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REVIEW

Diets, functional foods, and nutraceuticals as alternative therapies for inflammatory bowel disease: Present status and future trends

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Abstract

Inflammatory bowel disease (IBD) is a serious health concern among western societies. The disease is also on the rise in some East Asian countries and in Australia. Health professionals and dietitians around the world are facing an unprecedented challenge to prevent and control the increasing prevalence of IBD. The current therapeutic strategy that includes drugs and biological treatments is inefficient and are associated with adverse health consequences. In this context, the use of natural products is gaining worldwide attention. *In vivo* studies and clinical evidence suggest that well-planned dietary regimens with specific nutrients can alleviate gastrointestinal inflammation by modulating inflammatory cytokines, such as tumor necrosis factor α (TNF-α), interleukin 1 (IL-1), IL-6, IL-1β, and IL-10. Alternatively, the avoidance of high-fat and high-carbohydrate diets is regarded as an effective tool to eliminate the causes of IBD. Many functional foods and bioactive components have received attention for showing strong therapeutic effects against IBD. Both animal and human studies suggest that bioactive functional foods can ameliorate IBD by downregulating the pro-inflammatory signaling pathways, such as nuclear factor κB, STAT1, STAT6, and pro-inflammatory cytokines, including IL-1β, IL-4, IL-6, COX-2, TNF-α, and interferon γ. Therefore, functional foods and diets have the potential to alleviate IBD by modulating the underlying pathogenic mechanisms. Future comprehensive studies are needed to corroborate the potential roles of functional foods and diets in the prevention and control of IBD.

Key words: Inflammatory bowel disease; Colitis; Diets; Functional foods; Bioactive compounds; Inflammatory cytokines; Alternative therapy

Core tip: Diets and functional foods are two of the most potential alternative therapies for inflammatory bowel disease (IBD). Dietary supplementation of probiotics and non-starch polysaccharides demonstrated strong therapeutic actions on IBD. Likewise, functional foods have received more attention than ever as alternative therapies for IBD. Plant-derived extracts and bioactive compounds exhibited anti-inflammatory actions against IBD. Both diets and functional foods have a very important role to play in the near future. We have discussed the roles of both diets and functional foods in IBD management.

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic gastrointestinal disorder characterized by relapsing inflammation and severe mucosal damage in the intestine. There are two common forms of IBD, namely, ulcerative colitis (UC) and Crohn's disease (CD), which are generally associated with diarrhea, nausea, abdominal pain, fatigue, rectal bleeding, weight loss, anxiety, *etc*[1]. Currently, IBD is one of the most prevalent gastrointestinal diseases among the developed nations in the West, affecting nearly 1.6 million people in the United States and 2.5-3.0 million people in northern Europe[2,3]. Although IBD is mostly prevalent in North America and Europe, the adoption of western dietary habits and lifestyle has led to, countries like- China, South Korea, and Australia witnessing a significant rise in the incidence of IBD[4].

The exact etiology of IBD has yet to be defined, but it is believed that genetic susceptibility, environment, immunoregulatory dysfunction, intestinal microbiota, nutrition, and lifestyle are the key players in the pathogenesis of IBD[5]. Activation of macrophages and an uncontrolled production of pro- and anti-inflammatory cytokines, including tumor necrosis factor α (TNF-α), interleukins, and interferon γ (IFN-γ) in the intestinal mucosa, mediate the inflammation by inducing inflammatory pathways[6]. Conventional therapies based on steroidal and non-steroidal drugs and biological agents are inefficient in treating IBD and are often associated with adverse side effects. As a consequence, tremendous research attention is now being focused on finding alternative therapies based on plants and other natural products.

There is a growing consensus that diet and nutrition play a critical role in the etiopathogenesis of IBD, and hence dietary therapy has a great implication on the treatment of IBD[7]. Recent research evidence suggests that the supplementation of fruits and vegetables, probiotic bacteria, dietary fibers, and fat-soluble vitamins can substantially reduce the symptoms of IBD through their anti-inflammatory functions[7-11]. In contrast, as the high-fat and high-carbohydrate foods are supposedly involved in the etiology of IBD, eliminating these foods from the diet could be an essential tool in the management of IBD[12]. Bioactive natural compounds and functional foods have been a major focus of research throughout the last decade as potential therapies for IBD, and many research groups have demonstrated positive and outstanding results. Plant-derived extracts, antioxidants, phytochemicals, polyunsaturated fatty acids, and dietary peptides have demonstrated strong anti-inflammatory effects against IBD due to their modulatory actions on pro- and anti-inflammatory cytokines and signaling pathways[13-18]. Ongoing and future research is expected to provide more evidence and explanations regarding the use of diets and functional foods to control IBD. It appears that the alternative therapies based on diets and functional foods will be the future of IBD management. The present study therefore provides an overview on the current status and the future direction of the use of diets, functional foods, and bioactive compounds against IBD.

