



# Alternative Therapies for Inflammatory Bowel Diseases: The Growing Popularity of Nutritional Plans and Supplementation

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## Abstract

Crohn's disease (CD) and ulcerative colitis (UC) are inflammatory bowel disease (IBD). IBD is a long-term chronic disease that affects the gastrointestinal tract and causes inflammation. While these conditions have largely been associated with the industrialized world, they are increasing in prevalence and incidence worldwide. [1] UC refers to inflammation involving the colon. CD refers to transmural ulceration from the mouth to the anus, most often involving the terminal ileum. The severity of each disease phenotype can vary greatly among patients. At least up to 21% of patients with IBD use alternative treatment outside of the medications to supplement their medications [2]. Recent advances in the area of biologics and the use of the JAK-STAT pathway have significantly improved the natural history of patients suffering from IBD. However, recent data have shown that up to 50% of patients do not respond to therapy and up to 80% fail to achieve remission even with the most advanced therapies. [3,4,5,6] For this reason, many patients turn their hopes for a better quality of life to alternative therapies and various dietary programs. There is emerging evidence for diet and its role in inducing and maintaining remission, and recently dietary interventions have received a higher allocation of research dollars. In addition, patients often look for supplements or probiotic products to augment their pharmaceutical strategies for inducing or maintaining remission. As with diet, there is emerging information on supplements such as Qing Dai (QD, Indigo) and curcumin. [7] We will also discuss probiotics, which have undergone extensive research as potential adjunct therapies in IBD. Products containing these ingredients and other molecules are seeing significant interest in the private equity space because of studies with early, promising data with small patient cohorts. This article reviews the up-to-date information regarding dietary research and promising alternative therapies in the induction and maintenance of remission in IBD.

**Keywords:** Crohn Disease (CD); Ulcerative Colitis (UC); Curcumin, Qing Dai, Micronutrients, Macronutrients, Mild Colitis, Omega-3 fatty acids, Exclusive Elemental Diet, Vitamin D and Zinc, Irritable Bowel Syndrome (IBS); C-reactive Protein (CRP); Fecal Calprotectin (FC); and Complementary and alternative medicines (CAM)

## Introduction

With the advancement of research, patients with inflammatory bowel disease (IBD) have more medical and surgical options than ever. However, even with the medications currently available, up

to 80% of patients fail to reach remission with the use of modern medicines including biologics. [8,9,10] Conventional medicines for the treatment of IBD remain cost prohibitive in addition to side effects. While there is significant interest from patients regarding

the use of alternative complementary strategies, such as diet and supplements, the evidence is not as robust as for medications. This often leads to frustration among patients as clinicians are unable to provide evidence-based recommendations regarding these alternate strategies. In this review, we will highlight the up-to-date evidence and future directions for alternative complementary IBD.

## Supplements

### Curcumin and Qing Dai Products

The primary active polyphenol in turmeric root is curcumin. Cultures globally have historically regarded it as a powerful anti-inflammatory agent. Many believe its benefits stem from anti-inflammatory, antioxidant, and anticarcinogenic properties. These mechanisms influence various cellular processes, including the NF $\kappa$ B inflammatory pathway, and potentially alter gut microbiota [11]. The authors of a systematic review and meta-analysis by Yin et al. looked at six randomized trials that used curcumin and found that it was safe to use in all six of them. While it was able to induce clinical remission in CD (RR = 2.10, 95% CI 1.13 to 3.89); there was no evidence of clinical improvement or mucosal healing. [12] While these results are noteworthy, current medical standards prioritize achieving both mucosal healing and histological remission. Persistent microscopic inflammation from IBD can progress into dysplasia and eventually lead to adenocarcinoma if the intestinal lining does not fully heal. Consequently, clinicians now target “deep remission,” which specifically requires the successful healing of the mucosa [13].

