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Dietary (poly)phenols mitigate inflammatory bowel disease: Therapeutic targets, mechanisms of action, and clinical observations

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ABSTRACT

Inflammatory bowel diseases (IBD), which include Crohn's disease and ulcerative colitis, are a rapidly growing public health concern worldwide. These diseases are heterogeneous at the clinical, immunological, molecular, genetic, and microbial level, but characteristically involve a disrupted immune-microbiome axis. Shortcomings in conventional treatment options warrant the need for novel therapeutic strategies to mitigate these life-long and relapsing disorders of the gastrointestinal tract. Polyphenols, a diverse group of phytochemicals, have gained attention as candidate treatments due to their array of biological effects. Polyphenols exert broad anti-inflammatory and antioxidant effects through the modulation of cellular signaling pathways and transcription factors important in IBD progression. Polyphenols also bidirectionally modulate the gut microbiome, supporting commensals and inhibiting pathogens. One of the primary means by which gut microbiota interface with the host is through the production of metabolites, which are small molecules produced as intermediate or end products of metabolism. There is growing evidence to support that modulation of the gut microbiome by polyphenols restores microbially derived metabolites critical to the maintenance of intestinal homeostasis that are adversely disrupted in IBD. This review aims to define the therapeutic targets of polyphenols that may be important for mitigation of IBD symptoms, as well as to collate evidence for their clinical use from randomized clinical trials.

1. Introduction

Inflammatory bowel diseases (IBD), including the most common subtypes, Crohn's disease (CD) and ulcerative colitis (UC), have emerged as a public health challenge worldwide (Ananthakrishnan et al., 2020). IBD causes significant gastrointestinal symptoms including diarrhea, abdominal pain, and bleeding, as well as extra-intestinal manifestations, such as micronutrient malabsorption and weight loss (Hendrickson et al., 2002). The exact etiology of IBD symptoms, a spectrum of chronic and relapsing disorders of the gastrointestinal tract, is still under investigation. One of the main hallmarks of IBD is a disrupted immune-microbiome axis, sometimes linked to genetic predisposition. Diagnosis involves screening for hematological features, such as inflammatory markers and elevated white blood cell count, but is confirmed through endoscopic examination with biopsies (Hendrickson et al., 2002). Although IBD has been observed throughout history (Kirsner, 1988, 2001), the prevalence of IBD is steadily rising worldwide alongside the "westernization" of countries and will likely reach 1% of the population globally within this decade (Kaplan and Windsor, 2021). All age groups are affected and the unpredictable and incurable nature of these diseases contributes to its 3-fold higher cost in healthcare and considerable impact on quality of life (Park et al., 2020).

Conventional treatment for IBD includes various pharmacotherapies to interrupt inflammatory flare-ups or extend remission periods, including corticosteroids, immunosuppressive agents, antibiotics, aminosalicylates, and biologics (Cai et al., 2021). While many of these therapies can be effective for a proportion of patients, many do not respond to treatments or lose response over time. Additionally, conventional therapies are often limited due to harmful side effects. For example, long-term use of corticosteroids increases the risk of more serious sequela, such as osteoporosis (Piodi et al., 2014). Many patients discontinue the use of immunosuppressants and aminosalicylates due to intolerable side effects, such as increased risk of infection and gastrointestinal distress, respectively (Cai et al., 2021). Biologics, such as

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anti-tumor necrosis factor agents, are attractive therapeutics due to their effectiveness and low side effects, however, their use is limited by their cost (Park and Bass, 2011). Additionally, inflammatory bowel diseases are typically progressive diseases that require changes in treatment over a patient's lifetime. Collectively, the shortcomings of conventional therapies warrant the need for novel therapeutic strategies for IBD treatment.

Polyphenols are a large and structurally diverse group of natural compounds that have gained attention as potential therapeutic agents for IBD due to their range of biological activity and relatively low side effects. Prospective epidemiological evidence has linked polyphenol intake to reduced risk for cancers (Grosso et al., 2017a), type 2 diabetes (Rienks et al., 2018), metabolic syndrome (Grosso et al., 2017b), and Crohn's disease (Lu et al., 2017). They are one of the most numerous and widely distributed groups of phytochemicals in the plant kingdom and an integral part of the human diet, found in vegetables, fruits, nuts, and beverages such as coffee, tea, wine, and beer (Tsao, 2010). Estimates of daily intake are approximately 1 g in the U.S. but vary widely depending on diet (Huang et al., 2020). Polyphenols are defined by the presence of multiple phenolic units, but with more than 8000 structural varieties characterized, they represent a highly diverse group of compounds (Bravo, 1998). They range from low molecular weight molecules, such as coumarins, to highly polymerized compounds, such as tannins. Although by definition simple phenolic acids - with a single phenol group - are not polyphenolic, their similarity in structure and co-abundance with polyphenols in nature and human metabolism warrants including them in the discussion. As secondary metabolites in plants, polyphenols occur primarily in conjugation with one or more sugar residues as glycosides. Absent of conjugation with a sugar moiety, polyphenols are classified by structural similarity of their aglycone carbon skeleton. Fig. 1 illustrates the basic chemical structure of the main (poly)phenols, as well as examples of each listed throughout this review.

In this review, we discuss the protective mechanisms of polyphenol administration relative to IBD symptoms, focusing on isolated compounds, rather than whole food sources, when sufficient evidence is available. The potential protective mechanisms include transcription factor targets important in regulating inflammatory pathways, oxidative stress, intestinal barrier function, and pathogen defense; modulation of the gut microbiome; and influences on metabolite production from gut microbiota important in maintaining intestinal homeostasis. Finally, we summarize randomized, placebo-controlled clinical trials examining isolated polyphenols for the treatment of IBD.

2. IBD, risk factors & the cycle of disease progression

IBD pathologies, including Crohn's disease and ulcerative colitis, lead to a similar phenotype of relapsing intestinal inflammation, defective intestinal epithelial barrier function, abnormal expression of antimicrobial peptides, and persistent alterations in innate and adaptive immune responses (Abraham and Cho, 2009; Podolsky, 2002). Crohn's disease can affect any area of the small or large intestine, often in a noncontiguous manner, and is characterized by transmural inflammation. In contrast, ulcerative colitis is contained to the colon and is characterized by superficial mucosal inflammation. A hallmark of IBD is pronounced infiltration of the lamina propria by innate and adaptive immune cells, resulting in elevated levels of pro-inflammatory cytokines, including tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), and interferon-γ (IFN- γ) (Kakazu et al., 1999; Reimund et al., 1996). Overactivity of mucosal helper T cells, especially in contrast to reduced regulatory T cells, leads to differentiation into subsets (Th1, Th2, and Th17) that produce distinct pro-inflammatory cytokine profiles that

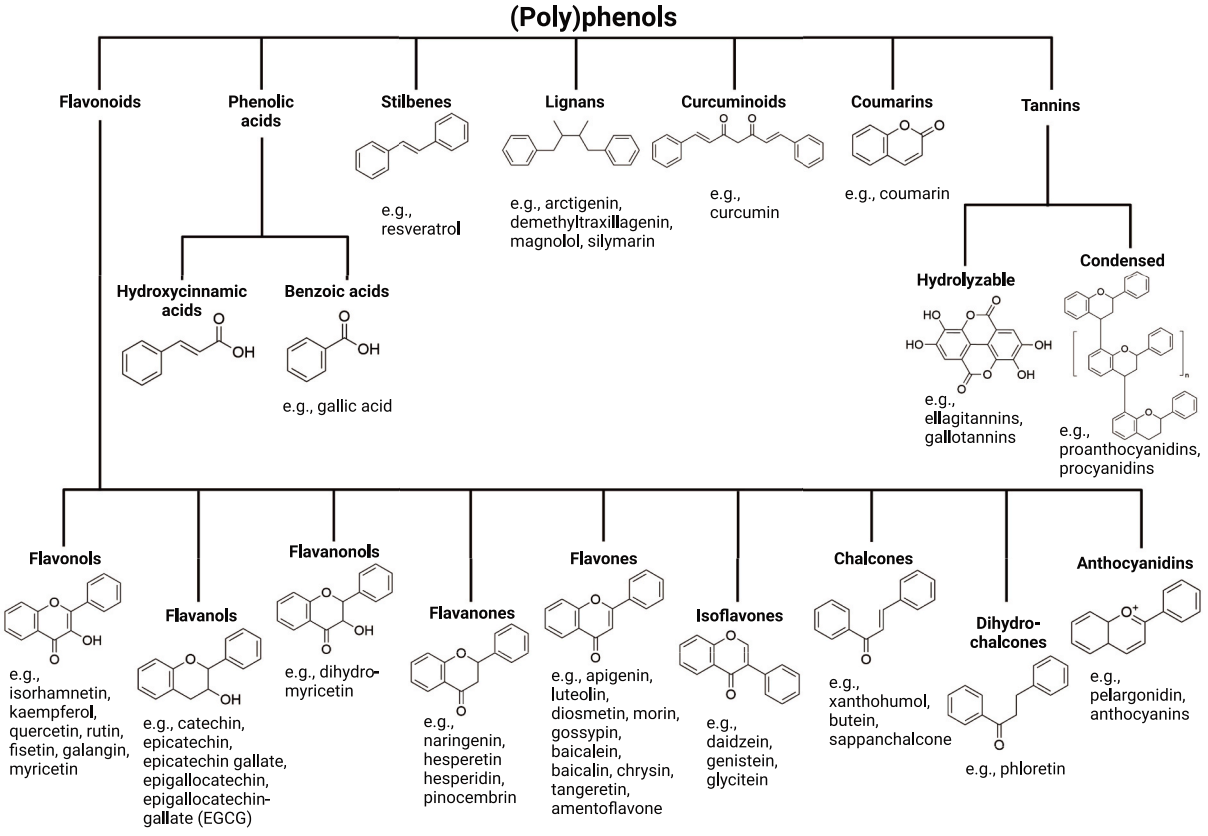

Fig. 1. The classification and chemical structures of (poly)phenols. Structures provided represent basic carbon skeletons. Examples listed are those which appear in this paper.

maintain chronic inflammation (Abraham and Cho, 2009). Experimental and observational studies in IBD suggest its pathology is characterized by this polarized T cell activity which ultimately leads to tissue damage and fibrosis (Hendrickson et al., 2002; Neuman, 2007). Considerable attention is given to the cytokine, TNF-α, in the pathogenesis of IBD due to its proinflammatory and apoptotic effect, as evidenced by therapeutic TNF-α antagonists capable of restoring the gut barrier (Vulliemoz et al., 2020).

The etiology of IBD is complex and thought to involve genetic and environmental interactions (Huang et al., 2017; Hugot et al., 2001; Piovani et al., 2019). Genomic drivers of IBD include more than 200 risk variants, many of which are involved in immune responses, maintenance of intestinal barrier function, pathogen sensing, and cellular stress response (Huang et al., 2017). Polymorphisms with the strongest associations are involved in immune response to microbes, such as nucleotide-binding oligomerization domain-containing protein 2 (NOD2), involved in sensing bacterial cell wall components; interleukin 23 receptor (IL23R), involved in inflammatory responses to microbes; and autophagy related 16 like 1 (ATG161), involved in autophagy and inflammasome activation in host defense (Abraham and Cho, 2009). However, since most IBD patients do not report a family history of disease and twin studies do not demonstrate high concordance, the attributable risk of heritability appears relatively low, suggesting environmental factors play a large part in disease etiology (Spehlmann et al., 2008). Dietary changes common to western diets may in part lead to maladaptive shifts in the host-microbiome relationship. Among western countries, dietary factors such as low-fiber diets and high dietary fat are associated with IBD, whereas the consumption of tea, a source of dietary polyphenols, is protective against IBD in Asia (Ananthakrishnan, 2015; Ananthakrishnan et al., 2013; Ng et al., 2015).

Whether genetics, pathogens, diet, or other environmental factors trigger IBD, symptoms of these diseases — namely, intestinal inflammation and gut microbiome dysbiosis — positively feedback on each other and contribute to disease progression (Britton et al., 2019; Lavelle and Sokol, 2020; Rigottier-Gois, 2013). The concept of dysbiosis remains incompletely defined, but refers to a stable disruption in the intestinal microbiome resulting in structural and often functional changes (Olesen and Alm, 2016; Tiffany and Bäumler, 2019). In IBD, dysbiosis may result in alterations to the gut metabolome, which includes anti-inflammatory, anti-microbial, and barrier-enhancing signaling molecules, resulting in disrupted barrier function. The disrupted physical barrier leads to increased exposure to intestinal microbes, amplifying inflammatory responses and perpetuating disease symptoms. These topics have been extensively reviewed previously and we would direct the reader to several references for more information (Lavelle and Sokol, 2020; Rigottier-Gois, 2013; Xavier and Podolsky, 2007). Polyphenols provide an attractive therapeutic strategy for IBD because they target multiple points along the cycle of disease progression. Polyphenols interact directly with molecular targets to inhibit inflammatory processes and protect against oxidative stress. Additionally, they modulate the gut microbiota and may influence its metabolic output. Thus, polyphenol supplementation may provide a suitable treatment to remit IBD flare-ups and maintain remission periods.

