

Functional foods, conventional treatment and bioactive compounds, and assistance in the management of inflammatory bowel disease

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ABSTRACT

Ulcerative colitis, ileitis, and colonic Crohn's disease are the most common inflammatory bowel diseases (IBS). The etiology of this group of diseases is complex and has still not been entirely elucidated. Nonetheless, IBS is at least partially attributed to microbiota imbalance, which leads to an abnormal immune response. Due to the gravity of this condition, its impact on the quality of life, and increasing incidence, many investigations have been conducted with conventional and alternative treatments. While conventional medicine is partially beneficial, it cannot completely control the disease. There are frequent relapses and symptomatology often persists. Accordingly, specific diets, functional foods, and herbal medicine may offer a solution to restore intestinal microbiota and gut health, in addition to improving symptomatology. This review will focus on the diagnosis and management of IBD with respect to functional foods, bioactive compounds, and the potential of conventional treatment.

Keywords: IBD, Crohn's disease, ulcerative colitis, inflammation, treatment, microbiota, functional foods, bioactive compounds, bioactive ingredients, remission, effect.

INTRODUCTION

According to the Centers for Disease Control and Prevention, about 1-1.3 million people in the United States currently suffer from intestinal bowel disease (IBD) [1]. IBD includes both Crohn's Disease (CD) and ulcerative colitis (UC). In IBD, the gut microbiota interferes with normal intestinal functions, becoming both the cause and recipient of abnormalities of intestinal motility,

sensitivity, and neuroimmune signaling. This results in alterations of mucosal barrier, pattern recognition receptors expression, and dysfunctions of hypothalamus-pituitary-adrenal axis [2].

The community of microorganisms residing in the human gastrointestinal (GI) tract is known as GI microbiota, and is composed of about one thousand commensals and/or symbiotic microbial species. This community includes viruses (including bacteriophages), bacteria, archaea, and unicellular eukaryotes comprised of fungi and other non-bacterial and non-archaeal microbial species [3]. Microbiota can alter the health or nutritional status of the host in order to fight against pathogens, a process that is a potential contributing factor to IBD [4]. Gut microbiota participate in host protection from pathogenic microbes, regulate metabolic pathways, and drive the maturation of the host immune system [5].

However, changes in the microbiota can also be associated with and are a feature of various diseases. Pathogens in the gut vary among animal species. In a study that compared different hosts (e.g. cattle, chimpanzees, and humans) in the same environment, similarities were observed between gut pathogens in humans and other species. These similarities may be the result of phylogenetic similarities in gut flora. Investigators additionally discovered that varieties of bacterial species may also be the result of dietary differences [6]. In humans, the intestinal tract contains a range of about 100 bacterial colonies, with the colon containing the majority of these bacterial colonies (about 10^{12}) [7]. The microbiome is located in the intestinal tract and defined as "...the collection of organisms and their genomes inhabiting locations both in and on humans."

The "collection of organisms" consists of anaerobic or aerobic bacteria (e.g. Bacteroidetes, Firmicutes, Actinobacteria, and Proteobacteria) [8]. Microbial implantation does not occur until birth. If delivery is vaginal, the infant will experience bacterial colonization when it contacts maternal fecal and vaginal microbiota [9].

If delivery is conducted via cesarean section, the infant will receive microbiota from the surrounding environment [9-10]. The microbiome, with its distribution and richness of microbiota can be influenced by either the environment or diet; this includes the expression of different immune responses within the niche habitats in the proximal and distal sections of the intestine [4]. Varying diets will also affect microbiome diversity. For example, the differences between a high protein, high fat "western" diet and a low fat "non-western" diet can alter the abundance of microbiota [11-12]. Studies have demonstrated how higher fat diets increased Firmicutes, Proteobacteria, and Clostridium while reducing the number of Bacteroidetes and Bifidobacterium [13-17].

When the microbiota equilibrium is disrupted, the host can develop an imbalance [18] called dysbiosis. Alteration of the host environment into a state of dysbiosis can affect mental health and may lead to depression [19].

A new term, "psychobiotic," has been established and defined as "a living organism, that when ingested in adequate amounts, produces health benefits in patients suffering from psychiatric illnesses" [20]. Brain-gut interactions have been identified which may be modulated by gut microbiota via immunological, neuroendocrine, and neural mechanisms that can induce systemic inflammation [21].