Since the 1960s, traditional Chinese medicine has used Qing Dai for ulcerative colitis (UC). Qing Dai is a dried powder made from several plants. It is made up of natural ingredients like indirubin, indigo, isoindigotin, and nimbosterol. [14] Indirubin has been implicated in the downregulation of the NF $\kappa$ B pathway resulting in anti-inflammatory effects. Additionally, studies have demonstrated that indigo specifically affects the aryl-hydrocarbon receptor (AhR) pathway through its biochemical effects. Indigo acts as a ligand at AhR, resulting in increased expression of IL-22. It is believed that this effect enhances mucosal regeneration, thereby promoting mucosal healing [15].

The most compelling evidence for the use of Qing Dai to date was a double-blinded placebo-controlled clinical trial presented at the Crohn's and Colitis Congress in 2023. This was an open-label study of 4 weeks of treatment using a combination of curcumin and Qing Dai. People in Israel and Greece who had active UC (as defined by an SCCAI score of 5 or more) and a Mayo endoscopic sub score of 2 or more were asked to take part in this study. They administered a 2:1 ratio of either oral enteric-coated curcumin and Qing Dai (3g/day) or placebo to these patients for a total of eight weeks. At 8 weeks, the primary outcome was to see if there was clinical response (a drop in SCCAI of at least 3 points) and objective response (an improvement in the Mayo endoscopic sub score of at least 1 or a 50% drop in calprotectin from baseline). Patients who

did respond continued their original intervention, whether it was the intervention or placebo, for an additional 8 weeks. Rectal mucosa expression of Cyp1A1 was followed by measuring AhR pathway activation. In the initial efficacy analysis of part one of the two-part study, 70% had a clinical response including 30% achieving clinical remission. Part two of the study screened 95 patients, including 42, and randomized them. Of these, 43% of the intervention patients and 8% of the placebo patients achieved the co-primary outcome (p=0.033). One interesting thing about this study is that 75% of people who took the supplement showed endoscopic improvement, which is defined as a decrease of 1 or more points on the endoscopic Mayo sub score. Only 20% of people who took the placebo showed endoscopic improvement (p=0.036); and the rate of adverse events was the same in both groups. The group ultimately observed a clinical response in 85.7% of those receiving curcumin and Qing Dai versus 30.7% of those receiving placebo (p<0.001). Mechanistically, the group observed upregulation of the AhR pathway determined by increased expression of CYP1A1 in the rectal mucosa. Patients receiving placebo, 5-ASA, or biologics did not exhibit this [16]. This was the largest randomized, placebo-controlled study involving a nutritional supplement to find statistically significant efficacy (p=<0.001) with respect to clinical response and clinical remission (p=0.01). Additionally, the study found objective improvement with a reduction in the inflammatory marker calprotectin (p=0.08) and endoscopic improvement (p=0.03). This randomized controlled trial showed that a combination of curcumin and Qing Dai was effective for inducing remission in active UC and that the AhR pathway may be a target for potential treatment in active UC.

While this data is promising, it is important to note that these supplements do not come without their own side effect profiles. In the study, the authors state that their clinical protocol involves induction with 8 weeks of the curcumin-Qing Dai combination followed by curcumin monotherapy for maintenance. Studies have linked chronic Qing Dai consumption to pulmonary arterial hypertension, gastrointestinal symptoms such as intussusception, and elevated liver enzymes. In this study, adverse events were discovered in 91 patients (10.3%). Elevation in liver enzymes was the most common adverse event (43.9%). These elevations were found to be mild and reversible. [17] It is also important to note that the primary endpoint, endoscopic improvement, is not equivalent to mucosal healing or histologic improvement. There is not yet sufficient data to globally recommend Qing Dai or curcumin supplements for IBD patients.