3. Polyphenols and their molecular targets

Polyphenols, including flavonoids, lignans, and stilbenes, are pharmacologically active compounds with well-known antioxidant and

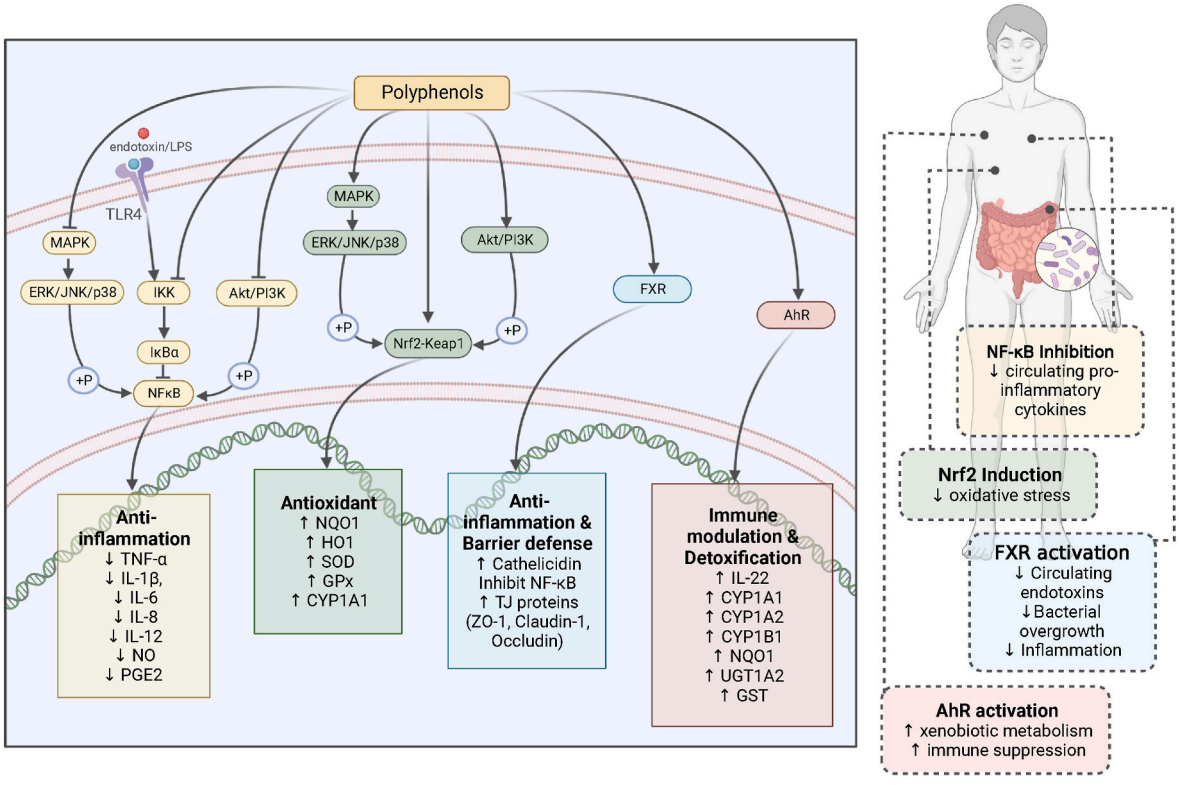

Fig. 2. Key molecular targets of polyphenols important in IBD and proposed systemic effects. Polyphenols exert diverse bioactive effects through the modulation of cellular signaling pathways and transcription factors. Polyphenols inhibit nuclear factor κ-B (NF-κB) through several mechanisms that results in inhibition of pro-inflammatory cytokine production and other gene expression products involved in inflammation. Polyphenols increase endogenous antioxidant defense and phase II xenobiotic metabolism through activation of nuclear factor erythroid 2-related factor 2 (Nrf2). Activation of farnesoid X receptor (FXR) by polyphenols increases the production of anti-microbial peptides (cathelicidin), enhances tight junction protein architecture, and inhibits NF-κB. Activation of aryl hydrocarbon receptor (AhR) by polyphenols increases expression of phase II xenobiotic metabolism enzymes and is important in promoting regulatory T cell differentiation and suppressing pro-inflammatory cytokine production. (P+) denotes phosphorylation.

immunomodulatory activity. Over time, the consensus regarding the mechanisms of action responsible for these effects *in vivo* has moved away from antioxidant effects due to physiochemical properties and towards polyphenol's modulation of cellular signaling pathways (Pompella et al., 2014). Here we focus on mechanisms that converge on transcription factors to categorize the broad modulation of cellular behavior by polyphenols (Fig. 2). Much of the research elucidating cellular mechanisms is necessarily confined to *in vitro* studies that utilize aglycone or glycosidic polyphenols. As we go into greater detail later, many dietary polyphenols are poorly absorbed, which limits their interaction with target tissues *in vivo*. For the treatment of IBD, the intestinal mucosa is the target tissue and poor bioavailability may actually increase mucosal exposure. However, polyphenols that remain in the intestinal lumen interact with intestinal microbiota which alter their pharmacokinetics and can produce metabolites with greater bioavailability and variable biological activity. Thus, some polyphenols that are heavily modified by intestinal microbiota are physically and pharmacologically different than those interacting with the colonic epithelia. From this perspective, some *in vitro* mechanistic studies may not be as meaningful from a translational standpoint. Yet, *in vivo* models that characterize downstream changes in transcriptional activity frequently support the involvement of the transcription factors outlined below. Concerning IBD, polyphenols influence the cellular behavior of innate and adaptive immune cells, as well as enterocytes, resulting in inhibition of inflammation, greater protection against oxidative stress, enhanced barrier function, and increased pathogen defenses.

3.1. Nuclear factor-kappa-B

In a healthy gut, the mucosal immune system ensures a balanced response between pro- and anti-inflammatory responses, which allows for appropriate defenses against pathogens and simultaneously, prevents an overwhelming immune response against a large amount of harmless antigens from food and commensal microbes. In IBD, the immunological response is shifted towards pro-inflammation, driven by the hyperactivation of immune effector cells producing high levels of pro-inflammatory cytokines, like TNF-α, IL-6, and IFN-γ. Central to the control and regulation of the mucosal immune system is the transcription factor, nuclear factor kappa B (NF-κB). NF-κB is responsible for inducing a number of pro-inflammatory genes, including pro-inflammatory cytokines, and is ubiquitously expressed in all cell types. NF-κB is markedly overactivated in IBD as evidenced by increased NF-κB p65 expression in biopsied tissue from IBD patients, particularly Crohn's disease (Ellis et al., 1998; Schreiber et al., 1998). There is a direct positive correlation between NF-κB activation in IBD patients and chronic mucosal inflammation (Ellis et al., 1998; Rogler et al., 1998; Schreiber et al., 1998). Activation of NF-κB can occur in response to a wide array of cellular stimuli, including inflammatory cytokines (e.g., TNF-α), microbial endotoxins (e.g., lipopolysaccharide, LPS), and reactive oxygen species (ROS) (Liu et al., 2017). Activation of NF-κB is mediated through the phosphorylation of its inhibitory subunit, IκB, by IκB kinases (IKK), resulting in the degradation of IκB and translocation of NF-κB to the nucleus, expression of inflammatory genes and activation of a number of immune cells (Karin et al., 2004).

A wide range of polyphenols show inhibitory effects on NF-κB, including flavones, isoflavones, flavonols, flavanones, chalcones, anthocyanins, lignans, stilbenes, and phenolic acids, described largely *in vitro*. Hämäläinen et al. (2007) compared 36 flavonoids on NF-κB activation in murine J774 macrophages and found daidzein (IC_{50} ~ 70 μM), genistein (IC_{50} ~ 30 μM), isorhamnetin (IC_{50} ~ 30 μM), kaempferol (IC_{50} ~25 μM), quercetin (IC_{50} ~ 25 μM), naringenin (IC_{50} ~ 80 μM), and pelargonidin (IC_{50} ~ 90 μM) inhibited NF-κB evaluated by reduced nitric oxide (NO) production. Stilbenes, such as resveratrol (IC_{50} ~ 17 μM) (D.-I. D.-I. Cho et al., 2002) and lignans, such as arctigenin (IC_{50} ~ 0.01 μM) and demethyltraxillagenin (IC_{50} ~ 50 μM) (M. K. M.K. Cho et al., 2002) are reported to inhibit NF-κB by similar mechanisms but varying degrees of potency. Comparatively, 5-aminosalicylic acid, a common anti-inflammatory medication taken for moderate to severe IBD, dose-dependently inhibited NO production in IL-1β- and IFN-γ-stimulated human intestinal epithelial (DLD-1; IC_{50} ~4.5 mM) and colon (Caco-2 BBE; IC_{50} ~2.5 mM) cells at millimolar concentrations (Kennedy et al., 1999). Polyphenols demonstrating NF-κB half maximal inhibitory concentrations in the low micromolar range may provide a more potent anti-inflammatory agent than some conventional IBD therapies, such as 5-aminosalicylates. Polyphenols modify the function of the IKK complex and prevent phosphorylation and degradation of IκB. Apigenin, quercetin, luteolin, and diosmetin have been reported to inhibit the IKK-γ regulatory subunit (Comalada et al., 2006; Nicholas et al., 2007), while other flavonoids, such as EGCG (Youn et al., 2006), butein (Pandey et al., 2007), morin (Manna et al., 2007), fisetin (Sung et al., 2007), and gossypin (Kunnumakkara et al., 2007) have been reported to inhibit the IKK-β regulatory subunit. In either case, degradation of IκB is prevented and NF-κB translocation to the nucleus is inhibited. A common approach for the assessment of NF-κB status is through measurement of IκB phosphorylation or total IκB levels (since phosphorylation targets IκB for proteasomal degradation). The vast majority of polyphenols are inhibitory to NF-κB activation at this level of measurement (Chen et al., 2007; Cho et al., 2003; Ge et al., 2007).

Toll-like receptors (TLRs) are primarily cell membrane receptors that mediate recognition of microbial molecules to eliminate pathogens or prevent overwhelming inflammatory responses towards commensal microbes (Round et al., 2011). Elevated expression of toll-like receptor 4 (TLR4), which binds the bacteria endotoxin, LPS, was detected in the intestinal mucosa of IBD patients, suggesting its activation may contribute to mucosal inflammation in IBD (Brown et al., 2014). Activation of TLRs leads to secretion of inflammatory cytokines through signaling pathways that largely converge on NF-κB (Round et al., 2011). TLR signaling diverges into two distinct signaling pathways, the MyD88-dependent and the TRIF-dependent pathway. The MyD88-dependent pathway is common to all TLRs except TLR3, and its primary effect is activation of NF-κB and mitogen-activated protein kinases (MAPKs). Polyphenols inhibit the MyD88-dependent pathway through suppression of IKK. The TRIF-dependent pathway is used by TLR3 and TLR4. Activation of the TRIF-dependent pathway leads to activation of kinases TBK1 and RIPK1. TBK1 activation results in transcriptional changes that produce Interferon type I inflammatory cytokines, while RIPK1 activation ultimately leads to NF-κB activation. Epigallocatechin-3-gallate (EGCG) inhibited the activation of the TRIF-dependent pathway through suppression of kinase activity of TBK1, as well as the MyD88-dependent pathway through inhibition of IKK in murine RAW264.7 macrophages (Youn et al., 2006). Luteolin (Lee et al., 2009) and resveratrol (Youn et al., 2005) were also reported to inhibit the TRIF-dependent pathway through TBK1 inhibition.

An additional level of control of NF-κB activity involves phosphorylation events that influence NF-κB DNA binding and transcription. Mitogen-activated protein kinases (MAPK) influence NF-κB activity through this level of control and are involved in directing cellular responses to a wide array of stimuli, including proinflammatory cytokines (Schulze-Osthoff et al., 1997). The mammalian MAPK family includes three subfamilies: extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinases (JNK), and p38 mitogen-activated protein kinases (p38). Flavonoids have been reported to modulate MAPKs, although not uniformly. For instance, quercetin was found to inhibit ERK and JNK, while catechin was found to inhibit p38 and JNK in stimulated THP-1 cells (Huang et al., 2006). Phosphorylation of NF-κB p50 subunit through the phosphatidylinositol 3-kinase (PI3K)/Akt pathway also influences DNA binding and transcriptional activity through this second level of control (Koul et al., 2001). Several flavonoids have been shown to inhibit this pathway through the inhibition of Akt or PI3K (Chen et al., 2007; Lee et al., 2006). Fisetin inhibited NF-κB activation and DNA binding by attenuating phosphorylation of Akt and p38, but not ERK and JNK, in dextran sulfate sodium (DSS)-induced colitis in mice (Sahu et al.,

2016). Proanthocyanidins suppressed NF-κB activation through JNK, ERK, and PI3K/Akt phosphorylation in a rat hepatic stellate cell line (Jiang et al., 2017). Additionally, quercetin (Cho et al., 2003), kaempferol (Huang et al., 2010), luteolin (Xagorari et al., 2002), apigenin (Masuelli et al., 2011), and EGCG (Bae et al., 2008) have been reported to modulate one or a combination of these kinases.