CURRENT STATUS AND TREATMENTS OF IBD

The chronic and recurrent inflammation of the gastrointestinal tract associated with IBD, represented by UC and CD accompanies several gastrointestinal and systemic disorders and mental illnesses[19]. Although the two forms of IBD share some common features, they are regarded as separate entities, as they possess distinct histopathological and symptomatic characteristics. UC is generally defined as a mucosal or submucosal inflammation of mainly the rectum and occasionally of the colonic area. The common symptoms of UC include abdominal pain, diarrhea, malnutrition, rectal pain and bleeding. CD is regarded as a transmural inflammation of the ileum and colon, though it can affect any part of the gastrointestinal tract and form granulomas, fistulas, and strictures in the intestine. Patients diagnosed with CD often have abdominal pain, diarrhea, fever, loss of appetite and weight, anemia, and intermittent anal fissures.

Although the exact etiology of IBD has yet to be specified, a number of factors including- diet, immunity, environment, heredity, and microbiota, contribute to the development of IBD[20]. A complex interaction of environmental, genetic, microbial, and immunological factors might cause the activation of the mucosal immune response and the release of numerous cytokines[21]. Cytokines are cell signaling molecules generated predominantly by immune cells that have specific roles in the communication and interaction between cells and

Table 1 Overview of the conventional therapies for inflammatory bowel disease

Therapeutic agent	Active compound	Mode of action	Ref.
Aminosalicylates (ASA)	5-ASA	Decreases MPO activity, inhibits β-catenin activation Inhibits the generation and activity of IL-1β, IL-4, IL-5, IL-8, granulocyte-macrophage colony stimulating factor, and TNF-α	[23]
Corticosteroids	Corticosteroids		[24]
Immunosuppressants	Azathioprine 6-mercaptopurine Cyclosporine A Tacrolimus Methotrexaten	Clinical remission Mucosal healing	[25]
Antibiotics	Metronidazole Ciprofloxacin	Decrease disease activity index Maintain remission	[26]
Biological therapy	Infliximab Adalimumab Certolizumab	Neutralizes TNF-α Reduces inflammation	[27]

TNF-α: Tumor necrosis factor α; IL: Interleukin.

the onset of local and systemic inflammation. Under normal conditions, the intestinal mucosa can maintain the balance between pro-inflammatory cytokines, such as TNF-α, IFN-γ, interleukin (IL)-1, IL-6, and IL-12 and anti-inflammatory cytokines, which includes IL-4, IL-10, and IL-11. In IBD patients, the intestinal homeostasis and the fine balance between pro- and anti-inflammatory cytokines is disrupted, causing an increased number and activities of pro-inflammatory cytokines in the mucosa, leading to tissue damage and inflammation. Furthermore, the weakened epithelial barrier function and the increased intestinal permeability in IBD subjects facilitate mucosal inflammation[22].

Currently, there is no effective therapy available that can completely cure IBD. Current therapeutic options are incapable of targeting the underlying pathogenic mechanisms of IBD; instead, they are specifically designed to instigate and maintain the remission of the disease and help mitigate complications in patients[1]. Aminosalicylates and corticosteroids are considered first-line therapy for IBD (Table 1). Both of these drugs have shown efficacies in ameliorating the severity and the symptoms of IBD through their abilities to down-regulate the pro-inflammatory cytokines and signaling pathways[23,24]. Immunosuppressive agents, including azathioprine, 6-mercaptopurine, cyclosporine A, and antibiotics, which are mostly used as adjunct therapies, can decrease intestinal inflammation by suppressing the mucosal immune response[25,26] (Table 1). A more recent and innovative approach is called "biological therapy," where monoclonal antibodies, such as infliximab and adalimumap, are applied to downregulate the immune response pathways[27].

Despite providing some symptomatic and temporary relief, current drug therapies are described as inadequate with serious side effects[28]. Biological therapies, which are currently a mainstay for of IBD treatment, are expensive and associated with adverse health effects.

Therefore, the development of alternative IBD therapies using natural products that are highly effective, safe, and inexpensive is in great demand.