### 4.2. Omega-3 Fatty Acids

Omega-3 fatty acids have historically been used for several inflammatory conditions. A study by Seidner et al. examined the use of omega-3 fatty acids in addition to vitamin E, vitamin C, and selenium in patients with mild-to-moderate disease. This randomized controlled trial assigned patients to an oral supplement including Omega-3s, vitamin E, vitamin C, and selenium or to placebo. Both groups were found to have statistically significant

improvements in the disease activity index (DAI); but only patients taking the oral supplement were found to require decreased doses of prednisone to control their clinical symptoms. [18] This formulation could therefore be useful as an adjunctive therapy to reduce glucocorticoid requirements.

Notably, a systematic review by Lev-Tzion et al. also found that there was an improvement in maintaining remission in CD when evaluating six total studies (RR 0.77, 95% CI 0.61 to 0.98). However, four of these studies had an unclear risk of bias. When the authors evaluated the two largest and lowest risk of bias studies, there was no statistically significant difference between the intervention group and placebo for maintaining remission in CD. [19] There is conflicting data regarding the efficacy of omega-3 fatty acids thus resulting in its exclusion from the guidelines. The evidence is more robust in other systemic autoimmune conditions such as rheumatoid arthritis (RA), psoriasis, or psoriatic arthritis. [20] In psoriatic arthritis, omega-3 fatty acids fared better than olive oil and had objective decreases in inflammation marker leukotriene B4 ( $p = 0.004$ ). There was also a significant reduction in the use of non-steroidal anti-inflammatory drug (NSAID) and paracetamol compared with controls ( $p = 0.04$ ) to alleviate clinical symptoms. [21] Based on these findings, researchers suggest that omega-3 fatty acids might help treat enteropathic arthritis related to IBD. Nevertheless, further studies are necessary to verify the effectiveness of omega-3 fatty acids for this specific condition [22-25].

### Probiotics in Inflammatory Bowel Disease

Changes in the intestinal mucosa and microbiota may alter the homeostasis between gut flora and the human immune system. [26] This along with genetics and environmental conditions may lead to the pathogenesis of IBD. [27,28] Specific intestinal microbes have been associated with active disease. [29] Researchers have found that compared to healthy controls, CD and UC patients have fewer Firmicutes and Bacteroidetes and more Proteobacteria and Actinobacteria. [29,30] Probiotics have been used for supplementation in these conditions. Probiotics are believed to enhance epithelial integrity, suppress inflammatory bacterial byproducts, and potentially decrease the production of mucin [30,31,32].

One of the most popular formulations of probiotics used in IBD is known as Visbiome®/VSL #3 ® made by Sigma-Tau Healthscience/Alfasigma. One randomized control trial in CD looked at VSL#3 and prevention of CD after surgery. This study demonstrated that early VSL#3 administration was associated with later recurrence after surgery. There were no statistical differences in endoscopic recurrence rates at day 90 between patients who received VSL#3 and patients who received placebo. Levels of inflammatory cytokines and recurrence rates leading to repeat surgery were lower among patients who received early VSL#3 for a total of one year. This indicated that this probiotic should be further

investigated for prevention of Crohn's disease recurrence. [33,34] Patients with UC who have had a total proctocolectomy and ileal pouch-anal anastomosis (IPAA) may be less likely to develop acute pouchitis if they take VSL#3 with Lactobacillus, Bifidobacterium, and Streptococcus. Furthermore, four clinical trials have demonstrated the potential of VSL#3 in preventing chronic pouchitis [35-38].

The future of IBD probiotics may lie in genetically modified bacteria designed to synthesize therapeutic compounds. These specialized organisms would detect intestinal inflammation in real-time and respond by releasing anti-inflammatory molecules directly at the site of the flare. This advancement could offer a more tailored approach to care, providing internal therapeutic benefits exactly where needed instead of relying on external biologic medications [39].

