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 is still not entirely understood. However, 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 prevalence, many investigations have been conducted into both conventional and alternative treatments. While treatment with conventional medicine is partially beneficial, it cannot completely control the disease. There are frequent relapses, and symptomatology often persists. Therefore, 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 and bioactive compounds in addition to 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. They include stress, changes in environment or diet, and pathogenic invasion. Genetic polymorphism, microbiota, and food hypersensitivity are factors which contribute to IBD pathology (T-Cell negative regulators, B Cells, epithelial junctions, and innate sensors). IBD has the potential to decrease the quality of life in some subjects.

In the article "Regional ileitis: a pathological and clinical entity that identified patients with a chronic inflammatory disease of unknown etiology," the chronic inflammatory disease was later identified as Crohn's disease [22]. Crohn's disease is an IBD characterized as a responsive disease for those at risk from pathogens, high intestinal permeability, genetic factors, the environment, dysbiosis, bacterial translocation, and inflammation [7]. CD can occur anywhere along the digestive system [23]. Those affected by CD have elevated levels of jejunal mucosa, which causes 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 which 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 p21, a cyclin-dependent kinase inhibitor, which can suppress neuronal cell proliferation. Unfortunately, p21 expression can increase due to inflammation [27]. Furthermore, conventional treatment alone is unable to control the symptoms of IBD. In light of this, functional foods may be a beneficial treatment when used alongside prescription medication. However, in order to improve outcomes, specific beneficial foods and the ideal amount and timing of their consumption still need to be identified. In light of this, a study with women participants discovered 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 the diagnostic capsule is ingested [29]. Magnetic resonance heterography (MRE) has been helpful in diagnosing IBD and CT. Diagnostic techniques are useful in respect to CD cross sectional diagnosis, in addition to identifying extra-intestinal and extra-luminal conditions.

However, these techniques increase children’s susceptibility to CD due to ionizing radiation [30]. Fortunately, MRE is radiation free and yields the same results as CT and MRI [30-32]. Another diagnostic method is confocal laser-induced endomicroscopy, which captures images of “virtual histology” of the gastrointestinal mucosa [33]. The benefits and limitations of these various diagnostic techniques are shown in Table 1.
Table 1. Comparison of a few IBD diagnosis methods.

<table>
<thead>
<tr>
<th>Diagnosis Method of IBD</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wireless Capsule Endoscopy (WCE)</td>
<td>• Can visualize small bowel mucosa</td>
<td>• Difficulty in differentiating ulcers from CD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 13% risk of capsule retention in CD patients</td>
</tr>
<tr>
<td>Magnetic Resonance Enterography (MRE)</td>
<td>• Diagnose IBD inflammation in CD</td>
<td>• Lower visual quality of images in contrast to CT</td>
</tr>
<tr>
<td></td>
<td>• Increase of blood flow could signal inflammation phase</td>
<td>• Difficult to differentiate between inflammation and fibrosis</td>
</tr>
<tr>
<td>Computed Tomography (CT)</td>
<td>• Identify strictures, abscesses, and fistulae</td>
<td>• May not detect early symptoms of CD as an MRE diagnosis</td>
</tr>
<tr>
<td></td>
<td>• Identify severity of CD</td>
<td>• 0.08% risk of cancer from radiation exposure</td>
</tr>
<tr>
<td>Confocal Laser-Induced Endomicroscopy</td>
<td>• Allow visualization of the pathology of mucosal epithelium</td>
<td>• Limited equipment and training in general practice</td>
</tr>
<tr>
<td></td>
<td>• Manage IBD patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Predict future relapse of the disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Responses of anti-TNF therapy</td>
<td></td>
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</tbody>
</table>

A recent, large international study investigating 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 examining the frequency of bowel movements, extent of rectal bleeding, endoscopic appearance, and effects on the patient’s quality of life and activities [36]. Plasma free amino acid concentrations can also be used to predict the risk of UC relapse within a year of diagnosis. 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 the absence of 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 indicate increased levels of this inflammatory marker. This has also been demonstrated in both UC and CD [39]. Another diagnostic method is $^1$H NMR, which can demonstrate inflammation-driven changes in the metabolic profile 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 to reveal the presence of various mucus phenotypes and differences 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 using healthy patients with active and inactive UC, butyrate was shown to reduce the expression of pro-inflammatory cytokines by
inhibiting the NF-kB pathway, thereby 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. In contrast, 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]. Overall, there are a variety of IBD diagnostic methods that can be used based on the level of frequency, age, or availability.

