: [10.4103/0974-8490.89748](https://doi.org/10.4103/0974-8490.89748).
- Cheng, A.-S., Y.-H. Cheng, C.-H. Chiou, and T.-L. Chang. 2012. Resveratrol upregulates Nrf2 expression to attenuate methylglyoxal-induced insulin resistance in Hep G2 cells. *Journal of Agricultural and Food Chemistry* 60 (36):9180–87. doi: [10.1021/jf302831d](https://doi.org/10.1021/jf302831d).
- Choy, Y. Y., P. Quifer-Rada, D. M. Holstege, S. A. Frese, C. C. Calvert, D. A. Mills, R. M. Lamuela-Raventos, and A. L. Waterhouse. 2014. Phenolic metabolites and substantial microbiome changes in pig feces by ingesting grape seed proanthocyanidins. *Food & Function* 5 (9):2298–308. doi: [10.1039/C4FO00325J](https://doi.org/10.1039/C4FO00325J).

- Clifford, M. N. 2004. Diet-derived phenols in plasma and tissues and their implications for health. *Planta Medica* 70 (12):1103–14. doi: [10.1055/s-2004-835835](https://doi.org/10.1055/s-2004-835835).
- Coates, E. M., G. Popa, C. I. Gill, M. J. McCann, G. J. McDougall, D. Stewart, and I. Rowland. 2007. Colon-available raspberry polyphenols exhibit anti-cancer effects on *in vitro* models of colon cancer. *Journal of Carcinogenesis* 6 (1):4. doi: [10.1186/1477-3163-6-4](https://doi.org/10.1186/1477-3163-6-4).
- Cueva, C., M. V. Moreno-Arribas, P. J. Martín-Álvarez, G. Bills, M. F. Vicente, A. Basilio, C. L. Rivas, T. Requena, J. M. Rodríguez, and B. Bartolomé. 2010. Antimicrobial activity of phenolic acids against commensal, probiotic and pathogenic bacteria. *Research in Microbiology* 161 (5):372–82. doi: [10.1016/j.resmic.2010.04.006](https://doi.org/10.1016/j.resmic.2010.04.006).
- Cueva, C., F. Sánchez-Patán, M. Monagas, G. E. Walton, G. R. Gibson, P. J. Martín-Álvarez, B. Bartolomé, and M. V. Moreno-Arribas. 2013. *In vitro* fermentation of grape seed flavan-3-ol fractions by human faecal microbiota: Changes in microbial groups and phenolic metabolites. *FEMS Microbiology Ecology* 83 (3):792–805. doi: [10.1111/1574-6941.12037](https://doi.org/10.1111/1574-6941.12037).
- D'Agostino, E. M., D. Rossetti, D. Atkins, D. Ferdinando, and G. E. Yakubov. 2012. Interaction of tea polyphenols and food constituents with model gut epithelia: The protective role of the mucus gel layer. *Journal of Agricultural and Food Chemistry* 60:3318–28. doi: [10.1021/jf205111k](https://doi.org/10.1021/jf205111k).
- D'Argenio, G., G. Mazzone, C. Tuccillo, M. T. Ribeco, G. Graziani, A. G. Gravina, S. Caserta, S. Guido, V. Fogliano, N. Caporaso, et al. 2012. Apple polyphenols extract (APE) improves colon damage in a rat model of colitis. *Digestive and Liver Disease* 44:555–62. doi: [10.1016/j.dld.2012.01.009](https://doi.org/10.1016/j.dld.2012.01.009).
- de Souza, E. L., A. S. dos Santos, T. M. de Albuquerque, and J. L. De Brito Alves. 2019. Effects of quercetin and resveratrol on *in vitro* properties related to the functionality of potentially probiotic *Lactobacillus* strains. *Frontiers in Microbiology* 10:2229. doi: [10.3389/fmicb.2019.02229](https://doi.org/10.3389/fmicb.2019.02229).
- Denis, M.-C., Y. Desjardins, A. Furtos, V. Marcil, S. Dudonné, A. Montoudis, C. Garofalo, E. Delvin, A. Marette, and E. Levy. 2015. Prevention of oxidative stress, inflammation and mitochondrial dysfunction in the intestine by different cranberry phenolic fractions. *Clinical Science* 128 (3):197–212. doi: [10.1042/CS20140210](https://doi.org/10.1042/CS20140210).
- Denis, M.-C., Roy, D. Yeganeh, Pantea, R. Desjardins, Y. Varin, T. Haddad, N. Amre, D. Sané, Alain, T. Garofalo, C. Furtos, A, et al. 2016. Apple peel polyphenols: A key player in the prevention and treatment of experimental inflammatory bowel disease. *Clinical Science* 130 (23):2217–37. doi: [10.1042/CS20160524](https://doi.org/10.1042/CS20160524).
- Denis, M. C., A. Furtos, S. Dudonné, A. Montoudis, C. Garofalo, Y. Desjardins, E. Delvin, and E. Levy. 2013. Apple peel polyphenols and their beneficial actions on oxidative stress and inflammation. *Plos One* 8 (1):e53725. doi: [10.1371/journal.pone.0053725](https://doi.org/10.1371/journal.pone.0053725).
- During, A., C. Debouche, T. Raas, and Y. Larondelle. 2012. Among plant lignans, pinosresinol has the strongest antiinflammatory properties in human intestinal Caco-2 cells. *The Journal of Nutrition* 142 (10):1798–805. doi: [10.3945/jn.112.162453](https://doi.org/10.3945/jn.112.162453).
- Eckburg, P. B., E. M. Bik, C. N. Bernstein, E. Purdom, L. Dethlefsen, M. Sargent, S. R. Gill, K. E. Nelson, and D. A. Relman. 2005. Diversity of the human intestinal microbial flora. *Science* 308 (5728):1635–8. doi: [10.1126/science.1110591](https://doi.org/10.1126/science.1110591).
- Edmunds, S. J., N. C. Roy, D. R. Love, and W. A. Laing. 2011. Kiwifruit extracts inhibit cytokine production by lipopolysaccharide-activated macrophages, and intestinal epithelial cells isolated from IL10 gene deficient mice. *Cellular Immunology* 270 (1):70–9. doi: [10.1016/j.cellimm.2011.04.004](https://doi.org/10.1016/j.cellimm.2011.04.004).
- Everard, A., and P. D. Cani. 2013. Diabetes, obesity and gut microbiota. *Best Practice & Research. Clinical Gastroenterology* 27 (1):73–83. doi: [10.1016/j.bpg.2013.03.007](https://doi.org/10.1016/j.bpg.2013.03.007).
- Fahlgren, A., S. Hammarstrom, A. Danielsson, and M. L. Hammarstrom. 2003. Increased expression of antimicrobial peptides and lysozyme in colonic epithelial cells of patients with ulcerative colitis. *Clinical and Experimental Immunology* 131 (1):90–101. doi: [10.1046/j.1365-2249.2003.02035.x](https://doi.org/10.1046/j.1365-2249.2003.02035.x).
- Ferrari, D., A. Speciale, M. Cristani, D. Fratantonio, M. S. Molonia, G. Ranaldi, A. Saija, and F. Cimino. 2016. Cyanidin-3-O-glucoside inhibits NF- κ B signalling in intestinal epithelial cells exposed to TNF- α and exerts protective effects via Nrf2 pathway activation. *Toxicology Letters* 264:51–8. doi: [10.1016/j.toxlet.2016.10.014](https://doi.org/10.1016/j.toxlet.2016.10.014).
- Fiesel, A., D. K. Gessner, E. Most, and K. Eder. 2014. Effects of dietary polyphenol-rich plant products from grape or hop on pro-inflammatory gene expression in the intestine, nutrient digestibility and faecal microbiota of weaned pigs. *BMC Veterinary Research* 10:196. doi: [10.1186/s12917-014-0196-5](https://doi.org/10.1186/s12917-014-0196-5).