### Vitamins and Micronutrients

Both vitamin D and zinc are known to be vital to physiological enzymatic reactions and the immune system. In IBD, it is known that the 25(OH)D receptor is downregulated. It has therefore been postulated that 25(OH)D may be useful as a predictive marker for disease improvement in IBD. With respect to CD, it is thought that lack of vitamin D is related to the bowel being unable to absorb significant inflammation. Serum 25(OH)D levels and zinc were examined in one retrospective study which found that CD patients with clinical or deep remission had significantly higher levels of serum 25(OH)D. In patients with UC, there was only a correlation with clinical remission. There was no correlation in disease activity with zinc in this study. 25(OH)D may be useful as a non-invasive marker of disease activity in IBD [40].

Vitamin D deficiency is more often associated with CD. There are emerging data suggesting a novel role for vitamin D in immune homeostasis and improved ability to control chronic inflammation. One clinically applicable study by Caviezel et al. compared IBD patients' 25-OH-D3 levels to those of patients with irritable bowel syndrome (IBS). It was found that vitamin D deficiency is common among all IBD patients. Patients with CD showed a significant decrease in 25-OH-D3, more so than those with UC. There was also a significant inverse association between C-reactive protein (CRP) and fecal calprotectin (FC) with 25-OH-D3 that was observed. This lends further credit to vitamin D as a predictor of disease improvement or activity [41].

Zinc is absorbed as an essential micronutrient in the small intestine with both anti-inflammatory and antioxidant properties. Patients with autoimmune disease have been shown to have lower serum and plasma levels of zinc. [42] There is evidence that up to 15% of IBD patients have some level of zinc insufficiency. [43] Research has linked zinc deficiency to poor clinical outcomes in both CD and UC. Siva et al. linked insufficient zinc to an increased risk of subsequent hospitalizations, surgeries, and disease-related complications in their study. Siva et al. also noted that normalizing

zinc levels was associated with improved outcomes for both UC and CD patients. This finding does support regular monitoring of zinc and replacement as indicated [44]. Manganese and selenium are trace minerals that have been shown to provide beneficial effects in studies examining experimental colitis. [45] Specifically, Choi et al. demonstrated that manganese-deficient mice with dextran sulfate sodium (DSS)-induced colitis had more severe weight loss and absence of recovery than manganese-adequate mice. They postulate that manganese helps maintain intestinal barrier integrity and limits existing colitis. [46] Selenium has been implicated in mitigating inflammation and can also influence the composition of gut microbiota. It is thought that selenium supplementation may have an anti-inflammatory effect via upregulation of the PPAR $\gamma$  pathway [47].

## Diet

### Mediterranean Diet

Although data have not favoured any singular diet decreasing the rate of flares in adult IBD patients, updated clinical practice guidelines by the American Gastroenterological Association (AGA) recommend that all patients without contraindications should be on a Mediterranean diet. [48] The benefits of this diet, which includes a variety of monounsaturated fats, complex carbohydrates, lean proteins, and foods that have been minimally processed, are thought to improve the gut microbiome and metabolome, which leads to lower rates of comorbid disease.

Several studies supported this practice recommendation. In a clinical trial by Chicco et al., 84 UC and 58 CD patients adhering to a Mediterranean diet were followed for 6 months. In conjunction with stable therapy, rates of active disease improved to 6.8% from 23.7% with UC and to 3% from 17.6% with CD patients. Inflammatory markers, BMI, waist circumference, and rates of liver steatosis of any grade also improved. [49] Another study showed no statistical difference between the Mediterranean diet and another well-known diet discussed below, the specific carbohydrate diet (SCD); in achieving responses in symptomatic remission, FC, and CRP. [50] The Mediterranean diet therefore provides a dietary option that is more likely to be adhered to than comparatively more complex diets such as SCD.