In this review, the function of gut microbiota and chronic diseases will be discussed along with possible treatments from the use of functional foods, medications, and therapies, in addition to an opinion regarding the investigation and treatment of IBD.

WHAT IS INFLAMMATORY BOWEL DISEASE?

Inflammatory bowel diseases (IBD) are a group of intestinal diseases characterized by chronic inflammation of the bowel associated with an abnormal immune response [2]. There are many triggers for IBD, including stress, changes in environment or diet, a pathogenic invasion, and stress. Genetic polymorphism, microbiota, and food hypersensitivity are factors which contribute to IBD pathology (T-Cell negative regulators, B Cells, epithelial junctions, innate sensors). Crohn's disease is characterized as a responsive disease for those at risk from pathogens, high intestinal permeability, genetic factors, the environment, dysbiosis, or bacterial translocation, in addition to inflammation [7].

In an article titled "Regional ileitis: a pathological and clinical entity that identified patients with a chronic inflammatory disease of unknown etiology," the disease was later described as Crohn's disease [22]. CD can occur anywhere along the digestive system [23]. Those affected have elevated levels of jejunal mucosa causing the reduced synthesis of brush border enzymes. Thus, Crohn's disease can be categorized as a diffuse lesion of the gastrointestinal tract [24].

Ulcerative colitis is an IBD present in the lining of the colon that causes chronic relapse or progressive inflammation and a decrease in microbiota diversity, especially among bacteria that produce butyrate, which represses pro-inflammatory cytokine secretion [25]. Steroids are often prescribed to control UC symptoms, despite well-known side effects including hyperglycemia, infections, bone loss, and more. [26].

All IBD can affect brain functions. For example, Zonis et. al discovered that UC can alter hippocampal neurogenesis due to a cyclin-dependent kinase inhibitor, p21, which can suppress neuronal cell proliferation. Unfortunately, p21 expression can increase due to inflammation [27]. Furthermore, conventional treatment by itself is unable to control the symptoms of IBD. In light of this, functional foods may potentially be used in addition to prescription medication. However, the amount, schedule, and particular foods capable of improving outcomes need to be identified. Interestingly, a study in women found that probiotic intake from fermented milk could alter brain activity in regions controlling emotion and sensory processing [28].

METHODS OF DIAGNOSIS

IBD is diagnosed using Magnetic resonance heterography (MRE) and Wireless capsule endoscopy (WCE). WCE is a user and patient-friendly sensor diagnosis that assists in diagnosing the severity of IBD when ingested [29]. Magnetic resonance heterography (MRE) has been proven to be helpful in the diagnosis of IBD and CT. Diagnostic techniques have been very useful in respect to CD cross sectional diagnosis, in addition to extra-intestinal and extra-luminal conditions.

However, these techniques make children more prone to CD due to ionizing radiation [30]. Fortunately, MRE is radiation free and constructs the same results as CT and MRI [30-32]. Another diagnostic method is confocal laser-induced endomicroscopy, which was introduced to capture

images of “virtual histology” of the gastrointestinal mucosa [33]. The benefits and limitations of various diagnostic techniques are shown in Table 1.

Table 1. Comparison of a few IBD diagnosis methods.		
Diagnosis Method of IBD	Pros	Cons
Wireless Capsule Endoscopy (WCE)	<ul style="list-style-type: none"> • Can visualize small bowel mucosa 	<ul style="list-style-type: none"> • Difficulty in differentiating ulcers from CD • 13% risk of capsule retention in CD patients
Magnetic Resonance Enterography (MRE)	<ul style="list-style-type: none"> • Diagnose IBD inflammation in CD • Increase of blood flow could signal inflammation phase 	<ul style="list-style-type: none"> • Lower visual quality of images in contrast to CT • Difficult to differentiate between inflammation and fibrosis
Computed Tomography (CT)	<ul style="list-style-type: none"> • Identify strictures, abscesses, and fistulae • Identify severity of CD 	<ul style="list-style-type: none"> • May not detect early symptoms of CD as an MRE diagnosis • 0.08% risk of cancer from radiation exposure
Confocal Laser-Induced Endomicroscopy	<ul style="list-style-type: none"> • Allow visualization of the pathology of mucosal epithelium • Manage IBD patients • Predict future relapse of the disease • Responses of anti-TNF therapy 	<ul style="list-style-type: none"> • Limited equipment and training in general practice