DIETS AND DIETARY INTERVENTIONS FOR IBD

Diets comprise the usual food and drink that a person regularly consume. Diets, among other factors, play a crucial role in the etiology of IBD. Dietary interventions in the form of either providing specific nutrients or dietary restrictions are regarded as effective tools in treating IBD. Currently, due to the lack of adequate data and research evidence, health professionals and dieticians often find it difficult to recommend dietary strategies for IBD patients. However, recent research outcomes are providing evidence that many nutrients and food elements can cure IBD symptoms; hence a dietary plan based on proper nutrients could be an effective therapeutic strategy against IBD.

Probiotics

Probiotics are described as live microorganisms that benefit humans by promoting gut health and the immune system upon ingestion in an acceptable amount. Numerous possible mechanisms through which probiotic bacteria exert their beneficial effects have been proposed. Probiotics can reduce harmful microorganisms and maintain the microbial balance inside the gut by blocking the site of adhesion, competing for nutrients, and killing pathogenic microorganisms[29]. Production of short-chain fatty acids (SCFA) and butyrate by probiotic bacteria lowers the pH level in the colon and limits the growth of pathogens[30]. In addition, probiotic bacteria can function as anti-inflammatory agents by modulating the NF-κB signaling pathway, inflammatory cytokines, and the regulatory T cell response[31]. Two of

the most widely studied genera that have been proven effective in alleviating gastrointestinal inflammation are *Lactobacillus* and *Bifidobacteria*. Lee *et al*[32] reported that *Lactobacillus suntoryeus* suppressed toll-like receptor (TLR)-4 linked NF-κB and IL-6 expression in TNBS-induced colitis (Table 2). In a mouse model of IBD induced by *E. coli* 0111 LPS, soy milk fermented with *Lactococcus lactis* subsp. *lactis* S-SU2 prevented colonic shortening and spleen enlargement, and repaired epithelial damage[33]. *Lactobacillus paracasei* LS2 isolated from kimchi decreased the number of neutrophils ($CD11b^+Gr\text{-}1^+$) and, macrophages ($CD11b^+$ $F4/80^+$), and decreased TNF-α and IFN-γ expression in DSS-induced UC[34]. An oral administration of *Lactococcus lactis* NZ9000 (NZ-HO) secreting an anti-inflammatory substance called recombinant mouse heme oxygenase (mHO-1) to mice decreased the disease activity index (DAI), increased the production of IL-10, and suppressed IL-1α and IL-6 expression[35]. A study by Yokota *et al*[36] revealed that supplying drinking water containing *Lactobacillus plantarum* AN1 isolated from fermented fish to an IBD mouse model increased the indigenous population of lactic acid bacteria in the colon, and their synergistic effects reversed colonic shortening, spleen enlargement, and colonic tissue damage significantly. Several other strains of *Lactobacillus plantarum* exhibited therapeutic effects on gastrointestinal inflammation through their modulatory functions against inflammatory cytokines[37]. A recent study indicated that *Lactobacillus sakei* attenuated the clinical symptoms and histological damage by suppressing inflammatory mediators, such as NF-κB, STAT1, and TL4[38]. A combined therapy consisting of *Lactobacillus casei,* butyrate, and *Pistacia atlantica* significantly improved histological scores and reduced MPO activity in a rat model of IBD[39].

The antimicrobial and anti-inflammatory effects of *Bifidobacteria* are also well-known, and this probiotic genus has a wide application against gastrointestinal inflammation. Reportedly, *Bifidobacterium adolescentis* IM38 alleviated inflammation by downregulating NF-κB expression and lipopolysaccharide production in high-fat diet-induced ulcerative colitis in mice[40]. An *in vitro* and *in vivo* study suggested that *Bifidobacteria bifidum* 231 enhanced the IL-10 production in IEC-6 cell lines and improved the macroscopic and histological conditions in TNBS-induced colitis[41]. *Bifidobacterium longum* CCM7952 strengthened the epithelial barrier function and reduced clinical symptoms in experimental colitis[31].

Non-starch polysaccharides

Non-starch polysaccharides (NPS), classified as dietary fiber and prebiotics, are obtained from various natural sources that have been studied extensively as therapeutics against inflammation and other immune-related problems. All of the major components of NPS, including cellulose, glucomannan, glucan, pectin, inulin, and oligosaccharides have exhibited anti-inflammatory and immunomodulatory functions[42]. It has been suggested that most of the NPS components reach the large intestine intact, where they are fermented by probiotic and useful bacteria to exert their anti-inflammatory functions[43].