### Exclusive Enteral Nutrition

One of the most frequently researched dietary strategies for Crohn's disease and ulcerative colitis is exclusive enteral nutrition (EEN). This approach utilizes a specific formula-based regimen that prohibits all other food and beverages. The paediatric population largely studied this and found that it occasionally led to clinical remission, maintenance, and induction [51]. One study by Lee et al. compared EEN, tumour necrosis factor alpha inhibitors (anti-TNF); and partial enteral nutrition (PEN) in 90 children with active Crohn's disease. They found that EEN and anti-TNF had comparable rates of clinical response, defined as PCDAI reduction greater than 15 or final PCDAI of less than 10. Similarly, they found that EEN and

anti-TNF significantly reduced fecal calprotectin [52]. In addition, studies have shown that the use of EEN in paediatric CD has been associated with decreased long-term risks of corticosteroid dependency and hospitalization in comparison with corticosteroid use [53].

The evidence for the effectiveness of EEN in the adult population has increased recently. In one study, 32 patients with active disease who completed 2 weeks of EEN had significant improvement in disease symptoms, serum CRP, IGF-1, and FC. These effects were largely sustained over an additional 6 weeks of intervention. [54] Another study compared biologic therapy with EEN versus biologic therapy alone. They found that the biologic-EEN group achieved higher rates of clinical response, clinical remission, and endoscopic response. This finding was sustained in maintenance [55].

It is believed that the EEN diet can improve nutritional deficiencies, correct dysbiosis, and have anti-inflammatory effects. One systematic review showed improvements in clinical, biomarker, endoscopic, and radiologic measures of disease activity in patients with IBD. Preoperative EEN administration has demonstrated a reduction in postoperative recurrence and complications. One major drawback to EEN is non-compliance. Compliance rates typically range from 50 to 80% [56].

### Crohn's Disease Exclusion Diet

One specific type of diet for CD is the Crohn's disease exclusion diet (CDED). The CDED, a whole food diet, aims to restrict foods that result in dysbiosis or alter the intestinal barrier. CDED is an approach that which specifically defines oral intake, via oral supplement or whole food, over three separate phases while also restricting particular foods. The restrictions lessen as the patient advances through these three phases. [48] In a prospective trial, CDED alone was compared to CDED plus partial enteral nutrition (PEN). The results demonstrated that CDED, with or without PEN, was effective for induction and maintenance of remission for biologic naïve CD patients with mild-to-moderate disease [57].

A randomized controlled trial compared CDED plus PEN with EEN in paediatric CD patients with mild to moderate disease. This group found that CDED plus PEN and EEN patients both achieved clinical remission at a significant and similar rate at week 6. However, once EEN patients transitioned to EEN and subsequently a free diet, they had recurrence of inflammatory biomarkers including fecal calprotectin. Additionally, once a regular diet was resumed, their microbiome composition reverted to its baseline state. At week 12, CDED plus PEN patients had significantly improved rates of maintenance of remission and a continued decrease in fecal calprotectin. This provides evidence that the foods excluded by CDED may drive dysbiosis and thus inflammation.

They also demonstrated a statistically significant difference in tolerance of the CDED diet compared to the EEN diet. At week 6, there was no statistically significant difference in compliance between the groups. This may explain the comparable rates of

clinical remission at week 6. However, once reintroduction of unrestricted table foods occurred in the EEN group after week 6 the groups diverged. The tolerance of CDED is key to the diet's success as increasing adherence to dietary therapy is associated with achieving clinical remission [58].

### Specific Carbohydrate Diet

The Specific Carbohydrate Diet (SCD) originated in the 1920s and was popularized by Elaine Gottschall. The primary consideration in the SCD is the exclusion of disaccharides and polysaccharides. Notable exclusions from this diet include lactose, sucrose, food additives, maltose, and preservatives. Notable foods included are meat, oil, nuts, and fruits [59].

Studies in paediatric patients have shown both clinical remission and improvement in inflammatory biomarkers with SCD. [60] Another paediatric study followed 10 patients with CD for one year on SCD. They found clinical improvement and mucosal improvement via video capsule endoscopy at both 12 and 52 weeks [61].