A recent large international study which investigated 34,819 patients with IBD genotyped by gene-microarray methodology was able to detect three phenotypic-location associations which categorized IBD as ileal Crohn’s disease, colonic Crohn’s disease, and ulcerative colitis [34]. The mathematical analysis of relatives with or without UC and or IBD has demonstrated that they share similar intestinal microbiota. In contrast, there are no relationships in non-relatives with or without IBD shared similar microbiota [35]. This relationship in microbiota is considered a biomarker of UC disease activity [35]. As for ulcerative colitis, assessing its severity includes the frequency of bowel movements, extent of rectal bleeding, endoscopic appearance, and effects on the patient’s quality of life and activities [36]. Because UC can relapse, using plasma free amino acid concentrations can predict the risk of relapse within a year of diagnosis. Additionally, this study also associated decreased histidine levels in PFAAs as a marker of an increased risk of relapse [37]. IBD in children has been difficult to diagnose, due to how there are no chronic symptoms in the early stages of IBD. However, colonic crypt distortion or rectosigmoid eosinophilia may be early signs of IBD in children [35-8]. Fecal lactoferrin can be used to detect IBD in pediatric patients, as patients with IBD will express increased levels of this inflammatory marker. This has also been demonstrated in both UC and CD [39]. Another diagnostic method is ¹H NMR, which is able to show inflammation-driven changes in the metabolic profile that are related to malabsorption and dysbiosis [40].

Microbial communities throughout the gut are evaluated using bacterial 16S ribosomal RNA gene sequencing, which act as a phylogenetic marker of microbiota that show there are different

mucus phenotypes, in addition to a difference in permeability. Limitations of the 16S RNA gene sequencing include its lack of diversity, specificity, and comparison of databases, in addition to this method also including many biases [41]. In a study employed on healthy patients with active and inactive UC, butyrate was shown to reduce the expression of pro-inflammatory cytokines by inhibiting the NF- κ B pathway, causing an anti-inflammatory effect [42]. Individuals with a high gene count (HGC) for microbiota, have a microbiome rich in butyrate-producing organisms, in addition to having lower risk for metabolic disorders and obesity. On the contrary, low gene count (LGC) gut microbial individuals have higher proportions of pro-inflammatory bacteria like *Bacteroides* and *Ruminococcus gnavus*, which are associated with IBD [43]. Infections can also be used as an IBD diagnostic factor for undiagnosed disease [44-45]. There are a variety of IBD diagnostic methods, with each being discriminatory based on the level of frequency, age, or availability. Multiple scientific studies and clinical trials have shown results from diagnosis and possible treatments.

FUNCTIONAL FOODS AND SYNBIOTICS

Changes in diet can greatly affect the type of microbiota and can potentially reduce the severity of IBD symptoms [44]. Prebiotics are "non-viable food components that confer a health benefit on the host associated with modulation of the microbiota." By definition, prebiotics are not absorbed or hydrolyzed in the gastro-intestinal tract. Prebiotics constitute a selective substrate for one or a limited number of beneficial bacteria and are able to alter the colonic microbiota in favor of a healthier composition. The probiotics definition was originally framed by the World Health Organization (WHO) and Food and Agriculture Organization of the United Nations (FAO) as the following: "live microorganisms which, when administered in adequate amounts confer a health benefit on the host." Probiotics and prebiotics combined synergistically can be more effective than when taken alone [46]. Functional foods are classified by the Functional Food Center (USA) as "Natural or processed foods that contain known or unknown biologically-active compounds; which, in defined, effective non-toxic amounts, provide a clinically proven and documented health benefit for the prevention, management, or treatment of chronic disease" [47]. Functional foods can act as a natural dietary supplementation that assist microbiota in regulating the health of hosts. Probiotics and prebiotics can be found in functional foods and benefit the host. A diet consisting of whole-grains or prebiotics can decrease the amount of bacterial endotoxins released into the bloodstream and regulate levels of inflammation [48]. This kind of diet can also increase bacteria capable of producing beneficial products from the fermentation of those carbohydrates [48]. An important source of probiotics is yogurt. When yogurt is consumed, concentrations of *Lactobacillus* and *Bifidobacterium* in stool are increased and levels of *Bacteroides* are decreased [49]. *Bacteroides* are considered to be "aggressive" bacteria due to the implications in the pathogenesis of IBD and is observed in ratio with *Firmicutes* to demonstrate the status of microbiota [50].