**FUNCTIONAL FOODS AND SYNBOTICS**

Changes in diet can greatly affect the type of microbiota and can potentially reduce the severity of IBD symptoms [44]. Functional foods can act as a natural dietary supplementation that assist microbiota in regulating the health of hosts. 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]. Prebiotics and probiotics can be found in functional foods and benefit the host. 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 World Health Organization (WHO) and Food and Agriculture Organization of the United Nations (FAO) define probiotics as the following: “live microorganisms which, when administered in adequate amounts confer a health benefit on the host.” When probiotics and prebiotics are combined synergistically, they can be more effective than when taken alone [46]. A diet consisting of whole-grains or prebiotics can decrease the number 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]. One significant 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 “aggressive” bacteria due to being implicated in the pathogenesis of IBD, and are observed in ratio with *Firmicutes* to demonstrate the status of microbiota [50].

There is also evidence that algae could have effective benefits for treating 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 algae abundantly. Research has demonstrated that Asian diets are associated with a reduced risk of cancer and diabetes. Additionally, diets with red seaweed contain anti-inflammatory, immunomodulatory, and neuroprotective effects through their prebiotic and antioxidant properties. The food and medical industries have become more interested and involved in investigating organisms that may have bioactive effects, including brown and red algae for undiscovered bioactive compounds or nutrients [51].
Brown alga or Dictyopteris undulata contains sesquiterpene zonarol, which inhibits inflammation and the apoptosis responsible for disrupting the mucosal barrier function. Currently, 5-aminosalicylic acid (5-ASA) is used to inhibit inflammation. However, zonarol also has potential [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 consist 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 or CAZymes extract energy from polysaccharides, which suggests that the human microbiome has developed the ability to degrade algal carbohydrates [55]. Fucoidans or fructose-rich polysaccharides are found in edible brown algae and have been known to have significant inflammatory effects. A study by Lean et al. treated mice with fucoidans and monitored them for signs of anti-inflammatory effect on colitis. 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 which 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 assist 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. Extra virgin olive oil may also 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]. As 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 affected mice via the down-regulation of genes 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 due to 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
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 outcome can be especially 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 possible effects on IBD.

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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Analysts</th>
<th>n</th>
<th>Subject</th>
<th>Duration</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kruis, 1997</td>
<td>Probiotics</td>
<td>120</td>
<td>120 human subjects with chronic UC</td>
<td>12 weeks</td>
<td>500 mg mesalazine t.d.s. or 200 mg E. coli Nissle</td>
<td>Probiotic treatment is an alternative option in maintenance therapy for UC. Relapse rate: 11.3% and 16.0% mesalazine and E. coli Nissle, respectively</td>
<td>Double-blind comparison</td>
</tr>
<tr>
<td>Langmead, 2004</td>
<td>Aloe Vera</td>
<td>44</td>
<td>44 human subjects with active UC</td>
<td>4 weeks</td>
<td>Aloe vera gel 100 mL twice daily</td>
<td>Reduces histological disease activity and provides inflammation inhibiting properties. More research is needed to see if the results stop if the intervention ceases</td>
<td>Double-blind, randomize, placebo controlled trial</td>
</tr>
<tr>
<td>Hanai, 2006</td>
<td>Curcumin</td>
<td>45</td>
<td>45 human subjects with UC</td>
<td>6 months</td>
<td>1 g curcumin twice daily plus mesalamine or placebo</td>
<td>Curcumin significantly improved both clinical activity and endoscopic indexes. Curcumin in combination with mesalamine was better in comparison to placebo. More research is needed to see if the results stop if the intervention ceases</td>
<td>Randomized, double-blind, placebo-controlled trial</td>
</tr>
<tr>
<td>Kanauchi, 2003</td>
<td>Germinated barley</td>
<td>21</td>
<td>21 patients with mild-moderate active UC</td>
<td>24 weeks</td>
<td>20-30 g of germinated barley foodstuff with continuation of baseline steroid treatment</td>
<td>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</td>
<td>Multicenter Open Trial</td>
</tr>
<tr>
<td>Kazi, 2009</td>
<td>Saffron (croetin</td>
<td>10</td>
<td>10 female BALB mice induced with UC</td>
<td>8 days</td>
<td>25, 50, or 100 mg/kg/d of croetin</td>
<td>50mg/kg/d was the most effective dose of croetin 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 the results stop when intervention ceases</td>
<td>In vivo trial</td>
</tr>
</tbody>
</table>
Table 3. The effects of functional food ingredients on Crohn’s Disease