Konjac glucomannan is a plant-derived polysaccharide that has been used to treat gastrointestinal inflammatory disorders. For example, supplementation with konjac glucomannan hydrolysate for fourteen days to IBD patients resulted in improved bowel movement, fecal consistence, reduced abdominal pain, and a better lifestyle[44] (Table 2). β-Glucan was orally administered to an animal model of IBD, which resulted in improved fecal output and reduced colorectal distension[45]. In another study, oat β-glucan reduced the levels of MPO, NO, and MDA, and suppressed the expression of IL-1β, IL-6, and iNOS in a DSS-induced colitis model in mice[46]. Bacterial β-(1,3)-glucan prevented IBD in mice by recovering regulatory T cells (Tregs) and the defects of natural killer (NK) cells and by suppressing the excessive production of IgA[47,48]. Azuma *et al*[49,50] reported that cellulose nanofibers obtained from seaweed and pear reversed colonic shortening, reduced colonic damage and, suppressed NF-κB expression and MPO activity in colitic mice.

Prebiotics are non-digestible polysaccharides, which generally includes oligosaccharides and inulin that act as nutrients for the native gut microbiota that offer health benefits to the host[30]. Providing fructooligosaccharides to colitic mice resulted in increased lactic acid bacteria in the gut and decreased pro-inflammatory cytokines such as, IFN-γ, IL-17, and TNF-α[51]. In a DSS-induced colitis mouse model, goat milk oligosaccharides reduced the colonic tissue damage and increased the favorable microbial population in the intestine[52]. Štofilová *et al*[53] demonstrated that prebiotic inulin together with *Lactobacillus plantarum* LS/07 CCM7766 symbiotically improved colonic and jejunal tissue damage by down-regulating IL-2, IL-6, IL-17, TNF-α, COX-2, and NF-κB expression in an N, N-dimethylhydrazin-induced colitis model in rats.

Vitamins

Fat soluble vitamins such as Vitamin A and D have protective roles against the pathogenesis of IBD. Accumulating evidence suggests that patients with IBD are frequently diagnosed with low levels of fat soluble vitamins, and therefore specific supplementations of those vitamins are often recommended[5]. Gubatan *et al*[54] recently reported that a low level of vitamin D in the patients with UC at the time of remission increased the risk of clinical relapse of IBD. Vitamin D deficiency in UC patients has been found to be associated with mucosal inflammation and disease activity[55]. Therefore, vitamin D supplementation can result in positive outcomes in IBD patients. It has been demonstrated that vitamin D, by downregulating pro-inflammatory cytokines, IL-6, IL-21, TNF-α, and IFN-γ and by stabilizing the intestinal barrier, can contribute to the amelioration of IBD symptoms[56]. According to Zhu

Table 2 Role of nutrients and diets against inflammatory bowel disease

Base material	Main compounds/agents	Mode of action	Ref.
Probiotics			
Lactic acid bacteria	*Lactobacillus suntoryeus*	Inhibited the activation of TLR-4-linked NF-κB activation	[32]
	Lactococcus lactis subsp. lactis S-SU2	Prevented the colonic shortening, lowering of liver and thymus weights, and spleen enlargement	[33]
	Lactobacillus paracasei LS2 (from kimchi)	Increased IL-10 Reduced TNF-α, IFN-γ, IL-1β and MPO activity	[34]
	Lactococcus lactis NZ9000 (NZ-HO)	Reduced CD11b+ F4/80+ and CD11b+ Gr-1+	[35]
	Lactobacillus plantarum AN1	Increased IL-10; reduced IL-1α and IL-6	[36]
	Lactobacillus sakei K040706	Ameliorated the atrophy of colon length, mucosal damage, and spleen enlargement	[38]
Bifidobacteria	*Bifidobacterium bifidum* 231	Reduced the expression of iNOS, TNF-α, IL-1β, and IL-6	[41]
	Bifidobacterium longum CCM7952	Suppressed NF-κB, STAT3, and TLR4 expression Increased IL-10; Decreased IL-1β Engaged TLR2; Contained NOD2 Improved epithelial barrier	[31]
Dietary fibers and prebiotics			
Konjac glucomannan	Konjac glucomannan hydrolysate	Reduced bowel movement, diarrhea, blood in feces, abdominal pain, and flatulence	[44]
Glucan	β-(1,3–1,6)-d-glucan	Improved fecal output	[45]
	Oat β-glucan	Reduced visceral pain Lowered MPO, NO, and MDA Inhibited the expressions of TNF-α, IL-1β, IL-6 and iNOS	[46]
	Glucan from mushroom (*Pleurotus pulmonarius*)	Reduced histological damage	[47]
	Bacterial β-(1,3)-glucan	Reduced the expression of IL-1β Reversed Treg reduction	[48]
Nanofiber	Cellulose nanofiber from seaweed	Decreased NK cell defects and IgA production	[49]
Prebiotics	Cellulose nanofiber from pear	Improved intestinal tissue injury Suppressed the activation of NF-κB	[50]
	Fructooligosaccharides	Suppressed colon atrophy Suppressed the activation of NF-κB	[51]
	Goat milk oligosaccharide	Decreased IFN-γ, IL-17, and TNF-α levels	[52]
	Inulin	Increased LAB population Decreased inflammation Improved mucosal damage Decreased TNFα, COX-2, IL-2, and IL-6	[53]
Vitamins	1alpha,25-dihydroxyvitamin D3	Suppressed TNF-α Enhanced IL-10 production	[57]
	1,25-dihydroxyvitamin D3	Reduced IFN-γ	[58]
	Vitamin D3	Increased CD+ T cells and IL-6 Protected mitochondria	[59]
	Vitamin A	Inhibited nuclear respiratory factor (NFR)-1 and mitochondrial transcription factor A (TFAM)	[60]

