The Use of Complementary and Alternative Medicine in Patients With Inflammatory Bowel Disease

Steven C. Lin, MD, MPH, and Adam S. Cheifetz, MD

Dr Lin is a clinical fellow in gastroenterology and hepatology at Beth Israel Deaconess Medical Center in Boston, Massachusetts. Dr Cheifetz is an associate professor of medicine at Harvard Medical School in Boston, Massachusetts and director of the Center for Inflammatory Bowel Disease at Beth Israel Deaconess Medical Center.

Address correspondence to:
Dr Adam S. Cheifetz
Center for Inflammatory Bowel Disease
Beth Israel Deaconess Medical Center
Harvard Medical School
330 Brookline Avenue
Boston, MA 02215
Tel: 617-667-2136
E-mail: acheifet@bidmc.harvard.edu

Keywords
Complementary and alternative medicine, Crohn's disease, ulcerative colitis, herbal supplement, curcumin, cannabis, acupuncture, exercise, probiotics

Abstract: Complementary and alternative medicine (CAM) includes products or medical practices that encompass herbal and dietary supplements, probiotics, traditional Chinese medicines, and a variety of mind-body techniques. The use of CAM in patients with inflammatory bowel disease (IBD) is increasing as patients seek ways beyond conventional therapy to treat their chronic illnesses. The literature behind CAM therapies and their application, efficacy, and safety is limited when compared to studies of conventional, allopathic therapies. Thus, gastroenterologists are often ill equipped to engage with their patients in informed and meaningful discussions about the role of CAM in IBD. The aims of this article are to provide a comprehensive summary and discussion of various CAM modalities and to appraise the evidence for their use.

Complementary and alternative medicine (CAM) consists of products and medical practices or disciplines that are not considered mainstream, or conventional, medicine.[1,2] CAM can include herbal therapy or phytotherapy, dietary supplementation, probiotics, Chinese medicinal practices (eg, herbal supplements or acupuncture), mindfulness, or other mind-body therapies. As the names imply, nonmainstream treatments used in conjunction with conventional (allopathic) medical therapy are considered complementary, whereas nonmainstream therapies used in lieu of conventional treatments are considered alternative.[2]

The use of CAM has increased in popularity over the past several decades, particularly in Western societies (specifically in North America and Europe).[3] This increase in the use of CAM is particularly true in patients with chronic diseases, such as inflammatory bowel disease (IBD).[2,4] Discordant with this trend is most gastroenterologists' knowledge of CAM and their ability to engage in informed discussions with patients who are interested in or who use CAM.[1,2] One of the major issues is the lack of well-designed, randomized,

controlled trials (RCTs) studying the safety and efficacy of CAM. Furthermore, the data behind CAM vary and are based mostly on survey studies, case reports, and case series, and only a few well-designed RCTs.[5] The aims of this article are to describe some of the most commonly used CAM therapies and summarize the data presently available on their safety and efficacy in order to better prepare gastroenterologists to engage with patients in discussion of this topic.

Epidemiology of Complementary and Alternative Medicine Use in Patients With Inflammatory Bowel Disease

The estimated prevalence of CAM use in patients with IBD is high, ranging between 21% and 60%.[1,4,6,7] Reasons for CAM use include a desire for holistic approaches to supplement conventional therapy[2,8]; the perception that herbal remedies are more natural, less toxic, or harmless; a lack of response to or undesirable side effects of conventional therapy[6,7]; and the desire for more control of the disease and symptoms to improve quality of life (QOL).[3,9] Predictors of CAM use include psychiatric comorbidities; dissatisfaction with the patient-doctor relationship; side effects from conventional therapies; use of CAM among friends or family[8]; vegetarianism; longer disease duration; high corticosteroid usage; female sex; and higher income, education, and socioeconomic status.[3,10,11] There is also geographic variation with regard to CAM use.[1,10] In the United States, CAM is more frequently used in the Mountain, Pacific, and Midwest regions compared to other parts of the country.[2]

However, despite the widespread use of CAM, up to 75% of patients with IBD do not discuss their usage of CAM with their physicians.[8,11] Some patients regard taking vitamins and supplements as normal practices and, thus, do not disclose this use.[1] Poor patient-doctor relationships may also deter open discussion, as well as physicians' lack of knowledge of CAM.[9] Being unaware of CAM use in IBD patients can be detrimental, as certain oral CAM therapies may have side effects, interactions, or organ-specific toxicities.[9] CAM use has also been associated with worse compliance with conventional therapies.[7,12]

Most CAM therapies fall into one of the following main categories: (1) herbal/botanical or dietary supplements and (2) mind-body practices, including hypnosis, yoga/exercise, mindfulness, and stress reduction. The most commonly used CAM therapies include probiotics, herbs (including Chinese medicines, curcumin, and cannabis), vitamins, and fish oil.[1,13] Other therapies include the use of traditional Chinese practices such as acupuncture and moxibustion.