There is evidence that algae could be beneficially effective towards IBD. Red seaweed includes many bioactive ingredients (sulfated polysaccharides, polyphenols, carotenoids, amino acids, protein/peptide, and lipids) and has the ability to beneficially change the mucosal barrier function in IBD [51]. Unfortunately, most people in western countries do not consume algae due to a lack of awareness and/or dietary customs. Asian countries consume this product abundantly and research has shown that traditional Asian diets are associated with a reduced risk of cancer, and diabetes. Additionally, diets that contain red seaweed confer anti-inflammatory, immunomodulatory, and neuroprotective effects through its prebiotic and antioxidant properties.

Food and medical industries have become increasingly interested in investigating related organisms for undiscovered bioactive compounds or nutrients [51].

Brown algae, *Dictyopterus undulata*, contain sesquiterpene zonarol, which works by inhibiting inflammation and the apoptosis responsible for disrupting the mucosal barrier function. Currently, 5-aminosalicylic acid (5-ASA) is used to inhibit inflammation. However, zonarol has the potential to be a suggested change [52]. A study conducted by Kang et al. investigated whether brown algae extract could induce apoptosis through inducing endoplasmic reticulum (ER) stress in human colonic cancerous cells. ER stress can be overwhelming and lead to the apoptotic death of a damaged cell [53]. Red algae consists of agarose and agarose oligosaccharides, which have demonstrated prebiotic effects. Fortunately, *Bacteroides uniformis* (L8), which is occasionally found in the gut, can degrade these compounds leading to antioxidant, anti-tumor, and anti-inflammatory effects [54]. Carbohydrate active enzymes, CAZymes that extract energy from polysaccharides suggest that the human microbiome has evolved with the ability to degrade algal carbohydrates [55]. Fucoidans, fructose-rich polysaccharides, are found in edible brown algae and have been known to have substantiality-inflammatory effects. A study by Lean et al. treated mice with fucoidans and monitored the signs of colitis for any effect the fucoidans may have towards inflammation. Fucoidans reduced colitis symptoms, diarrhea, and the relative weight of the colon and spleen, implying they had reduced inflammation and edema [56].

Vitamin D is a bioactive signaling compound that modulates inflammatory responses via regulation of pro-inflammatory gene expressions, their transcription factors, and the activation of signaling cascades that mediate inflammatory responses [57]. Vitamin D supplementation has the potential for efficient therapeutic use, due to its ability to stimulate the production of T-regulatory lymphocytes and assists with recovery from IBD [58]. Low vitamin D levels are associated with increased cancer and IBD risk. Furthermore, higher levels of vitamin D are associated with reduced risks of *Clostridium difficile* [59].

Oxidative stress (OS) can have a negative impact in IBD because it can lead to tissue damage. Interestingly, extra virgin olive oil could increase antioxidant enzyme activity, modulate responses against OS, and reduce the effects of IBD [60]. A study conducted by Bouzid et al. used malondialdehyde (MDA) as a biological marker to identify IBD [61]. A marker of lipid peroxidation, MDA indicates the presence of oxidative stress and suggests that oxygen radicals are released in the inflammatory process associated with IBD [58]. There are some dietary fats that have been necessary or beneficial in treating health issues. However, omega-3 polyunsaturated fatty acid effects differ by location in IBD and induce changes to microbiota that can cause pro-/anti-inflammatory effects [62].

Dioscoreaceae, is a type of yam plant with the bioactive compound methyl protodioscin (MPD), a substance shown to be beneficial in treating IBD [63]. In mice, colitis was induced using dextran sulfate sodium and subsequently treated with MPD [63]. MPD ameliorated inflammation in the intestinal mucosa by enhancing intestinal barrier differentiation. Furthermore, MPD protected colonic mucosa from *Citrobacter rodentium*, while also preventing the colonization of bacteria [63]. Another study by Gil et. al focused on how this type of yam plant extract effected mice via the down-regulation of genes that were related to inflammation [64].

C. difficile is a gram-positive, anaerobic, and dormant spore-forming bacterium, which can cause many infections and gastroenteritis-associated deaths because of its natural antibiotic resistance and ability to spread spores [65]. Intestinal microbiota can fight against *C. difficile* through resource competition, inhibition of germination or vegetative growth, or enhancement of the host's defenses [66]. Increased use of antibiotics may increase *C. Difficile* incident in healthy

individuals by damaging microbiota [67]. Patients with UC have higher risk of *C. difficile* infection (CDI) and the outcomes can be significantly more severe [68]. To correct the imbalance and restore the health of intestinal microbiota, CDI can be treated using fecal microbial transport (FMT). [69]. Additionally, other alternative methods of treating ulcerative colitis or Crohn’s disease can be seen in Tables 2 and 3. Each table lists functional food ingredients that have known possible effects on IBD.