TLR: Toll-like receptor; TNF-α: Tumor necrosis factor α; IFN-γ: Interferon γ; IL: Interleukin; NF-κB: Nuclear factor κB.

et al[57] (2005), 1α,25-dihydroxyvitamin D3 together with calcium substantially reduced TNF-α expression and relieved the symptoms of IBD in IL-10 knockout mice. In human CD4+ cells, 1,25-dihydroxyvitamin D3 increased the level of IL-10 and inhibited the proliferation of T cells[58]. Patients suffering from Crohn's disease have shown an increased level of IL-6 after vitamin D3 treatment[59]. The protective effects of vitamin A have been investigated in a TNBS-induced colitis mouse model, and after 21 days of treatment, vitamin A substantially increased the proliferation of mitochondrial transcription factors NFR-1 and TFAM and prevented intestinal tissue damage[60].

Specific carbohydrate diets and FODMAP

The specific carbohydrate diet (SCD) was first designed and mentioned by Sydney Haas in 1914 to cure celiac disease[20]. The term became popularized when Elaine

Gottschall published his book entitled "Breaking the Vicious Cycle: intestinal health through diet" in 2012 about how he and his daughter were cured from IBD by strictly following this diet plan[61]. The SCD plan allows the intake of only monosaccharides and the complete avoidance of disaccharides and polysaccharides, because they remain undigested and unabsorbed in the digestive tract and lead to the overproduction of yeast and bacteria, which eventually causes intestinal injury. In a clinical study, children with Crohn's disease under this dietary plan for 12 and 52 wk had remarkably reduced mucosal damage and improved clinical symptoms[62]. FODMAPs are specific carbohydrate foods that contain mono-, di-, and oligosaccharides and polyols[63]. These carbohydrates are poorly digested, but easily fermented by the colonic bacteria, leading to bloating, abdominal cramping and discomfort, and diarrhea, which are also associated with IBD[64]. As a consequence, scientists developed the idea of eliminating FODMAPs from the diet for IBD patients as a cure. The efficacies of FODMAP diets have been demonstrated through human studies, and patients who adhered to FODMAP elimination have experienced fewer abdominal disorders and better quality of life[65,66].

FUNCTIONAL FOODS AND NUTRACEUTICALS FOR IBD

Functional foods are any fresh or processed foods that provide health benefits and have disease prevention activities beyond their basic nutritional value. Nutraceuticals are foods or food supplements that deliver concentrated form of bioactive substances with medicinal properties. Although functional foods have been used as traditional medicines to treat chronic diseases for several centuries, it is modern scientific discoveries that are establishing the health benefits of functional foods and natural bioactive compounds providing the underlying mechanisms of their actions. Potential roles of functional foods against IBD have been broadly studied over the last decade, and overwhelming research evidence suggests that plant extracts, polyphenols, fatty acids, and amino acids can attenuate IBD symptoms by interfering with inflammatory pathways[6,67] (Table 3).