- Georgiades, P., P. D. A. Pudney, S. Rogers, D. J. Thornton, and T. A. Waigh. 2014. Tea derived galloylated polyphenols cross-link purified gastrointestinal mucins. *Plos One* 9 (8):e105302. doi: [10.1371/journal.pone.0105302](https://doi.org/10.1371/journal.pone.0105302).
- Ghanim, H., C. L. Sia, K. Korzeniewski, T. Lohano, S. Abuaysheh, A. Marumganti, A. Chaudhuri, and P. Dandona. 2011. A resveratrol and polyphenol preparation suppresses oxidative and inflammatory stress response to a high-fat, high-carbohydrate meal. *Journal of Clinical Endocrinology and Metabolism* 96 (5):1409–14. doi: [10.1210/jc.2010-1812](https://doi.org/10.1210/jc.2010-1812).
- Ghoshal, U. C., R. Shukla, U. Ghoshal, K.-A. Gwee, S. C. Ng, and E. M. M. Quigley. 2012. The gut microbiota and irritable bowel syndrome: Friend or foe? *International Journal of Inflammation* 2012:151085. doi: [10.1155/2012/151085](https://doi.org/10.1155/2012/151085).
- González-Reyes, S., S. Guzmán-Beltrán, O. N. Medina-Campos, and J. Pedraza-Chaverri. 2013. Curcumin pretreatment induces Nrf2 and an antioxidant response and prevents hemin-induced toxicity in primary cultures of cerebellar granule neurons of rats. *Oxidative Medicine and Cellular Longevity* 2013:1–14.
- Gu, L., N. Li, J. Gong, Q. Li, W. Zhu, and J. Li. 2011. Berberine ameliorates intestinal epithelial tight-junction damage and down-regulates myosin light chain kinase pathways in a mouse model of endotoxemia. *The Journal of Infectious Diseases* 203 (11):1602–12. doi: [10.1093/infdis/jir147](https://doi.org/10.1093/infdis/jir147).
- Guinane, C. M., and P. D. Cotter. 2013. Role of the gut microbiota in health and chronic gastrointestinal disease: Understanding a hidden metabolic organ. *Therapeutic Advances in Gastroenterology* 6 (4):295–308. doi: [10.1177/1756283X13482996](https://doi.org/10.1177/1756283X13482996).
- Gumbiner, B. M. 1993. Breaking through the tight junction barrier. *The Journal of Cell Biology* 123 (6):1631–1633. doi: [10.1083/jcb.123.6.1631](https://doi.org/10.1083/jcb.123.6.1631).
- Guo, W., E. Kong, and M. Meydani. 2009. Dietary polyphenols, inflammation, and cancer. *Nutrition and Cancer* 61 (6):807–10. doi: [10.1080/01635580903285098](https://doi.org/10.1080/01635580903285098).
- Gwiazdowska, D., K. Juś, J. Jasnowska-Malecka, and K. Kluczyńska. 2015. The impact of polyphenols on *Bifidobacterium* growth. *Acta Biochimica Polonica* 62 (4):895–901. doi: [10.18388/abp.2015_1154](https://doi.org/10.18388/abp.2015_1154).
- Haklar, G., E. Sayin-Özveri, M. Yüksel, A. Ö. Aktan, and A. S. Yalçin. 2001. Different kinds of reactive oxygen and nitrogen species were detected in colon and breast tumors. *Cancer Letters* 165 (2):219–24. doi: [10.1016/S0304-3835\(01\)00421-9](https://doi.org/10.1016/S0304-3835(01)00421-9).
- Halliwell, B. 2008. Are polyphenols antioxidants or pro-oxidants? What do we learn from cell culture and *in vivo* studies? *Archives of Biochemistry and Biophysics* 476 (2):107–12. doi: [10.1016/j.abb.2008.01.028](https://doi.org/10.1016/j.abb.2008.01.028).
- Han, M., P. Song, C. Huang, A. Rezaei, S. Farrar, M. A. Brown, and X. Ma. 2016. Dietary grape seed proanthocyanidins (GSPs) improve weaned intestinal microbiota and mucosal barrier using a piglet model. *Oncotarget* 7 (49):80313–26. doi: [10.18632/oncotarget.13450](https://doi.org/10.18632/oncotarget.13450).
- Kim, H., N. Banerjee, R. C. Barnes, C. M. Pfent, S. T. Talcott, R. H. Dashwood, and S. U. Mertens-Talcott. 2017. Mango polyphenolics reduce inflammation in intestinal colitis—involvement of the miR-126/PI3K/AKT/mTOR axis *in vitro* and *in vivo*. *Molecular Carcinogenesis* 56:197–207.
- Isabel, V., S. F. Susana, and D. L. L. C. Alarcón. 2011. Chemopreventive effect of dietary curcumin on inflammation-induced colorectal carcinogenesis in mice. *Molecular Nutrition & Food Research* 55:259–67.
- Jang, S., J. Sun, P. Chen, S. Lakshman, A. Molokin, J. M. Harnly, B. T. Vinyard, J. F. Urban, Jr., C. D. Davis, and G. Solano-Aguilar. 2016. Flavanol-enriched cocoa powder alters the intestinal microbiota, tissue and fluid metabolite profiles, and intestinal gene expression in

- pigs. *The Journal of Nutrition* 146 (4):673–80. doi: [10.3945/jn.115.222968](https://doi.org/10.3945/jn.115.222968).
- Jones, E., and R. Hughes. 1982. Quercetin, flavonoids and the life-span of mice. *Experimental Gerontology* 17 (3):213–7. doi: [10.1016/0531-5565\(82\)90027-4](https://doi.org/10.1016/0531-5565(82)90027-4).
- Jung, H., L. Eckmann, S. Yang, A. Panja, J. Fierer, E. Morzycka-Wroblewska, and M. Kagnoff. 1995. A distinct array of proinflammatory cytokines is expressed in human colon epithelial cells in response to bacterial invasion. *Journal of Clinical Investigation* 95 (1):55–65. doi: [10.1172/JCI117676](https://doi.org/10.1172/JCI117676).
- Kamiloglu, S., C. Grootaert, E. Capanoglu, C. Ozkan, G. Smagghe, K. Raes, and J. Camp. 2017. Anti-inflammatory potential of black carrot (*Daucus carota* L.) polyphenols in a co-culture model of intestinal Caco-2 and endothelial EA.hy926 cells. *Molecular Nutrition & Food Research* 61 (2):1600455. doi: [10.1002/mnfr.201600455](https://doi.org/10.1002/mnfr.201600455).
- Kau, A. L., P. P. Ahern, N. W. Griffin, A. L. Goodman, and J. I. Gordon. 2011. Human nutrition, the gut microbiome and the immune system. *Nature* 474 (7351):327–36. doi: [10.1038/nature10213](https://doi.org/10.1038/nature10213).
- Khan, H. Y., H. Zubair, M. Faisal, M. F. Ullah, M. Farhan, F. H. Sarkar, A. Ahmad, and S. M. Hadi. 2014. Plant polyphenol induced cell death in human cancer cells involves mobilization of intracellular copper ions and reactive oxygen species generation: A mechanism for cancer chemopreventive action. *Molecular Nutrition & Food Research* 58 (3):437–46. doi: [10.1002/mnfr.201300417](https://doi.org/10.1002/mnfr.201300417).
- Kilua, A., R. Nomata, R. Nagata, N. Fukuma, K. Shimada, K.-H. Han, and M. Fukushima. 2019. Purple sweet potato polyphenols differentially influence the microbial composition depending on the fermentability of dietary fiber in a mixed culture of swine fecal bacteria. *Nutrients* 11 (7):1495. doi: [10.3390/nu11071495](https://doi.org/10.3390/nu11071495).