Table 2. The effects of functional food ingredients on Ulcerative Colitis

Reference	Analysts	n	Subject	Duratio n	Interventio n	Outcome	Study
Kruis, 1997 [73]	Probiotic s	12 0	120 human subjects with chronic UC	12 weeks	500 mg mesalazine t.d.s. or 200 mg E. coli Nissle	Probiotic treatment is an alternative option in maintenance therapy for UC. Relapse rate: 11.3% and 16.0% mesalazine and E. coli Nissle, respectively	Double-blind comparison
Langmead, 2004 [74]	Aloe Vera	44	44 human subjects with active UC	4 weeks	Aloe vera gel 100 mL twice daily	Reduces histological disease activity and provides inflammation inhibiting properties. More research is needed to see if the results stop if the intervention ceases	Double-blind, randomize, placebo controlled trial
Hanai, 2006 [75]	Curcumi n	45	45 human subjects with UC	6 months	1 g curcumin twice daily plus mesalamine or placebo	Curcumin significantly improved both clinical activity and endoscopic indexes. Curcumin in combination with mesalamine better in comparison to placebo. More research is needed to see if the results stop if the intervention ceases	Randomized, double-blind, placebo-controlled trial
Kanauchi, 2003 [76]	Germinat ed barley foodstuff	21	21 patients with mild- moderate active UC	24 weeks	20-30 g of germinated barley foodstuff with continuation of baseline steroid treatment	Decrease clinical activity index (degree of visible blood in stools and diarrhea). More research is needed to see if the results stop if the intervention ceases	Multicenter Open Trial
Kazi, 2009 [77]	Saffron (crocetin extract)	10	10 female BALB mice induced with UC	8 days	25, 50, or 100 mg/kg/d of crocetin	50mg/kg/d was the most effective dose of crocetin in the mice. Reduction in neutrophil infiltration, lipid peroxidation, nitric oxide levels, also down regulation of nuclear factor-kB with favorable expression of TH1 and TH2. More research is needed if	In vivo trial

						the results stop when intervention ceases	
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Table 3. The effects of functional food ingredients on Crohn's Disease

Reference	Analysts	n	Subject	Duration	Intervention	Outcome	Study
Yang, 2013 [78]	Vitamin D	18	18 human subjects with confirmed Crohn's disease between 18-70 years old	24 weeks	Vitamin D3 initiated at 1,000 IU/d. After 2 weeks, incrementally increased to maximum 5,000 IU/d.	A safe dose to induce remission in mild-to-moderate CD is 5,000 IU/d	Clinical Trial
Kaliora, 2007 [79]	Mastic	10	10 patients with mild-moderate active Crohn's Disease	4 weeks	2.2 g mastic daily (6 caps total)	Mastic supplementation concluded as a tumor necrosis factor- α inhibitor and migration inhibitory factor stimulator	Double-blind, randomized placebo-controlled trial
Omer, 2007 [80]	Wormwood herb and prednisone	40	40 patients with CD	20 weeks	3 weeks 40 mg prednisone and wormwood herb 3 x 500 mg/d for 10 weeks. 5-aminosalicylates for at least 4 weeks, azathioprine at least 8 weeks, or methotrexate for at least 6 weeks as concomitant medications	Remission of CD symptoms and a strong suggestion that wormwood herb has a steroid sparing effect	Double-blind, randomized placebo-controlled
Ren, 2013 [81]	Tripterygium wilfordii (GTW)	45	45 postoperative CD patients between the ages 18-60	52 weeks	1 mg/kg GTW or 4 g 5-ASA daily for 52 weeks. Baseline analysis at weeks 13, 26, and 52	GTW was more effective than 5-ASA in minimizing clinical and endoscopic recurrence of CD	Prospective, single-center, randomized single-blind study
Holtmeier, 2011 [82]	Boswellia serrata	108	108 patients with active Crohn's disease	52 weeks	2400 mg/d or placebo to check for maintaining remission	There was no distinguishable difference or superiority between the placebo and boswellian serrata	Randomized double-blind, placebo-controlled, parallel study