Plant and fruit extracts

The history of using plant extracts as alternative therapies for boosting the immune system and treating chronic inflammatory disorders dates back to ancient times. The anti-inflammatory activities of the plant extracts derive mainly from their abilities to modulate inflammatory cytokines. Several plant-derived extracts have strong therapeutic effects against IBD, and there is a growing interest in developing an effective IBD therapy based on plant extracts. *Coriolus versicolor,* mostly grown in China is a medicinal mushroom that has well-known health benefits. This mushroom contains polysaccharides, including krestin, lignin, and glucan. Our investigation on the effect of *Coriolus versicolor* extract (CVE) on UC in mice demonstrated that CVE could relieve the symptoms of colitis by decreasing the level of IgE in the serum and lymph nodes and, by suppressing the expression of TNF-α, IFN-γ, IL-4, IL-1β and IL-6[68]. *Cordyceps militaris,* a folk medicinal mushroom found in East Asia, also has proven health benefits against inflammation, most likely due to its polysaccharide contents[69]. A study by Han *et al*[70] reported that *Cordyceps militaris* prevented epithelial damage, inflammatory cell migration, and colonic shortening by decreasing TNF-α and iNOS levels. Interestingly, recent studies claim that the mushrooms grown on germinated cereal grains are rich in antioxidants and other bioactives and possess potent antioxidative and anti-inflammatory functions[71,72]. The chaga mushroom grown on germinated brown rice suppressed the expression of COX-2, TNF-α, IL-4, STAT1 and STAT6, and reduced the levels of IgE and IgA[73]. Additionally, *Ganoderma lucidum* grown on germinated rice reduced the inflammation in colitic mice by downregulating NF-κB and MAPK pathways[74].

Fruit extracts, due to their potential nutraceutical properties, have been investigated as therapeutic agents to treat IBD. A *Prunus mume* mixture in a DSS-induced colitis mouse model ameliorated inflammation by decreasing inflammatory cytokines and the immune response[75]. Pomegranate (*Punica granatum*), a tropical fruit rich in polyphenols especially ellagitannins and ellagic acid, has antioxidant and anti-inflammatory properties[76]. Pomegranate extracts, in TNBS-induced colitis rats, decreased TNF-α, MAPK phosphorylation, and NF-κB translocation[77]. Berry fruits are known for being rich in bioactive compounds and their therapeutic actions against numerous health problems[78]. The oral administration of blueberry extracts to colitic mice alleviated inflammation by a three-fold mechanism: antioxidation, inhibition of NF-κB translocation, and suppression of inflammatory cytokines[79]. The application of *Aronia melanocarpa* Elliot, also known as black chokeberry, relieved colitis symptoms in mice through its antioxidative and anti-inflammatory activities[80,81]. Ginger, which has been traditionally used as a spice and a natural remedy, has shown anti-inflammatory properties. Ginger extract, when administered to colitic mice, ameliorated colonic inflammation by downregulating NF-κB and IL-1β expression[82].

Marine foods and extracts have lately received attention as bioactive substances for IBD. The ethanol extract from *Haliotis discus hannai* Ino remarkably decreased mucosal tissue damage and lowered the expressions of IL-4, IFN-γ, STAT1, and STAT6 in a mouse model of colitis[83]. Green algae extract also exhibits strong remedial effects against DSS-induced colitis[84].

Phytochemicals

Phytochemicals perform important bioactive functions against oxidative and inflammatory disorders. Plant-

Table 3 Role of natural extracts and phytochemicals against inflammatory bowel disease

Base material	Main compound/agent	Mode of action	Ref.
Extracts			
Mushroom	*Coriolus versicolor* extract	Reduced TNF-α, IL-1β and IL-6 Reduced STAT1 and STAT6	[68]
	Cordiceps militaris extract	Decreased epithelial damage Suppressed iNOS and TNF-α mRNA expression	[70]
	Inonotus obliquus extract	Suppressed TNF-α, COX-2, and IFN-γ	[73]
	Ganoderma lucidum extract	Inhibited MAPK phosphorylation and NF-κB activation Decreased histological score	[74]
Fruit extracts			
Prunus mume	*Prunus mume* extract	Suppressed mucosal damage, TNF-α, and iNOS expressions	[75]
Pomegranate	Pomegranate extract (ellagitannins and ellagic acid)	Decreased the expression of TNF-α, COX-2, IL-4, and STAT6	[77]
		Prevented the translocation of NF-κB	[78]
Cranberry	Cranberry fruit/extract Blueberry extract	Modulated NF-κB and IL-1β signaling Attenuated colon shortening	[79]
		Suppressed pro-inflammatory cytokines	[80]
Averrhoa bilimbi	*Averrhoa bilimbi* L. extract	Prevented oxidation Inhibited pro-inflammatory mediators	[81]
Aronia melanocarpa	*Arronia melanocarpa* juice	Reduced NF-κB translocation	
Ginger	Ginger extract (zingerone)	Decreased mucosal injury	[82]
Marine food		Decrease the level of pro-inflammatory cytokines	[83]
	Haliotis discus hannai Ino extract	Improved colonic damage Decreased TBARS concentration Suppressed NF-κB and IL-1β	[84]
	Green algae extract	Suppressed colonic tissue damage Downregulated IFN-γ and IL-4 Ameliorated colonic tissue damage Decreased pro-inflammatory cytokines	
Phytochemicals	Apple polyphenols	Reduced COX-2 and TNF-α Recovered transglutaminase protein	[85]
	Resveratrol	Suppressed NF-κB and TNF-α Reduced clinical score	[86]
	Cardamonin	Reduced histopathological damage Reduced iNOS, NF-κB, TNF-α, COX-2, and caspase-3 Suppressed IL-1β and TNF-α	[18]
	Ginsenoside Rg1	Reduced colonic damage and DAI Improved colon shortening and DAI	[90]
	Sulforaphane	Suppressed STAT3 expression	[91]
	Curcumin	Reduced TNF-α, IL-1β, and MPO Attenuated morphological damage	[92]