- Kim, H., N. Banerjee, M. A. Sirven, Y. Minamoto, M. E. Markel, J. S. Suchodolski, S. T. Talcott, and S. U. Mertens-Talcott. 2017. Pomegranate polyphenolics reduce inflammation and ulceration in intestinal colitis—involved of the miR-145/p70S6K1/HIF1 α axis *in vivo* and *in vitro*. *Journal of Nutritional Biochemistry* 43:107–15. doi: [10.1016/j.jnutbio.2017.02.005](https://doi.org/10.1016/j.jnutbio.2017.02.005).
- Kim, Y. H., H.-S. Kwon, D. H. Kim, H. J. Cho, H. S. Lee, J.-G. Jun, J. H. Y. Park, and J.-K. Kim. 2008. Piceatannol, a stilbene present in grapes, attenuates dextran sulfate sodium-induced colitis. *International Immunopharmacology* 8 (12):1695–702.
- Kim, Y. S., and S. B. Ho. 2010. Intestinal goblet cells and mucins in health and disease: Recent insights and progress. *Current Gastroenterology Reports* 12 (5):319–30. doi: [10.1007/s11894-010-0131-2](https://doi.org/10.1007/s11894-010-0131-2).
- Krajmalnik-Brown, R., Z.-E. Ilhan, D.-W. Kang, and J. K. DiBaise. 2012. Effects of gut microbes on nutrient absorption and energy regulation. *Nutrition in Clinical Practice* 27 (2):201–14. doi: [10.1177/0884533611436116](https://doi.org/10.1177/0884533611436116).
- Lee, H. C., A. M. Jenner, C. S. Low, and Y. K. Lee. 2006. Effect of tea phenolics and their aromatic fecal bacterial metabolites on intestinal microbiota. *Research in Microbiology* 157 (9):876–84. doi: [10.1016/j.resmic.2006.07.004](https://doi.org/10.1016/j.resmic.2006.07.004).
- Lee, J. S., S.-Y. Park, D. Thapa, M. K. Choi, I.-M. Chung, Y.-J. Park, C. S. Yong, H. G. Choi, and J.-A. Kim. 2010. *Grifola frondosa* water extract alleviates intestinal inflammation by suppressing TNF- α production and its signaling. *Experimental and Molecular Medicine* 42 (2):143. doi: [10.3858/emmm.2010.42.2.016](https://doi.org/10.3858/emmm.2010.42.2.016).
- Lee, W.-L., J.-Y. Huang, and L.-F. Shyur. 2013. Phytoagents for cancer management: Regulation of nucleic acid oxidation, ROS, and related mechanisms. *Oxidative Medicine and Cellular Longevity* 2013:1–22. doi: [10.1155/2013/925804](https://doi.org/10.1155/2013/925804).
- León-González, A. J., C. Auger, and V. B. Schini-Kerth. 2015. Pro-oxidant activity of polyphenols and its implication on cancer chemoprevention and chemotherapy. *Biochemical Pharmacology* 98 (3): 371–80. doi: [10.1016/j.bcp.2015.07.017](https://doi.org/10.1016/j.bcp.2015.07.017).
- Li, H. L., Z. J. Li, Z.-S. Wei, T. Liu, X. Z. Zou, Y. Liao, and Y. Luo. 2015. Long-term effects of oral tea polyphenols and *Lactobacillus brevis* M8 on biochemical parameters, digestive enzymes, and cytokines expression in broilers. *Journal of Zhejiang University-Science B* 16 (12):1019–26. doi: [10.1631/jzus.B1500160](https://doi.org/10.1631/jzus.B1500160).
- Lian, P. Y., T. Maseko, M. Rhee, and K. Ng. 2012. The antimicrobial effects of cranberry against *Staphylococcus aureus*. *Food Science and Technology International* 18 (2):179–86. doi: [10.1177/1082013211415159](https://doi.org/10.1177/1082013211415159).
- Lindén, S. K., T. H. J. Florin, and M. A. McGuckin. 2008. Mucin dynamics in intestinal bacterial infection. *Plos One* 3 (12):e3952. doi: [10.1371/journal.pone.0003952](https://doi.org/10.1371/journal.pone.0003952).
- Linden, S. K., P. Sutton, N. G. Karlsson, V. Korolik, and M. A. McGuckin. 2008. Mucins in the mucosal barrier to infection. *Mucosal Immunology* 1 (3):183–97. doi: [10.1038/mi.2008.5](https://doi.org/10.1038/mi.2008.5).
- Ling, K., L. Wan, H. El-Nezami, and M. Wang. 2016. Protective capacity of resveratrol, a red wine constituent polyphenol against deoxynivalenol-induced intestinal barrier dysfunction and bacterial translocation. *Chemical Research in Toxicology* 29 (5):823–33. doi: [10.1021/acs.chemrestox.6b00001](https://doi.org/10.1021/acs.chemrestox.6b00001).
- Link, A., F. Balaguer, and A. Goel. 2010. Cancer chemoprevention by dietary polyphenols: Promising role for epigenetics. *Biochemical Pharmacology* 80 (12):1771–92. doi: [10.1016/j.bcp.2010.06.036](https://doi.org/10.1016/j.bcp.2010.06.036).
- Liou, G.-Y., and P. Storz. 2010. Reactive oxygen species in cancer. *Free Radical Research* 44 (5):479–96. doi: [10.3109/10715761003667554](https://doi.org/10.3109/10715761003667554).
- Liu, H., X. Liu, C. Zhang, H. Zhu, Q. Xu, Y. Bu, and Y. Lei. 2017. Redox imbalance in the development of colorectal cancer. *Journal of Cancer* 8 (9):1586–97. doi: [10.7150/jca.18735](https://doi.org/10.7150/jca.18735).
- Lombardo Bedran, T. B., K. Feghali, L. Zhao, D. M. Palomari Spolidorio, and D. Grenier. 2014. Green tea extract and its major constituent, epigallocatechin-3-gallate, induce epithelial beta-defensin secretion and prevent beta-defensin degradation by *Porphyromonas gingivalis*. *Journal of Periodontal Research* 49 (5):615–23. doi: [10.1111/jre.12142](https://doi.org/10.1111/jre.12142).
- Lombardo Bedran, T. B., M.-P. Morin, D. Palomari Spolidorio, and D. Grenier. 2015. Black tea extract and its theaflavin derivatives inhibit the growth of periodontopathogens and modulate interleukin-8 and β -defensin secretion in oral epithelial cells. *Plos One* 10 (11): e0143158. doi: [10.1371/journal.pone.0143158](https://doi.org/10.1371/journal.pone.0143158).
- Ma, C., Y. Wang, L. Dong, M. Li, and W. Cai. 2015. Anti-inflammatory effect of resveratrol through the suppression of NF- κ B and JAK/STAT signaling pathways. *Acta Biochimica et Biophysica Sinica* 47 (3):207–13. doi: [10.1093/abbs/gmu135](https://doi.org/10.1093/abbs/gmu135).
- Madara, J. L. 1983. Increases in guinea pig small intestinal transepithelial resistance induced by osmotic loads are accompanied by rapid alterations in absorptive cell tight junction structure. *The Journal of Cell Biology* 97 (1):125–36. doi: [10.1083/jcb.97.1.125](https://doi.org/10.1083/jcb.97.1.125).
- Madara, J. L., and J. S. Trier. 1994. The functional morphology of the mucosa of the small intestine. In *Physiology of the gastrointestinal tract*, ed. L. R. Johnson, 1577–1622. New York: Raven.
- Maity, S., A. Ukil, S. Karmakar, N. Datta, T. Chaudhuri, J. R. Vedasiromoni, D. K. Ganguly, and P. K. Das. 2003. Thearubigin, the major polyphenol of black tea, ameliorates mucosal injury in trinitrobenzene sulfonic acid-induced colitis. *European Journal of Pharmacology* 470 (1-2):103–12. doi: [10.1016/S0014-2999\(03\)01760-6](https://doi.org/10.1016/S0014-2999(03)01760-6).
- Manach, C., A. Scalbert, C. Morand, C. Remesy, and L. Jimenez. 2004. Polyphenols: Food sources and bioavailability. *The American Journal of Clinical Nutrition* 79 (5):727–47. doi: [10.1093/ajcn/79.5.727](https://doi.org/10.1093/ajcn/79.5.727).