Phytochemicals found in cocoa and in red wine contain antioxidants beneficial to intestinal and overall health. Some polyphenols have antioxidant activities. In particular, cocoa is rich in polyphenols that contain antioxidant, anti-inflammatory, and antitumor qualities. These can help prevent tumor formation in UC patients who are at risk of developing colorectal cancer due to blocked expression of a signal transducer and transcription activation in the intestinal epithelial cells that take part in IBD and colorectal cancer [70]. The abundant non-alcoholic polyphenol portion of red wine includes: falvan-3-ol, flavanols, anthocyanins, catechin, epicatechin,

proanthocyanadins, benzoic, and hydroxycinnamic acids. Red wine can prevent or delay the progression of IBD by reducing oxidative stress and inflammation through polyphenols acting as free radical scavengers and modulators of inflammation-related genes [71]. Additionally, red wine derived polyphenols can also act as prebiotics and antimicrobial agents. The alcohol within red wine at low concentrations can alter gastrointestinal (GI) pathogens such as *Salmonella enterica* and *E. coli* [71]. *Ficus bengalensis* refers to the “banyan tree” that produces sap from the bark, which also has an antioxidant phenolic compound that can assist towards the treatment of inflammation, dysentery, and diarrhea in IBD patients [72].

NUTRITION interventions for IBD

Prebiotics, probiotics, and synbiotics can have a beneficial temporary effect towards IBD. However, fecal transplants also show promise. FMT, which is also known as bacteriotherapy, is a process of donating fecal material to the intestinal tract of a patient [85]. The FDA initially classified human fecal material as drugs due to its medical usage. As fecal material is now considered a human tissue, FMT is easier to perform as there is no drug-regulation policy for human tissue [85]. The first fecal transplant was recorded in 1989 when a man with ulcerative colitis conducted a self-administered fecal microbiota transplant (FMT) on himself from a healthy donor, which reduced symptoms and induced remission [83]. In another case, an individual with *C. difficile* and chronic IBD underwent FMT as a rescue therapy, which led to remission and improved overall well-being [84]. A study conducted in IBD patients who had fecal transplants indicated that the procedure was associated with clinical remission and improvement in CD and UC [84].

E. coli strain Nissle 1917 has been identified as clinically effective towards IBD because it has been reported to be equivalent to Mesalazine (an anti-inflammatory drug) treatment for patients with UC but not CD [86]. As *E. coli* strain Nissle 1917 is an apathogenic strain that lives in an anaerobic environment, it can thrive in the large intestine as a carrier of specific molecules into the intestine, often in places where a carrier and its products are undesirable [86]. *E. coli* strains can multiply rapidly, adhere, and invade epithelial cells, negatively modify the intestinal barrier function, or induce inflammatory responses in cells [86]. All animals, including cold-blooded animals, are infected with *E. coli*, which is usually the first bacterium to colonize the body once nutrients are obtained from the mucus layer [86]. *E. coli* is resistant to the acid contained in the stomach through a protective system and can use the mucus layer to colonize itself, in addition to acting as a nutrient reservoir [86].

Faecalibacterium prausnitzii (*F. prausnitzii*) is a butyrate-producing species that can induce gut homeostasis and has a protective role in IBD, especially CD [87]. Miquel et al. conducted a study that involved colitis affected mice prone to this bacterial species, discovering there was a protective modulation of metabolites along the gastrointestinal tract, reducing colitis [88]. This species, along with *Clostridium leptum*, are not very abundant in fecal samples in IBD patients, especially CD patients, due to the numerous butyrate-producing bacteria. However, they represent a huge source of energy for colonic epithelial cells and are associated with the inhibition of inflammation [89].