TLR: Toll-like receptor; TNF-α: Tumor necrosis factor α; IFN-γ: Interferon γ; IL: Interleukin; NF-κB: Nuclear factor κB.

derived bioactive compounds can repress inflammation by inhibiting oxidative damage and interacting with the immune system. In a previous study, apple polyphenol extract reduced mucosal inflammation by reversing transglutaminase depletion in a TNBS-induced colitis rat model[85]. Resveratrol is an important polyphenol found abundantly in peanut, berries, and red grapes. This polyphenol exhibits versatile biological functions that are generally attributed to its modulating actions against oxidative processes and inflammatory pathways[86]. A randomized controlled trial conducted by Samsami-Kor *et al*[87] revealed that patients with UC supplemented with resveratrol had lower inflammation and decreased levels of TNF-α and NF-κB compared with the placebo group. A component from Chinese traditional medicine called cardamonin was administered to rats with acetic acid-induced colitis, and at the end of the trial, the rats had a reduced DAI score and improved histopathological conditions[18]. Cardamonin supplementation also reduced MDA and MPO activities, and NF-κB, TNF-α, and COX-2 expression. Previous reports suggest that NLRP12, a NOD-like receptor, can attenuate colonic inflammation by downregulating inflammatory cytokines and promoting the growth of useful bacteria in the gut[88,89]. Zhu *et al*[90] reported that Ginsenoside Rg1, a red ginseng compound, inhibited the inflammatory response and colonic damage by upregulating NLRP12 in mice with UC. A broccoli-derived isothiocyanate compound sulforaphane, exhibited anti-colitic activities by preventing colonic atrophy and increasing the expression of the Nrf2-dependent gene in

mice[91]. Curcumin, which is isolated from turmeric, has medicinal application in some Eastern Asian countries, and it is one of the most studied phytochemicals against ulcerative colitis. A study conducted on colitic mice found that curcumin supplementation could improve the histopathological score in the colon by suppressing the activity and the DNA-binding ability of STAT3, and by reducing TNF-α and IL-1β expression[92]. A combined therapy with curcumin, green tea polyphenol, and selenium exhibited outstanding results with decreased inflammatory symptoms and DAI both in human subjects with colitis and in DSS- and TNBS-induced colitic mice[93].

Fatty acids

Polyunsaturated fatty acids (PUFAs) are important pharmaconutrients that can exert therapeutic functions to control inflammatory disorders by modulating the immune response. Therapeutic effects of PUFAs against IBD have been demonstrated over the years, and growing evidence suggests that supplementing with PUFAs through ~~the~~ diet could be an interesting strategy for managing IBD[94]. The role of omega-3 fatty acids, including EPA and DHA, has been investigated in rats. The results indicate that EPA and DHA combined with olive oil and quercitrin reduced the levels of iNOS, COX-2, TNF-α, LTB_4, and IL-1β in colitic rats[95]. It is assumed that EPA and DHA-derived metabolites, namely, protectin, resolvin, and maresin are the factors responsible for the anti-inflammatory functions[96]. An adjunct therapy of omega-3 PUFAs with ~~to~~ 5-ASA showed that the dual therapy was more effective in downregulating NF-κB and inducing PPARγ in a rat model of colitis than a higher concentration of 5-ASA alone[97]. Administering EPA together with arachidonic acid (AA) to colitic mice resulted in decreased TNF-α and IL-6 and increased PPARγ[98]. The protective role of conjugated linoleic acid (CLA) on IBD was investigated by Bassaganya-Riera and Hontecillas (2006), and they concluded that CLA could efficiently delay the onset of colitis and decrease the severity of inflammation by influencing PPARγ expression[99]. Alpha linoleic acid from sage oil significantly lowered the inflammatory damage in experimental colitis by decreasing the levels of IL-6, COX-2, and TNF-α[100].