- Mandel, S., and M. B. Youdim. 2004. Catechin polyphenols: Neurodegeneration and neuroprotection in neurodegenerative diseases. *Free Radical Biology and Medicine* 37 (3):304–17. doi: [10.1016/j.freeradbiomed.2004.04.012](https://doi.org/10.1016/j.freeradbiomed.2004.04.012).
- Mansoorian, B., E. Combet, A. Alkhalidi, A. Garcia, and C. Edwards. 2019. Impact of fermentable fibres on the colonic microbiota metabolism of dietary polyphenols rutin and quercetin. *International Journal of Environmental Research and Public Health* 16: E292.
- Mantis, N. J., N. Rol, and B. Corthesy. 2011. Secretory IgA's complex roles in immunity and mucosal homeostasis in the gut. *Mucosal Immunology* 4 (6):603–11. doi: [10.1038/mi.2011.41](https://doi.org/10.1038/mi.2011.41).
- Marín, L., E. M. Miguélez, C. J. Villar, and F. Lombó. 2015. Bioavailability of dietary polyphenols and gut microbiota metabolism: Antimicrobial properties. *Biomed Research International* 2015: 1–18. doi: [10.1155/2015/905215](https://doi.org/10.1155/2015/905215).

- Marín, M., R. María Giner, J.-L. Ríos, and M. Carmen Recio. 2013. Intestinal anti-inflammatory activity of ellagic acid in the acute and chronic dextrane sulfate sodium models of mice colitis. *Journal of Ethnopharmacology* 150 (3):925–34. doi: [10.1016/j.jep.2013.09.030](https://doi.org/10.1016/j.jep.2013.09.030).
- Martin, A. R., I. Villegas, C. La Casa, and C. A. de la Lastra. 2004. Resveratrol, a polyphenol found in grapes, suppresses oxidative damage and stimulates apoptosis during early colonic inflammation in rats. *Biochemical Pharmacology* 67:1399–410.
- Massot-Cladera, M., M. Abril-Gil, S. Torres, À. Franch, M. Castell, and F. J. Pérez-Cano. 2014. Impact of cocoa polyphenol extracts on the immune system and microbiota in two strains of young rats. *British Journal of Nutrition* 112 (12):1944–54. doi: [10.1017/S0007114514003080](https://doi.org/10.1017/S0007114514003080).
- Massot-Cladera, M., À. Franch, C. Castellote, M. Castell, and F. Pérez-Cano. 2013. Cocoa flavonoid-enriched diet modulates systemic and intestinal immunoglobulin synthesis in adult Lewis rats. *Nutrients* 5 (8):3272–86. doi: [10.3390/nu5083272](https://doi.org/10.3390/nu5083272).
- Massot-Cladera, M., T. Pérez-Berezo, A. Franch, M. Castell, and F. J. Pérez-Cano. 2012. Cocoa modulatory effect on rat faecal microbiota and colonic crosstalk. *Archives of Biochemistry and Biophysics* 527 (2):105–12. doi: [10.1016/j.abb.2012.05.015](https://doi.org/10.1016/j.abb.2012.05.015).
- Mayta-Apaza, A. C., E. Pottgen, J. De Bodt, N. Papp, D. Marasini, L. Howard, L. Abranko, T. Van de Wiele, S.-O. Lee, and F. Carbonero. 2018. Impact of tart cherries polyphenols on the human gut microbiota and phenolic metabolites *in vitro* and *in vivo*. *The Journal of Nutritional Biochemistry* 59:160–72. doi: [10.1016/j.jnutbio.2018.04.001](https://doi.org/10.1016/j.jnutbio.2018.04.001).
- Mazzon, E., C. Muià, R. D. Paola, T. Genovese, M. Menegazzi, A. De Sarro, H. Suzuki, and S. Cuzzocrea. 2005. Green tea polyphenol extract attenuates colon injury induced by experimental colitis. *Free Radical Research* 39 (9):1017–25. doi: [10.1080/10715760500197177](https://doi.org/10.1080/10715760500197177).
- Middleton, E., C. Kandaswami, and T. C. Theoharides. 2000. The effects of plant flavonoids on mammalian cells: Implications for inflammation, heart disease, and cancer. *Pharmacological Reviews* 52 (4):673–751.
- Mihye, K., M. Akira, M. Shingo, T. Takuji, and O. Hajime. 2010. The modifying effects of green tea polyphenols on acute colitis and inflammation-associated colon carcinogenesis in male ICR mice. *BioFactors* 36:43–51.
- Molan, A., M. Lila, J. Mawson, and S. De. 2009. *In vitro* and *in vivo* evaluation of the prebiotic activity of water-soluble blueberry extracts. *World Journal of Microbiology and Biotechnology* 25 (7):1243–49. doi: [10.1007/s11274-009-0011-9](https://doi.org/10.1007/s11274-009-0011-9).
- Morgan, X. C., T. L. Tickle, H. Sokol, D. Gevers, K. L. Devaney, D. V. Ward, J. A. Reyes, S. A. Shah, N. LeLeiko, S. B. Snapper, et al. 2012. Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. *Genome Biology* 13 (9):R79. doi: [10.1186/gb-2012-13-9-r79](https://doi.org/10.1186/gb-2012-13-9-r79).
- Ni, J., G. D. Wu, L. Albenberg, and V. T. Tomov. 2017. Gut microbiota and IBD: Causation or correlation? *Nature Reviews Gastroenterology & Hepatology* 14 (10):573–84. doi: [10.1038/nrgastro.2017.88](https://doi.org/10.1038/nrgastro.2017.88).
- Nicod, N., G. Chiva-Blanch, E. Giordano, A. Dávalos, R. S. Parker, and F. Visioli. 2014. Green tea, cocoa, and red wine polyphenols moderately modulate intestinal inflammation and do not increase high-density lipoprotein (HDL) production. *Journal of Agricultural and Food Chemistry* 62 (10):2228–32.
- Nohynek, L. J., H.-L. Alakomi, M. P. Kähkönen, M. Heinonen, I. M. Helander, K.-M. Oksman-Caldentey, and R. H. Puupponen-Pimiä. 2006. Berry phenolics: Antimicrobial properties and mechanisms of action against severe human pathogens. *Nutrition and Cancer* 54 (1):18–32.
- Nunes, C., E. Ferreira, V. Freitas, L. Almeida, R. M. Barbosa, and J. Laranjinha. 2013. Intestinal anti-inflammatory activity of red wine extract: Unveiling the mechanisms in colonic epithelial cells. *Food & Function* 4 (3):373–83. doi: [10.1039/C2FO30233K](https://doi.org/10.1039/C2FO30233K).
- Okayasu, I., S. Hatakeyama, M. Yamada, T. Ohkusa, Y. Inagaki, and R. Nakaya. 1990. A novel method in the induction of reliable experimental acute and chronic ulcerative colitis in mice. *Gastroenterology* 98 (3):694–702. doi: [10.1016/0016-5085\(90\)90290-H](https://doi.org/10.1016/0016-5085(90)90290-H).
- Okazaki, Y., Y. Han, M. Kayahara, T. Watanabe, H. Arishige, and N. Kato. 2010. Consumption of curcumin elevates fecal immunoglobulin A, an index of intestinal immune function, in rats fed a high-fat diet. *Journal of Nutritional Science and Vitaminology* 56 (1):68–71.
- Okubo, T., N. Ishihara, A. Oura, M. Serit, M. Kim, T. Yamamoto, and T. Mitsuoka. 1992. *In vivo* effects of tea polyphenol intake on human intestinal microflora and metabolism. *Bioscience, Biotechnology, and Biochemistry* 56 (4):588–91. doi: [10.1271/bbb.56.588](https://doi.org/10.1271/bbb.56.588).