Medications used for IBD treatment depend on the severity and location of the lesion and include amino salicylates and antibiotics when the disease is limited to the mucosa, corticosteroids for moderate severe cases, and biological molecules when fistula is present [90]. Biological therapies include the use of antibodies to inhibit pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF α) that can induce apoptosis or block growth factors and induce remission of IBD [91]. Adalimumab is anti-TNF α , which has been shown to maintain remission in CD, even in severe cases [92]. With respect to CDI (*Clostridium difficile* infection), especially

in IBD, vancomycin treatment is often successful. According to a study conducted by Horton et al., subjects treated with this antibiotic showed fewer readmissions and shorter lengths of hospital stays, especially when steroids were not used concomitantly, as steroids increased the severity and risk of CDI [93]. Antibiotics are a common form of therapy in CDI, but they can change the environmental conditions for microbiota and even trigger resistance [94]. Furthermore, antibiotics can affect the fecal environment and reduce the numbers of butyrate-producing species [95]. However, biosynthesis of antibiotics in the gut does not occur naturally, which suggests that antibiotic resistant genes are controlled independently by the presence of antibiotics. This is consistent with the rich expression of these genes in the intestinal area [96]. On the other hand, antibiotics are presumed to potentially induce beneficial effects in the treatment of active luminal CD via alteration of microbiota [97]. Metronidazole has been used in multiple studies to treat CD. One study found no objective difference in patients treated with Metronidazole, although patients did report an enhanced feeling of well-being and comfort [98]. In a crossover study using metronidazole and sulphasalazine, metronidazole was shown to be more effective [99]. An additional study compared metronidazole and cotrimoxazole separately and together, and consequently detected no significant differences [100]. Overall, metronidazole was determined to be beneficial towards the suppression of CD via fighting anaerobic bacteria and possibly acting as an immunosuppressant rather than an antibiotic [98].

There are other medications that have been found to cause changes in IBD, either through changing the disease course or by inducing remission. Monoclonal antibodies have also been shown to be beneficial in treating IBD patients. Examples include golimumab, natalizumab, vedolizumab, and biosimilars. Golimumab is an anti-TNF monoclonal antibody that was shown to be effective in reducing symptoms, inducing remission, and mucosal healing in UC patients [101]. Anti-TNF therapy has been shown to induce mucosal healing in IBD patients [102]. However, some CD and UC patients do not respond to this treatment [102]. Natalizumab is another monoclonal antibody that prevents symptoms of Crohn's disease and regulates α_4 integrin whose expression in endothelium luminal cells causes inflammation in IBD [103]. Vedolizumab is a monoclonal antibody which, similarly to Natalizumab, is specific towards $\alpha_4\beta_7$ integrin which associates itself with inflammation of the intestinal epithelium [104]. Vedolizumab can induce clinical remission and mucosal healing within a year of exposure [105]. Lastly, biosimilars are copy versions of biological drugs targeting liver and gastrointestinal diseases, whose amino acid and glycosylation patterns are similar to other licensed medications [106]. According to the European Crohn's and Colitis Organization, biosimilars may be effective and safe for some causes but potentially not for others. Consequently, the accurate assessment of their strengths and weaknesses is needed in order to benefit patients [106]. Overall, medications and/or antibiotics can have positive therapeutic effects.

Herbal therapy has been categorized as a natural agent supporting IBD treatment. It is considered to be a complementary and alternative medicine (CAM), as it is administered outside of centers where conventional medicine is provided [107]. A study investigating the effects of herbal medicine in IBD patients indicated that these substances could be more effective than other CAM, representing a more cost efficient alternative [108]. Traditional Chinese medicine (TCM) diagnoses and treats symptoms through inspection, listening, smelling, inquiry, and palpitation [109]. TCM uses YunNan BaiYao (YNBY), *Wedelia chinensis*, Changtai granules, and Xilei-san. YNBY is a mix of different herbs and plants, which can suppress the severity of colitis through immune-suppression and wound-healing mechanisms [110]. *W. chinensis* water extract is beneficial through relief of diarrhea, rectal bleeding, body weight loss, and colonic inflammation [110]. Changtai granules (CTG), exhibits anti-diarrheal, anti-inflammatory, anti-bacterial, and analgesic effects [110]. Xilei-san (traditional Chinese herb) is another type of TCM that was found

to reduce inflammation in colitis patients administered together with mesalazine or corticosteroids in a clinical trial, 86% of patients went through remission, suggesting that Xilei-san had remission potential [110]. Therefore, herbal medicine demonstrates favorable outcomes in IBD patients,

The introduction of stem cells may be an alternative treatment of IBD. Differentiation of hematopoietic and non-hematopoietic stem cells are likely involved in the pathogenesis of IBD [111]. Hematopoietic stem cells (HSC) and mesenchymal stem cells (MSC), are involved in resetting the immune system of patients on myeloablation therapy, which causes elimination of T-lymphocyte and memory T-cells [112]. Mesenchymal stromal cells are adult stem cells that can have multiple effects towards the immune system including activation, proliferation, or repair of tissue. Furthermore, these cells can have anti-inflammatory effects in IBD patients [113]. Once a patient receives transplanted MSC's, remission will begin, accompanied by the release of anti-inflammatory cytokines to balance the immune system [114]. PROM1 has been identified and used as a stem cell marker for prediction of colon cancer or IBD, but can possibly assist in intestinal healing [115]. Bone marrow stem cells may be able to regenerate damaged mucosa in the gastrointestinal tract and restore damaged intestinal permeability [116]. Table 4 describes more common nutrition approaches that may be beneficial or ineffective.