Probiotics

Probiotics are among the most popular CAM therapies and come in various forms, including single or multiple strains of bacteria and/or yeast.[1] The probiotic market has grown rapidly over the past decade. However, the current regulation of probiotics—as well as of most herbal and dietary supplements—is inadequate to protect consumers and doctors, as different formulations can vary tremendously in quality and potency.[14] Probiotics are thought to be anti-inflammatory and to impact immune-modulatory pathways, such as by downregulating the expression of Toll-like receptors and inflammatory cytokines as well as by inhibiting the phosphoinositide 3-kinase/Akt pathway and the nuclear factor κ–light chain enhancer of activated B cells (NF-κB) pathway.[15,16]

The most robust data for the use of probiotics in IBD are for the prevention of recurrent pouchitis, an inflammatory condition of the ileal pouch–anal anastomosis (IPAA) that occurs in over 50% of patients after surgery.[17] Pouchitis is likely caused by aberrant immune responses and bacterial dysbiosis.[1] VSL#3 is the most-studied probiotic. It is a high-concentration probiotic preparation of 8 live bacterial strains: *Streptococcus thermophilus*, 4 strains of *Lactobacilli* (*L paracasei, L plantarum, L acidophilus,* and *L delbrueckii*), and 3 strains of *Bifidobacteria* (*B longum, B breve,* and *B infantis*). This probiotic appears to work by decreasing tumor necrosis factor (TNF)-α, interferon-γ, and matrix metalloproteinases 2 and 9.[16]

Prevention of a First Episode of Pouchitis and of Recurrent Pouchitis

One RCT suggested that VSL#3 decreased the risk of developing a first episode of acute pouchitis within a year after an IPAA.[18] Forty patients were randomized to either VSL#3 (900 billion bacteria daily) or placebo immediately following an IPAA. Fewer patients receiving VSL#3 vs placebo developed their first episode of pouchitis over 12 months (10% vs 40%; $P<.05$). Furthermore, VSL#3 may decrease the risk of recurrent pouchitis. Mimura and colleagues reported in a small RCT (N=36) that 85% of patients taking VSL#3 at 6 g daily (300 billion bacteria/g) vs 6% of patients on placebo maintained remission after 12 months of follow-up.[19] However, not all studies have had positive findings. In a cohort of 31 patients with antibiotic-dependent pouchitis who were placed on VSL#3 6 g/day following 2 weeks of ciprofloxacin, 80% of patients stopped taking the probiotic due to recurrence or adverse effects (bloody bowel movements, constipation, bloating, gas in 2 patients).[20] The 20% of patients who continued taking VSL#3 remained in clinical remission at 8 months, although without significant improvement of endoscopy scores.

Induction of Remission in Active Mild-to-Moderate Ulcerative Colitis

There is some evidence that certain probiotics, especially VSL#3, may be effective for achieving clinical response and remission in mild-to-moderate ulcerative colitis (UC). In a RCT (N=147), more patients with active mild-to-moderate UC receiving VSL#3 (900 billion bacteria/day) at 6 weeks had 50% improvement in the Ulcerative Colitis Disease Activity Index (UCDAI) compared to those receiving placebo (32.5% vs 10.0%; *P*=.001). At week 12, 42.9% of patients on VSL#3 achieved remission vs 15.7% of patients in the placebo group (*P*<.001).[21] Similar results were reported from a RCT conducted by an Italian group around the same time.[22] A meta-analysis found that VSL#3, when added to conventional therapy at a dose of 3.6×10^{12} colony-forming units/day, is safe and more effective than conventional therapy alone in achieving higher rates of response and remission in patients with mild-to-moderate UC.[23]

A positive signal has been observed with other probiotic formulations as well. Tamaki and colleagues conducted a RCT investigating the efficacy of *B longum* 536 for induction of remission in active mild-to-moderate UC.[24] Although there was no difference in remission rates, UCDAI scores decreased by more points in the probiotic group vs the placebo group (3.8 vs 2.6 points; *P*<.01).[24] However, in a RCT using nonpathogenic strains of *Escherichia coli* Nissle 1917 in patients with active UC as an add-on to conventional therapies, no benefit was seen in the probiotic group.[25]

Maintenance of Remission in Ulcerative Colitis

In patients with quiescent UC, the current literature suggests that probiotics may also reduce rates of relapse.[16,26] The only RCT studying the add-on use of VSL#3 (weight-based 450-1800 billion bacteria/day) to a 5-aminosalicylate (5-ASA) in the maintenance of remission involves a small pediatric cohort (N=29) with mild-to-moderate UC.[27] Fewer patients treated with VSL#3 (21.4% vs 73.3%) relapsed within 1 year of follow-up. At 6 months, 12 months, and time of relapse, endoscopic and histologic scores were lower in the VSL#3 group. Another RCT compared *Lactobacillus* GG (18 billion bacteria/day) use with 5-ASA therapy, and found no added benefit when using both therapies together in terms of relapse rate in adult patients with quiescent UC.[28] Overall, the choice of probiotic varies across existing studies, and the optimal dose, duration, and mode of administration are still unclear.[16,26]

Crohn's Disease

In Crohn's disease (CD), the data on the efficacy of probiotics for inducing or maintaining remission are very limited. In a RCT of 119 patients with CD randomized to VSL#3 (900 billion bacteria/day) or placebo within 30 days after ileocolonic resection and reanastomosis, no difference in the proportion of patients with severe endoscopic lesions was observed at 90 days.[29] However, the VSL#3 group had lower mucosal inflammatory cytokine levels than the placebo group. Overall, 2 recent meta-analyses found no benefit associated with probiotics in patients with active CD or for preventing relapse, nor in patients with postoperative CD.[16,26]

As previously discussed, probiotics vary in cost, formulation, potency, and efficacy in UC and CD, and require doses as high as 900 billion to 1.8 trillion bacteria daily. The Toronto consensus guidelines on the medical management of nonhospitalized patients with UC do not recommend probiotics to induce or maintain complete remission outside the setting of a clinical trial, attesting to the lack of larger, more robustly designed RCTs in this domain.[30] Limitations of probiotics, specifically VSL#3, include cost, the need for high potency administration to achieve efficacy, and the lack of coverage by insurance. Adverse events are rare and generally limited to bloating.[1,23]

Herbal and Dietary Supplementation

Curcumin (Turmeric)