A randomized trial compared the SCD and Mediterranean diets in CD, with the primary outcome being clinical remission at week 6. Both groups were found to have symptomatic improvement at week 6 and neither group was found to have a statistically significant change in CRP at week 6 or 12. These authors postulate that the Mediterranean diet may be preferable over the SCD due to its easier adherence and extraintestinal health benefits [62].

### Low FODMAP Diet

The low FODMAP diet focuses on foods low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols, which form the acronym FODMAP. People often use this diet to improve symptoms of irritable bowel syndrome (IBS). An Italian randomized trial demonstrated that short-term low-FODMAP protocols enhanced disease activity scores and lowered calprotectin levels in IBD patients. The quality of life also showed a mild improvement. However, it should be noted that the patients in this trial either had mild disease activity or were in remission. [63] Other randomized control trials have found improvements in symptoms without statistically significant improvements in inflammatory markers. [64,65] It is important to note that studies have found that organisms that are reduced via the low FODMAP diet are associated with both clinical and endoscopic remission [66,67]. Clinicians must weigh the potential nutritional risks of restrictive protocols like the low FODMAP diet, particularly for IBD patients who face an existing threat of malnutrition. Because research regarding its efficacy remains inconsistent, this diet should be implemented carefully and viewed as a short-term measure. In each study, it has been used temporarily prior to the reintroduction of restricted foods, either gradually for responders to gain tolerance or immediately for non-responders. Recent AGA guidelines suggest utilizing low-FODMAP diets potentially during active flares but with a return to a Mediterranean diet thereafter

[48].

### Fiber-Restricted Diet

Newer clinical practice guidelines are deviating from long-held recommendations in support of fiber-restricted diets. These diets are limited in variety and may contribute to negative outcomes in nutritional status, gut microbiome composition, and CD remission rates. [68] Therefore, the vast majority of IBD patients do not require fiber restriction. Fiber restriction does maintain a role in IBD patients with intestinal strictures or other symptomatic disease flares who are unable to achieve food consistency through additional food processing steps that may limit these symptoms [48].

### Conclusions and Future Direction

IBD is associated with a state of malnutrition in micro- and macronutrients. [69] There have been significant advances and better understanding of the effect of dieting in IBD patients. This rising evidence has thus led to greater priority on dietary interventions in the treatment of IBD patients. While each patient's treatment plan should be individualized, clear recommendations are emerging surrounding dietary interventions in IBD as the recent AGA Clinical Guidelines have outlined. Evidence has shown that dietary therapy can be useful both as primary therapy or complementary to pharmacotherapy. It is essential for practitioners to be cognizant of the evidence surrounding dietary therapy in IBD and to work closely with patients and dieticians for individualized patient plans. As modern medicine continues to progress, there is increasing interest and research in the realm of alternative therapies. It is now clearer that diet, use of supplements, and the manipulation of IBD patients' microbiota may eventually become commonplace in the treatment of the disease.

### Future directions

Nutritional strategies and supplements remain subjects of vibrant interest and hold great potential for preventing or managing IBD. A primary objective in IBD care is to pair the appropriate dietary or supplemental plan with a patient's specific disease characteristics and their existing medication. While the choice of therapy depends on the individual, it is certain that a one-size-fits-all strategy is not effective for these patients. Furthermore, increasing evidence suggests these alternative approaches can therapeutically alter gut microorganisms. Consequently, managing a patient's microbiota will necessitate a more precise method than current knowledge of host-flora interactions currently permits. Future progress requires long-term, intervention-focused research to determine how different dosages of supplements and diets impact disease severity. Achieving this is challenging due to the clinical intricacies of IBD. Patients with coexisting IBS can also significantly confound studies based on subjective improvements in interventions. Additionally, the fact that the success of dietary changes can fluctuate depending on a patient's current disease load introduces further complications. The synergistic therapeutic

effects of combining medications with diet and nutritional therapies show promise. This approach is underutilized by providers and may benefit patients with IBD [70,71].

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