3.2. Nuclear factor erythroid 2-related factor 2

Chronic mucosal inflammation in IBD results in elevated infiltration by granulocytes and macrophages which produce large amounts of reactive oxygen species (ROS) as signaling molecules that activate inflammatory responses through NF-κB (Naito et al., 2007; Roessner et al., 2008). With prolonged inflammation, ROS can cause extensive damage to mucosal tissue. Imbalances between oxidative stress and antioxidant defenses have been observed in biopsied tissue of IBD patients compared to healthy individuals and may be directly related to tissue damage (Naito et al., 2007; Rezaie et al., 2007). Polyphenols have free radical scavenging capabilities *in vitro*, but it is largely understood that antioxidant and anti-inflammatory effects *in vivo* stem from their induction of endogenous antioxidant defense systems that mitigate oxidative stress. In this regard, the nuclear factor erythroid 2-related factor 2 (Nrf2) is a major transcriptional regulator of numerous detoxification and antioxidant enzymes.

Nrf2 is a member of the basic leucine zipper transcription factor family, which binds to the antioxidant response element (ARE) of DNA initiating transcription of many Phase II detoxifying and antioxidant genes. Nrf2 plays a pleiotropic role in the regulation of inflammation, immune responses, metabolism, autophagy, and mitochondrial physiology (He et al., 2020). In its inactive form, Nrf2 is bound to the repressor protein, Kelch-like ECH-associated protein (Keap1) in the cytosol, which tags Nrf2 for ubiquitination, thus resulting in low cytosolic Keap1-Nrf2 levels (Itoh et al., 1999). In periods of cellular oxidative or electrophilic stress, the activity of Keap1 is diminished and Nrf2 translocates to the nucleus, binds antioxidant responsive element (ARE), and initiates target gene expression. Nrf2 is important in the constitutive and inducible expression of detoxifying and antioxidant enzymes, such as UDP-glucuronyl transferase (UGT), glutathione S-transferase (GST), and NAD(P)H: quinone oxidoreductase (NQO1).

Numerous flavonoids and related-polyphenolic compounds regulate the Nrf2-Keap1-ARE pathway and can largely be classified into two schemes: Keap1-dependent and Keap1-independent (Qin and Hou, 2016). Modification of cysteine residues of Keap1 prevents Nrf2 ubiquitination and is a critical event in the Nrf2-dependent induction of protective genes in response to oxidative stress (Zhang and Hannink, 2003). Keap1 cysteine residues display reactivity towards polyphenol-derived quinones and chalcone-type flavonoids, resulting in conformation changes in Keap1, and increased stability and accumulation of Nrf2 (Stevens et al., 2018). *In vitro* studies have shown quercetin (Tanigawa et al., 2007), resveratrol (Kode et al., 2008), baicalein (Qin et al., 2012, 2014), xanthohumol (Dietz et al., 2005; Luo et al., 2007), and others (Qin and Hou, 2016) are capable of Nrf2 induction. Xanthohumol, a prenylated chalcone, doubled induction of quinone reductase in Hepa 1c1c7 murine hepatoma cells at 1–2 μM concentrations, whereas structurally related flavonoids from the same plant showed weak or no activity (Dietz et al., 2005). Incubation of xanthohumol with isolated Keap1 protein revealed covalent modification of cysteine sulfhydryl residues in a dose-dependent manner.

Polyphenols also influence the fate of the Keap1-Nrf2-ARE pathway, independent of Keap1, through the modification of protein kinases. Phosphorylation of Nrf2 at Ser40, Ser408, Degron domain, and other unknown sites leads to an increase in its stability and subsequent transactivation activity (Huang et al., 2002; Nguyen et al., 2003, 2004). Mitogen-activated protein kinases (MAPKs), including extracellular signal-regulated kinases (ERK), c-Jun NH_2-terminal kinases (JNK), and p38 influence Nrf2 induction. Quercetin (Yao et al., 2007), resveratrol (Chen et al., 2005), lycopene (Yang et al., 2012), luteolin (Lin et al., 2010), procyanidins (Rodríguez-Ramiro et al., 2012), anthocyanins (Hwang et al., 2011), hesperidin (Chen et al., 2010), EGCG (Wu et al., 2006), and epicatechin (Granado-Serrano et al., 2010) have been reported to upregulate the Nrf2-ARE pathway through ERK; quercetin (Yao et al., 2007), lycopene (Yang et al., 2012), EGCG (Pullikotil et al., 2012), and procyanidins (Bak et al., 2012; Rodríguez-Ramiro et al., 2012) through p38; and kaempferol (Gao et al., 2010) and sappanchalcone (Jeong et al., 2010) through JNK. Resveratrol (Chen et al., 2005), EGCG (Wu et al., 2006), epicatechins (Granado-Serrano et al., 2010), and procyanidins (Bak et al., 2012) have been reported to activate Nrf2-ARE through phosphatidylinositol 3-kinases (PI3K). Lastly, Nrf2-ARE activity can be modulated by a variety of transcription factors, including nuclear factor kappa B (NF-κB) (Qin and Hou, 2016). Increasing evidence suggests that the Nrf2 and NF-κB signaling pathways bidirectionally interfere with one another at the transcriptional level (Sivandzade et al., 2019). Thus, inhibition of NF-κB by polyphenols likely plays a role in the induction of the Nrf2-ARE pathway (S. S. Wu et al., 2022).

3.3. Farnesoid X receptor

The farnesoid X receptor (FXR) is a member of the nuclear receptor superfamily, endogenously activated by bile acids. The primary bile acid, chenodeoxycholic acid (CDCA) is reported to be the most potent endogenous activator, but it is also strongly activated by deoxycholic acid (DCA), lithocholic acid (LCA), and cholic acid (CA) (Wang et al., 1999). Additionally, glycine- and taurine-conjugates of primary bile acids strongly activate FXR but require membrane transporters for entry into the cell. FXR is primarily recognized for its role in regulating bile acid metabolism and fatty acid oxidation but has also been implicated in immune modulation and barrier function in the intestine (Gadaleta et al., 2011b). FXR activation reduces the expression of proinflammatory cytokines and preserves epithelial barrier function both *in vivo* and *in vitro* (Gadaleta et al., 2011b). A counter-regulatory network appears to exist between FXR and NF-κB, as pro-inflammatory cytokines, which activate NF-κB, repress FXR activity (Gadaleta et al., 2011a). Additionally, it was demonstrated in mouse studies that FXR plays a critical role in preventing bacterial overgrowth through cathelicidin expression, an anti-microbial and biofilm-disrupting peptide (D'Aldebert et al., 2009; Inagaki et al., 2006). Ileal biopsies of Crohn's disease patients reveal reduced FXR activation assessed by mRNA expression of small heterodimer partner (SHP), a target of FXR activation (Nijmeijer et al., 2011). Similarly, circulating plasma fibroblast growth factor 19 (FGF19), another target of FXR activation with anti-inflammatory activity, is found to be reduced in Crohn's disease patients compared to controls (Gadaleta et al., 2020).

Several polyphenols have been identified as modulators of FXR. Epigallocatechin-3-gallate (EGCG), a catechin in green tea, has been reported as an FXR modulator, together with (−)-epigallocatechin and (−)-epicatechin-3-gallate. In a reporter gene assay, EGCG dose-dependently activates FXR with an EC_{50} of 2.99 μM, increasing expression of SHP and bile salt export pump (BSEP) in HepG2 cells (Li et al., 2012). Conversely, when cells are co-treated with either FXR agonist, CDCA or GW4064, EGCG dose-dependently antagonizes FXR activation. A coactivator recruitment assay suggests EGCG blocks the FXR coactivator, SRC-2, induced by GW4064, resulting in reduced FXR target gene expression and FXR mRNA levels. Alternatively, xanthohumol, a prenylated chalcone, dose-dependently increased FXR activity both alone (0.5–20 μM) or with CDCA (CDCA, 50 μM; XN, 0–10 μM) in HepG2 cells (Nozawa, 2005). Hydrogen-deuterium exchange mass spectrometry along with molecular docking studies reveal xanthohumol, and related prenylated flavonoids, occupy the canonical ligand binding domain with low affinity within the human FXR protein (Yang et al., 2016). The stilbene, resveratrol, is reported to have FXR agonist activity as well *in vitro* and *in vivo* (Ding et al., 2018), and the synthetic

stilbenoid, GW4064, was the first non-steroidal FXR agonist identified with a stronger potency than CDCA (Maloney et al., 2000).

Several polyphenols appear to act as co-agonists for FXR alongside steroidal compounds. Grape seed procyanidin extract dose-dependently increased FXR expression, evaluated by a luciferase reporter assay, in HeLa cells when co-treated with CDCA, but not alone (Del Bas et al., 2009). Interestingly, the grape seed procyanidin extract did not increase transactivation of FXR by the nonsteroidal FXR agonist, GW4064, suggesting procyanidins may co-modulate FXR with steroidal compounds specifically, such as endogenous bile acids. It was later demonstrated by the same group that procyanidin dimers and dimer gallates are the most potent co-agonists within grape seed extracts (Rodriguez and Ricketts, 2017). In a similar study, date palm extract — abundant in proanthocyanidins, hydroxycinnamic acids, and lipophilic phenolics — was also found to activate FXR dose-dependently when co-treated with CDCA in Caco-2 cells. Similarly, date palm extract did not affect FXR when administered alone, suggesting a co-agonist effect with steroidal compounds (Alfaro-Viquez et al., 2018).

It is important to note that evidence for FXR modulation by polyphenols is still developing and studies so far have primarily investigated *in vitro* models. Several lines of evidence suggest polyphenols also influence bile acid composition, as we report later. Although many bile acids are FXR agonists, greater proportions of conjugated bile acids appear to have an antagonistic effect on intestinal FXR (Paraiso et al., 2021; Zhang et al., 2020). While this effect may prove therapeutic for metabolic diseases and certain cancers (Sun et al., 2021), it is unclear whether it would be beneficial for IBD treatment. Further *in vivo* studies are needed to fully elucidate the relationship between polyphenol intake, FXR activation, and modulation of endogenous FXR signaling.

3.4. Aryl hydrocarbon receptor

The Aryl hydrocarbon receptor (AhR) is a transcription factor primarily recognized for its role in xenobiotic metabolism. It binds to a variety of exogenous and endogenous ligands. Activation through the canonical pathway leads to transcription of Phase I and Phase II xenobiotic metabolizing enzymes, such as glutathione-S-transferase and NAD(P)H: quinone oxidoreductase, which facilitates the biotransformation and elimination of exogenous substances (Denison and Nagy, 2003; Nebert et al., 2000). AhR is also an important regulator of innate and adaptive immunity and interacts directly with NF-κB through the non-canonical pathway, inducing the expression of several cytokines and chemokines, including the tumor necrosis factor family (Vogel et al., 2007). AhR plays a critical role in barrier function, recovery from inflammatory responses, and protection against pathogen colonization (Monteleone et al., 2011). The AhR has been implicated in IBD pathogenesis as mononuclear cells from the lamina propria of IBD patients demonstrate decreased expression of AhR (Monteleone et al., 2011). The cause of this downregulation is unknown. However, AhR ligands, especially those derived from gut microbiota such as indoles, are decreased in IBD patients (Lamas et al., 2016). It is possible that reduced AhR expression in immune cells is related to decreased ligand availability.

Many polyphenols are ligands for AhR, although some are agonistic, while others are antagonistic. Substrates for AhR are planar aromatic compounds with few substituent groups, similar to many low molecular weight polyphenols. Using an AhR-responsive luciferase reporter assay, 22 polyphenols were compared for AhR agonistic activity in murine Hepa lclc7 cells (Amakura et al., 2008). Isoflavones, such as daidzein (EC_{25} ~ 3.0 μM), glycitein (EC_{25} ~ 4.2 μM), and genistein (EC_{25}~ 2.4 μM), as well as flavones, including baicalein (EC_{25} ~ 2.8 μM) and baicalin (EC_{25} ~ 3.2 μM), exhibited the greatest agonistic activity. Flavanones, naringenin (EC_{25} ~ 53 μM) and hesperetin (EC_{25} ~ 38 μM), and the stilbene, resveratrol (EC_{25} ~ 30 μM), elicited weaker agonistic activity, as did the flavone, chrysin (EC_{25} ~ 14 μM) and most of the flavonoid glycosides. Conversely, apigenin, luteolin, myricetin, and morin exhibited only very weak agonist activity at very high (100 μM) concentrations and thus, are thought to have antagonistic effects. And flavanones and flavanols, such as (+)-catechin and (−)-epicatechin, showed very poor induction activity. Polyphenols, such as isoflavones and flavones, appear to activate AhR in a similar range of potency as the microbially-derived endogenous agonists, indoles (EC_{50} ~3 μM in HepG2 cells) (Hubbard et al., 2015).