<table>
<thead>
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<th>Reference</th>
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</thead>
</table>

Phytochemicals 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 include 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 can alter gastrointestinal (GI) pathogens such as Salmonella enterica and E. coli, at low concentrations [71]. Ficus bengalesis refers to the “banyan tree” which produces sap from the bark that also has an antioxidant phenolic compound which 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 a drug due to its medical usage. Now that fecal material is 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 on 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. This strain has been reported to be equivalent to the 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. In this study, they discovered there was a protective modulation of metabolites along the gastrointestinal tract which reduced colitis [88]. This species and *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 (TNFα) which can induce apoptosis or block growth factors and induce remission of IBD [91]. Adalimumab is anti-TNFα, which has been shown to maintain remission in CD, even in severe cases [92]. With respect to CDI (*Clostridium difficile* infection) and especially IBD, vancomycin treatment is often successful. In a study conducted by Horton et al., subjects treated with this antibiotic demonstrated fewer readmissions and shorter 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 may 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 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 which prevents symptoms of Crohn’s disease and regulates α4 integrin whose expression in endothelium luminal cells causes inflammation in IBD [103]. Vedolizumab is a monoclonal antibody which, like Natalizumab, is specific towards αβ7 integrin and is involved in the inflammation of the intestinal epithelium [104]. Vedolizumab can induce clinical remission and mucosal healing within a year of exposure [105]. Furthermore, 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 required for patients to benefit [106]. Overall, medications and/or antibiotics can have positive therapeutic effects.

Herbal therapy has been categorized as a natural agent supporting IBD treatment. Herbal therapy is a complementary and alternative medicine (CAM) therapy which is administered outside of centers providing conventional medicine [107]. A study investigating the effects of herbal medicine in IBD patients indicates 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 contributes to the relieving of diarrhea, rectal bleeding, body weight loss, and colonic inflammation [110]. Changtai granules (CTG) exhibit anti-diarrheal, anti-inflammatory, antibacterial, and analgesic effects [110]. Xilei-san (traditional Chinese herb) is another type of TCM discovered to reduce inflammation in colitis patients when administered together with mesalazine or corticosteroids in a clinical trial; 86% of the patients went through remission, thereby suggesting that Xilei-san has 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 to be 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 MSCs 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 the 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**

<table>
<thead>
<tr>
<th>Alternative Therapies</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
</table>
| Probiotics [117]      | • Adding beneficial bacteria, in the digestive tract may have beneficial effect against IBD  
• There is some evidence to support these claims | • Research is limited  
• Does not have significant evidence to support the benefits of probiotics  
• Probiotic therapy is not regulated by the FDA  
• May have unknown side effects |
| Fish Oil [118]        | • Fish oil present anti-inflammatory activities  
• Combining fish oil with aminosalicylates increases effectiveness | • 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]       | • Acts as a natural anti-inflammatory for UC | • May cause diarrhea  
• Aloe Vera therapy is not regulated by the FDA  
• May cause unknown side effects |
| Turmeric [120]        | • The active ingredient in turmeric, curcumin, has been used in clinical trials of UC and have shown promising results | • Not significant evidence to support the claims  
• Turmeric therapy is not regulated by the FDA  
• May cause unknown side effects  
• Research is limited |
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 which have investigated different pharmacological immunotherapies, 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. Accordingly, functional analysis should be used to observe metabolic shifts in intestinal microenvironments of IBD. Functional analysis is a method of studying interactions between microbes and diseases to analyze microbiome biological properties [122]. Existing biomarkers that distinguish CD from UC are limited in predicting the long-range course of a disease [123]. Therefore, research should focus on identifying markers of prognosis [123]. A healthy diet can also influence IBD, especially with the 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 a significant and important disease, research should continue to be undertaken. Research and studies will be difficult and time-consuming as microbiota evolve and can become resistant to treatment. However, 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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REFERENCES


59. Ferguson LR. Nutritional Modulation of Gene Expression: Might This be of Benefit to Individuals with Crohn’s Disease? Frontiers in Immunology. 2015; 6:467.


95. Zaura E, Brandt BW, Teixeria de Mattos MJ, et al. Same Exposure but Two Radically Different Responses to Antibiotics: Resilience of the Salivary Microbiome versus Long-