- Oz, H. S., and J. L. Ebersole. 2010. Green tea polyphenols mediated apoptosis in intestinal epithelial cells by a FADD-dependent pathway. *Journal of Cancer Therapy* 1:105–13. doi: [10.4236/jct.2010.13018](https://doi.org/10.4236/jct.2010.13018).
- Ozdam, T., D. A. Sela, J. Xiao, D. Boyacioglu, F. Chen, and E. Capanoglu. 2016. The reciprocal interactions between polyphenols and gut microbiota and effects on bioaccessibility. *Nutrients* 8 (2):78. doi: [10.3390/nu8020078](https://doi.org/10.3390/nu8020078).
- Pandey, K. B., and S. I. Rizvi. 2009. Plant polyphenols as dietary antioxidants in human health and disease. *Oxidative Medicine and Cellular Longevity* 2 (5):270–8. doi: [10.4161/oxim.2.5.9498](https://doi.org/10.4161/oxim.2.5.9498).
- Pandurangan, A. K., N. Mohebbi, N. Mohd. Esa, C. Y. Looi, S. Ismail, and Z. Saadatdoust. 2015. Gallic acid suppresses inflammation in dextran sodium sulfate-induced colitis in mice: Possible mechanisms. *International Immunopharmacology* 28 (2):1034–43. doi: [10.1016/j.intimp.2015.08.019](https://doi.org/10.1016/j.intimp.2015.08.019).
- Parker, S. G., T. M. Trower, and D. E. Stevenson. 2013. Fecal microbial metabolism of polyphenols and its effects on human gut microbiota. *Anaerobe* 23:12–19. doi: [10.1016/j.anaerobe.2013.07.009](https://doi.org/10.1016/j.anaerobe.2013.07.009).
- Pastene, E., H. Speisky, A. García, J. Moreno, M. Troncoso, and G. Figueroa. 2010. *In vitro* and *in vivo* effects of apple peel polyphenols against *Helicobacter pylori*. *Journal of Agricultural and Food Chemistry* 58 (12):7172–9. doi: [10.1021/jf100274g](https://doi.org/10.1021/jf100274g).
- Patil, A., A. L. Hughes, and G. Zhang. 2004. Rapid evolution and diversification of mammalian α -defensins as revealed by comparative analysis of rodent and primate genes. *Physiological Genomics* 20 (1):1–11. doi: [10.1152/physiolgenomics.00150.2004](https://doi.org/10.1152/physiolgenomics.00150.2004).
- Pérez-Berezo, T., A. Franch, C. Castellote, M. Castell, and F. J. Pérez-Cano. 2012. Mechanisms involved in down-regulation of intestinal IgA in rats by high cocoa intake. *Journal of Nutritional Biochemistry* 23 (7):838–44. doi: [10.1016/j.jnutbio.2011.04.008](https://doi.org/10.1016/j.jnutbio.2011.04.008).
- Perše, M. 2013. Oxidative stress in the pathogenesis of colorectal cancer: Cause or consequence? *Biomed Research International* 2013:1–9. doi: [10.1155/2013/725710](https://doi.org/10.1155/2013/725710).
- Phalipon, A., A. Cardona, J. P. Kraehenbuhl, L. Edelman, P. J. Sansonetti, and B. Corthesy. 2002. Secretory component: A new role in secretory IgA-mediated immune exclusion *in vivo*. *Immunity* 17 (1):107–15. doi: [10.1016/S1074-7613\(02\)00341-2](https://doi.org/10.1016/S1074-7613(02)00341-2).
- Pierre, J. F., A. F. Heneghan, R. P. Feliciano, D. Shanmuganayagam, C. G. Krueger, J. D. Reed, and K. A. Kudsk. 2014. Cranberry proanthocyanidins improve intestinal sIgA during elemental enteral nutrition. *Journal of Parenteral and Enteral Nutrition* 38 (1):107–14. doi: [10.1177/0148607112473654](https://doi.org/10.1177/0148607112473654).
- Pineiro, M., N. Asp, G. Reid, S. Macfarlane, L. Morelli, O. Brunser, and K. Tuohy. 2008. FAO technical meeting on prebiotics. *Journal of Clinical Gastroenterology* 42:S156–S9. doi: [10.1097/MCG.0b013e31817f184e](https://doi.org/10.1097/MCG.0b013e31817f184e).
- Puleston, J., M. Cooper, S. Murch, K. Bid, S. Makh, P. Ashwood, A. H. Bingham, H. Green, P. Moss, A. Dhillon, et al. 2005. A distinct subset of chemokines dominates the mucosal chemokine response in inflammatory bowel disease. *Alimentary Pharmacology and Therapeutics* 21 (2):109–20. doi: [10.1111/j.1365-2036.2004.02262.x](https://doi.org/10.1111/j.1365-2036.2004.02262.x).
- Puupponen-Pimiä, R., L. Nohynek, C. Meier, M. Kähkönen, M. Heinonen, A. Hopia, and K.-M. Oksman-Caldentey. 2001. Antimicrobial properties of phenolic compounds from berries. *Journal of Applied Microbiology* 90:494–507. doi: [10.1046/j.1365-2672.2001.01271.x](https://doi.org/10.1046/j.1365-2672.2001.01271.x).
- Qin, B., H. D. Dawson, N. W. Schoene, M. M. Polansky, and R. A. Anderson. 2012. Cinnamon polyphenols regulate multiple metabolic pathways involved in insulin signaling and intestinal lipoprotein

- metabolism of small intestinal enterocytes. *Nutrition* 28 (11-12): 1172-9. doi: [10.1016/j.nut.2012.03.020](https://doi.org/10.1016/j.nut.2012.03.020).
- Queipo-Ortuño, M. I., M. Boto-Ordóñez, M. Murri, J. M. Gomez-Zumaquero, M. Clemente-Postigo, R. Estruch, F. Cardona Diaz, C. Andrés-Lacueva, and F. J. Tinahones. 2012. Influence of red wine polyphenols and ethanol on the gut microbiota ecology and biochemical biomarkers. *The American Journal of Clinical Nutrition* 95 (6):1323-34. doi: [10.3945/ajcn.111.027847](https://doi.org/10.3945/ajcn.111.027847).
- Radovanović, B. C., A. S. M. Andelković, A. B. Radovanović, and M. Z. Andelković. 2013. Antioxidant and antimicrobial activity of polyphenol extracts from wild berry fruits grown in Southeast Serbia. *Tropical Journal of Pharmaceutical Research* 12:813-9.
- Rainis, T., I. Maor, A. Lanir, S. Shnizer, and A. Lavy. 2007. Enhanced oxidative stress and leucocyte activation in neoplastic tissues of the colon. *Digestive Diseases and Sciences* 52 (2):526-30. doi: [10.1007/s10620-006-9177-2](https://doi.org/10.1007/s10620-006-9177-2).
- Ramos, S. 2008. Cancer chemoprevention and chemotherapy: Dietary polyphenols and signalling pathways. *Molecular Nutrition & Food Research* 52 (5):507-26. doi: [10.1002/mnfr.200700326](https://doi.org/10.1002/mnfr.200700326).
- Ridaura, V. K., J. J. Faith, F. E. Rey, J. Cheng, A. E. Duncan, A. L. Kau, N. W. Griffin, V. Lombard, B. Henrissat, J. R. Bain, et al. 2013. Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science* 341 (6150):1241214. doi: [10.1126/science.1241214](https://doi.org/10.1126/science.1241214).
- Rodríguez-Ramiro, I., S. Ramos, E. López-Oliva, A. Agis-Torres, L. Bravo, L. Goya, and M. A. Martín. 2013. Cocoa polyphenols prevent inflammation in the colon of azoxymethane-treated rats and in TNF- α -stimulated Caco-2 cells. *British Journal of Nutrition* 110 (2): 206-15. doi: [10.1017/S0007114512004862](https://doi.org/10.1017/S0007114512004862).