Short chain fatty acids (SCFAs) including acetate, propionate, and butyrate have exhibited therapeutic benefits for colitis. Butyrate limits the immune response and modulates the inflammatory mediators to alleviate mucosal inflammation[101]. In a previous study, butyrate supplementation to colitic rats maintained the integrity of the colonic mucosa by enhancing the production of regulatory T cells (Tregs) in blood and the plasma levels of IL-10 and IL-12[102]. Segain *et al*[103] reported that butyrate inhibited the NF-κB activation and degraded IκBα level in a rat model of colitis. Other SCFAs, including acetate and propionate also showed preventive activity against IBD in mice by inhibiting the expression of immune-related genes and inflammatory mediators, such as NF-κB and IL-6[104].

Bioactive peptides

Dietary peptides have displayed bioactive functions against several illnesses, including chronic inflammation, diabetes, hypertension, and oxidation[105]. Therefore bioactive peptides have the potential to be used as an alternative therapy for IBD and other chronic inflammatory disorders. According to Hou *et al*[106], treatment with alanyl-glutamine in a mouse model of colitis suppressed Th-17 cytokines and macrophage migration to the peritoneal cavity, indicating a reduction in the inflammatory response. Propionyl-L-carnitine, an essential factor of transporting fatty acids in mitochondria reduced mucosal inflammation through antioxidative effects in TNBS-induced colitis[107]. Bovine glycomacropeptide resulted in decreased mucosal damage in the colon, decreased MPO activity, and increased IL-10 in lymphocyte-driven colitis[108]. In a study by Azuma *et al*[109], fish scale gelatin peptide demonstrated anti-inflammatory functions in ulcerative colitis through its inhibitory actions against the activation of NF-κB and the accumulation of monocyte chemotactic protein-1 (MCP-1) in serum. Bioactive peptides isolated from salmon also showed anti-inflammatory functions in experimental colitis in mice[110].

FUTURE TRENDS

The inefficiency of current drug therapies along with the increasing prevalence of IBD from the West towards East Asian and other westernized countries and its recent globalization have triggered a significant amount of research aiming to develop alternative therapies based on natural substances that are highly effective and safe. A coordinated effort based on identifying and solving the environmental and dietary risk factors for IBD will be a priority in the future[111]. As diet is one of the key etiological factors of the disease, a multifaceted dietary intervention involving the elimination of certain foods and the inclusion of food components that can target the underlying causes of IBD is immensely needed. Manipulation of the gut ecosystem with probiotic bacteria is an interesting topic of research in the management of IBD. However, current data for the recommendation of probiotics for chronic metabolic illnesses are still insufficient. Recently, "designer probiotics" has drawn attention as an innovative approach, where genetically engineered bacteria with specific functionalities are administered to patients[112]. Promising results were found when recombinant *Bifidobacteria were* used as carriers for alpha-melanocyte and manganese superoxide dismutase in experimental colitis[113,114]. In recent years, "specific targeting" which allows nutrients or bioactive compounds to reach and target the specific site of inflammation to exert their effects, has become a trending topic of research for IBD control and will

be of tremendous importance in future research[115]. Development of novel cell models that can simulate the GI tract is considered to be a futuristic model of research in the quest for natural alternative therapies for IBD[116]. More importantly, the complete and precise understanding of the pathogenic mechanisms of IBD is necessary, as it will help researchers find suitable and efficacious treatments for IBD using available and prospective natural therapeutic agents. Therefore, future research studies will be centered upon the development of more effective therapeutic strategies for IBD based on health functional materials that will be capable of reaching the target site and exerting their functions to control the underlying pathogenic mechanisms of IBD.

CONCLUSION

Diets and functional foods have emerged as promising alternatives for the prevention and treatment of IBD during the past decade. While diets and dietary habits are key modulating factors involved in the pathogenesis of IBD, several food components such as dietary fibers, probiotics, non-starch polysaccharides, and fat soluble vitamins, have been effective in ameliorating gastrointestinal inflammation. Functional foods and bioactive compounds, including plant-derived extracts, phytochemicals, antioxidants, omega-3 fatty acids, and dietary peptides, have exhibited strong anti-inflammatory effects against IBD both in animal models and human subjects. Functional foods can modulate inflammatory cytokines and can interact with the immune system to produce anti-inflammatory functions against IBD. Therefore, diets and functional foods will play a significant role to control IBD in near future. At the same time, regular food intake, well-managed lifestyle, rest, and medication would require enough attention for the efficient management of IBD.

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