Table 4. Common Nutritional Approaches		
Alternative Therapies	Pros	Cons
Probiotics [117]	<ul style="list-style-type: none"> • Adding beneficial bacteria, in the digestive tract may have beneficial effect against IBD • There is some evidence to support these claims 	<ul style="list-style-type: none"> • Research is limited • Does not have significant evidence to support the benefits of probiotics • Probiotics therapy is not regulated by the FDA • May have unknown side effects
Fish Oil [118]	<ul style="list-style-type: none"> • Fish oil present anti-inflammatory activities • Combining fish oil with aminosalicylates increases effectiveness 	<ul style="list-style-type: none"> • May cause diarrhea • Limited evidence that proves its claims • Fish Oil therapy is not regulated by the FDA • May have unknown side effects
Aloe Vera [119]	<ul style="list-style-type: none"> • Acts as a natural anti-inflammatory for UC 	<ul style="list-style-type: none"> • May cause diarrhea • Aloe Vera therapy is not regulated by the FDA • May cause unknown side effects

<p>Turmeric [120]</p>	<ul style="list-style-type: none"> • The active ingredient in turmeric, curcumin, has been used in clinical trials of UC and have shown promising results 	<ul style="list-style-type: none"> • Not significant evidence to support the claims • Turmeric therapy is not regulated by the FDA • May cause unknown side effects • Research is limited
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SUMMARY

IBD is a chronic disease that affects large numbers of individuals worldwide. Dysbiosis caused by antibiotics, diet, and genetic predisposition may increase the risk of acquiring IBD. Currently there are no treatments that are totally or uniformly effective for all forms of IBD, despite many clinical trials that have associated different pharmacological immunotherapy, natural medications, and other therapies. FMT is being studied for its potential to alleviate this disease, and has been shown to be effective. Unfortunately, most IBD patients are treated with bacterial therapeutics after serious symptoms are present. Thus, functional analysis, a method of studying interactions between microbes and diseases to analyze microbiome biological properties, should be used to observe metabolic shifts in intestinal microenvironments of IBD [122]. Existing biomarkers that distinguish CD from UC are limited in predicting the long-range course of a disease [123]. Therefore, research should be targeted at identifying markers of prognosis [123]. Consuming a healthy diet can also influence IBD, including consumption of functional foods. Enteral diets and semi-vegetarian diets, can increase the likelihood of remission in patients. Functional foods and bioactive compounds, such as probiotics or vitamins, have a significant effect in the regeneration of intestinal microbiota, which thereby causes remission or treatment of some IBD with respect to inflammation. Further studies are necessary to examine how microbes, bioactive components, and functional foods can be beneficial in facilitating anti-inflammatory responses, butyrate producing species, or restoration of mucosal barrier function and healing. As IBD is still an important disease, much research is required. This will be time-consuming as microbiota evolve and can become resistant to treatment. With ongoing investigation and persistence, the future of patients with IBD can be brighter.

List of Abbreviations: Complementary alternative medicine, CAM; Crohn’s disease, CD; *Clostridium difficile* infection, CDI; Endoplasmic reticulum, ER; Food and Drug Administration, FDA; Fecal microbiota transplantation, FMT; Gastrointestinal, GI; Hematopoietic stem cells, HSC; Intestinal bowel disease, IBD; Low gene count, LGC; Malondialdehyde, MDA; Methyl protodioscin, MPD; Magnetic resonance enterography, MRE; Mesenchymal stem cells, MSC; PROM1Oxidative stress, OS; Traditional Chinese medicine, TCM; Tumor necrosis factor alpha, TNFα; Ulcerative colitis, UC; Wireless Capsule Endoscopy, WCE; YunNan BaiYao, YNBY; 5-aminosalicylic acid, 5-ASA;

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