Curcumin, a major phytochemical active ingredient of turmeric, is derived from a rhizomatous plant (*Curcuma longa)* of the ginger family. Curcumin has a characteristic yellow appearance and is a popular herbal remedy among patients with IBD. It has been shown to have anti-inflammatory and antioxidative properties on human lymphocytes and gut epithelial cell lines,[31] and reduces histologic features of inflammation and colitis in mice.[32]

A multicenter RCT (N=50) showed some benefit of curcumin in inducing remission in patients with active mild-to-moderate UC who had failed 5-ASA therapy. Lang and colleagues randomized patients with active mild-to-moderate UC despite oral and topical mesalamine therapy to either continued mesalamine and placebo or continued mesalamine and curcumin (3 g/day).[31] In this trial, 53.8% of patients who received curcumin vs 0% of the placebo group achieved clinical remission at week 4 (*P*=.01). Additionally, endoscopic remission (partial Mayo score ≤1) was observed in 38% of the curcumin group vs 0% of the placebo group (*P*=.043).[31] Curcumin may also be efficacious in maintaining remission in patients with UC on sulfasalazine or a 5-ASA. Hanai and colleagues randomized 89 patients with quiescent UC on sulfasalazine or a 5-ASA to receive curcumin (1 g twice daily) or placebo, and demonstrated that fewer patients in

the curcumin group relapsed during 6 months of follow-up (4.7% vs 20.5%; *P*=.04).[33]

The results of these trials should be taken with the caveat that investigators used very pure curcumin compounds. Retail brands and formulations may not be potent enough or may not be as pure.[34] Side effects of curcumin are mild and include bloating, nausea, and transiently loose stools.[31,35] Based on the aforementioned evidence and safety of curcumin, it can be considered as a complement to standard therapy in active and quiescent UC, but only as an additive in conventional treatment algorithms.

Cannabis (Medical Marijuana)

Marijuana is derived from the plant *Cannabis sativa* and has been used for centuries as a treatment for numerous ailments. It contains over 70 different cannabinoid compounds, but the 2 major active compounds include cannabinol and δ-9-tetrahydrocannabinol (THC).[1,36,37] In the United States, cannabis is a Schedule I substance, which means that it is illegal for both recreational and medicinal use, per federal law.[38] However, individual state laws have allowed marijuana for recreational use (in 9 states) and medical use (in 29 states) as of 2018.

Cannabis acts via the endocannabinoid system (ECS), which includes the cannabinoid receptors 1 and 2 (CB1, CB2). These can be activated by a variety of synthetic or plant-derived cannabinoids, as well as ligands of the ECS (anandamide and 2-arachidonoyl glycerol).[37,38] Animal models have shown that activation of CB1 and CB2 attenuates experimental colitis.[38] Furthermore, CB2 activation reduces reactive oxygen species production by the intestinal epithelium and decreases macrophage production of nitric oxide.[39] Patients with UC have experienced downregulation of their ECSs, with altered levels of endogenous anandamide and increased CB2 expression.[40]

The use of cannabis among patients with IBD is substantial, with up to 17.6% reporting prior or current use for disease symptoms; 84% of cannabis users report that it improves abdominal pain.[41,42] Approximately 10% to 15% of patients with IBD report active use, mostly for relief of symptoms (nausea, abdominal pain, and diarrhea).[1] These patients tend to have more active disease and prior abdominal surgeries and tend to use chronic pain medications and other CAM therapies.[43]

Small, observational, and prospective pilot studies indicate that cannabis use by patients with IBD generally improves QOL, general health perceptions, social function, and the ability to work, and may reduce corticosteroid use and Harvey-Bradshaw Index scores.[44,45] In a small prospective RCT, 21 patients with CD and Crohn's Disease Activity Index (CDAI) scores over 200 who had not responded to therapy with corticosteroids, immunomodulators, or anti-TNF agents were randomized to receive cannabis, twice daily, in the form of cigarettes (115 mg of THC) or placebo (cigarettes with cannabis flower, THC extracted).[46] Clinical response (CDAI decrease of >100) was observed in 90% of the cannabis group vs 40% of the placebo group (*P*=.028), and there was a significant increase in QOL in the cannabis group. However, the primary outcome of clinical remission was not met in the majority of patients, as only 45% of patients in the cannabis group vs 10% of patients in the placebo group achieved clinical remission (CDAI <150; *P*=.43). Furthermore, cannabis did not improve C-reactive protein (CRP). However, 19 of the 21 patients were able to distinguish which group they were assigned to due to the psychotropic effects of cannabis, essentially unblinding the study.

Since this initial RCT of cannabis, 2 other RCTs have been conducted. In a recent small RCT, 20 patients with active CD on various therapies were randomized to receive cannabidiol 20 mg/day or placebo. No significant difference in CDAI score was noted between the 2 groups after 8 weeks.[47] The more recent trial, by Irving and colleagues, showed that among patients with left-sided or extensive UC stable on 5-ASAs, a cannabidiol-rich botanical extract was superior to placebo in improving QOL outcomes, although remission rates at 10 weeks were similar between the 2 groups.[48]

Aside from the lack of objective evidence that marijuana decreases inflammation in IBD, there are also legal and psychosocial risks involved with its use, particularly among younger patients.[49] Side effects of marijuana use include confusion, ataxia, dizziness, nausea, and vomiting.[42] Chronic use is associated with cognitive impairments and deficits in motivation, learning, and memory, as well as increased risk of motor vehicle crashes and decreased fertility.[38] Furthermore, the use of cannabis for more than 6 months at any time was a strong predictor for surgery in patients with CD, comparable to tobacco smoking.[42] Thus, we cannot recommend the use of cannabis in patients with IBD outside of clinical trials until studies emerge showing that it improves clinical and endoscopic outcomes and its safety is established.