4. Pharmacokinetics of polyphenols and the gut microbiome

A diverse collection of microorganisms, consisting of bacteria, fungi, viruses, archaea, and protozoa, rivaling the number of human cells, inhabit the gastrointestinal tract. Collectively, the large and flexible genome of the gut microbiome has adapted to the intestinal environment and complements the host, such that it may be regarded as a kind of auxiliary metabolic organ (Flint et al., 2012; Hou et al., 2022). Microorganisms within the gut microbiome are capable of enzymatic conversion of polyphenols. Thus, the composition of the gut microbiome may alter the pharmacokinetics of dietary polyphenols and may produce metabolites that differ pharmacologically from the parent compound (Lavefve et al., 2020; Rodríguez-Daza et al., 2021). A prime example are microbially-derived urolithin metabolites, thought to drive the health-promoting benefit of ellagic acid (García-Villalba et al., 2022). For example, urolithin A and urolithin B (10 μM) inhibited prostaglandin E2 production, by 85% and 40%, respectively, after IL-1β administration in human colonic fibroblasts, whereas ellagic acid did not show any effect (González-Sarrías et al., 2010). These observations have raised the question of whether polyphenols exert their health-promoting effects indirectly by interacting with the gut microbiota and modulating its composition (Lavefve et al., 2020; Rodríguez-Daza et al., 2021). Indeed, many polyphenols appear to exert a bidirectional influence on the gut microbiome, enhancing abundance of beneficial species while inhibiting potentially pathogenic species. The bidirectional effect of polyphenols on modulating the gut microbiome and the microbially derived polyphenol metabolites that are produced confer benefit to the host (Fig. 3) (Duda-Chodak et al., 2015). Many polyphenols are produced as secondary metabolites of plants to modulate the soil microbiome and their impact on the intestinal microbiome may parallel their primary action in nature (Kennedy, 2014; Ramírez-Puebla et al., 2013).

Although trends of dysbiosis are commonly reported in IBD, no single microorganism has been consistently implicated in pathogenesis. It is difficult to determine if dysbiosis is a cause or consequence of IBD due to the inherent limitations of observational studies on patients that are already diagnosed. Over 90% of the gut microbiome is composed of four major phyla: Firmicutes (49–76%), Bacteroidetes (16–23%), Proteobacteria, and Actinobacteria (Eckburg et al., 2005). Most studies report reduced bacterial diversity and richness in IBD compared to healthy controls (Gevers et al., 2014; Manichanh et al., 2006; Moustafa et al., 2018; Willing et al., 2009). Reductions in Firmicutes and increased Proteobacteria, driven by a loss in Firmicutes diversity, are consistently observed in IBD (Frank et al., 2007; Manichanh et al., 2006). Decreases in notable genera of Bacteroidetes (e.g., *Alistipes* and *Barnesiella*) and Firmicutes (e.g., *Faecalibacterium*, *Oscillibacter*, *Agathobacter*, *Ruminococcus*) are reported (Liguori et al., 2016; Manichanh et al., 2006; Moustafa et al., 2018), as well as reductions or absence in specific anti-inflammatory or butyrate-producing genera, such as *Faecalibacterium prausnitzii*, *Roseburia* spp., and *Bifidobacterium adolescentis* (Takahashi et al., 2016; Willing et al., 2010). Conversely, an enrichment in Enterobacteriaceae (Liguori et al., 2016; Willing et al., 2010), including *Escherichia coli* (Baumgart et al., 2007; Fang et al., 2018; Kotlowski et al., 2007; Moustafa et al., 2018; Willing et al., 2009) and *Fusobacterium* (Liguori et al., 2016; Ohkusa et al., 2003; Strauss et al., 2011; Tahara et al., 2015) have been reported, as well as other species including *Clostridium perfringens* (Moustafa et al., 2018) and *Ruminococcus gnavus* (Schirmer et al., 2018).

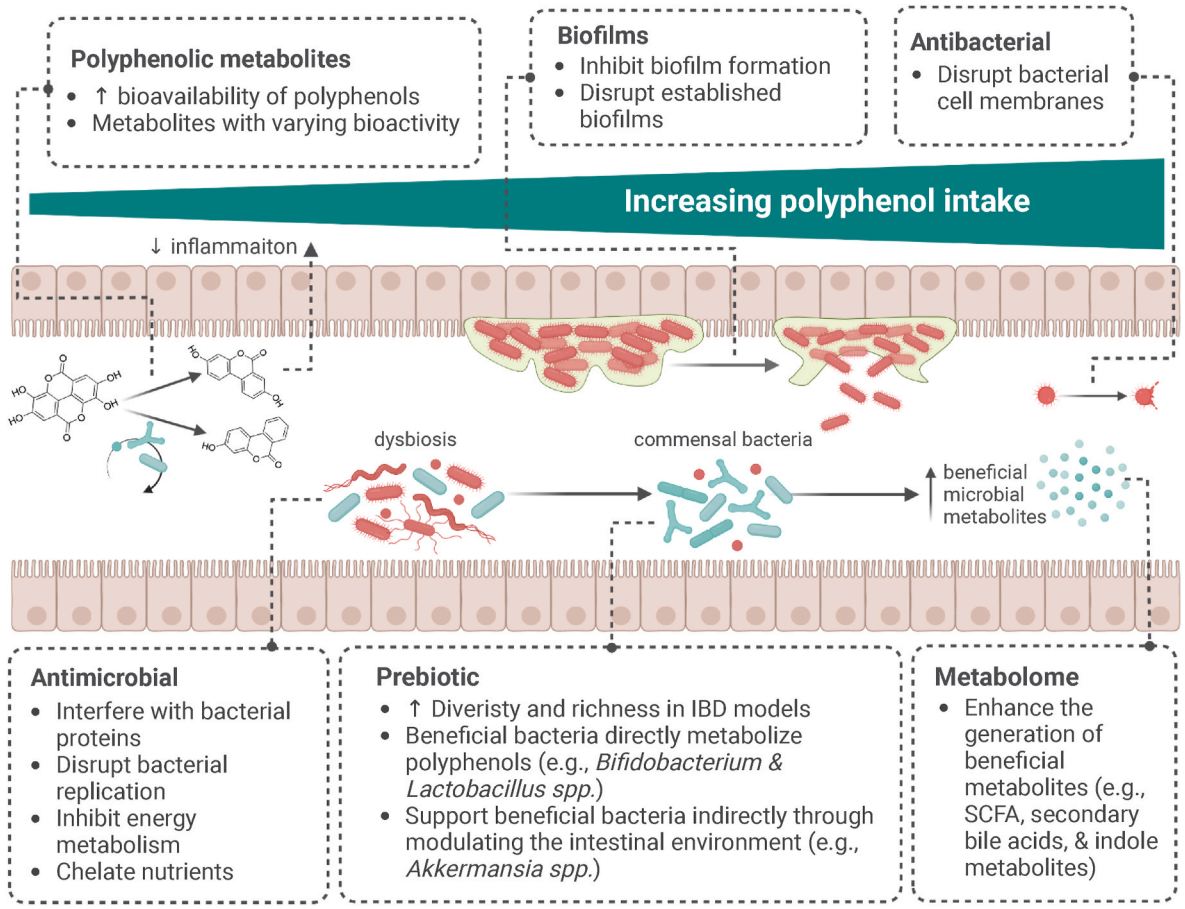

Fig. 3. Putative mechanisms of multi-directional modulation of the gut microbiome by polyphenols. Polyphenols appear to interact with the gut microbiome in ways important for IBD that may be categorized into three general schemes. 1) Polyphenols are metabolized by gut microbiota, producing bioactive metabolites (i.e., anti-inflammatory metabolites). 2) Polyphenols enhance the growth of certain beneficial bacteria that provide vital functions for the host (e.g., production of SCFAs, secondary bile acids, or indoles) or inhabit important ecological niches. 3) Polyphenols exert antimicrobial activity by interfering with microbial enzymes, energy and replication mechanisms, nutrient availability, or biofilm formation, which are all important in the pathogenicity of some microbes.

4.1. *Pharmacokinetics of polyphenols*

The absorption and metabolism of polyphenols are determined by their chemical structure, including glycosylation or degree of polymerization, molecular size, and solubility (Bravo, 1998). In this light, the pharmacokinetics of polyphenols can be significantly variable and influence their biological effect by restricting bioavailability and interaction with target tissues. In food, polyphenols are typically present as complex mixtures and mostly exist as esters, glycosides, or polymers, which are not readily absorbed (Bravo, 1998). Conversely, polyphenols administered as supplements likely have greater bioavailability since they are extracted from a complex food matrix. A large portion of glycosidic polyphenols are hydrolytically converted into their corresponding aglycone in the acidic environment of the stomach or by β-glucosidase enzymes within enterocytes of the small intestine where they are absorbed by passive diffusion (King et al., 1996; Manach et al., 1997). Alternatively, the sodium-dependent glucose transporter (SGLT)-1 may facilitate the absorption of glycosides into the enterocyte where they are hydrolyzed to their aglycone in the cytosol (Gee et al., 2000; Wolffram et al., 2002). Estimates of small intestine absorption of isolated aglycones or glycosides range from 0% to 60% (Manach and Donovan, 2004). Once absorbed, mammalian metabolic transformation of polyphenols is largely accomplished by phase I and II detoxifying enzymes in enterocytes or hepatocytes, giving rise to hydroxylation of aromatic rings, *O*-methylation, *O*-demethylation, and conjugation of hydroxy groups to yield glucuronides and sulfates. Glucuronide conjugate polyphenols are frequently found in circulation at significantly higher concentrations than their aglycones (Legette et al., 2014; Wiese et al., 2015). A variable proportion of conjugated polyphenols are excreted in the urine or into the bile where they re-enter the small intestine.

Whether polyphenols re-enter the gut lumen through bile or remain in the gut lumen, a considerable proportion of orally consumed polyphenols reach the large intestine, where the vast majority of gut microbiota reside. Gut microbiota glucosidase and glucuronidase enzymes influence polyphenol bioavailability by hydrolytic release of aglycones from *O*-glycosides and phase II-derived *O*-glucuronides, respectively, converting them back to aglycones available for re-absorption (Piwowarski et al., 2015; Wilson and Nicholson, 2017). This action by the gut microbiota likely explains the biphasic peaks in plasma concentration observed in many pharmacokinetic profiles of polyphenols (Legette et al., 2014; Zhong et al., 2017). This enterohepatic recycling aided by the gut microbiota may enhance polyphenol bioavailability, extend their half-life, and increase their exposure to the gut mucosa. The increased exposure to the inflamed gut mucosa is especially important to IBD as it is the target tissue for treatment. Within the large intestine, polyphenols may undergo further metabolic biotransformations by microbiota, yielding metabolites with greater bioavailability and variable pharmacological properties compared to the parent compound (Piwowarski et al., 2015). *In vitro* studies with culturable microbes demonstrate gut microbes can perform enzymatic carbon-carbon cleavage of heterocyclic and aromatic rings in flavonoids, dehydroxylation, decarboxylation, and hydrogenation of alkene moieties in a range of compounds (Cortés-Martín et al., 2020; Stevens and

Maier, 2016). These metabolic conversions do not occur randomly but follow a sequence of reactions guided by chemical principles. The metabolic end-products depend on the presence of microbiota capable of those conversions. Thus, considerable variation in the metabolism of polyphenols exists between individuals.

4.2. Microbiota-generated metabolites of polyphenols and their physiological effects

Polyphenols are extensively catabolized by microbiota to a highly diverse group of derivative compounds, largely phenolic acids, which vary in biological activity. A diverse range of species belonging to the four most abundant phyla in the human gut microbiome (Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria) are capable of initiating the first reaction, to hydrolyze *O*-glycosides to aglycones. Both *in vitro* and *in silico* studies identify members of Lactobacilli and *Bifidobacterium* as primarily involved in *O*-deglycosylation reactions (Goris et al., 2021). These taxa are recognized for their anti-inflammatory and short-chain fatty acid-producing effects, likely contributing to the health-promoting effects of polyphenols. Although a limited number of commensal microbes are culturable, *in vitro* studies have confirmed certain anaerobes capable of enzymatic transformation of polyphenolic aglycones (Cortés-Martín et al., 2020). These reactions involve C-ring and lactone fission, demethylation, decarboxylation, reduction, and isomerization. In recent years, considerable progress has been made in identifying phenolic-derived metabolites generated by the gut microbiota, including equol from isoflavones, urolithins from ellagitannins, enterolactone and enterodiol from lignans, as well as phenylvaleric acids, phenylpropionic acids, phenylacetic acids, and hydroxybenzoic acids arising from a number of polyphenols. Interestingly, despite the diverse enzymatic conversions required for further metabolism of polyphenolic aglycones, microbes capable of these conversions appear to be limited to two bacterial phyla — Firmicutes and Actinobacteria (Cortés-Martín et al., 2020). The majority of bacteria identified as capable of polyphenol biotransformations are within the phylum Firmicutes, including members within the families Clostridiaceae, Eubacteriaceae, Lachnospiraceae, Ruminococcaceae, Lactobacillaceae, Peptostreptococcaceae, and Streptococcaceae (Cortés-Martín et al., 2020). Fewer families within the Actinobacteria phyla are known to transform polyphenols and include Bifidobacteriaceae and Eggerthellacea.

In some cases, microbially generated metabolites of polyphenols exceed circulating concentrations of the parent compound and have greater bioactivity (Wiese et al., 2015). Hydroxybenzoic acid is a common phenolic metabolite of flavonoids, including hesperetin, naringenin, quercetin, and epicatechin. In human THP-1 monocytes stimulated with LPS, 1 μM of 4-hydroxybenzoic acid was sufficient to inhibit the release of IL-1β by nearly 50% compared to controls, while none of the parent flavonoids produced a change in inhibition at the same concentration (di Gesso et al., 2015). In humans receiving ellagitannin-rich pomegranate extract (1 g), peak plasma concentrations of urolithin A glucuronide reached over 80-fold the C_{max} of ellagic acid (2.47 μM compared to 0.02–0.061 μM), indicative of greater bioavailability of the microbial metabolite (Seeram et al., 2008). When urolithin A, B, and C were compared for anti-inflammatory activity, minimum effective concentrations to inhibit the production of NO in LPS-stimulated RAW 264.7 cells were 2.5, 20, and 40 μM, respectively (Piwowarski et al., 2015). Distinct variation in human production of these microbial metabolites led to the discovery of metabotypes — variable functional composition of the gut microbiome resulting in distinct profiles of polyphenol metabolites (Cortés-Martín et al., 2018). Understanding the role of metabotypes on polyphenol metabolism will be crucial in determining the efficacy, potency, and administration of polyphenols for IBD treatment.

4.3. Prebiotic effects of polyphenols

It is still unclear what drives the beneficial effects of polyphenol consumption — whether it is the generation of microbially-derived metabolites or the modulation of microbiota composition, or both. Polyphenols appear to confer a prebiotic effect, whereby they are selectively utilized by and encourage the growth of beneficial microorganisms with subsequent health benefits. Microbial clades that appear to be most affected provide a physiological benefit to the host, such as production of short-chain fatty acids. In animal models of IBD, polyphenol administration typically rescues changes to the gut microbiota that parallel dysbiosis in human IBD (Table 1). Polyphenol treatment restores community diversity and richness, as well as increases Firmicutes abundance, which are often reported to be reduced in IBD (Frank et al., 2007; Manichanh et al., 2006). For example, tangeretin, a flavone, increased Firmicutes abundance and increased alpha diversity in DSS-induced colitis in mice (Chen et al., 2021). Tangeretin supplementation (at 0.08% of diet) increased Lachnospriaceae and suppressed Rikenellaceae and Enterobacteriaceae compared to DSS treatment alone. Lachnospiraceae produce short-chain fatty acids through fermentation of soluble fiber, which were significantly increased with tangeretin supplementation and may contribute to its protective effect. Administration of the dihydrochalcone, phloretin (100 mg kg^{-1}), normalized DSS-induced changes to the gut microbiota in mice, resulting in increased Lactobacilli and decreased *Escherichia coli*, which coincided with decreased plasma levels of the bacterial endotoxin, LPS (Zhang et al., 2019). Luteolin administration by gastric gavage (34.6 mg kg^{-1}) ameliorated DSS-induced colitis in rats, partially mediated by increases in Lactobacilli, *Bacteroides*, *Roseburia* and *Butyricicoccus* abundance (B. Li et al., 2021). Lactobacilli are important lactic acid producers and overwhelmingly seen as beneficial, and *Roseburia* and *Butyricicoccus* are butyrate producers that are frequently found reduced in IBD patients (Devriese et al., 2017; Machiels et al., 2014). In mice given anthocyanins from black raspberry (3.5 or 7.0 μmol/g total diet), gut microbiota changes induced by DSS were reversed, including reductions in *Desulfovibrio* spp. and *Enterococcus* spp., as well as increases in *Eubacterium rectale*, *Faecalibacterium prausnitzii*, and Lactobacilli (Chen et al., 2018). Many Firmicutes species, in particular butyrate producers such as *Faecalibacterium prausnitzii*, are reported to be poorly represented in patients with active IBD compared to healthy subjects (Sokol et al., 2009). Exemplifying the requisite function of specific species, administration of *F. prausnitzii* in mice significantly decreased the severity of trinitrobenzene sulfonic acid (TNBS)-induced colitis (Martín et al., 2014).

Akkermansia muciniphila has frequently been reported to increase with polyphenol-rich diets, particularly in combination with high-fat diets (Anhê et al., 2015; Axling et al., 2012; Kemperman et al., 2013; Roopchand et al., 2015), although appears to occur independent of dietary fat (Zhang et al., 2018). *Akkermansia* spp. are thought to mediate the protective effects of polyphenols against inflammation and metabolic dysfunction. The effect of polyphenols on *Akkermansia* abundance observed *in vivo* is likely mediated indirectly, for instance, through the production of mucins for which *A. muciniphila* selectively degrade or the inhibition of a competitive microbe that normally limits *A. muciniphila* growth. Thus, increase in *Akkermansia* abundance is likely a biomarker of beneficial impact of polyphenols on the gut mucosal integrity. *Akkermansia* reside in a specific ecological niche near the gut lining and may confer protection by limiting interaction with other microorganisms. In a mouse model of IBD, proanthocyanidins from grape seed extract at 50 mg kg^{-1} for 21 days ameliorated colitis symptoms and rebalanced DSS-altered gut microbiota, including restoring *Akkermansia* and Ruminococcaceae, as well as Firmicutes abundance (Sheng et al., 2020). Consistently, *A. muciniphila* administration rescued against chemical-induced colitis in mice, resulting in reduced inflammatory markers (TNF-α and IFN-γ) and normalization of the gut microbiome (Bian et al., 2019; Zhai et al., 2019). A specific strain of *A. muciniphila*

Table 1
Summary of animal models of IBD examining polyphenol supplementation as isolated compounds or plant extracts included in this review.

Polyphenol	IBD model	Experimental design	Changes to gut microbiota	Other effects	Author (year)
Anthocyanins (as black raspberry extract)	AOM/DSS-induced colitis and colon cancer in mice	3 cycles of AOM (10 mg kg^{-1}) injection followed by 7-day DSS (2% w/v) challenge followed by 12-weeks PP (3.5 or 7.0 μmol/g of diet)	↑ *Eubacterium rectale*, ↑ *Faecalibacterium prausnitzii*, ↑ *Lactobacilli*, ↓ *Desulfovibrio*, ↓ Enterococcus	↓ IL-1β, IL-6, IL-10, COX2, TNF-α; Reduced colon tumor formation	Chen et al. (2018)
Curcumin/curcuminoids (as turmeric extract)	DSS-induced colitis in mice	4 cycles of 4-day DSS (1.5% w/v) challenge followed by 7-day recovery with PP (8% of diet w/w)	↑ Bacteroidetes, ↑ Muribaculaceae, ↑ *Ileibacterium*, ↑ Lactobacilli, ↑ *Alloprevotella*, ↑ *Bifidobacterium*, ↓ Firmicutes, ↓ Lachnospiraceae	↑ indole-3-acetic acid and indole-3-propionic acid, ↓ tryptophan; ↑ total SCFA, acetic, propionic, butyric, valeric acid; ↑ Ahr, IL-22, ↓ TNF-α, IL-10; ↑ TJP (occludin, ZO-1, claudin-1); Reduced colon injury	Yang et al. (2022)
Dihydromyricetin	DSS-induced colitis in mice and rats	7-day DSS (3% w/v) challenge concurrent with PP (100 or 200 mg/kg/day)	↑ Lactobacillaceae, ↑ Lactobacilli, ↑ *Akkermansia*, ↓ Streptococcaceae, ↓ Bacteroidaceae, ↓ Lachnospiraceae, ↓ Peptostreptococcaceae, ↓ *Romboutsia*, ↓ *Turicibacter*, ↓ *Lachnoclostridium*, ↓ *Bacteroides*, ↓ *Blautia*, ↓ *Streptococcus*, ↓ *Enterococcus*	↑ LCA, CDCA, α-MCA, TCDCA, ↓ isoLCA, CA; ↑ Tgr5 and Fxr expression (rats); ↑ TJP (ZO-1, claudin-1, occludin); ↓ MPO, IL-6, TNF-α, IL-1β, ↑ IL-10; Reduced colonic injury	Dong et al. (2021)
Galangin	DSS-induced colitis in mice	7-day DSS (3% w/v) challenge followed by 7-day PP (15 mg/kg/day)	↑ Alpha-diversity, ↑ Firmicutes, ↑ Lactobacilli, ↑ *Butyricimonas*, ↑ *Mucispirillum*, ↓ Bacteroidetes	↑ total SCFA, acetic, propionic, and butyric acid; ↓ TNF-α, IL-1β, IL-6, MPO; Reduced colonic injury	Xuan et al. (2020)
Hesperetin glucoside	DSS-induced colitis in mice	7-day DSS (1.5% w/v) challenge concurrent with PP (1 mg/kg/day)	↑ Bacteroidetes, ↑ Patescibacteria, ↑ Ruminococcaceae, ↑ Enterorhabdus, ↑ *Enterococcus*, ↓ Cyanobacteria, ↓ Desulfobacterota, ↓ Prevotellaceae, ↓ *Eubacterium*, ↓ *Intestinimonas*	↑ propionic and butyric acid; ↑ indole-3-propionic acid & indole acetic acid; ↓ TNF-α, IL-1β, IL-22, IL-6; Reduced colonic injury	Wu et al. (2021)
Luteolin	DSS-induced colitis in rats	10-day DSS (3.5% w/v) challenge followed by PP (34.6 mg/kg/day)	↑ Alpha-diversity, ↑ Bacteroides, ↑ Lactobacilli, ↑ *Roseburia*, ↑ *Butyricicoccus*	NF-κB inhibition; ↓ IL-23; Reduced colon injury	(B) Li et al. (2021)
Magnolol	DSS-induced colitis in mice	5-day DSS (2% w/v) challenge followed by 7-day DSS + PP (5, 10, or 15 mg/kg/day)	NR	↑ 5-hydroxyindolacetic acid, indoleacetic acid, indoleactic acid, indoxylsulfuric acid, kynurenic acid; ↓ MPO, TNF-α, IL-1β, IL-6; Reduced colon injury	Zhao et al. (2017)
Monogalloyl glucoside, gallic acid (as mango extract)	DSS-induced colitis in rats	3 cycles of DSS (3% w/v) challenge followed by 14-day recovery with PP (475 mg/L *ad libitum*)	↑ *Lactobacillus plantarum*, ↑ *Lactococcus lactis*, ↑ *Clostridium butyrium*	↑ butyric and valeric acid; ↑ Gpr43 & Gpr109a mRNA	Kim et al. (2018)
Phloretin	DSS-induced colitis in mice	14-day PP (25, 50, or 100 mg/kg/day) followed by 7-day DSS (2.5% w/v) challenge with PP	↑ Lactobacilli, ↓ *Escherichia coli*	↓ TNF-α, IL-1β, IL-12, IL-17, IFN-γ; NF-κB inhibition; ↓ TLR4 expression; ↑ TJP (ZO-1, occludin); ↓ plasma endotoxin; Reduced colon injury	Zhang et al. (2019)
Phloretin	DSS-induced colitis in mice	2-week PP (100 mg/kg/day) followed by 7-day DSS (3% w/v) challenge + PP	↓ Alpha-diversity, ↑ Bacteroides, ↑ *Akkermansia*, ↓ *Ruminiclostridium-9*, ↓ *Intestinimonas*, ↓ *Tyzzerella*, ↓ *Barnesiella*	↑ total bile acids, DCA and LCA, ↓ HDCA; ↑ Tgr5 expression; ↓ IL-6; ↑ TJP (ZO-1, occludin); Reduced colonic injury	Liu et al. (2021)
Proanthocyanidins (as grape seed extract)	DSS-induced colitis in mice	21-day DSS (2.5% w/v) challenge concurrent with PP (50 mg/kg/day)	↑ Firmicutes, ↑ Verrucomicrobia, ↑ Ruminococcaceae, ↑ *Akkermansia*, ↓ Bacteroidetes, ↓ Muribaculaceae, ↓ Lactobacilli, ↓ *Dubosiella*, ↓ *Veillonella*	↓ TNF-α, IL-1β, ↑ IL-10; ↓ MDA, ↑ SOD, GSH; ↑ TJP (ZO-1, occludin, claudin); Reduce colon injury	Sheng et al. (2020)
Resveratrol	DSS-induced colitis in mice	4 cycles of a 4-day DSS (1.5% w/v) challenge followed by 7-day recovery with PP (0.025% of diet w/w)	↑ Alpha-diversity, ↑ *Bifidobacterium*, ↓ *Akkermansia*, ↓ *Bilophila*, ↓ *Dorea*, ↓ *Sutterella*	↓ IFN-γ, IL-10, IL-2, IL-1β, IL-6, TNF-α; Reduced colon injury	Li et al. (2020)

(*continued on next page*)

Table 1 (*continued*)

Polyphenol	IBD model	Experimental design	Changes to gut microbiota	Other effects	Author (year)
Rutin, cholorogenic acid, quercetin (as *Eucommia ulmoides* extract)	DSS-induced colitis in mice	7-day DSS (2% w/v) challenge + PP (200 or 400 mg/kg/day) followed by 4-day PP	↑ Alpha-diversity, ↑ Verrucomicrobia, ↑ Burkhoderiaceae, ↑ Akkermansiaceae, ↑ Ruminococcaceae, ↓ Erysipelotrichaceae, ↓ Bacteroidaceae	↓ total BA, primary BA, ↑ DCA, TCA; ↓ IL-6; ↑ Tgr5 expression; ↑ TJP (claudin-1, occludin); Reduced colon injury	Zhai et al. (2021)
Tangeretin	DSS-induced colitis in mice	4 cycles of 4-day DSS (1.5% w/v) challenge followed by 7-day recovery with PP (0.04% or 0.08% of diet w/w)	↑ Alpha-diversity, ↑ Firmicutes ↑ Lachnospiraceae, ↑ Lactobacillaceae, ↓ Bacteroidetes, ↓ Rikenellaceae, ↓ Marinifilaceae, ↓ Enterobacteriaceae, ↓ Rikenellaceae RC9, ↓ *Alistipes*,	↑ acetic, butyric, valeric acid; ↓ IL-1β & TNF-α; ↑ TJP (claudin-1, ZO-1); Reduced colonic injury	Chen et al. (2021)

Findings reported here are statistically significant findings from animal studies covered throughout this paper. Outcomes are compared to colitis (DSS-only) controls. Outcomes are typically comparable to healthy controls. AOM: azoxymethane; DSS: dextran sulfate sodium; PP: polyphenols; IL-1β: interleukin 1β; IFN-γ: interferon γ; IL-2: interleukin 2; IL-6: interleukin 6; IL-10: interleukin 10; IL-12: interleukin 12; IL-17: interleukin 17; IL-22: interleukin 22; IL-23: interleukin 23; COX2: cyclo-oxygenase 2; MPO: myeloperoxidase; TJP: tight junction proteins; ZO-1: zonula occludens 1; BA: bile acids; CA: cholic acid; LCA: lithocholic acid; DCA: deoxycholic acid; TCA: taurocholic acid; HDCA: hyodeoxycholic acid; CDCA: chenodeoxycholic acid; α-MCA: α muricholic acid; TCDCA: taurochenodeoxycholic acid; isoLCA: isolithocholic acid; Tgr5: G protein-coupled bile acid receptor 1; Fxr: farnesoid x receptor; Ahr: aryl hydrocarbon receptor; NF-κB: nuclear factor κ B; Gpr43: G protein-coupled 43; Gpr109a: G protein-coupled 109a; TLR4: toll-like receptor 4; MDA: malondialdehyde; SOD: superoxide dismutase; GSH: glutathion

(strain ATCC) has been shown to modulate the differentiation of T regulatory cells and increase the production of short-chain fatty acids, indicating species-specific effects on intestinal homeostasis (Zhai et al., 2019). Compared to healthy people, the abundance of *A. muciniphila* has been found significantly decreased in patients with UC (Bajer et al., 2017; Earley et al., 2019; Presti et al., 2019) and CD (Dunn et al., 2016; Presti et al., 2019). Therefore, *A. muciniphila* is generally regarded as a beneficial microbe and promising probiotic.

Bifidobacterium bacteria fulfill important functions within the human colon, including production of acetate and lactate, which can be converted to butyrate through cross-feeding interactions with butyrate-producing species (Rios-Covian et al., 2015; Rivière et al., 2016). *Bifidobacterium* hydrolyze glycosides as well as metabolize isoflavones, lignans, and stilbenes *in vitro* and appear to be supported by polyphenol supplementation *in vivo* (Cortés-Martín et al., 2020). Administration of resveratrol (0.025% of diet w/w), a stilbene, showed strong prebiotic effects by increasing the abundance of *Bifidobacterium*, although reducing genera *Akkermansia* and *Dorea,* as well as ameliorating intestinal inflammation in DSS-induced colitis in mice (Li et al., 2020). Resveratrol treatment also significantly preserved microbiome diversity and richness compared to mice treated with DSS only. Culture medium from *Bifidobacterium adolescentis* co-cultured with flavonols (galangin, quercetin, and fisetin) had an anti-inflammatory effect when exposed to LPS-stimulated RAW 264 cells (Kawabata et al., 2013). HPLC analysis determined negligible changes in the flavonols concentrations, ruling out the possibility of microbial conversion into more bioactive compounds. The authors assert that exposure to the flavonols enhanced an anti-inflammatory agent originating from *B. adolescentis*. In a subsequent study by the same group, culture medium from a co-culture with *B. adolescentis* and quercetin maintained the anti-inflammatory activity after washout of quercetin. Stearic acid was tentatively identified as the anti-inflammatory compound originating from *B. adolescentis* after quercetin exposure (Kawabata et al., 2018). This suggests that polyphenols may not only encourage abundance of probiotic species but enhance the beneficial properties of those present.

4.4. Antimicrobial effects of polyphenols

Gut bacteria play a key role in initiating and maintaining inflammatory responses in the gut of IBD patients by supplying antigens or stimulatory signals that trigger immune cell activation. Polyphenols exert antimicrobial activity against pathogenic microbes through a variety of mechanisms, including interactions with bacterial proteins, disruption of DNA synthesis and replication, interference with bacterial cell walls, disruption of biofilms, and inhibition of energy metabolism (Makarewicz et al., 2021). Multiple lines of evidence suggest that polyphenols inhibit potentially pathogenic microbes to a greater extent than neutral or beneficial microbes (Chan et al., 2018; Duda-Chodak et al., 2015; Ferreira de Brito et al., 2022). Many *in vitro* studies have investigated the antimicrobial activity of polyphenols against *E. coli*, as a model pathogenic anaerobe and an important pathobiont in IBD (Baumgart et al., 2007; Fang et al., 2018; Kotlowski et al., 2007; Moustafa et al., 2018; Willing et al., 2009). Epigallocatechin gallate (EGCG) has been found to bind to membrane porins in Gram-negative bacteria, limiting their permeability (Yoda et al., 2004), which inhibited the growth of *E. coli in vitro* (Nakayama et al., 2013). Several polyphenols, including quercetin (Ohemeng et al., 1997; Plaper et al., 2003), apigenin (Ohemeng et al., 1997), pentahydroxyflavone (Ohemeng et al., 1997), EGCG, epicatechin gallate (ECG), and epigallocatechin (EGC) (Gradišar et al., 2007), and coumarins (Marko Oblak et al., 2007) bind and inhibit DNA gyrase, a prokaryotic enzyme in *E. coli* responsible for bacterial DNA synthesis. Highly polymerized proanthocyanidins bind LPS in the outer membrane of Gram-negative bacteria, such as *E. coli*, and prevent interactions with mammalian membrane receptors (Delehanty et al., 2007). Thus, an anti-inflammatory mechanism of polyphenols may result from disarming microbial endotoxins. The negative charge of LPS within the outer membrane of Gram-negative bacteria provides some resistance to lipophilic polyphenols that would otherwise diffuse across membranes (Ignasimuthu et al., 2019). Conversely, Gram-positive bacteria that lack negatively charged LPS, seem to be more susceptible to the membrane disruptive action of polyphenols due to polyphenolic diffusion within bacterial cell walls (Cueva et al., 2010; Vattem et al., 2004). Among several polyphenols tested, a positive relationship was found between antibacterial activity against *E. coli* and membrane rigidification related to the lipophilicity of the compound (Wu et al., 2013). Substituents that increase the lipophilicity of the molecule, such as prenyl groups, alkyl chains, and nitrogen or oxygen-containing heterocyclic moieties, enhance antibacterial effects (Xie et al., 2015). Polyphenols also inhibit microbial growth by chelating and depriving microbes of essential micronutrients, such as

iron or zinc. Illustrating this effect, *E. coli* growth was inhibited *in vitro* with tannic acid, but restored by the addition of iron (Chung et al., 1998). Conversely, beneficial bacteria such as *Bifidobacterium* and Lactobacilli spp., which are also capable of metabolizing polyphenols, do not require iron for growth, likely contributing to their resistance to the antimicrobial activity of polyphenols.

Although many polyphenols show prominent antimicrobial activity, their strongest utility may lie in their anti-virulent properties. Quorum sensing is an intercellular bacterial communication mechanism, which depends on bacterial population density, that controls the pathogenicity of many microorganisms by regulating gene expression, virulence factors, and biofilm formation. Biofilms are assemblages of microbes bound within an extracellular matrix of biopolymers that make them especially resistant to antimicrobial stimuli. Mucosal biofilms have been found in subsets of UC (Baumgartner et al., 2021) and CD (Abdelhalim et al., 2020) that correlate with dysbiosis and the presence of pathogens, such as adherent-invasive *Escherichia coli*. Curcumin (25–100 μg/mL) (Packiavathy et al., 2014), quercetin (10–80 μg/mL; MIC: 4.1 μg/mL) (Gopu et al., 2015; Veloz et al., 2019), kaempferol (16–128 μg/mL) (Ming et al., 2017), naringenin (5–60 μg/mL) (Wen et al., 2021), phloretin (5–100 μg/mL) (Lee et al., 2011), EGCG (12.5–200 μg/mL) (Serra et al., 2016), pinocembrin (MIC: 1.4 μg/mL) (Veloz et al., 2019), and apigenin (MIC: 1.3 μg/mL) (Veloz et al., 2019) have been reported to disrupt quorum sensing or inhibit biofilm formation of various bacteria in cell culture in a dose-dependent manner. Evidence suggests that higher concentrations are needed to disrupt established biofilms compared to inhibiting initial formation (Serra et al., 2016). In an *in vitro* comparison of 9 flavonoids, phloretin was most effective at impairing enterohemorrhagic *E. coli* O157:H7 biofilm formation and growth (89% inhibition at 25 μg/mL) (Lee et al., 2011). Interestingly, phloretin was effective in inhibiting pathogenic *E. coli* strains, but did not harm biofilms of a commensal *E. coli* K-12 strain. In an *in vivo* study, phloretin-rich polyphenol extract (200 mg or 400 mg kg^{-1}) protected against intestinal inflammation and *Clostridioides difficile* infection in mice (Z. Z. Wu et al., 2022).

5. Polyphenols impact the gut metabolome

Studying states of gut health and disease can be especially complex due to interactions between host metabolism, the gut microbiome, and the diet. Advances in next generation sequencing have allowed for rapid profiling of microorganisms within a biological sample, no longer dependent on whether or not microbes are culturable. Still, some limitations persist. Methods that utilize 16S rRNA gene sequencing cannot predict the functional profile of a microbiome. While shotgun metagenomic sequencing reveals the functional potential of the gut microbiome, analysis is highly reliant on prior knowledge of how genes relate to enzymes. And even still, evidence suggests that a substantial proportion of transcriptional activity of the gut microbiome is not reflected in genomic abundances (Franzosa et al., 2014). Increasingly researchers are looking to metabolomic methods — which measure small molecules within a biological system — to elucidate functional changes within the gut microbiome. Gut microbiota can modulate a myriad of host physiological functions through small molecule metabolites — derived from dietary sources, host molecules, or directly from bacteria. In turn, these signaling molecules can have a range of effects on the host such as immune modulation, host energy metabolism, and maintenance of the mucosal lining (Lavelle and Sokol, 2020). Several classes of microbial metabolites, including short-chain fatty acids (SCFAs), secondary bile acids, and indoles (tryptophan metabolites) are the focus of current research due to their association with intestinal homeostasis and altered metabolome profiles in IBD (Fig. 4).

5.1. Short-chain fatty acids

Short-chain fatty acids (SCFAs) are quintessential examples of

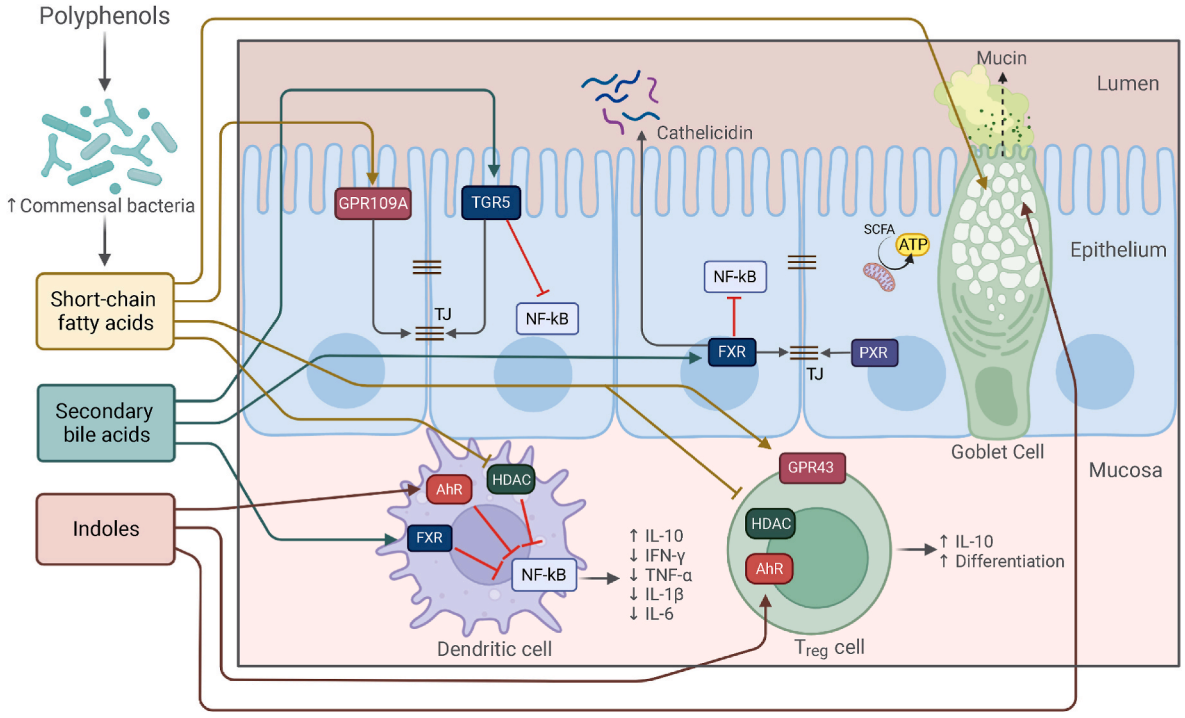

Fig. 4. Polyphenols enhance the generation of microbial metabolites with a range of beneficial effects on the host. Short-chain fatty acids (SCFAs) mediate diverse effects on intestinal homeostasis. They provide substrate for energy metabolism, increase the production of mucins, promote expansion of regulatory T (T_{reg}) cells, and increase tight junction (TJ) proteins. Secondary bile acids (as well as deconjugated primary bile acids) reduce inflammation through NF-κB inhibition, increase production of antimicrobial peptides (cathelicidin), and increase tight junction proteins. Indoles reduce inflammation through NF-κB inhibition, promote expansion of T_{reg} cells, and increase production of mucins.

microbial metabolites that regulate intestinal homeostasis. They are derived from fermentable dietary fibers and regulate host immune response (Jin et al., 2017), susceptibility to pathogens (Wu et al., 2017), and epithelial barrier function (Jin et al., 2017; Kelly et al., 2015). Acetate, propionate, and butyrate account for ~90% of SCFAs produced by microbial fermentation and can reach peak concentrations of 130 mM in the proximal colon prior to absorption (Cummings et al., 1987). Their proportion in the colonic environment is variable by diet and microbiome composition. Acetate, which is produced by multiple bacterial groups, accounts for ~50–70%; propionate, which is produced by members of the phyla Bacteroidetes and Firmicutes, accounts for ~10–20%; and butyrate, produced by a small number of *Clostridia*, accounts for less than 10% (Miller and Wolin, 1996; Salonen et al., 2014). Critical for the maintenance of the intestinal barrier, SCFAs are an important source of energy for the intestinal epithelium. Commensal bacteria produce SCFAs, which reduce intestinal pH and limit the colonization of enteric pathogens (Kamada et al., 2013). In human and mouse colon cell lines, SCFAs promote differentiation of regulatory T cells, important in suppressing immune responses (Jin et al., 2017; Smith et al., 2013). Fig. 4 provides more detail regarding mechanisms of SCFA signaling in intestinal homeostasis. A reduction in SCFAs, particularly butyrate, is reported in IBD patients (Louis et al., 2004; Marchesi et al., 2007; Takahashi et al., 2016; Piero Vernia et al., 1988; P. Vernia et al., 1988). Consistently, microbial dysbiosis observed in IBD is associated with a loss of butyrate-producing species, such as *Faecalibacterium prausnitzii* (Sokol et al., 2008, 2009) and *Roseburia hominis* (Machiels et al., 2014).

In vitro fecal cultures with polyphenols show increases in total and individual short-chain fatty acids (Shengyong Mao, 2011) as an end product of bacterial catabolism (Wong et al., 2006). However, the contribution of polyphenols directly to SCFA production is likely negligible compared to what is produced from dietary soluble fiber. Instead, polyphenols may encourage the growth of SCFA-producing taxa, such as Lactobacilli and *Bifidobacterium*, increasing the capacity of the gut microbiome to generate SCFAs from dietary sources. In animal models of IBD, several studies have measured the production of SCFAs in response to polyphenol administration. Rats allowed to drink a mango-derived, polyphenol-rich (475 mg gallic acid equivalent/L) beverage with soluble fiber enzymatically removed for 3 weeks showed increased butyric and valeric acid production after a DSS challenge compared to controls (Kim et al., 2018). HPLC-MS analysis characterized the polyphenol content as consisting of monogalloyl glucoside, gallic acid, p-hydroxybenzoic acid glycoside, coumaric glycoside, and dihydrophaseic acid glucoside. Gallotannins were present at relatively low concentrations. The increase in SCFAs coincided with increases in *Lactiplantibacillus plantarum* (previously known as *Lactobacillus plantarum*) and *Lactococcus lactis*, as well as butyrate-producing *Clostridium butyrium*. Mice administered tangeretin (0.08% diet by weight), a citrus-derived flavone, recovered from DSS-induced colitis similar to healthy controls, which corresponded with recovered production of acetic, butyric, and valeric acid (Chen et al., 2021). Additionally, tangeretin increased the abundance of beneficial bacteria, *Lachnospiraceae* and *Lactobacillaceae*, while decreasing the abundance of *Enterobacteriaceae* and *Alistipes*. Decreased inflammatory cytokines and increased expression of tight junction proteins, claudin-1 and ZO-1, in tangeretin-supplemented mice may have partially resulted from improved SCFA production. Galangin, a flavonol, administered at 15 mg kg^{-1} for 1 week before a DSS challenge, protected against colitis in mice, accompanied by significantly increased levels of acetic, propionic, and butyric acid, and recovery of Lactobacilli and *Butyricimonas* abundance (Xuan et al., 2020). In a similar experimental model, 1 mg kg^{-1} of hesperetin-7-O-glucoside administered for 7 days alleviated DSS-induced colitis in mice with significant increases in fecal propionic and butyric acid, as well as indole metabolites (Wu et al., 2021). These changes were accompanied by significant changes in gut microbiome composition similar to healthy control animals, suggesting it is crucial to mediating the polyphenol-driven protection against colitis.

5.2. Bile acids

Bile acids are a family of amphipathic molecules generated from cholesterol in the liver which facilitate the digestion of lipids. Primary bile acids, cholic acid (CA) and chenodeoxycholic acid (CDCA), are conjugated to either glycine or taurine before excretion into the intestinal lumen. While 95% of the bile acid pool is reabsorbed in the ileum by enterohepatic circulation, ~5% of bile acids escape and are available for modification by intestinal microbes, producing secondary bile acids with a range of important biological activity. The "gateway reaction" of bile acid metabolism by intestinal bacteria is the deconjugation of primary bile salts by bile salt hydrolases (BSHs) which are found in all major bacterial phyla and some archaea (Fiorucci et al., 2021). This initial step is followed by the dehydroxylation at the C7 position by 7α-dehydroxylase expressing bacteria such as *Clostridium* and *Eubacterium,* giving rise to the main secondary bile acids, deoxycholic acid (DCA) from CA and lithocholic acid (LCA) from CDCA. Bile acids exert a range of effects on intestinal homeostasis through binding receptors including the farnesoid X receptor (FXR) and the transmembrane G protein-coupled receptor 5 (TGR5) (Schaap et al., 2014). Intestinal FXR activation inhibits bacterial overgrowth, translocation, and intestinal inflammation (Gadaleta et al., 2011b; Inagaki et al., 2006). Bile acids can have direct antimicrobial effects by damaging bacterial membrane integrity (Kurdi et al., 2006; Watanabe et al., 2017), as well as indirect effects through inducing host production of antimicrobial peptides, such as cathelicidin (D'Aldebert et al., 2009), angiogenin I (Inagaki et al., 2006), and inducible nitric oxide synthase (iNOS) (Gadaleta et al., 2011b). In rodent models, Tgr5 modulates intestinal immune response and expression of tight junction proteins (Cipriani et al., 2011). In human IBD, disrupted bile acid composition is characterized by increased fecal conjugated primary bile acids, decreased secondary bile acids, and higher levels of 3-OH-sulfated bile acids, suggesting functional shifts in the microbiome (Duboc et al., 2013; Franzosa et al., 2019; Jansson et al., 2009; Takaishi et al., 2008). Reduced secondary bile acids found in IBD may support the colonization of pathogens (Buffie et al., 2015; Kang et al., 2019). In human and murine cell lines, TGR5 activation, for which secondary bile acids have the greatest affinity, inhibits NF-κB (Calmus et al., 1992; Wang et al., 2011). Selective secondary bile acids, 3-oxoLCA and isoalloLCA, have been found to modulate adaptive immunity through T helper cell differentiation, attenuating intestinal inflammation (Hang et al., 2019). Consistently, administration of secondary bile acids, LCA and DCA, alleviated DSS- and TNBS-induced colitis in mice (Sinha et al., 2020).

Several animal models of IBD have shown polyphenol supplementation restores bile acid profiles concurrent with ameliorating colitis symptoms, presumably through the remodeling of the gut microbiome, although outcomes are not always consistent. In a mouse model of IBD, dihydromyricetin (200 mg kg^{-1}), a flavanonol, restored decreases in LCA and CDCA, which were significantly altered with DSS treatment (Dong et al., 2021). The authors note LCA and CDCA are endogenous agonists for bile acid receptors, TGR5 and FXR, respectively, which are important in maintaining intestinal homeostasis. The increases in bile acids were positively correlated with the abundance of Lactobacilli and *Akkermansia*. In rats, dihydromyricetin with DSS treatment significantly upregulated Tgr5 and Fxr expression compared to the DSS-only treated group (Dong et al., 2021). Antibiotic treatment blunted the increase in expression, suggesting Tgr5 and Fxr upregulation was dependent on gut microbiota. Consistently, Caco-2 cells exposed to LCA (10 μM) and CDCA (50 μM) increased mRNA expression of TGR5 and FXR, respectively, while dihydromyricetin (10–100 μM) showed no effect on its own, demonstrating bile acids on the causal path. In a similar IBD model, mice treated with phloretin (100 mg kg^{-1}) for 2 weeks, then phloretin and DSS for 1 week, were partially protected from developing colitis with bile acid composition similar to controls (Liu et al., 2021).

Compared to the DSS-only treated group, phloretin significantly increased mRNA expression of Tgr5, total bile acids, and concentrations of secondary bile acids, DCA and LCA, similar to controls. The secondary bile acids likely mitigated intestinal inflammation by inhibiting NF-κB through Tgr5 receptor activation. Phloretin also significantly decreased hepatic Fxr mRNA expression, which was upregulated in the DSS-treated group. Extract from *Eucommia ulmoides* (200 mg kg^{-1} 11 days), a traditional Chinese herbal medicine rich in flavonoids and phenolic acids, prevented intestinal inflammation and damage from a DSS challenge in mice (Zhai et al., 2021). Treatment with *Eucommia ulmoides* extract restored DSS-induced alteration in bile acids, reducing primary bile acids (CA, β-MCA), and increasing the secondary bile acid, DCA. Additionally, the restoration in bile acids coincided with significantly increased Tgr5 mRNA, gut barrier integrity, and tight junction proteins, claudin-1 and occludin, compared to controls that received DSS alone.

It is important to note that some polyphenols, such as caffeic acid phenethyl ester (Zhong et al., 2022) and amentoflavone (Li et al., 2022), inhibit microbial bile salt hydrolase (BSH) activity, the key enzyme required for de-conjugation of primary conjugated bile acids and the gateway reaction in further microbial conversions of bile acids. Thus, some polyphenols inhibit the microbial conversion of conjugated primary bile acids to secondary bile acids. Some lines of evidence suggest the increase in conjugated bile acids has a net antagonistic effect on intestinal FXR (Paraiso et al., 2021; Zhang et al., 2020). While this effect appears therapeutic in models of metabolic syndrome and gastrointestinal cancers (Sun et al., 2021), the consequences for IBD are less clear.

5.3. Indoles

Tryptophan is an essential, aromatic amino acid that can be metabolized by gut microbiota to produce a range of indole metabolites that act as aryl hydrocarbon receptor (AhR) agonists. AhR-dependent production of IL-10 and IL-22 by immune T cells promote antimicrobial immunity, mediate recovery from inflammatory responses, and induce epithelial proliferation (Monteleone et al., 2011; Sonnenberg et al., 2011). In murine dendritic cells, administration of indole-3-carbinol suppressed production of proinflammatory mediators, TNF-α, IL-1β, IL-6, IL-12, and NO, as well as increased anti-inflammatory IL-10 levels after LPS-activation (Benson and Shepherd, 2011). Like SCFAs, indoles can improve first-line defenses against pathogens by increasing mucus production (Chimerel et al., 2014), mucins (MUC2 and MUC4) from goblet cells (J. Li et al., 2021), and tight junction proteins (Bansal et al., 2010). The AhR has been implicated with IBD pathogenesis and reduced levels of indoles are reported in IBD patients (Nikolaus et al., 2017). While supplementation with Lactobacilli strains, known indole-producers, and synthetic AhR agonists maintained remission in IBD patients (Zocco et al., 2006).

In animal models of IBD, polyphenolic-rich extract from turmeric supplemented within a standard diet (8% w/w) ameliorated colitis symptoms caused by a 37-day DSS challenge in mice (Yang et al., 2022). Turmeric extract significantly elevated tryptophan metabolites, indole-3-acetic acid and indole-3-propionic acid, while reducing tryptophan compared to DSS-only treated mice. A strong negative correlation was found between tryptophan concentration and the relative abundance of Lactobacilli, which are known to metabolize tryptophan to indoles. *In vitro* and *in vivo* evidence suggest polyphenols support Lactobacilli, overwhelmingly seen as beneficial bacteria (Cortés-Martín et al., 2020). Consistently, turmeric extract in DSS-treated mice significantly restored colonic AhR and IL-22 levels, as well as tight junction proteins, occludin, ZO-1, and claudin-1, similar to healthy control animals (Yang et al., 2022). In mice, oral hesperetin-7-O-glucoside (1 mg kg^{-1} for 7 days) concurrent with a 7-day DSS challenge protected against colitis (Wu et al., 2021). DSS-induced colitis resulted in significant reductions in plasma indole-3-propionic and indole-3-acetic acid, while treatment with hesperetin-7-O-glucoside significantly increased plasma levels of these indoles similar to control mice. Hesperetin-7-O-glucoside also alleviated inflammatory status, significantly increased IL-22 levels, and restored histopathological measures. Magnolol, a lignan from *Magnolia officinalis*, given to mice through intragastric gavage (10 mg kg^{-1}) for 7 days following a 5-day DSS challenge significantly attenuated colitis activity, histopathological changes, and pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) compared to DSS-only treated mice (Zhao et al., 2017). Metabolomics analysis of serum revealed that magnolol treatment significantly elevated several tryptophan metabolites compared to DSS-treated mice, including 5-hydroxyindoleacetic acid, indoleacetic acid, indolelactic acid, and indoxylsulfuric acid. Although sequencing of the gut microbiome was absent from this study, *in vitro* evidence suggests that microbial taxa capable of biotransformation of lignans are also important indole producers. *Bifidobacterium* spp. have been shown to convert tryptophan to indole-3-lactic acid in culture (Aragozzini et al., 1979). Lactobacilli spp., which carry out *O*-deglycosylation reactions, are important and well-known producers of indole metabolites (Niu et al., 2022; Shi et al., 2020).

6. Evidence from randomized controlled clinical trials

Clinical trials evaluating the therapeutic value of polyphenols in IBD are currently ongoing as results, so far, are promising but far from unequivocal. Part of the ambiguity arises from inconsistent experimental conditions such as specific polyphenol supplements, dose, duration, route of administration, use with conventional medications, and outcome measures. To date, 10 randomized controlled trials (RCTs) have been conducted to evaluate the therapeutic potential of single polyphenol dietary supplements on clinical outcomes of ulcerative colitis (UC) (Table 2). To the best of our knowledge, no RCTs to date have investigated polyphenol supplementation in Crohn's disease or nonspecific IBD.

The majority of clinical trials have examined the efficacy of curcumin in UC. Hanai et al. (2006) investigated the use of 1 g of curcumin taken orally twice daily alongside sulfasalazine or mesalamine treatment for 6 months in 89 quiescent ulcerative colitis patients. Curcumin treatment significantly reduced relapse recurrence in patients during 6 months of treatment, with no significant difference after 6 months of further follow up, suggesting therapeutic benefit with continual use. Significantly better disease activity and endoscopic indexes were observed in the treatment group, suggesting improvement in disease activity without serious side effects. Singla et al. (2014) examined the effect of enema with NCB-02, a standardized extract of *Curcuma longa* containing 72% curcumin, 18% demethoxy curcumin, and 9% bis-demethoxy curcumin, on disease activity in patients with mild-to-moderate ulcerative colitis. Patients in the treatment group received one enema daily alongside 5-aminosalicylates for eight weeks. Participants that completed that protocol had significantly better measures of clinical remission, clinical response, and improved endoscopic disease activity; however, outcomes lost significance when participants that dropped out due to worsening symptoms or were lost to follow-up were included. Lang et al. (2015) investigated whether 3 g of oral curcumin taken daily for 1 month in combination with 5-aminosalicylate could induce remission in patients with mild to moderate UC. Improvements in clinical remission, defined as a Simple Clinical Colitis Activity Index (SCCAI) score less than or equal to 2, and endoscopic remission was found significantly more frequently in the treatment group compared to the placebo group, suggesting curcumin was an effective complementary treatment for moderate UC.

Conversely, a randomized, placebo-controlled trial of mild-to-moderate UC patients receiving curcumin found no significant outcomes (Kedia et al., 2017). Oral curcumin (150 mg) taken 3 times daily alongside mesalamine (5-aminosalicylic acid) for 8 weeks was not effective in inducing remission or reducing disease activity, although the study only reported intention to treat with a high loss to follow up. Another randomized, placebo-controlled, clinical trial examined the

Table 2
Summary of randomized clinical trials (RCTs) examining polyphenol supplementations in ulcerative colitis (UC).

Polyphenol	Intervention	Disease	Participants (ITT) treat./con.	Participants (PP) treat./con.	Other treatment	Outcome	Country	Author (year)
Curcumin	1 g twice daily for 6 months	UC, inactive	45/44	43/39	5-ASA	Improved remission rate, CAI & EI scores	Japan	Hanai et al. (2006)
	140 mg (NCB-02) enema daily for 8 weeks	UC, mild-to-moderate	23/22	14/16	5-ASA	Improved clinical remission & endoscopic response (NS in ITT group)	India	Singla et al. (2014)
	3 g daily for 1 month	UC, mild-to-moderate	26/24	25/22	5-ASA	Improved clinical remission & endoscopic remission	Israel, Hong Kong, Cyprus	Lang et al. (2015)
	150 mg 3 times daily for 8 weeks	UC, mild-to-moderate	29/33	16/25	5-ASA	Insignificant changes in ITT group	India	Kedia et al. (2017)
	80 mg (curcuminoid nanomicelles) 3 times daily for 8 weeks	UC, mild-to-moderate	28/29	28/28	5-ASA	Improved SCCAI score	Iran	Masoodi et al. (2018)
	500 mg 3 times daily for 8 weeks	UC, mild-to-moderate	35/35	31/32	NR	Improved clinical remission, ↓ESR & hs-CRP	Iran	Sadeghi et al. (2020)
EGCG	400 or 800 mg twice daily for 8 weeks	UC, mild-to-moderate	16/4	15/4	Inclusion criteria allowed 5-ASA and 6-MP	↑ clinical remission (UCDAI ≤2)	U.S.	Dryden et al. (2013)
Resveratrol	500 mg daily for 6 weeks	UC, mild-to-moderate	25/25	25/24	Inclusion criteria allowed 5-ASA, CS, & IS	Improved IBDQ-9 & SCCAI scores, ↓ hs-CRP, TNF-α, & PBMC NF-κB p65	Iran	Samsami-kor et al. (2015)
	500 mg daily for 6 weeks	UC, mild-to-moderate	28/28	26/27	Inclusion criteria allowed 5-ASA, CS, & IS	↓ MDA, ↑ SOD, & TAC	Iran	Samsamikor et al. (2016)
Silymarin	140 mg daily for 6 months	UC, inactive	42/38	38/32	Inclusion criteria allowed 5-ASA, CS, & IS	Improved remission rate & DAI scores, ↑ Hb, ↓ ESR	Iran	Rastegarpanah et al. (2015)

Treat: treatment; con: control; UC: ulcerative colitis; ITT: intention to treat; PP: per protocol; NR: not reported; NS: not significant; 5-ASA: 5-aminosalycilates; 6-MP: 6-mercaptopurine; CS: corticosteroid; IS: immunosuppressant; CAI: clinical activity index; EI: endoscopic index; UCDAI: ulcerative colitis disease activity index; SCCAI: simple clinical colitis activity index; IBDQ-9: inflammatory bowel disease questionnaire 9; ESR: erythrocyte sedimentation rate; hs-CRP: high sensitivity C-reactive protein; TNF-α: tumor necrosis factor alpha; PBMC NF-κB p65: peripheral blood mononuclear cell nuclear factor kappa B p65; MDA: malondialdehyde; SOD: superoxide dismutase; TAC: total antioxidant capacity; Hb: hemoglobin.

efficacy of 80 mg of curcuminoids taken orally 3 times daily plus mesalamine for 4 weeks in 56 patients with mild-to-moderate UC (Masoodi et al., 2018). Curcuminoid supplementation significantly reduced disease activity evaluated by SCCAI score, with no significant difference in side effects. In another randomized, placebo-controlled study, the effects of curcumin supplementation on changes in serum inflammatory serum biomarkers, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and tumor necrosis factor-α (TNF-α), were examined in mild-to-moderate UC patients (Sadeghi et al., 2020). Curcumin treatment (500 mg 3 times daily) for 8 weeks significantly reduced CRP and ESR, with no significant change in TNF-α. Additionally, curcumin supplementation significantly improved clinical remission compared to the placebo group.

Another polyphenolic compound that has been investigated for therapeutic value in UC is epigallocatechin gallate (EGCG). A randomized, placebo-controlled pilot study examined EGCG at 2 doses (400 mg or 800 mg twice daily) for 56 days as a complementary treatment in mild-to-moderate UC (Dryden et al., 2013). Participants were allowed to maintain established use of medication. EGCG treatment significantly improved clinical remission and response scores defined as a score less than or equal to 2 or a drop in score by 3 on the UC disease activity index (UCDAI), respectively.

Resveratrol has also been evaluated for therapeutic value in IBD. In a study that evaluated the effects of resveratrol on serum inflammatory markers, supplementation taken orally (500 mg daily for 6 weeks) significantly reduced serum levels of CRP and TNF-α, as well as activity of NF-κB p65 in peripheral blood mononuclear cells (PBMC) in mild to moderate UC patients compared to the placebo group (Samsami-kor et al., 2015). Resveratrol also significantly improved disease activity scores, evaluated by the Inflammatory Bowel Disease Questionnaire-9 (IBDQ-9) and the Simple Colitis Clinical Activity Index (SCCAI). In a follow-up study by the same group, the effect of resveratrol on measures of oxidative stress was evaluated by serum levels of malondialdehyde (MDA), superoxide dismutase (SOD), and total antioxidant capacity (TAC) (Samsamikor et al., 2016). Six weeks of daily resveratrol supplementation (500 mg) significantly increased SOD and TAC, and decreased serum concentration MDA, indicating improvements in antioxidant capacity. Supplementation also resulted in a significant reduction in disease activity and improved quality of life in UC patients.

A final randomized, placebo-controlled, clinical trial examined silymarin supplementation at 140 mg daily for 6 months in UC patients in remission (Rastegarpanah et al., 2015). At the end of 6 months, the treatment group maintained clinical remission significantly more frequently than the placebo group. This effect was accompanied by significantly reduced ESR and disease activity scores (UCDAI), indicating long-term polyphenol treatment positively influenced disease outcome.

Collectively, clinical trials examining the use of polyphenols as a complementary treatment in UC appear to elicit beneficial effects in disease activity, remission rates, and quality of life. Further studies with Crohn's disease and nonspecific IBD patients are needed as presently, all evidence comes from patients with ulcerative colitis. Additional studies in humans investigating the effects of polyphenol supplementation on inflammatory biomarkers, gut microbiota, and metabolic profiles may

elucidate mechanisms of polyphenol supplementation for IBD treatment. Additional studies are warranted to examine efficacy, dose, and treatment schedule, as well as optimal polyphenolic compounds.

7. Conclusion

In this review, we have summarized mechanisms of action regarding polyphenols for the mitigation of IBD symptoms. These include direct cellular targets, modulation of the intestinal microbiome, and influences on microbial metabolites as a product of microbiome modulation. Additionally, we summarize evidence from randomized controlled trials for polyphenol treatment in IBD. Preclinical evidence suggests that polyphenols act, broadly, through two general schemes. First, polyphenols interact with cellular signaling pathways and transcription factors that critically regulate inflammation, protection against oxidative stress, epithelial barrier function, and pathogen defense. Second, polyphenols exert both prebiotic and antimicrobial action towards the intestinal microbiome. Modulation of the gut microbiome by polyphenols supports the growth of beneficial microorganisms that may provide vital functions for the host or inhabit important ecological niches. Simultaneously, polyphenols inhibit pathogenic microbes that may contribute to intestinal inflammation or gut microbiome dysbiosis. One of the primary modes by which gut microbiota interface with the host is through the production of metabolites. Through modulation of the gut microbiome, polyphenols appear to help restore microbially derived metabolites critical to the maintenance of intestinal homeostasis that are adversely disrupted in IBD. Short-chain fatty acids, bile acids, and indole metabolites comprise some of the most meaningful classes of microbially generated compounds regarding IBD pathology, through their modulation of immune regulation, epithelial repair, and pathogen defense.

8. Future directions

Clinical trials with polyphenols for IBD are promising, yet their clinical value is still undetermined, in part due to the variety of phenolic compounds examined and a range of experimental designs used. Investigations are further complicated by the numerous mechanisms that may be at play and the inherent difficulty in observing interactions between host metabolism, the gut microbiome, and the exposome *in vivo*. Furthermore, IBD trials may be particularly sensitive to the placebo effect (Estevinho et al., 2018) and outcomes that solely rely on patient-reported questionnaires for disease activity or quality of life may be difficult to replicate in broader sample populations. Additionally, these measures do not provide information on polyphenols mechanisms of action, which will be important in determining their use as a therapy. We propose clinical trials would benefit from independent and objective measures to complement these primary clinical outcomes. Advances in next generation sequencing techniques now allow for the rapid and relatively affordable detection of microbial signatures within a biological system. Metabolomics provides a comprehensive 'snapshot' of small-molecule metabolites and can be used in parallel with microbiome sequencing to elucidate functional changes within a system. Together, multi-omic integration methods may elucidate complex treatment-host, treatment-microbe, and host-microbe interactions that certainly play an important role in IBD pathology and response to treatment. These relatively new approaches to investigating the role of the gut microbiome in polyphenol and host metabolism may provide critical insight that determines the clinical value of polyphenols for IBD therapy.

CRediT authorship contribution statement

Paige E. Jamieson: Conceptualization, Data curation, illustrations, Writing – original draft. **Franck Carbonero:** Conceptualization, Writing – review & editing. **Jan F. Stevens:** Conceptualization, Supervision, Funding acquisition, Writing – review & editing.

Declaration of competing interest

The authors have no conflicts of interest to declare.

Data availability

No data was used for the research described in the article.

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