- Romier, B., Y.-J. Schneider, Y. Larondelle, and A. During. 2009. Dietary polyphenols can modulate the intestinal inflammatory response. *Nutrition Reviews* 67 (7):363-78. doi: [10.1111/j.1753-4887.2009.00210.x](https://doi.org/10.1111/j.1753-4887.2009.00210.x).
- Romier, B., J. Van De Walle, A. During, Y. Larondelle, and Y.-J. Schneider. 2008. Modulation of signalling nuclear factor- κ B activation pathway by polyphenols in human intestinal Caco-2 cells. *British Journal of Nutrition* 100 (03):542-51. doi: [10.1017/S0007114508966666](https://doi.org/10.1017/S0007114508966666).
- Romier-Crouzet, B., J. Van De Walle, A. During, A. Joly, C. Rousseau, O. Henry, Y. Larondelle, and Y.-J. Schneider. 2009. Inhibition of inflammatory mediators by polyphenolic plant extracts in human intestinal Caco-2 cells. *Food and Chemical Toxicology* 47 (6): 1221-30. doi: [10.1016/j.fct.2009.02.015](https://doi.org/10.1016/j.fct.2009.02.015).
- Rosillo, M. A., M. Sanchez-Hidalgo, A. Cárdeno, and C. Alarcón de la Lastra. 2011. Protective effect of ellagic acid, a natural polyphenolic compound, in a murine model of Crohn's disease. *Biochemical Pharmacology* 82 (7):737-45. doi: [10.1016/j.bcp.2011.06.043](https://doi.org/10.1016/j.bcp.2011.06.043).
- Ross, J., and C. Kasum. 2002. Dietary flavonoids: Bioavailability, metabolic effects, and safety. *Annual Review of Nutrition* 22 (1):19-34. doi: [10.1146/annurev.nutr.22.1.1401.144957](https://doi.org/10.1146/annurev.nutr.22.1.1401.144957).
- Ruan, Z., S. Liu, Y. Zhou, S. Mi, G. Liu, X. Wu, K. Yao, H. Assaad, Z. Deng, Y. Hou, et al. 2014. Chlorogenic acid decreases intestinal permeability and increases expression of intestinal tight junction proteins in weaned rats challenged with LPS. *Plos One* 9 (6):e97815. doi: [10.1371/journal.pone.0097815](https://doi.org/10.1371/journal.pone.0097815).
- Ruiz, P. A., A. Braune, G. Hölzlwimmer, L. Quintanilla-Fend, and D. Haller. 2007. Quercetin inhibits TNF-induced NF- κ B transcription factor recruitment to proinflammatory gene promoters in murine intestinal epithelial cells. *The Journal of Nutrition* 137 (5):1208-15. doi: [10.1093/jn/137.5.1208](https://doi.org/10.1093/jn/137.5.1208).
- Ruiz, P. A., and D. Haller. 2006. Functional diversity of flavonoids in the inhibition of the proinflammatory NF- κ B, IRF, and Akt signalling pathways in murine intestinal epithelial cells. *The Journal of Nutrition* 136 (3):664-1. doi: [10.1093/jn/136.3.664](https://doi.org/10.1093/jn/136.3.664).
- Rupasinghe, H. P. V., I. Parmar, and S. V. Neir. 2019. Biotransformation of cranberry proanthocyanidins to probiotic metabolites by enhances their anticancer activity in HepG2 cells. *Oxidative Medicine and Cellular Longevity* 2019:1-14. doi: [10.1155/2019/4750795](https://doi.org/10.1155/2019/4750795).
- Sabu, M., K. Smitha, and R. Kuttan. 2002. Anti-diabetic activity of green tea polyphenols and their role in reducing oxidative stress in experimental diabetes. *Journal of Ethnopharmacology* 83:109-16. doi: [10.1016/S0378-8741\(02\)00217-9](https://doi.org/10.1016/S0378-8741(02)00217-9).
- Sahin, K., M. Tuzcu, H. Gencoglu, A. Dogukan, M. Timurkan, N. Sahin, A. Aslan, and O. Kucuk. 2010. Epigallocatechin-3-gallate activates Nrf2/HO-1 signaling pathway in cisplatin-induced nephrotoxicity in rats. *Life Sciences* 87 (7-8):240-5. doi: [10.1016/j.lfs.2010.06.014](https://doi.org/10.1016/j.lfs.2010.06.014).
- Sánchez-Fidalgo, S., A. Cárdeno, I. Villegas, E. Talero, and C. A. de la Lastra. 2010. Dietary supplementation of resveratrol attenuates chronic colonic inflammation in mice. *European Journal of Pharmacology* 633 (1-3):78-84. doi: [10.1016/j.ejphar.2010.01.025](https://doi.org/10.1016/j.ejphar.2010.01.025).
- Sánchez-Patán, F., E. Barroso, T. van de Wiele, A. Jiménez-Girón, P. J. Martín-Alvarez, M. V. Moreno-Arribas, M. C. Martínez-Cuesta, C. Peláez, T. Requena, and B. Bartolomé. 2015. Comparative *in vitro* fermentations of cranberry and grape seed polyphenols with colonic microbiota. *Food Chemistry* 183:273-82.
- Sánchez-Patán, F., C. Cueva, M. Monagas, G. E. Walton, G. R. Gibson, M. J. E. Quintanilla-López, R. Lebrón-Aguilar, P. J. Martín-Alvarez, M. V. Moreno-Arribas, and B. Bartolomé. 2012. *In vitro* fermentation of a red wine extract by human gut microbiota: Changes in microbial groups and formation of phenolic metabolites. *Journal of Agricultural and Food Chemistry* 60 (9):2136-47. doi: [10.1021/jf2040115](https://doi.org/10.1021/jf2040115).
- Scalbert, A., and G. Williamson. 2000. Dietary intake and bioavailability of polyphenols. *The Journal of Nutrition* 130 (8):2073S-85S. doi: [10.1093/jn/130.8.2073S](https://doi.org/10.1093/jn/130.8.2073S).
- Schoefer, L., R. Mohan, A. Schwiertz, A. Braune, and M. Blaut. 2003. Anaerobic degradation of flavonoids by *Clostridium orbiscindens*. *Applied and Environmental Microbiology* 69 (10):5849-54. doi: [10.1128/AEM.69.10.5849-5854.2003](https://doi.org/10.1128/AEM.69.10.5849-5854.2003).
- Selma, M. V., J. C. Espín, and F. A. Tomás-Barberán. 2009. Interaction between phenolics and gut microbiota: Role in human health. *Journal of Agricultural and Food Chemistry* 57 (15):6485-501. doi: [10.1021/jf902107d](https://doi.org/10.1021/jf902107d).
- Sergeant, T., N. Piron, J. Meurice, O. Toussaint, and Y.-J. Schneider. 2010. Anti-inflammatory effects of dietary phenolic compounds in an *in vitro* model of inflamed human intestinal epithelium. *Chemico-Biological Interactions* 188 (3):659-67. doi: [10.1016/j.cbi.2010.08.007](https://doi.org/10.1016/j.cbi.2010.08.007).
- Serra, D., J. Paixão, C. Nunes, T. C. P. Dinis, and L. M. Almeida. 2013. Cyanidin-3-glucoside suppresses cytokine-induced inflammatory response in human intestinal cells: Comparison with 5-aminosalicylic acid. *Plos One* 8 (9):e73001. doi: [10.1371/journal.pone.0073001](https://doi.org/10.1371/journal.pone.0073001).
- Shakibaei, M., T. John, G. Schulze-Tanzil, I. Lehmann, and A. Mobasher. 2007. Suppression of NF- κ B activation by curcumin leads to inhibition of expression of cyclo-oxygenase-2 and matrix metalloproteinase-9 in human articular chondrocytes: Implications for the treatment of osteoarthritis. *Biochemical Pharmacology* 73 (9): 1434-45. doi: [10.1016/j.bcp.2007.01.005](https://doi.org/10.1016/j.bcp.2007.01.005).
- Shapiro, H., P. Singer, Z. Halpern, and R. Bruck. 2007. Polyphenols in the treatment of inflammatory bowel disease and acute pancreatitis. *Gut* 56 (3):426-36. doi: [10.1136/gut.2006.094599](https://doi.org/10.1136/gut.2006.094599).
- Shen, X., X. Sun, Q. Xie, H. Liu, Y. Zhao, Y. Pan, C.-A. Hwang, and V. C. H. Wu. 2014. Antimicrobial effect of blueberry (*Vaccinium corymbosum* L.) extracts against the growth of *Listeria monocytogenes* and *Salmonella enteritidis*. *Food Control* 35 (1):159-65. doi: [10.1016/j.foodcont.2013.06.040](https://doi.org/10.1016/j.foodcont.2013.06.040).
- Shin, H. S., H. Satsu, M.-J. Bae, Z. Zhao, H. Ogiwara, M. Totsuka, and M. Shimizu. 2015. Anti-inflammatory effect of chlorogenic acid on the IL-8 production in Caco-2 cells and the dextran sulphate sodium-induced colitis symptoms in C57BL/6 mice. *Food Chemistry* 168:167-75. doi: [10.1016/j.foodchem.2014.06.100](https://doi.org/10.1016/j.foodchem.2014.06.100).
- Singh, R., S. Chandrashekhara, S. R. Bodduluri, B. V. Baby, B. Hegde, N. G. Kotla, A. A. Hiwale, T. Saiyed, P. Patel, M. Vijay-Kumar, et al. 2019. Enhancement of the gut barrier integrity by a microbial metabolite through the Nrf2 pathway. *Nature Communications* 10 (1):89. doi: [10.1038/s41467-018-07859-7](https://doi.org/10.1038/s41467-018-07859-7).

- Singh, U. P., N. P. Singh, B. Singh, L. J. Hofseth, R. L. Price, M. Nagarkatti, and P. S. Nagarkatti. 2010. Resveratrol (trans-3,5,4'-trihydroxystilbene) induces silent mating type information regulation-1 and down-regulates nuclear transcription factor-kappaB activation to abrogate dextran sulfate sodium-induced colitis. *Journal of Pharmacology and Experimental Therapeutics* 332 (3):829–39.
- Skyberg, J. A., A. Robison, S. Golden, M. F. Rollins, G. Callis, E. Huarte, I. Kochetkova, M. A. Jutila, and D. W. Pascual. 2011. Apple polyphenols require T cells to ameliorate dextran sulfate sodium-induced colitis and dampen proinflammatory cytokine expression. *Journal of Leukocyte Biology* 90 (6):1043–54. doi: [10.1189/jlb.0311168](https://doi.org/10.1189/jlb.0311168).
- Smet, K. D., and R. Contreras. 2005. Human antimicrobial peptides: Defensins, cathelicidins and histatins. *Biotechnology Letters* 27: 1337–47. doi: [10.1007/s10529-005-0936-5](https://doi.org/10.1007/s10529-005-0936-5).
- Son, D. O., H. Satsu, and M. Shimizu. 2005. Histidine inhibits oxidative stress- and TNF- α -induced interleukin-8 secretion in intestinal epithelial cells. *FEBS Letters* 579 (21):4671–77. doi: [10.1016/j.febslet.2005.07.038](https://doi.org/10.1016/j.febslet.2005.07.038).
- Sourabh, A., S. S. Kanwar, R. G. Sud, A. Ghabru, and O. P. Sharma. 2013. Influence of phenolic compounds of Kangra tea [*Camellia sinensis* (L) O Kuntze] on bacterial pathogens and indigenous bacterial probiotics of Western Himalayas. *Brazilian Journal of Microbiology* 44 (3):709–15. doi: [10.1590/S1517-83822013000300007](https://doi.org/10.1590/S1517-83822013000300007).
- Stadnyk, A. W. 2002. Intestinal epithelial cells as a source of inflammatory cytokines and chemokines. *Canadian Journal of Gastroenterology and Hepatology* 16:241–6. doi: [10.1155/2002/941087](https://doi.org/10.1155/2002/941087).
- Suzuki, T., and H. Hara. 2009. Quercetin enhances intestinal barrier function through the assembly of zonula occludens-2, occludin, and claudin-1 and the expression of claudin-4 in Caco-2 cells. *The Journal of Nutrition* 139 (5):965–74. doi: [10.3945/jn.108.100867](https://doi.org/10.3945/jn.108.100867).
- Suzuki, T., and H. Hara. 2011. Role of flavonoids in intestinal tight junction regulation. *The Journal of Nutritional Biochemistry* 22 (5): 401–8. doi: [10.1016/j.jnutbio.2010.08.001](https://doi.org/10.1016/j.jnutbio.2010.08.001).
- Syed, U., and S. Ganapasam. 2010. Differential inhibitory effects of the polyphenol ellagic acid on inflammatory mediators NF-kappaB, iNOS, COX-2, TNF-alpha, and IL-6 in 1,2-dimethylhydrazine-induced rat colon carcinogenesis. *Basic and Clinical Pharmacology and Toxicology* 107:650–5.
- Taguchi, C., Y. Kishimoto, Y. Fukushima, E. Saita, M. Tanaka, Y. Takahashi, Y. Masuda, T. Goda, and K. Kondo. 2017. Dietary polyphenol intake estimated by 7-day dietary records among Japanese male workers: Evaluation of the within-and between-individual variation. *Journal of Nutritional Science and Vitaminology* 63 (3):180–5. doi: [10.3177/jnsv.63.180](https://doi.org/10.3177/jnsv.63.180).
- Taguri, T., T. Tanaka, and I. Kouno. 2004. Antimicrobial activity of 10 different plant polyphenols against bacteria causing food-borne disease. *Biological & Pharmaceutical Bulletin* 27 (12):1965–9. doi: [10.1248/bpb.27.1965](https://doi.org/10.1248/bpb.27.1965).
- Taira, T., S. Yamaguchi, A. Takahashi, Y. Okazaki, A. Yamaguchi, H. Sakaguchi, and H. Chiji. 2015. Dietary polyphenols increase fecal mucin and immunoglobulin A and ameliorate the disturbance in gut microbiota caused by a high fat diet. *Journal of Clinical Biochemistry and Nutrition* 57 (3):212–6. doi: [10.3164/jcbn.15-15](https://doi.org/10.3164/jcbn.15-15).
- Tang, Y.-T, X.-Q. Guan, L. Liu, L. Liu, and L.-J. Wang. 2009. Effect of tea polyphenols on expression of nuclear factor kappa B. *Zhonghua Gan Zang Bing za Zhi = Zhonghua Ganzangbing Zazhi = Chinese Journal of Hepatology* 17 (4):301–5.
- Tipoe, G. L., T.-M. Leung, M.-W. Hung, and M.-L. Fung. 2007. Green tea polyphenols as an anti-oxidant and anti-inflammatory agent for cardiovascular protection. *Cardiovascular & Hematological Disorders-Drug Targets* 7:135–44. doi: [10.2174/187152907780830905](https://doi.org/10.2174/187152907780830905).
- Toaldo, I. M., J. Van Camp, G. B. Gonzales, S. Kamiloglu, M. T. Bordignon-Luiz, G. Smagghe, K. Raes, E. Capanoglu, and C. Grootaert. 2016. Resveratrol improves TNF- α -induced endothelial dysfunction in a coculture model of a Caco-2 with an endothelial cell line. *Journal of Nutritional Biochemistry* 36:21–30. doi: [10.1016/j.jnutbio.2016.07.007](https://doi.org/10.1016/j.jnutbio.2016.07.007).
- Torres, J. L. T. y., and J. P. N. Rosazza. 2001. Microbial transformations of *p*-coumaric acid by *Bacillus megaterium* and *Curvularia lunata*. *Journal of Natural Products* 64:1408–14. doi: [10.1021/np010238g](https://doi.org/10.1021/np010238g).
- Tunon, M., M. Garcia-Mediavilla, S. Sanchez-Campos, and J. Gonzalez-Gallego. 2009. Potential of flavonoids as anti-inflammatory agents: Modulation of pro-inflammatory gene expression and signal transduction pathways. *Current Drug Metabolism* 10 (3):256–71. doi: [10.2174/138920009787846369](https://doi.org/10.2174/138920009787846369).
- Tzounis, X., A. Rodriguez-Mateos, J. Vulevic, G. R. Gibson, C. Kwik-Urbe, and J. P. E. Spencer. 2011. Prebiotic evaluation of cocoa-derived flavanols in healthy humans by using a randomized, controlled, double-blind, crossover intervention study. *The American Journal of Clinical Nutrition* 93 (1):62–72.
- Tzounis, X., J. Vulevic, G. G. C. Kuhnle, T. George, J. Leonczak, G. R. Gibson, C. Kwik-Urbe, and J. P. E. Spencer. 2008. Flavanol monomer-induced changes to the human faecal microflora. *British Journal of Nutrition* 99 (4):782–92. doi: [10.1017/S0007114507853384](https://doi.org/10.1017/S0007114507853384).
- Umeno, A., M. Horie, K. Murotomi, Y. Nakajima, and Y. Yoshida. 2016. Antioxidative and antidiabetic effects of natural polyphenols and isoflavones. *Molecules* 21 (6):708. doi: [10.3390/molecules21060708](https://doi.org/10.3390/molecules21060708).
- Varilek, G. W., F. Yang, E. Y. Lee, W. J. S. deVilliers, J. Zhong, H. S. Oz, K. F. Westberry, and C. J. McClain. 2001. Green tea polyphenol extract attenuates inflammation in interleukin-2-deficient mice, a model of autoimmunity. *The Journal of Nutrition* 131 (7):2034–9.
- Veldhuizen, E., H. Hendriks, A. Hogenkamp, A. van Dijk, W. Gastra, P. Tooten, and H. Haagsman. 2006. Differential regulation of porcine [beta]-defensins 1 and 2 upon *Salmonella* infection in the intestinal epithelial cell line IPI-21. *Veterinary Immunology and Immunopathology* 114 (1-2):94–102.
- Veldhuizen, E. J. A., M. Rijnders, E. A. Claassen, A. van Dijk, and H. P. Haagsman. 2008. Porcine β -defensin 2 displays broad antimicrobial activity against pathogenic intestinal bacteria. *Molecular Immunology* 45 (2):386–94. doi: [10.1016/j.molimm.2007.06.001](https://doi.org/10.1016/j.molimm.2007.06.001).
- Veldhuizen, E. J. A., A. van Dijk, M. H. G. Tersteeg, S. I. C. Kalkhove, J. van der Meulen, T. A. Niewold, and H. P. Haagsman. 2007. Expression of β -defensins pBD-1 and pBD-2 along the small intestinal tract of the pig: Lack of upregulation *in vivo* upon *Salmonella typhimurium* infection. *Molecular Immunology* 44 (4):276–83. doi: [10.1016/j.molimm.2006.03.005](https://doi.org/10.1016/j.molimm.2006.03.005).
- Vendrame, S., S. Guglielmetti, P. Riso, S. Arioli, D. Klimis-Zacas, and M. Porrini. 2011. Six-week consumption of a wild blueberry powder drink increases *bifidobacteria* in the human gut. *Journal of Agricultural and Food Chemistry* 59 (24):12815–20. doi: [10.1021/jf2028686](https://doi.org/10.1021/jf2028686).
- Viveros, A., S. Chamorro, M. Pizarro, I. Arija, C. Centeno, and A. Brenes. 2011. Effects of dietary polyphenol-rich grape products on intestinal microflora and gut morphology in broiler chicks. *Poultry Science* 90:556–78.
- Wan, L., K. Ling, M. Wang, and H. El-Nezami. 2016. Green tea polyphenol epigallocatechin-3-gallate improves epithelial barrier function by inducing the production of antimicrobial peptide pBD-1 and pBD-2 in monolayers of porcine intestinal epithelial IPEC-J2 cells. *Molecular Nutrition & Food Research* 60:1048–58. Epub Ahead of Print.
- Wan, M. L. Y., K. H. Ling, H. El-Nezami, and M. F. Wang. 2018. Influence of functional food components on gut health. *Critical Reviews in Food Science and Nutrition* 59 (12):1927–36.
- Wehkamp, J., K. Fellermann, K. R. Herrlinger, S. Baxmann, K. Schmidt, B. Schwind, M. Duchrow, C. Wohlschlager, A. C. Feller, and E. F. Stange. 2002. Human beta-defensin 2 but not beta-defensin 1 is expressed preferentially in colonic mucosa of inflammatory bowel disease. *European Journal of Gastroenterology & Hepatology* 14 (7):745–52. doi: [10.1097/00042737-200207000-00006](https://doi.org/10.1097/00042737-200207000-00006).
- Wehkamp, J., J. Harder, M. Weichenthal, O. Mueller, K. R. Herrlinger, K. Fellermann, J. M. Schroeder, and E. F. Stange. 2003. Inducible and constitutive beta-defensins are differentially expressed in Crohn's disease and ulcerative colitis. *Inflammatory Bowel Diseases* 9 (4):215–23. doi: [10.1097/00054725-200307000-00001](https://doi.org/10.1097/00054725-200307000-00001).

- Westfall, S., N. Lomis, and S. Prakash. 2018. A novel polyphenolic prebiotic and probiotic formulation have synergistic effects on the gut microbiota influencing *Drosophila melanogaster* physiology. *Artificial Cells, Nanomedicine, and Biotechnology* 46 (Suppl 2):441–55. doi: [10.1080/21691401.2018.1458731](https://doi.org/10.1080/21691401.2018.1458731).
- Yang, D., A. Biragyn, L. W. Kwak, and J. J. Oppenheim. 2002. Mammalian defensins in immunity: More than just microbicidal. *Trends in Immunology* 23 (6):291–6. doi: [10.1016/S1471-4906\(02\)02246-9](https://doi.org/10.1016/S1471-4906(02)02246-9).
- Yang, D., O. Chertov, and J. Oppenheim. 2001. The role of mammalian antimicrobial peptides and proteins in awakening of innate host defenses and adaptive immunity. *Cellular and Molecular Life Sciences* 58 (7):978–89. doi: [10.1007/PL00000914](https://doi.org/10.1007/PL00000914).
- Yoshioka, Y., H. Akiyama, M. Nakano, T. Shoji, T. Kanda, Y. Ohtake, T. Takita, R. Matsuda, and T. Maitani. 2008. Orally administered apple procyanidins protect against experimental inflammatory bowel disease in mice. *International Immunopharmacology* 8 (13-14): 1802–7. doi: [10.1016/j.intimp.2008.08.021](https://doi.org/10.1016/j.intimp.2008.08.021).
- Zamora-Ros, R., V. Knaze, J. A. Rothwell, B. Hémon, A. Moskal, K. Overvad, A. Tjønneland, C. Kyrø, G. Fagherazzi, M.-C. Boutron-Ruault, et al. 2016. Dietary polyphenol intake in Europe: The European Prospective Investigation into Cancer and Nutrition (EPIC) study. *European Journal of Nutrition* 55 (4):1359–75. doi: [10.1007/s00394-015-0950-x](https://doi.org/10.1007/s00394-015-0950-x).
- Zhang, G., C. Ross, and F. Blecha. 2000. Porcine antimicrobial peptides: New prospects for ancient molecules of host defense. *Veterinary Research* 31 (3):277–96. doi: [10.1051/vetres:2000121](https://doi.org/10.1051/vetres:2000121).
- Zitvogel, L., L. Galluzzi, S. Viaud, M. Vétizou, R. Daillère, M. Merad, and G. Kroemer. 2015. Cancer and the gut microbiota: An unexpected link. *Science Translational Medicine* 7:271. doi: [10.1126/scitranslmed.3010473](https://doi.org/10.1126/scitranslmed.3010473).