Fish Oil

Fish oil is typically derived from oily fishes, such as tuna, salmon, mackerel, or sardines. The main components behind its potential therapeutic effects include omega-3 polyunsaturated fatty acids (n-3 PUFAs), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA), the latter 2 being the main bioactive forms synthesized from the precursor n-3 PUFA α-linolenic acid.[50,51] Recently, n-3 PUFAs have been implicated in favorable shifts in the gut microbiota, including decreases in *Faecalibacterium* and an increase in *Bacteroidetes*.[50]

Two large, well-designed trials studying the role of n-3 PUFAs in CD (EPIC-1 and -2 [Epanova Program in Crohn's Study 1 and 2]) had negative results.[52] These trials found that treatment with 4 g/day of n-3 PUFAs was not better than placebo for preventing relapse in patients with quiescent CD. In patients with UC, the evidence is mixed. Although 1 study found that n-3 PUFA supplementation in patients with mild-to-moderate UC decreased corticosteroid requirement, its efficacy on prevention of relapse in patients in remission is debatable.[53] A RCT in patients with quiescent UC demonstrated that n-3 PUFA supplementation (γ-linolenic acid 1.6 g, EPA 270 mg, DHA 45 mg, daily) was no better than placebo in preventing relapse during 12 months of follow-up.[54] However, a recent RCT examined a cohort of patients in clinical remission (partial Mayo score <2) but with fecal calprotectin (FC) at least 150 μg/g, and randomized patients to receive EPA (1 g twice daily) or placebo.[55] The researchers found that 63.3% of patients receiving EPA vs 13.3% of patients receiving placebo had at least a 100-point reduction in FC (P<.001), and 76.7% of patients receiving EPA (vs 50% of patients receiving placebo) maintained remission (odds ratio, 3.29; 95% CI, 1.08-9.95).

Fish oil is generally safe, although many patients experience fishy breath odors.[1] With the lack of evidence for its efficacy in CD and mixed evidence in patients with UC, we do not recommend use of fish oil to maintain remission in IBD. However, we recognize that fish oil is generally safe and commonly used by the population at large for its known benefits in various cardiovascular diseases such as hyperlipidemia.[50]

Chinese Herbal Medicine

Traditional Chinese medicine (TCM) is one of the most developed branches of CAM in the world. TCM encompasses the application of various herbal agents and has been used for thousands of years.[6,56] There have been several recent RCTs of 2 agents in particular.

Andrographis paniculata, a member of the plant family Acanthaceae, is an herbal remedy used in China and many other Asian countries.[57] In a well-designed, multicenter RCT of patients with active mild-to-moderate UC, its extract, HMPL-004, produced similar rates of clinical remission, response, and endoscopic remission when compared with 5-ASAs at 8 weeks.[58] In another RCT, HMPL-004 was compared to placebo and was found to be superior in producing significantly higher rates of clinical response.[59] In these 2 trials, the most common adverse events were abdominal pain, diarrhea, and headache.[58,59] However, the frequency of adverse events was similar in both the treatment and control groups.

Indigo naturalis (IN, also known as Qing-Dai) is an herbal medicine extracted from indigo plants (ie, *Indigofera tinctoria*) and used predominantly in China.[60] It has been used as an antipyretic and as a hemostatic agent for centuries in TCM.[5] The anti-inflammatory effect of IN is thought to be due to inhibition of TNF-α, interleukin (IL)-1 and -6, and NF-κB, as well as promotion of IL-22 production.[61] In rat models with dextran sodium sulfate–induced colitis, IN reduced myeloperoxidase activity and expression of inflammatory cytokines while increasing expression of colonic mucosal repair–related cytokines and proteins.[62]

The largest well-designed, multicenter RCT evaluated the benefit of IN among 86 patients with active UC (Mayo score ≥6) refractory to conventional treatments. Those patients randomized to receive a daily dose of IN (doses of 0.5 g, 1.0 g, or 2.0 g) for 8 weeks had significantly higher rates of clinical response, remission, and mucosal healing vs patients in the placebo group.[60] Side effects included diarrhea, abdominal pain, nausea, vomiting, and headaches. Mild liver dysfunction was also observed in 10 patients who received IN. The trial was terminated early due to a report of a patient with UC (outside of the trial) who developed pulmonary arterial hypertension (PAH) after ingesting IN for 6 months. Thus, despite promising results, the authors cautioned the use of IN because of the potential for adverse events such as PAH and liver dysfunction.

A summary of evidence and recommendations involving select probiotic and oral dietary or herbal supplementation is shown in Table 1.

Acupuncture and Moxibustion

Acupuncture and moxibustion are therapeutic Chinese practices that have been used for thousands of years for numerous ailments.[63] Acupuncture is the practice of placing thin needles into the skin at certain acupoints to achieve a desired benefit.[64] One variation of this practice is to use small, electrical currents at certain frequencies applied through the acupuncture needles (electroacupuncture).[65] Moxibustion is the practice of burning dried mugwort (moxa) cones on acupoints (or other parts of the body) to generate warmth stimulation. Sometimes different herbs are added to the burning cones to reach a certain desired effect; this practice is called herb-partitioned moxibustion (HPM).[64]

There has been much research looking at the mechanisms of action of acupuncture and moxibustion in rat models of colitis. HPM was noted to promote repair of damaged colonic tissue and secretion of mucin in rats with colitis, and this response was correlated with an increased number of moxa cones and frequency of therapy.[66] Bao and colleagues examined the effect of acupuncture and moxibustion (with no control group)

Table 1. Summary of Evidence and Recommendations Regarding Select Probiotic and Oral Dietary or Herbal Supplementation for IBD Patients

	Summary of Evidence	General Recommendations
Probiotic		
VSL#3[a]	Pouchitis • Prevention of initial pouchitis: VSL#3 decreases risk for developing first episode of pouchitis 1 year after IPAA (1 RCT)[18] • Maintenance of remission in pouchitis: Evidence supporting VSL#3 for maintenance of remission in recurrent or refractory pouchitis after induction of remission with antibiotics (2 RCTs)[19,20] Ulcerative colitis • Active mild-to-moderate ulcerative colitis: Evidence supporting VSL#3 for induction of remission (2 RCTs)[21,22] • Quiescent ulcerative colitis: Evidence supporting VSL#3 for maintenance of remission along with 5-ASA (1 pediatric RCT, no adult RCT)[27] Crohn's disease • Limited evidence supporting efficacy[16,29]	Pouchitis • Reasonable to use • Prevention of pouchitis after IPAA: 900 billion bacteria daily • Prevention of recurrent pouchitis: 1.8 trillion bacteria daily Ulcerative colitis • Can consider use with conventional therapy in active mild-to-moderate and quiescent ulcerative colitis, but not as monotherapy (Toronto consensus) • Active mild-to-moderate ulcerative colitis: 900 billion to 3.6 trillion bacteria daily as add-on therapy • Maintenance of remission in ulcerative colitis: At least 1.8 trillion bacteria daily (extrapolated from pediatric RCT)[27] Crohn's disease • Not recommended
Herbs and Dietary Supplements		
Curcumin	Ulcerative colitis • Active mild-to-moderate ulcerative colitis: Evidence supporting benefit in patients failing oral or topical 5-ASAs (1 RCT)[31] • Quiescent ulcerative colitis: Evidence supporting use in patients on sulfasalazine or 5-ASA (1 RCT)[33] Crohn's disease • No evidence	Ulcerative colitis • Reasonable to use for both active and quiescent ulcerative colitis in addition to conventional therapy • Induction of remission: 3 g/daily + standard therapy • Maintenance of remission: 2-3 g/daily + standard therapy Crohn's disease • Not recommended
Cannabis	Ulcerative colitis • Improves QOL but no difference in remission rates in patients with quiescent ulcerative colitis (small, observational, and prospective pilot studies[44,45] and 2 RCTs[46,48]) • Similar rates of remission when cannabis added on to 5-ASA in stable ulcerative colitis patients[48] Crohn's disease • In 1 RCT, more patients (initial CDAI >200) with clinical response in cannabis vs placebo group, but no difference in clinical remission rates, no changes in inflammation (CRP), and increased QOL[46]	Ulcerative colitis and Crohn's disease • Not recommended outside of clinical trial
Fish Oil	Ulcerative colitis • May decrease corticosteroid requirement (1 RCT),[53] but does not prevent relapse (2 RCTs)[53,54] • Decreases fecal calprotectin, may help maintain remission (1 RCT)[55] Crohn's disease • Not better than placebo for prevention of relapse (2 RCTs)[52]	Ulcerative colitis and Crohn's disease • Not recommended

(Table continues on the following page.)

Table 1. *(Continued)* Summary of Evidence and Recommendations Regarding Select Probiotic and Oral Dietary or Herbal Supplementation for IBD Patients

	Summary of Evidence	General Recommendations
Andrographis paniculata	Ulcerative colitis • Active mild-to-moderate ulcerative colitis: Similar rates of clinical response, remission, and endoscopic remission vs 5-ASAs (1 RCT)[58]; superior to placebo in producing higher rates of clinical response (1 RCT)[59] • Quiescent ulcerative colitis: Limited evidence for maintenance of remission Crohn's disease • No evidence	Ulcerative colitis • Awaiting phase 3 studies Crohn's disease • Not recommended
Indigo naturalis	Ulcerative colitis • Active mild-to-moderate ulcerative colitis: significantly higher rates of clinical response, remission, and mucosal healing vs placebo (1 RCT)[60] Crohn's disease • No evidence	Ulcerative colitis • Not recommended due to early RCT termination after report of a community case of pulmonary arterial hypertension Crohn's disease • Not recommended

[a]VSL#3 formulation: 1 double-strength packet contains 900 billion bacteria, 1 single-strength packet contains 450 billion bacteria, and 2 capsules contain 225 billion bacteria.

5-ASA, 5-aminosalicylate; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; IBD, inflammatory bowel disease; IPAA, ileal pouch–anal anastomosis; QOL, quality of life; RCT, randomized, controlled trial.

on patients with quiescent CD.[65] Both groups underwent pre- and postintervention resting-state functional magnetic resonance imaging of the brain. Both groups had reduced CDAI values, but the 2 therapies varied in how they changed brain connectivity and perhaps symptomology.[65]

One study randomized 92 patients with active CD not on any conventional therapy (CDAI 151-350) to acupuncture with HPM (treatment) or wheat bran–partitioned moxibustion with superficial acupuncture (control). This RCT found that patients in the treatment group had greater reductions in CDAI (primary endpoint) as well as lower CRP and lower histopathology scores (secondary endpoints).[67] Another study randomized 51 patients with active CD (CDAI >150) to receive either acupuncture or control (sham acupuncture points) for 12 weeks.[68] The mean CDAI score (primary endpoint) decreased by 87 points in the treatment group vs 39 points in the control group (P=.003).

A meta-analysis of English and Chinese RCTs reported that the overall efficacy of acupuncture alone, moxibustion alone, or acupuncture combined with moxibustion (without sulfasalazine) was greater than the efficacy of oral sulfasalazine monotherapy for the treatment of UC.[69] However, there was low heterogeneity among the studies and low methodologic quality. Furthermore, many of these studies varied in the use of acupuncture and moxibustion sites and outcomes.

Acupuncture and moxibustion are generally safe and well tolerated. Adverse events include small, local superficial hematomas; mild bleeding; infections; and mild superficial burns (only with moxibustion).[64] Although the current evidence of acupuncture and moxibustion is promising in human RCTs, limitations such as low-quality methodology, lack of blinding, and variance in endpoints do exist in studies published in English. Thus, it is difficult to make recommendations as to the frequency and duration of acupuncture and moxibustion. However, these therapies can be considered as complements to conventional therapy in the right patient.

Cognitive-Physical (Mind-Body) Therapies

Mind-body therapies encompass an array of cognitive or psychodynamic therapies, stress management or relaxation, mindfulness, hypnosis, yoga, or exercise-based practices.[1,4] It is well known that psychological stress and IBD are related, and many patients with IBD have higher rates of depression, anxiety, and stress, as well as lower QOL than patients without IBD.[70,71] Cognitive-physical therapies are noted to be very common among patients with IBD. A Swedish study found that up to 21% of

patients with IBD use massage therapy, 15.3% practice relaxation or meditation techniques, 8% engage in yoga, and 0.6% have tried hypnosis.[72]

Cognitive Techniques and Therapies

The evidence on the efficacy of cognitive behavioral therapy (CBT) in patients with IBD is mixed, and existing studies vary widely on endpoints. A recent RCT (N=118) found that CBT improved disease-specific QOL based on self-reported questionnaires and lowered rates of depression and anxiety.[73] In a study of 176 patients with UC and CD, CBT plus standard therapy vs standard therapy alone did not influence the course of IBD (as measured by changes in CDAI, Simple Clinical Colitis Activity Index, CRP) over 24 months of follow-up.[74] A recent meta-analysis found that psychological therapies—particularly CBT—might have small short-term benefits on depression scores and QOL, although it noted the lack of well-designed RCTs in this domain.[75] CBT did not have any effect on disease activity indices when compared with control groups.

Another type of mind-body therapy is the practice of mindfulness. In a RCT, 60 patients with UC and CD were randomized to receive mindfulness-based stress reduction intervention or control. The mindfulness intervention included a mental body scan, sitting and walking meditations, yoga, group discussions, and sharing of experiences. Patients receiving the mindfulness intervention had significantly higher improvements in anxiety and QOL. Six months after intervention, reductions in depression and improvements in QOL were maintained.[76] No significant differences in FC, serum cytokines, or CRP were noted in another RCT employing mindfulness in patients with UC in remission.[77]

Gut-directed hypnotherapy has been shown to decrease the risk of disease relapse in patients with UC in remission. In a single-center RCT conducted by Keefer and colleagues, 54 patients with quiescent UC were randomized to 7 sessions of gut-directed hypnotherapy or attention control (encouraged questions, motivational interviewing), and were followed for 1 year.[78] A higher proportion of patients in the group receiving hypnotherapy stayed in clinical remission vs placebo (68% vs 40%; P=.04).[78] Although this is the only RCT studying hypnotherapy in IBD to date,[79] the established efficacy of this therapy in improving gastrointestinal (GI)-related symptoms among patients with irritable bowel syndrome (IBS) suggests a potential adjunctive role in patients with both IBS and IBD.[80]

Yoga, another type of mind-body therapy, has also been studied in patients with UC. Cramer and colleagues conducted a RCT of 77 patients with UC in remission but impaired QOL, who were randomly assigned to yoga (12 supervised weekly sessions, 90 minutes each) or to read self-care advice.[81] Patients practicing yoga had higher disease-specific QOL vs those reading self-care advice at 12 and 24 weeks.[81] A RCT studying yoga in patients with quiescent UC and CD saw improvements in anxiety and abdominal pain, but no difference in markers of immune response.[82]

Exercise

Exercise is linked to higher QOL,[83] improved bone mineral density,[84] and lower rates of relapse in both patients with UC and CD.[85,86] Potential mechanisms of benefit include an increase in IL-6 release during exercise, which has been shown to increase glucagon-like peptides involved in the repair of damaged intestinal mucosa.[87] In animal models of colitis, exercise decreases expression of proinflammatory cytokines such as TNF-α and IL-1, and increases expression of IL-6 and -10.[85] However, there are many potential barriers for patients with IBD to exercise. These include fatigue, joint pain related to arthritis or arthropathy, abdominal pain, diarrhea, or fecal urgency.[85] Although the overall benefits of exercise and the universally safe profile of most exercise regimens are clear, excessive exercise may be detrimental and perhaps dangerous, especially in patients with more moderate or severe disease activity and sequelae of chronic disease (eg, anemia, osteoporosis). Exercise is probably best for patients in remission.

Overall, cognitive and physical or mind-body therapies are safe complements to conventional therapies. There is abundant evidence for their efficacy in improving QOL, depression, and anxiety in patients with IBD (Table 2). However, little evidence indicates a positive impact on inflammation or disease activity indices.

Holistic or Comprehensive Health Wellness Retreats

Given the popularity and high prevalence of CAM use among patients with chronic diseases such as IBD, health wellness resorts or retreats have become increasingly popular. Using a combination of search terms such as IBD, health wellness, retreat, or GI in a standard search engine, we were able to find a number of health wellness resorts for patients with IBD. Some of these retreats are aimed at health wellness in general, whereas others specifically target patients with chronic diseases, such as autoimmune disorders, arthritis, cardiopulmonary diseases, IBS, and IBD. Benefits include relaxation, stress reduction, and exposure to mind-body therapies. Risks include cost, exposure to sham therapies, herbal-medication interactions, excessive laboratory or imaging

Table 2. Summary of Evidence and Recommendations Regarding Select Chinese Practices and Cognitive-Physical (Mind-Body) Therapies for IBD Patients

	Summary of Evidence	General Recommendations
Acupuncture and Moxibustion	Ulcerative colitis • Active mild-to-moderate ulcerative colitis: Some evidence suggesting superiority to oral sulfasalazine monotherapy, although limited due to low methodologic quality[69] Crohn's disease • May decrease CDAI and CRP (2 RCTs)[67,68]	Ulcerative colitis and Crohn's disease • Can consider as a complement to conventional therapy due to overall safety profile
CBT	Ulcerative colitis and Crohn's disease • Evidence on efficacy of CBT points toward some improvements in QOL and lower rates of depression and anxiety (1 RCT)[73,75] • CBT does not influence course of IBD or changes in CDAI, SCCAI, or CRP (1 RCT)[74]	Ulcerative colitis and Crohn's disease • Can consider as a complement to conventional therapy for improving QOL, anxiety, and depression
Mindfulness	Ulcerative colitis and Crohn's disease • Evidence indicates improvements in QOL, anxiety, and depression (1 RCT)[76] • No improvements in fecal calprotectin, serum cytokines, and CRP were noted (1 RCT)[77]	Ulcerative colitis and Crohn's disease • Can consider as a complement to conventional therapy for improving QOL, anxiety, and depression
Hypnotherapy	Ulcerative colitis and Crohn's disease • Gut-directed hypnotherapy increases clinical remission in patients with quiescent ulcerative colitis (1 RCT)[78]	Ulcerative colitis and Crohn's disease • Can consider as a complement to conventional therapy for improving symptoms
Yoga	Ulcerative colitis and Crohn's disease • Improves QOL, anxiety, and abdominal pain, but has no effect on disease activity (2 RCTs)[81,82] • No difference in inflammatory markers[82]	Ulcerative colitis and Crohn's disease • Can consider as a complement to conventional therapy for improving QOL and anxiety
Exercise	Ulcerative colitis and Crohn's disease • Associated with higher QOL (1 RCT)[83] • Improves bone mineral density (1 RCT)[84] • Predicts lower rates of relapse (1 prospective study)[86]	Ulcerative colitis and Crohn's disease • Can consider as a complement to conventional therapy for improving QOL and bone density • Exercise regimen should be individually tailored; avoid strenuous exercise in patients with more than mild active disease activity.

CBT, cognitive behavioral therapy; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; IBD, inflammatory bowel disease; QOL, quality of life; RCT, randomized, controlled trial; SCCAI, Simple Clinical Colitis Activity Index.

testing, misinterpretation of these tests, nonadherence to conventional therapy, and exposure to endemic infections and diarrheal diseases.

Conclusion

CAM use is very common among patients with IBD and spans an array of therapies, including herbal remedies, probiotics, and cognitive-physical (mind-body) practices. Although many types of CAM are generally safe, issues of purity, contamination with toxic metals, lacing with prescription drugs, and side effects of some traditional Chinese herbal remedies must be considered. Furthermore, larger well-designed RCTs are needed to validate specific CAM therapies in order for doctors to incorporate them into their traditional treatment algorithms.

It is important for gastroenterologists to ask all patients about CAM use. In addition to maintaining a good doctor-patient relationship, providing informed guidance will help set realistic, evidence-based expectations about particular therapies. Although the majority of patients regard CAM as more natural, it is not necessarily better or safe. Side effects of the CAM of interest should be reviewed. Ultimately, the goal should be to recognize CAM as having a potential supplemental role—but not an alternative one—to the conventional armamentarium for the treatment of IBD.

The authors have no relevant conflicts of interest to disclose.

References

1. Cheifetz AS, Gianotti R, Luber R, Gibson PR. Complementary and alternative medicines used by patients with inflammatory bowel diseases. *Gastroenterology*. 2017;152(2):415-429.e15.
2. Peregoy JA, Clarke TC, Jones LI, Stussman BJ, Nahin RL. Regional variation in use of complementary health approaches by U.S. adults. *NCHS Data Brief*. 2014;(146):1-8.
3. Koning M, Ailabouni R, Gearry RB, Frampton CM, Barclay ML. Use and predictors of oral complementary and alternative medicine by patients with inflammatory bowel disease: a population-based, case-control study. *Inflamm Bowel Dis*. 2013;19(4):767-778.
4. Langhorst J, Wulfert H, Lauche R, et al. Systematic review of complementary and alternative medicine treatments in inflammatory bowel diseases. *J Crohns Colitis*. 2015;9(1):86-106.
5. Ye BD. Introducing traditional herbal medicine into conventional health care in treating ulcerative colitis: primum non nocere. *Gastroenterology*. 2018;154(4):792-795.
6. Yanai H, Salomon N, Lahat A. Complementary therapies in inflammatory bowel diseases. *Curr Gastroenterol Rep*. 2016;18(12):62.
7. Nguyen GC, Croitoru K, Silverberg MS, Steinhart AH, Weizman AV. Use of complementary and alternative medicine for inflammatory bowel disease is associated with worse adherence to conventional therapy: the COMPLIANT study. *Inflamm Bowel Dis*. 2016;22(6):1412-1417.
8. Mountifield R, Andrews JM, Mikocka-Walus A, Bampton P. Doctor communication quality and friends' attitudes influence complementary medicine use in inflammatory bowel disease. *World J Gastroenterol*. 2015;21(12):3663-3670.
9. Lindberg A, Ebbeskog B, Karlen P, Oxelmark L. Inflammatory bowel disease professionals' attitudes to and experiences of complementary and alternative medicine. *BMC Complement Altern Med*. 2013;13:349.
10. Bertomoro P, Renna S, Cottone M, et al. Regional variations in the use of complementary and alternative medicines (CAM) for inflammatory bowel disease patients in Italy: an IG-IBD study. *J Crohns Colitis*. 2010;4(3):291-300.
11. Park DI, Cha JM, Kim HS, et al. Predictive factors of complementary and alternative medicine use for patients with inflammatory bowel disease in Korea. *Complement Ther Med*. 2014;22(1):87-93.
12. Mountifield R, Andrews JM, Mikocka-Walus A, Bampton P. Covert dose reduction is a distinct type of medication non-adherence observed across all care settings in inflammatory bowel disease. *J Crohns Colitis*. 2014;8(12):1723-1729.
13. Ong F, Seah Lee W, Lin C, et al. Complementary and alternative medicine (CAM) practices and dietary patterns in children with inflammatory bowel disease in Singapore and Malaysia [published online December 26, 2017]. *Pediatr Neonatol*. doi:10.1016/j.pedneo.2017.12.007.
14. de Simone C. The unregulated probiotic market [published online March 14, 2018]. *Clin Gastroenterol Hepatol*. doi:10.1016/j.cgh.2018.01.018.
15. Ng SC, Plamondon S, Kamm MA, et al. Immunosuppressive effects via human intestinal dendritic cells of probiotic bacteria and steroids in the treatment of acute ulcerative colitis. *Inflamm Bowel Dis*. 2010;16(8):1286-1298.
16. Shen J, Zuo ZX, Mao AP. Effect of probiotics on inducing remission and maintaining therapy in ulcerative colitis, Crohn's disease, and pouchitis: meta-analysis of randomized controlled trials. *Inflamm Bowel Dis*. 2014;20(1):21-35.
17. Singh S, Stroud AM, Holubar SD, Sandborn WJ, Pardi DS. Treatment and prevention of pouchitis after ileal pouch-anal anastomosis for chronic ulcerative colitis. *Cochrane Database Syst Rev*. 2015;(11):CD001176.
18. Gionchetti P, Rizzello F, Helwig U, et al. Prophylaxis of pouchitis onset with probiotic therapy: a double-blind, placebo-controlled trial. *Gastroenterology*. 2003;124(5):1202-1209.
19. Mimura T, Rizzello F, Helwig U, et al. Once daily high dose probiotic therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. *Gut*. 2004;53(1):108-114.
20. Shen B, Brzezinski A, Fazio VW, et al. Maintenance therapy with a probiotic in antibiotic-dependent pouchitis: experience in clinical practice. *Aliment Pharmacol Ther*. 2005;22(8):721-728.
21. Sood A, Midha V, Makharia GK, et al. The probiotic preparation, VSL#3 induces remission in patients with mild-to-moderately active ulcerative colitis. *Clin Gastroenterol Hepatol*. 2009;7(11):1202-1209.e1.
22. Tursi A, Brandimarte G, Papa A, et al. Treatment of relapsing mild-to-moderate ulcerative colitis with the probiotic VSL#3 as adjunctive to a standard pharmaceutical treatment: a double-blind, randomized, placebo-controlled study. *Am J Gastroenterol*. 2010;105(10):2218-2227.
23. Mardini HE, Grigorian AY. Probiotic mix VSL#3 is effective adjunctive therapy for mild to moderately active ulcerative colitis: a meta-analysis. *Inflamm Bowel Dis*. 2014;20(9):1562-1567.
24. Tamaki H, Nakase H, Inoue S, et al. Efficacy of probiotic treatment with Bifidobacterium longum 536 for induction of remission in active ulcerative colitis: a randomized, double-blinded, placebo-controlled multicenter trial. *Dig Endosc*. 2016;28(1):67-74.
25. Petersen AM, Mirsepasi H, Halkjær SI, Mortensen EM, Nordgaard-Lassen I, Krogfelt KA. Ciprofloxacin and probiotic Escherichia coli Nissle add-on treatment in active ulcerative colitis: a double-blind randomized placebo controlled clinical trial. *J Crohns Colitis*. 2014;8(11):1498-1505.
26. Derwa Y, Gracie DJ, Hamlin PJ, Ford AC. Systematic review with meta-analysis: the efficacy of probiotics in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2017;46(4):389-400.
27. Miele E, Pascarella F, Giannetti E, Quaglietta L, Baldassano RN, Staiano A. Effect of a probiotic preparation (VSL#3) on induction and maintenance of remission in children with ulcerative colitis. *Am J Gastroenterol*. 2009;104(2):437-443.
28. Zocco MA, dal Verme LZ, Cremonini F, et al. Efficacy of Lactobacillus GG in maintaining remission of ulcerative colitis. *Aliment Pharmacol Ther*. 2006;23(11):1567-1574.
29. Fedorak RN, Feagan BG, Hotte N, et al. The probiotic VSL#3 has anti-inflammatory effects and could reduce endoscopic recurrence after surgery for Crohn's disease. *Clin Gastroenterol Hepatol*. 2015;13(5):928-935.e2.
30. Bressler B, Marshall JK, Bernstein CN, et al. Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto consensus. *Gastroenterology*. 2015;148(5):1035-1058.e3.
31. Lang A, Salomon N, Wu JC, et al. Curcumin in combination with mesalamine induces remission in patients with mild-to-moderate ulcerative colitis in a randomized controlled trial. *Clin Gastroenterol Hepatol*. 2015;13(8):1444-1449.e1.
32. Sugimoto K, