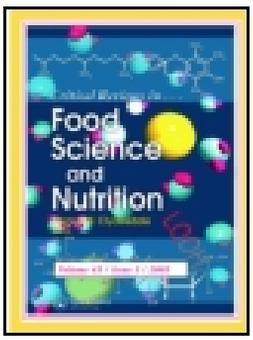

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REVIEW

Therapeutic implications of functional tea ingredients for ameliorating inflammatory bowel disease: a focused review

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ABSTRACT

Inflammatory bowel disease (IBD) is a chronic gastro-intestinal disorders of unknown etiology. There are several drugs approved for treating IBD patients with active disease, including first-line use of aminosalicylates, and secondary choices of immunomodulators and other therapies. These medications might manage disease symptoms, but have also shown significant side-effects in IBD patients. Tea is the second largest beverage in the world and its main active ingredients including tea polyphenols, polysaccharides and tea pigments have been shown promising anti-inflammatory and antioxidant properties. In this review, we summarize the influence of different tea varieties including green tea, black tea and dark tea as potential nutritional therapy for preventing and treating IBD, and discuss the mechanisms of tea ingredients involved in the regulation of oxidative stress, inflammation, signaling pathways, and gut microbiota that could benefit for IBD disease management. Our observation directs further basic and clinical investigations on tea polyphenols and their derivatives as novel IBD therapeutic agents.

KEYWORDS

Tea ingredients; polyphenol derivatives; nutritional therapy; inflammatory bowel disease

Introduction

Inflammatory bowel diseases (IBD) is characterized with chronic gastrointestinal inflammation with diarrhea, rectal bleeding and colonic mucous membrane congestion, erosion and recurrent intractable disease, and mainly refers to ulcerative colitis (UC) and Crohn's disease (CD), which are highly prevalent worldwide especially in developed countries (Benchimol et al. 2009; Molodecky et al. 2012; Benchimol et al. 2014). For example, about 1.6 million people in the United States are affected by IBD each year, including 910,000 UC and 785,000 CD patients (Aniwan, Park, and Loftus 2017). Epidemiological trends in the occurrence of IBD indicate an association with western lifestyle (Zuo et al. 2018), this is evidenced by the increased incidence of IBD in Asia, particularly in Japan and India, as well as in Middle East as a result of popularity of western diet (Ng et al. 2013). In particular, consumption of a Western diet high in saturated fat, food additives and refined carbs is associated with high risk of IBD (Dixon et al. 2015). Furthermore, IBD condition not only predisposes patients to intestinal surgeries and the risk of colon cancer, but also is associated with high mortality rate (Tenesa and Dunlop 2009).

Although the precise etiology of IBD is not entirely understood, the current consensus states that the disease initiation or induction is often linked to the interactions among human genetics, environmental factors, host immune response and intestinal microbiota (Figure 1). Such complicate mechanisms challenge the drug design for curing IBD, thus current clinical guidance has mainly focused on managing the symptoms of IBD to achieve remission state, especially suppressing host immune responses for reducing tissue inflammation. Unfortunately, most of IBD drugs cause serious adverse effects such as fatigue, nausea, diarrhea, pulmonary fibrosis, vomiting, and abdominal pain, etc (Rogler 2010; Ben-Horin and Yehuda 2014). Effectiveness in reducing mucosal inflammation is highly desirable. In addition, from the modern standpoint of public health, disease prevention is the main focus of epidemiologists and gastroenterologists. Apart from drug-based remission purpose, nutritional therapy has been included for long-term disease management of IBD patients. For centuries, due to the wide and frequent consumption of tea-based products, their functionalities have gained great attention and been extensively studied for preventing various diseases. Interestingly, Epidemiologic studies of green-tea-consuming regions have indicated daily tea consumption exerts a protective effect in both UC and CD patients (Dryden et al. 2013).

As the second most frequently consumed beverage worldwide, tea (*Camellia sinensis*) has been cultivated and its leaves have been processed and consumed for centuries. It can be classified as non-fermented (oxidation) green tea, fully fermented black tea and post-fermentation (microbial associated) dark tea based on their manufacturing processes. These types of tea are usual difference in the appearance,

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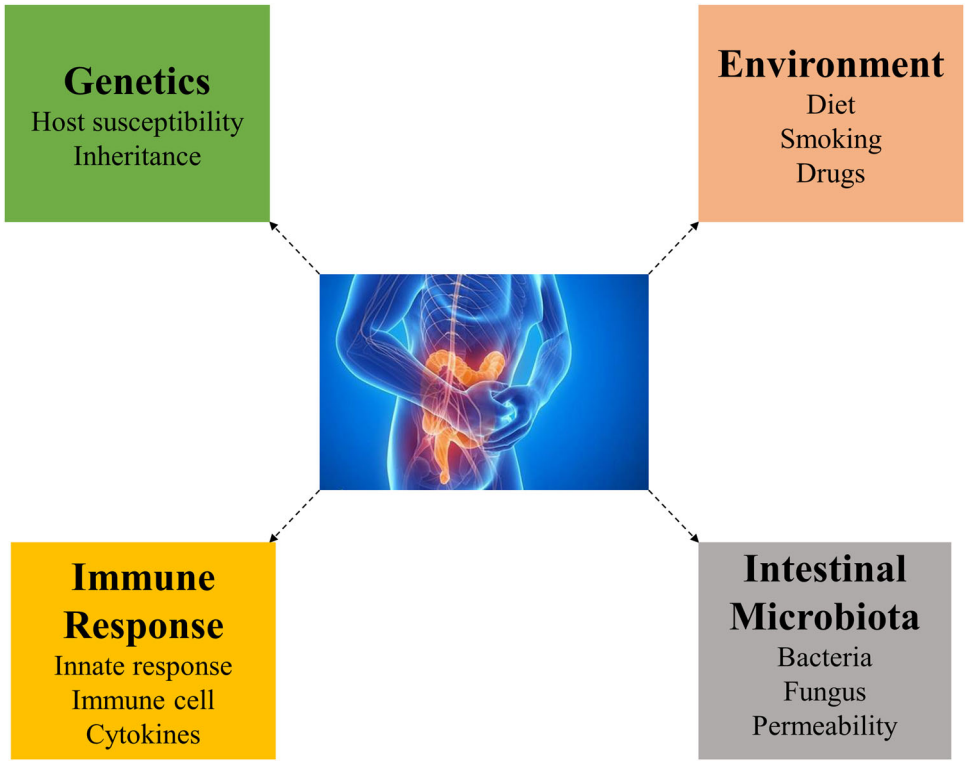


Figure 1. Mechanisms of inflammatory bowel disease. The pathogenesis of IBD is associated with the interactions among genetic, environmental, immune response factors and intestinal microbiota.

taste, infusion color, and aroma (Figure 2), such difference is highly linked with biotransformation events of tea ingredients during manufacturing. It is well known that tea is an important source of polyphenols, polysaccharides, theanine and tea-pigments that are believed to minimise the risk of many disease conditions including intestinal disorders (Yang et al. 2001; Biasi et al. 2011). For example, our recent study showed that ripened Pu-erh tea could significantly improve DSS-induced colitis in mice by modulating NF-κB and HIF-1α pathways (Huang et al. 2020). One of the pioneer studies – oral administration of Fuzhuan brick tea (dark tea) extracts (60 mg/kg/day) remarkably improved the characteristics of experimental colitis such as diarrhea, rectal bleeding and loss of body weight in a mouse model (Liu et al. 2016). Therefore, after biotransformation, tea would be a natural reservoir of novel functional compounds that could intervene the initiation and active state of IBD. However, different types of tea often vary in their chemical composition and functional efficacy. Keywords-based literature searching using Web of Science website indicates that most of studies focus on green tea, followed by black tea, but functional investigation of dark tea effect on IBD is limited (Figure 2). Unlike other reviews with a broad summary on effects of tea ingredients on various diseases, our review focuses on IBD based on prior reports (Huang et al. 2020) and our recent work on experimental colitis (Huang et al. 2021, in revision). Specifically, we firstly summary the pathogenesis of IBD, followed by assessing the effects of three tea varieties (green tea, black tea and dark tea) on IBD to provide theoretical basis for improving IBD management, with emphasis on novel constituents from black tea and dark tea as promising therapeutic candidates for disease management of IBD; we also discuss the colon-targeted delivery strategy for promoting the bioavailability of novel tea components.

Cellular and molecular mechanisms of IBD

The epidemiological evidence indicates that environmental triggers play a vital role in the progress of IBD (Shouval and Rufo 2017). Such environmental factors could mediate IBD pathogenesis by disrupting gut microbiome homeostasis which could lead to inappropriate and continuing inflammation, as well as destruction of intestinal barrier. Finally, activation of the innate immune cells and production of cytokines and chemokines, are not only accounted for the onset of clinical symptoms, but also regulating the imbalance regulatory and effector cells in the intestinal mucosa; such, immune dysregulation is often observed in IBD patients (Figure 3). Therefore, gastrointestinal tract is not only for nutritional absorption, but also for the maintaining host immune homoeostasis; any dysregulation could lead to different medical conditions, including IBD.

The gastrointestinal tract constitues three barriers to prevent harmful factors and hold intestinal homeostasis (Perez-Lopez et al. 2016). Mucosa, as the first barrier, about 100 trillion (10^{14}) microbes reside at here (Wells et al. 2011; Furusawa et al. 2013). In healthy humans, the host and gut microbiome in a state of mutual benefits form a co-evolutionary relationship (Donaldson, Lee, and Mazmanian 2016). Microbiota-derived components promote mucosal immune system maturity, and decolonize pathogenic microorganisms (Honda and Littman 2012). However, compared

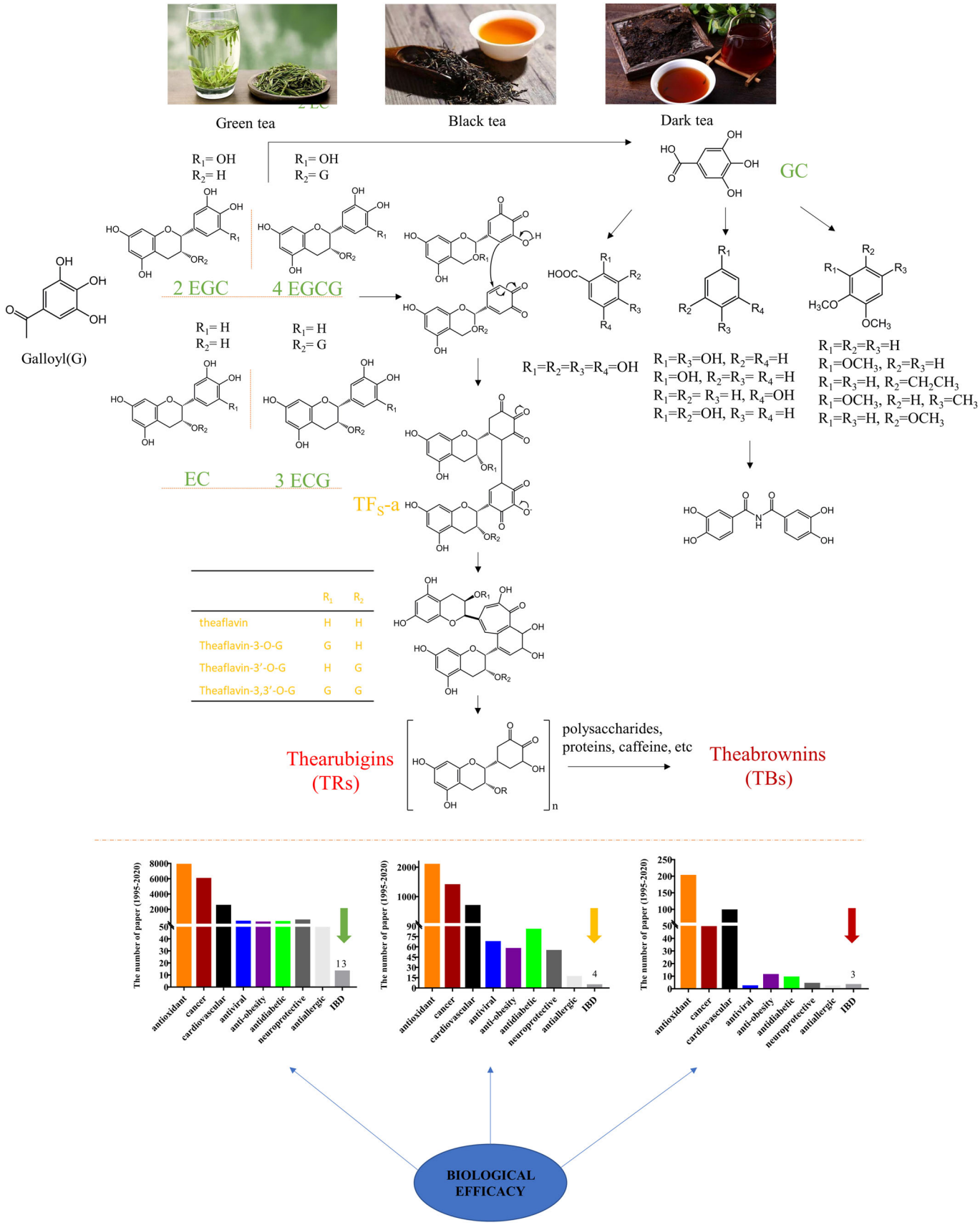


Figure 2. Green tea, black tea and dark tea differ in the appearance, infusion color, taste, and aroma.

to antibiotic-induced major shifts in gut microbiome composition, IBD patients present lesser changes but are often reported with the loss of protective species and the occurance of harmful bacteria (Sun, Nava, and Stappenbeck 2011; Ijssennagger, Meer, and Mil 2016). The intestinal epithelial cells (IECs), consisting of absorptive cells such

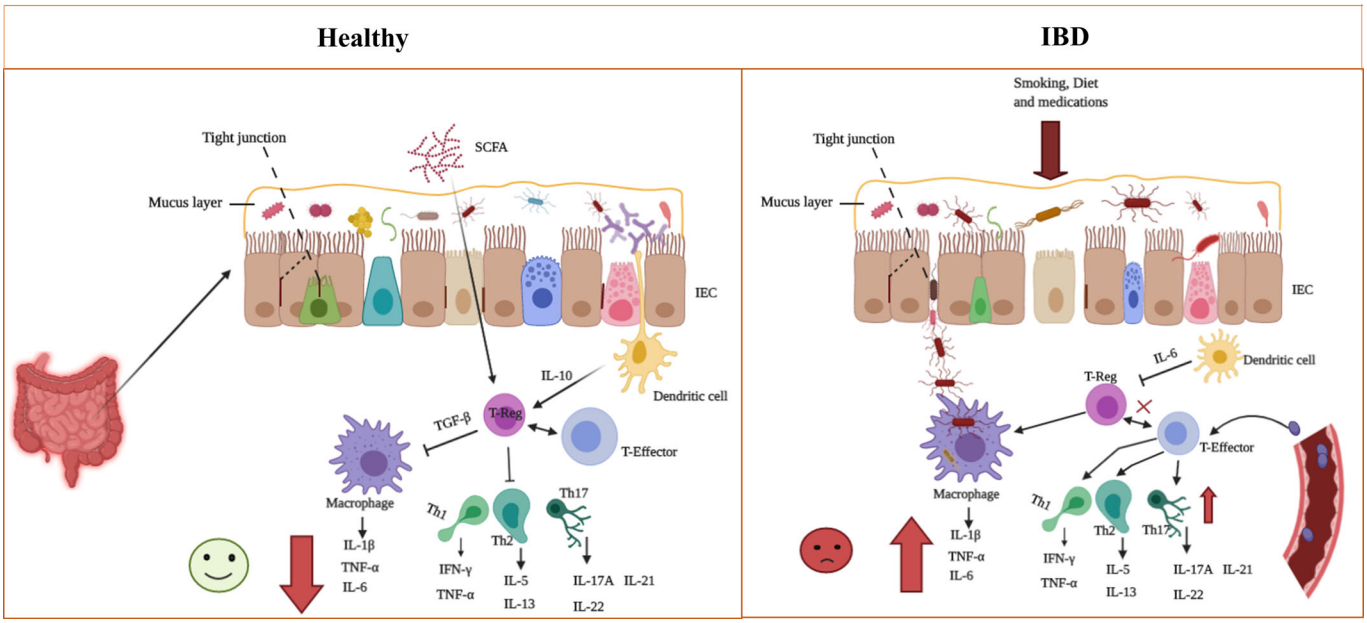


Figure 3. Gut microbiota alteration and immune responses in IBD. In healthy, gut microbes metabolize non-digestion food into SCFA, and induce an immune tolerance phenotype in the host. In the IBD, environment factors induce microbiota dysbiosis and immunological dysregulation. Microbiota dysbiosis involves decreasing bacteria diversity and metabolites depletion, e.g., SCFA, and engraftment of pathogenic microorganisms, which could increase intestinal permeability and invade intestinal tissue. Finally, imbalanced immune system decrease T-Reg cells and increase Th1, Th2 and Th17 cell, resulting in excessive production of pro-inflammatory interleukins such as IL-1β, TNF-α, IL-6 and IL-17, driving chronic inflammation.

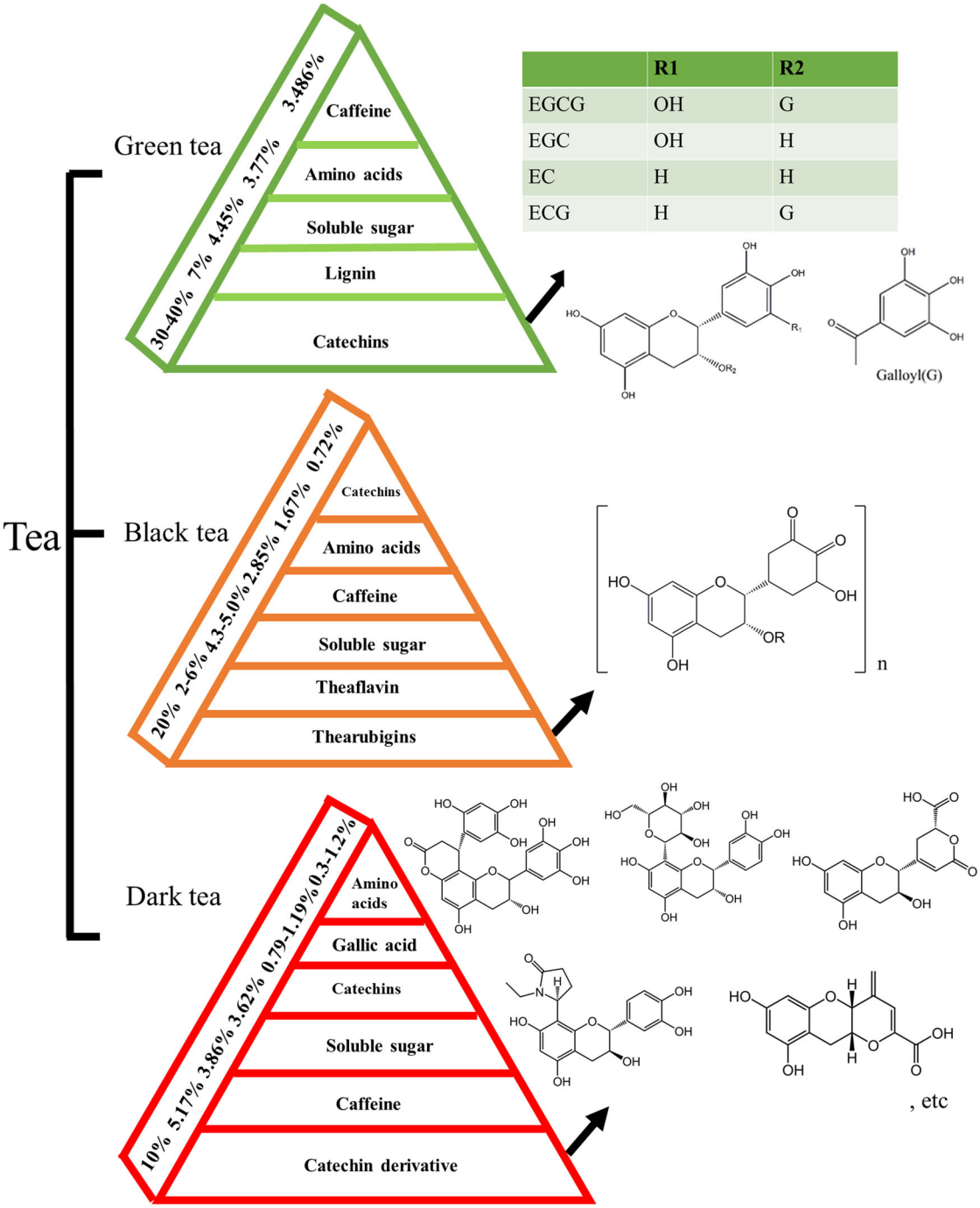
ascolumnar epithelial cells and secretory cells (e.g., goblet, enteroendocrine, and tuft cells) serve as the second barrier between microbes and the lamina propria. The immune cells, dendritic cells (DCs), macrophages, neutrophils, monocytes, natural killer (NK) cells, eosinophils, basophils and adaptive immune cells, form the third barrier. These cells could confer tolerance or initiate inflammation by producing chemokines, cytokines and antimicrobial agents. Inflammation or diseases occur when inflammatory cytokines were secreted in excessive amounts.

Epithelial-cell barrier performs crucial effect in maintaining the mucosal homeostasis. IBD patients are inclined to abnormal intestinal permeability (Söderholm et al 2002). In this setting, innate immunity is the first non-specific defence line against pathogens. For example, goblet cells, secrete gel-forming mucin, especially MUC2 covering the epithelium, which is important to both mucosal defense and repair (Johansson et al. 2011). In addition, some of the cells, such as macrophages and DCs, can recognize specific microorganisms via pattern recognition receptors (PRR), such as NOD-like (NOD) and Toll-like receptors (TLRs) (Mogensen 2009; Bernardo, Chaparro, and Gisbert 2018; Elisa et al. 2019). On the one hand, innate immune cells produce mass of cytokines and chemokine as an attempt to contain the inflammation, on the other hand, they also regulate naïve T-cells division into effector T helper (Th) cells (e.g., Th1, Th2, and Th17 cell types), thus reducing the immune tolerance to commensal bacteria in the intestinal tract. Patients with CD are often defective in innate immune responses, facilitated inflammatory macrophage infiltration that expresses dendritic cell markers, including CD14, and produces a mass of proinflammatory cytokines e.g., tumor necrosis factor and IL-6 (Kamada et al. 2008; Smith et al. 2009).

Tea varieties and its composition

Tea is categorized into nonfermented green tea, fermented black tea and post-fermented tea with great differences in composition and structure according to manufacturing processes (Figure 4) (Kapoor et al. 2013; Tan et al. 2011; Gong et al. 2020; Hua et al. 2018; Liang, Zhang, and Lu 2005; Qu et al. 2019; Zheng, Wan, and Bao 2015; Sang et al. 2011). Catechins were regarded as the main component of green tea, which accounts for 30–40% of total tea polyphenols (Sang et al. 2011; Balentine, Wiseman, and Bouwens 1997). There are four major catechins in tea: (−)-epigallocatechin gallate (EGCG), (−)-epigallocatechin (EGC), (−)-epicatechin gallate (ECG), and (−)-epicatechin (EC), thereof EGCG is dominant one and may be up to 60–65% of the total catechins in tea.

Black tea belongs to the category of fully fermented tea, and its production generally includes withering, rolling, fermentation and drying processes. Catechins are converted into thearubigins (TRs) and theaflavin (TF) during the fermentation-process mainly involving oxidation; those metabolites are the source of color formation of tea infusion and the key factors for evaluating the quality of black tea. Black tea is mainly composed of thearubigins, accounting for 15%–20% dry matter of black tea (Sang et al. 2011; Balentine, Wiseman, and Bouwens 1997). Compared to high catechins content in green tea, TRs were one of an important functional composition of black tea for quality assessment. At present, studies report that black tea shows great



	R1	R2
EGCG	OH	G
EGC	OH	H
EC	H	H
ECG	H	G

Figure 4. Tea varieties and its composition. Green tea enriched in catechins, and catechins is further oxidized into thearubigins in black tea production process. Catechins-derivates and thearubigins may be polymerized with proteins, lipids and polysaccharides to form theabrownins.

potential for the prevention of cancer, cardiovascular diseases, chronic inflammation and obesity etc.

Unlike green and black tea, dark tea is a uniquely post-fermented tea, involving solid-state microbial fermentation (Li et al. 2018). According to the source of raw material and manufacturing method in China, dark tea is divided into Fu brick tea, Pu-erh tea, Qing brick tea, and Liu pao tea etc. The chemical composition of dark tea, especially ripe Pu-erh tea and Fu brick tea, contains catechin derivatives, which accounts for 10%. Theaflavins and thearubigins are enriched in fully fermented black tea, whereas theabrownins, the main polyphenolic compounds in dark teas, is formed by further degradation, oxidation, condensation and polymerization of polyphenols during post-fermentation stage.

Effects of green tea on IBD

The mechanism of antioxidant for IBD

The pathogenesis of IBD involves an excessive oxidative stress level in the intestinal tract, including both overproduction of reactive nitrogen species (RNS) and reactive oxygen species (ROS) etc, result in lipid peroxidation, DNA damage, protein modification, cell apoptosis and pro-

inflammatory response (Valko et al. 2007; Denis et al. 2015). ROS includes super-oxide anion radical, hydrogen peroxide and hydroxyl radical. Studies have shown that these free radicals could damage mucosal layer and disturb the intestinal environment stimulating inflammatory responses by changing the concentration of several enzymes and proinflammatory cytokines (Urszula et al. 2018; Fabiana et al. 2020).

There have been numerous studies demonstrating that consumption of tea drinks could reduce oxidation stress and free radical damage, among which catechin plays a major role, and tea is an important source of catechin in our daily diet considering its large consumption worldwide. Markus et al. found that the combination of EGCG and piperin significantly reduced the concentration of lipid peroxide malonaldehyde (MDA), but increased glutathione oxidase and superoxide dismutase in colon tissue, and alleviated colonic injury in mice with colitis (Markus et al. 2012). Helieh et al. investigated the effect and mechanism of epigallocatechin-3-gallate (EGCG) treatment in colitis rats and observed that EGCG supplementation increased GSH oxidase levels in colon tissues in a dose-dependent manner (Helieh et al. 2013). Compared with the DSS model group, EGCG increased antioxidant levels in colon tissues and reduced the degree of colon inflammation (Zhi, Chen, and Xiao 2008). Mazzon et al. explored the effect of green tea extract on colitis mice, and found that green tea extract-treated mice significantly reduced intercellular adhesion molecule-1 expression in colon tissues, and increased levels of hemeoxygenase-1, an inducible enzyme against oxidative stress (Mazzon et al. 2005). The antioxidant mechanism of green tea is mainly linked to the structure characteristics of polyhydroxyl groups in TP. Those studies showed that green tea prevented host from continuous damage to colon tissues caused by elevated oxidative stress during the development of IBD.

Cytokine regulation

Apart from oxidative stress, a large number of antigens stimulate mucosal immune cells to accumulate and activate, thus inducing mucosal immune overreaction and misrecognition response, then activate macrophages and lymphocytes to release a series of cytokines and inflammatory mediators. The imbalance between pro-inflammatory and anti-inflammatory factors, amplifies the mucosal inflammation cascade which eventually damage colon tissue. Under normal circumstances, anti-inflammatory cytokines, such as interleukin (IL)-4, IL-10, IL-11, and IL-13 etc, maintain normal tissue homeostasis and-permeability of intestine. However, the production of pro-inflammatory cytokines such as tumor necrosis factor-a (TNF-a), IL-1β, and IL-6 boosts to disrupt the normal physiological condition.

Zachary et al. found that mice supplement with EGCG reversed DSS-induced splenomegaly and colon shortening. In another similar study, EGCG also reduced expression of inflammatory factors such as TNF-α, IL-1β, IL-6, and colonic lipid peroxides when compared with DSS-induced group (Zachary et al. 2016). In another study, A Gerges et al. observed a significant decrease in the number of mast cells in the submucosa of the colon by 84%, less expression of IL-6, TNF-α and NF-κB, and TNF-α overexpression to prevent colonic injury (A Gerges et al. 2017). Helieh et al. investigated the roles of GT, ECGC, and sulfasalazine in a BALB/c mice model and suggested that those compounds may improve colitis symptoms by reducing serum IL-6, TNF-α and amyloid A levels (Helieh et al. 2013). The above experiments showed that green tea extract EGCG demonstrated great potential to improve colitis by reducing the accumulation of inflammatory cells and the cascade of inflammatory factors.

Signaling modulation

Different signaling pathways play important roles in the occurrence and progress of IBD. Studies have shown that inflammatory factors could cause colonic injury through signal transduction via Janus kinase (JAK), mitogen-activated protein kinase (MAPK), signal transduction and transcriptional activator (STAT) proteins, and nuclear factor (NF-KB) pathways.

The JAK/STAT signaling pathway, including JAK1, JAK2, JAK3, TYK2 and STAT proteins, is an important downstream pathway of cytokines. The activation process of the JAK/STAT signaling is as follows: cytokines or growth factors bind to their receptors to form dimers, and then bind to JAK and phosphorylate it. Activation of JAK catalyzes receptor itself or downstream target protein phosphorylation of tyrosine residues to form corresponding dock STAT sites, makes the STAT combination with receptors through the SH2 domain under phosphorylation-induced activation of JAK tyrosine kinases. Finally, STAT forms homo- or heterodimerize and rapidly translocates from the cytoplasm into the nucleus, and combines with the corresponding target gene promoter. The JAK/STAT pathway signals regulate mucosal injury, inflammation, initiation and progression of tumor, as well as its apoptosis (Hua, Pardoll, and Jove 2009; George and Darnell 2012; Alejandro, Kanno, and O'Shea 2017). Numerous studies have shown that flavonoids inhibit the JAK/STAT signaling pathway. Liu et al. explored green tea polysaccharides effect on colitis-associated colorectal cancer (CAC) and found that green tea polysaccharides decreased inflammatory cells infiltrated into the tumor tissue regions as compared to those in the AOM/DSS-induced mice. Moreover, the levels of phosphorylated STAT3 [p-STAT3 (Tyr705)] and total STAT3 (t-STAT3) were significantly reduced in mice receiving the green tea polysaccharides (100 mg/kg and 200 mg/kg) treatment. It was implied that green tea polysaccharides alleviated the progression of CAC by inhibition of IL-6/STAT3 signal pathway (Liu et al. 2018). Xi et al reported that green tea polyphenols improved TNBS-induced colitis by down-regulating the JAK2/STAT3 signaling pathway as well (Xi et al. 2018).

NF-κB, an important promoter of chronic inflammatory disease, significantly increases phosphorylation levels in IBD patients. Therefore, the development of effective natural NF-κB inhibitors draws great attention for the treatment of inflammatory bowel disease. Yang et al. established an inflammatory model of intestinal epithelial cells and found

that green tea polyphenols inhibited IKB protein phosphorylation and NF-B activation (Yang et al. 2001). Eui-Baek et al. treated LPS-induced HT-29 inflammatory cells with EGCG, which increased the expression of cell surface protein 67LR and subsequently upregulated Tollip protein expression, thus inhibiting MAPK and NF-κB signaling pathways (Eui-Baek et al. 2018). These results indicated that the mechanism of EGCG intervention in colitis was not only contributed by single signaling pathway, but also combined with other cytokines and associated signaling pathways.

MAPKs signaling pathway, as one of the classical inflammatory signaling pathways, is a kind of serine/threonine protein kinases commonly exited in mammals, which can be activated by external stimulus. MAPK activation pathway mainly involves of protein kinase (ERK), C-Jun N-terminal kinase (JNK) and p38 (Marie and Philippe 2011). Its three-stage kinase cascade pathway was as follows: MAP-KKK activation is stimulated by mitogen leading to the activation and phosphorylation of the MAPKK which then arouses MAPK activity (Robbins et al. 1993). It has been shown that the expression of NF-κB (p65) and MAPK (P38) protein in colonic tissue of DSS-induced colitis mice was significantly up-regulated suggesting the involvement of MAPK pathway in such disease model (Gao et al. 2018). Interestingly, there have been many studies reporting that green tea improves several diseases through the MAPK signaling pathway, for example, Yu et al. manifested that EGCG inhibited high glucose-induced miR-1 augmentation in rats by down-regulating the p38MAPK pathway, thus playing a protective role in myocarditis (Yu et al. 2016). Moreover, some studies report the functions of EGCG for preventing colonic inflammation in vitro. Joo et al. established LPS-induced inflammation model of macrophages and demonstrated that EGCG not only inhibited the phosphorylation of NF-κB, but also reduced the phosphorylation of erK1/2, JNK, and P38 protein kinases in the MAPK pathway, thus decreased the transcription levels of inflammatory cytokines such as IL-6, MCP-1, ICAM-1 and VCAM-1 (Jooet al. 2012).

In summary, the major ingredient of green tea effect on colitis is tea polyphenols, which play roles in disease prevention through its strong antioxidant capacity i.e., reducing inflammatory cell infiltration and the production of pro-inflammatory factors by inhibition of JAK/STAT, NF-κB and MAPK pathways, such mechanistic insights demonstrate the potential of green tea for achieving IBD remission (Figure 5). However, there is new evidence indicating that EGCG or green tea extract at high doses exacerbates colitis. Comparing to non-treated colitic mice, oral gavage of 0.5% EGCG aggravates weight loss and rectal bleeding DSS-induced mice (Fei et al. 2012). Similarly, doses of 1% green tea extract worsens colitis symptoms (Hirofumi et al. 2013). Therefore, EGCG as an alternative therapy for treating colitis should be cautious, thus requiring further evidence on its safety and bioavailability.

Effects of black tea on IBD

Oxidative stress could damage tissues though the persistent presence of inflammatory factors, which directly causes

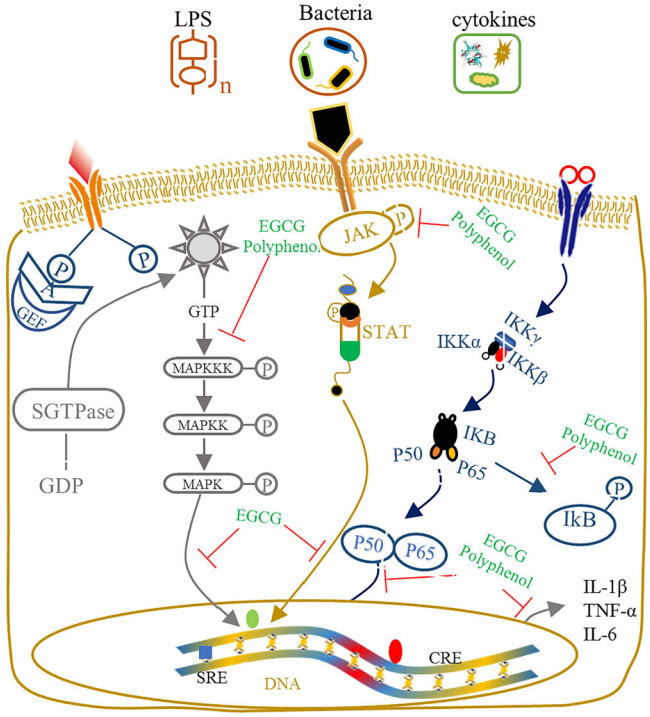


Figure 5. Green tea ameliorates IBD by different signaling pathways. JAK-STAT signaling pathway: Janus Kinases (JAK) is activated through ligand binding with receptors including cytokines or growth factors, activated-JAK catalyzes receptor itself or phosphorylates of tyrosine residues to form corresponding dock STAT sites, activated STAT are released from the receptor, and translocate to the nucleus to bind target genes. NF-κB signaling pathway: NF-κB protein complex (p65–p50) is bound and inhibited by IκB proteins, pro-inflammatory cytokines phosphorylates IκB proteins resulting in degradation NF-κB and translocation to the nucleus. The MAPK activation pathway: MAP-KKK is activated by mitogen stimulation, and MAPKK activation phosphorylation evokes MAPK activity. ati-inflammatory activity of green tea polyphenol may be related to inhibition of JAK, MAP-KKK and IκB phosphorylation and blocking STAT, MAPK and p65–p50 transfer to the nucleus.

chronic inflammation. Studies have shown that black tea and its extracts exhibit inhibition against inflammation. Swapna et al. treated colitis mice with 40 mg/kg TR, and found that TR significantly reduced the infiltration of neutrophils and lipid peroxidation in the lesion colon. Furthermore, the levels of nitric oxide (NO) and inducible nitric oxide synthase (INOS) were decreased compared to non-treated group (Swapna et al. 2003). NO is a pleiotropic free radical produced from L-arginine under the action of INOS. Under normal physiological condition, low concentration of NO has a protective effect on intestinal inflammation, but pro-inflammatory factors induce macrophages to secrete a large amount of INOS that up-regulates the level of NO during inflammation status (Alderton, Cooper, and Knowles 2001; Riku et al. 2005).

NO further interacts with superoxide anions to produce peroxynitrite, which enhances oxidative stress and tissue damage (Paul and Donna-Marie 2000). Song et al. indicated that 200 μg/mL black tea extract significantly reduced the mRNA transcription levels of IL-12p40, IL-23P19, IL-6 and IL-1β induced by LPS from in vitro experiments; to further assess the effect of NF-κB pathway on the inhibition of inflammatory mediators, the authors found that black tea extract not only prevented cytoplasmic IκBa degradation, but also reduced nuclear phosphorylation of NF-κB/P65

(Song et al. 2011). Fabiola et al. explored green and black tea extracts effect on IL-1β-induced gastric adenocarcinoma cell inflammation, and indicated that concentrations of 25 μg/mL green tea and black tea extracts significantly reduced the levels of IL-8 production. These anti-inflammatory actions were regulated, partly, by suppression of NF-κB activity (Fabiola et al. 2010). Ukil et al. reported that 5 mg/kg TF significantly decreased TNF-a, IL-12, IFN-γ and iNOS levels in the intestinal mucosa of mice with TNBS-induced colitis, and further detected increased expression levels of IκBa protein in colon tissues and reduced levels of NF-κB/P65 phosphorylation (Ukil, Maity, and Das 2006). The above experiments showed that theanine and theaflavin, the main functional components of black tea, could reduce intestinal inflammation mainly via restraining the NF-κB pathway, thus reducing the release of inflammatory factors, for alleviating the degree of colon inflammation.

Effects dark tea on IBD

Dark tea is traditionally regarded as remedy against gastrointestinal diseases, such as dyspepsia, bloating and constipation in China (Zheng, Wan, and Bao 2015). At present, the prevalence of IBD in the Western countries is as high as0.5% of general population, furthermore, the rising rate in the incidence of IBD is considerably higher which challenges current health-care systems (Molodecky et al. 2012). Therefore, tea, as the second largest beverage in the world, has great potential in improving IBD. Although the effects of dark tea on anti-tumor, hypoglycemia, weight loss and antioxidant activities are observed, there have been fewer studies on dark tea effect on IBD than green tea or black tea. Liu et al. showed that 30 mg/kg and 60 mg/kg Fu brick tea extract significantly reduced rectal bleeding, shortened the colon length, and decreased the production of inflammatory cytokine (Liu et al. 2016). Wang et al. found that kidney and liver were protected by Fu brick tea extract via increasing colonic microbiota species including *Lactobacillus*, *Bacteroides*, and *Clostridium* in *Escherichia coli* O157:H7-infected mice (Wang et al. 2015; Du, Wang, and Yang 2019). However, exploring other dark teas (e.g ripe Pu-erh tea) effect on intestinal functions is rare. We showed that ripe Pu-erh tea (RPT) significantly alleviated colitis such as improving loss of body weight, colon shortening, inflammatory cytokines, and infiltration of inflammatory cells. In addition, the activation of NF-κB pathway and HIF-1α expression was inhibited by RPT (Huang et al. 2020). And we also found that Ripened Pu-erh tea extract promotes gut microbiota resilience against dextran sulfate sodium-induced colitis (Huang et al. 2021, in revision). Liu et al. also reported that ripe Pu-erh tea extract improved DSS-induced colitis in mice (Liu et al. 2020). Furthermore, transplantation of fecal microbiota from donor mice treatment with Pu-erh tea extract-treated to DSS-induced colitic recipient mice could significantly ameliorated the loss of body weight and barrier integrity as well as gut microbiota dysbiosis (Liu et al. 2020).

Interactions between tea ingredients and gut microbiota benefiting for IBD treatment

Rapid development of nutrition and metabolism have given us great insights into the relationship between human health and colon. Nourishing substances that are difficult to digest and absorb in the upper gastrointestinal (GI) tract need to be delivered successfully to the colon and perform their effectiveness to improve their bioavailability. It is not only due to the characteristics of colonic physiology, but also related with the dense bacteria in the colon (10^{11} CFU/g) compared to small intestine (10^{4} CFU/g) (Dave et al. 2012). For example, bioactive phytochemicals from fruits or vegetables exhibit the capacity of reducing inflammation, suppressing colon cancer and facilitating the growth of potential probiotics in the colon (Prakash, Charu, and Girish 2012; Sun et al. 2018). Therefore, It is great meaningful to elucidate the two-way interaction on tea active ingredients and gut microbiota for the treatment of IBD.

Biotransformation of tea ingredients by gut microbiota

Polyphenols, also known as phenolics, comprise a large category of compounds, main comprising EGCG, (−)-epigallocatechin (EGC), (−)-epicatechin gallate (ECG) and and (−)-epicatechin (EC). Several studies have indicated that 90–95% polyphenols were not absorbed but accumulated in the colon, and degraded by gut microbiota to promote its absorptivity (Table 1) (Chen et al. 1997; Lambert et al. 2003; Misaka et al., 2013). Aout 31.2% of EC, 13.7% of EGC, and 0.1% of EGCG were directly absorbed (Chen et al. 1997). Similarly, Pereira-Caro et al. also showed that theaflavins were poor relative bioavailability because their phase II metabolites were not detected in the urine excreted from 0 to 30 h after intake (Pereira-Caro et al. 2017). The colon contains a large number of microbiotas with a set of different enzymes that transform various non-digestible ingredients for promoting absorption. These bacteria carry out a variety of metabolic reactions via hydrolysis, C-ring cleavage and reduction including lactonization, decarboxylation, dihydroxylation and oxidation reactions (Braune and Blaut 2016). The majority of catechins reach the colon, first transformed into1-(3,4-dihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl) propan-2-ol by *Eggerthella lenta* and *Eubacterium* sp. strain SDG-2, and then the latter was converted into

Table 1. Pharmacokinetic parameters of catechins catechins in green tea.

Compounds	Object of study	Dosage (mg/kg)	Tmax (min)	Cmax (μg/mL)	Bioavailability	Reference
EGCG	Mouse	75	89.8 ± 25.5	0.128 ± 0.04	26.5%±7.5%	(Lambert et al. 2003)
EGCG	Rat	75	85.5 ± 42	19.8 ± 3.5	1.6%	(Chen et al. 1997)
EGC	Rat	400	48 ± 6	0.76 ± 0.2	6.7%	(Misaka et al. 2013)

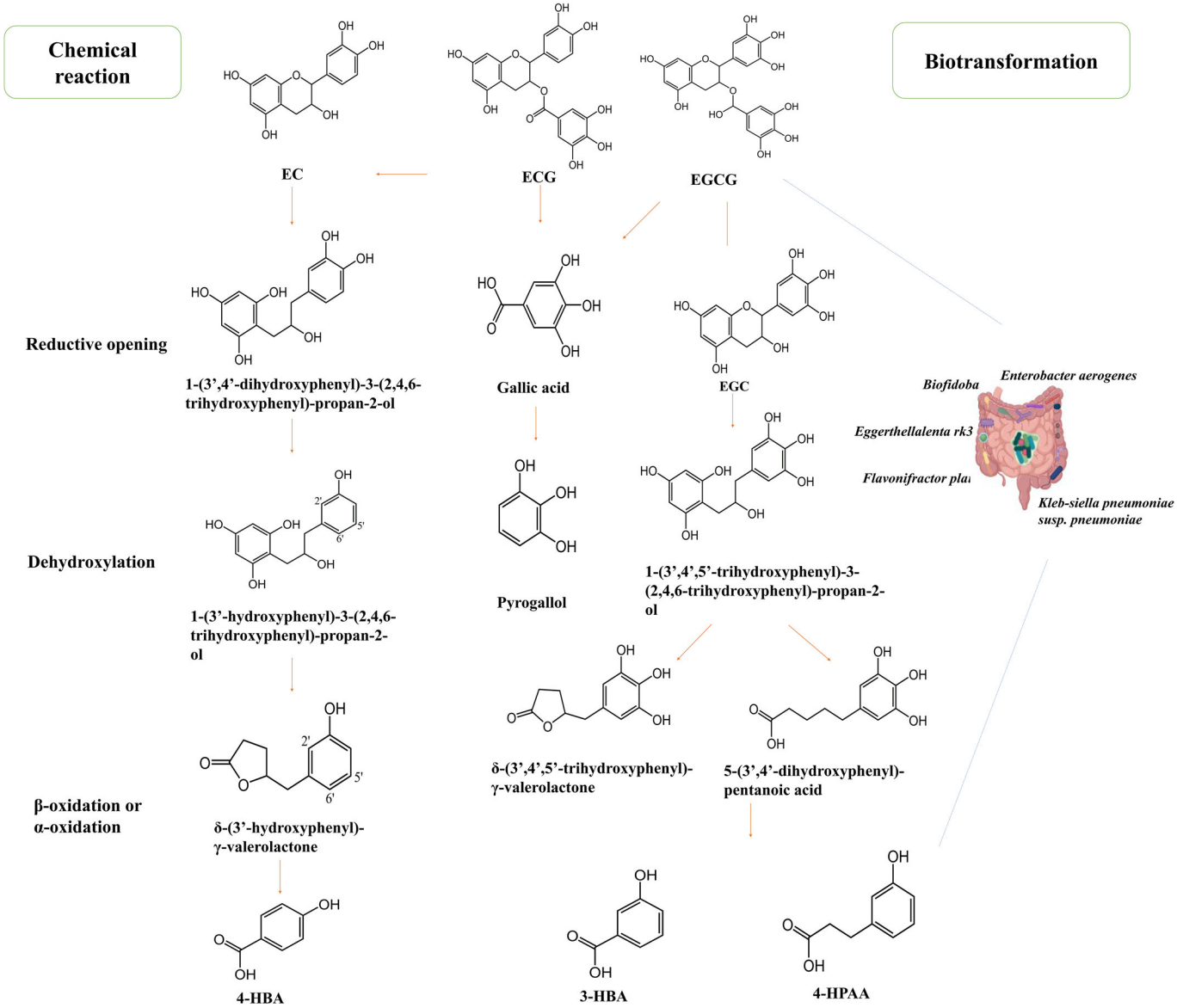


Figure 6. Biotransformation of tea polyphenol by gut microbiota.

3-hydroybenzoic acid (3-HBA), 4-hydroybenzoic acid (4-HBA), 3,4-dihydroxyphe-nylacetic acid (3,4-DHPAA) and 4-hydroxyphenylacetic acid (4-HPAA) by *Flavonifractor plautii*. (Figure 6) (Chen and Sang 2014; Wu et al. 2020). The information on microbial metabolism pathways for black tea components such as theaflavins, theasinensins and thearubigins is relatively limited. Theaflavins has been demonstrated to be low systematic bioavailability. Chen et al. demonstrated that *Lactobacillus plantarum* 299v and *Bacillus subtilis* transformed theaflavin-3,3′-digal-late into theaflavin-3-gallate, theaflavin-3′-gallate and gallic acid (Chen et al. 2012). Therefore, there is large variation in terms of biotransformation of tea ingredients in the gut, and such process is highly dependent on the composition and structure of intestinal microbiota.

Modulation of tea ingredients on gut microbiota

Along with the metabolism of tea ingredients via gut microbiota, in turn, the composition of gut microbiota may also shift in structural composition. Tea and its metabolites were proved to regulate the composition and relative abundance of gut microbiota, where specific enzymes could be enriched to catabolizing tea phytochemicals (Gan et al. 2018). Although, increasing findings have suggested that intestinal bacteria are altered by these tea ingredients for obesity, hyperlipidemia, nonalcoholic steatohepatitis and metabolomic disorder (Henning et al. 2018; Huang et al. 2019; Zhu et al. 2020; Jeong et al. 2020; Li et al. 2020; Ning et al. 2020), but there is less focus on these tea for improving IBD by modulating gut microbiota.Yuan et al indicated that green tea treatment increased the ratio of *Firmicutes*/*Bacteroidetes*, enriched the abundance of bacteria including *Blautia*, *Roseburia*, *Faecalibacterium*, *Bifidobacterium*, *Eubacterium* and *Coprococcus* about producing short-chain fatty acid, and decreased bacterial lipopolysaccharide synthesis and the functional pathways abundance relevance to cancer, relieved the inflammation and suppressed colorectal cancer (Yuan et al. 2018). Liu et al. demonstrated that mice receiving green tea and dark tea extracts enriched potentially beneficial bacteria e.g.,

Table 2. Green tea, black tea and dark tea effect on IBD.

Class of tea	Compound	Optimal doses	Model	Cytokine	Oxidative stress alleviation	Signal pathway	Reference
Green tea	EGCG	6.9 mg/kg	DSS-induced colitis model with C57BL/ mice	—	MPO↓MDA↓	—	(Markus et al. 2012)
	EGCG	0.25% 0.5%	DSS-induced colitis model with BALB/c mice	TNF-α↓ IL-6↓	GSH↑	—	(Helieh et al. 2013)
	EGCG	50 mg/kg	8% acetic acid-induced colitis model with SD rats	TNF-α↓ IFN-γ↓	MDA↓SOD↑	Blocks nuclear trans-	(Zhi, Chen, and Xiao 2008)
	Green tea extract	0.6%	Mdr1a$^{-/-}$ mice	—	—	location of NF-κB	(Barnett et al. 2013)
	Polyphenol extract	50 mg/g	DSS-induced colitis model with SD rats	TNF-α↓	MPO↓ICAM-1↓	—	(Mazzon et al. 2005)
	EGCG	3.2 mg/g	DSS-induced colitis model with CF-1 mice	TNF-α↓ IL-6↓ IL-1β↓		—	(Zachary et al. 2016)
	EGCG	1 mg/kg	TNBS-induced colitis model with SD rats	TNF-α↓ IL-6↓ IL-6↓	ROS↓	—	(A Gerges et al. 2017)
	EGCG	20 mg/kg 50 mg/kg	DSS-induced colitis model with C57BL/ mice	TNF-α↓ MCP-1↓	—	—	(Du et al. 2019)
Black tea	polysaccharides	100 mg/kg 200 mg/kg	AOM/DSS-induced colorectal cancer BALB/c mice	TNF-α↓ IL-6↓ IL-2↓	—	Suppressing IL-6/ STAT3 pathway	(Liu et al. 2018)
	polyphenols	100 mg/kg	TNBS-induced colitis model with C57BL/ mice	TNF-α↓ IL-6↓	—	Inhibiting JAK2/ STAT3 pathway	(Xi et al. 2018)
	EGCG	0-0.4 mg/mL	*In vitro*: intestinal epithelial cell line (IEC-6)	—	—	Inhibiting IκB protein phosphorylation and NF-κB activation	(Yang et al. 2001)
	EGCG	20 μM	In vitro: intestinal epithelial cells (HT-29)	IL-8↓	—	Inhibiting activation of MAPKs and NF-κB signaling pathways	(Eui-Baek et al. 2018)
	EGCG	100 μM	In vitro: bone marrow-derived macrophages (BMMs)	IL-12↓ IL-6↓ MCP-1↓	—	blocking NF-κB and MAPK signaling pathways	(Joo et al. 2012)
	Thearubigin	40 mg/kg	TNBS-induced colitis model with BALB/c mice	—	iNOS↓MDA↓ NO↓	Suppressed NF-κB activation	(Swapna et al. 2003)
Dark tea	Black tea extract	1%	DSS-induced colitis model with C57BL/ mice	—	—	Blocking phosphorylation of IκBa and NF-κB/p65	(Song et al. 2011)
	Black tea extract	25 μg/mL	*In vitro*: IL-1β-induced inflammation with gastric adenocarcinoma cell inflammation	IL-18	—	Inhibition of NF-κB activity	(Fabiola et al. 2010)
	TFDG	5 mg/kg	TNBS-induced colitis model with BALB/c mice	TNF-α↓ IFN-γ↓ IL-12↓	—	Decreasing phosphorylation of IκB and IKK	(Ukil, Maity, and Das 2006)
	Fu brick tea extract	30 mg/kg 60 mg/kg	DSS-induced colitis model with ICR mice	TNF-α↓ IL-1β↓ IFN-γ↓	MDA↓MPO↓	—	(Liu et al. 2016)
	Pu-erh tea extract	3%	DSS-induced colitis model with C57BL/ mice	TNF-α↓ IL-6↓ IL-1β↓	—	suppressing the activation of NF-κB pathway and down-regulated the expression of the HIF-1α.	(Huang et al. 2020)
	Pu-erh tea extract	5 mg/kg	DSS-induced colitis model with C57BL/mice	—	—	Downregulated TLR4/ MyD88/NF-κB pathway	(Liu et al. 2020)

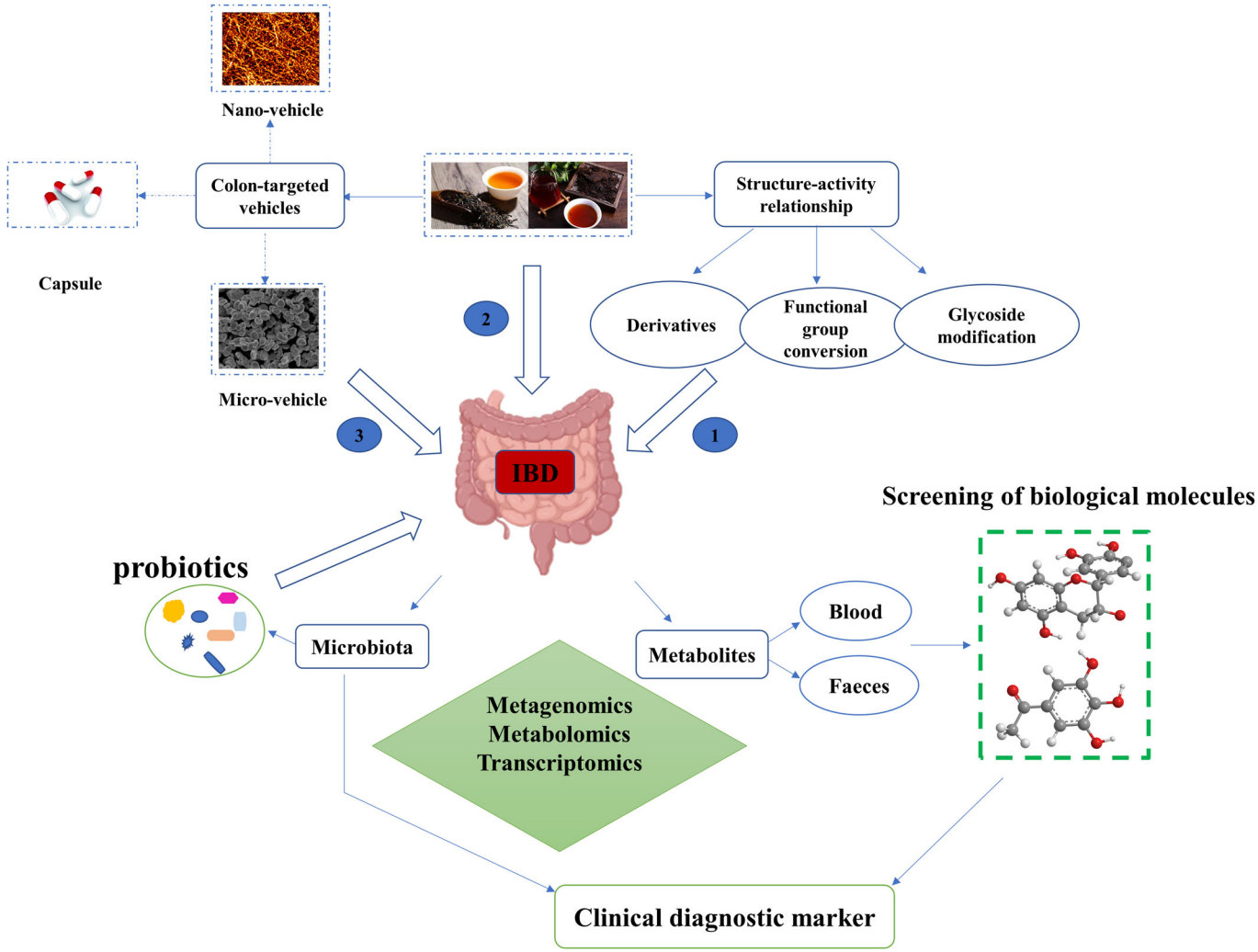


Figure 7. Future research directions for emphasizing on the mechanisms of novel tea ingredients in IBD intervention.

Lactococcus and *Akkermansia*, and lower the abundance of potentially harmful bacteria e.g., *Turicibacter*, *Romboutsia*, *Parasutterella* and *Lachnoclostridium*. Moreover, colitis mice increased beneficial gut microbial bacteria e.g., *Akkermansia* or *Bifidobacterium*, and decreased harmful bacteria e.g., *Bacteroides* or *Parasutterella* after fecal transplant with green tea and dark tea-treated donor mice; FMT-treated mice significantly alleviated colitis-related symptoms, for example loss of body weight and colonic inflammation via inhibition of TLR4/MyD88/NF-κB pathway (Liu et al. 2020). We also indicated that RPT treatment improved DSS-induced colitis by partially reversing the dysbiosis state of gut microbiota, which might be associated with an increase in SCFAs level and PPAR-γ expression (Huang et al. 2021, in revision).

Concluding remarks and future perspectives

Massive studies report antioxidant properties of green tea which are highly associated with the high content of unoxidized flavanols, however, a new trend has been centered on the investigation of underlying pharmaceutical activities of novel tea ingredient from fully fermented tea and post-fermented tea. During tea manufacturing, polyphenols undergo extensive oxidation by endogenous polyphenol oxidase (PPO) and peroxidase (POD), resulting in the formation of dimeric and oligomeric compounds, such as theaflavins, thearubigins and theabrownins. The complex structures of thearubigins and theabrownins limit further studies on their biological efficacy due to the difficulty in compound separation and purification.

Although the potential of three types of tea for the prevention and treatment of IBD is mechanistically observed including signal pathway regulations for reducing inflammatory cell infiltration and inflammatory factors (Table 2), the structure-function of tea ingredients and their regulations on dysbiotic gut microbiota of colitis mouse models remains largely unclear. Therefore, there have been three main research directions needed to be emphasized on: (1) identification of active components and structure-activity relationship of novel tea ingredients by modern separation technology; (2) multi-omics (metagenomics, metabolomics and transcriptomics) integration strategy to dissect certain bacteria from tea ingredients-regulated gut microbiota to reverse gut dysbiosis of IBD; (3) colon-targeted delivery of bioactive tea compounds as an alternative strategy to improve the biological efficacy for IBD intervention (Figure 7).

Disclosure statement

There are no conflicts of interest to declare.

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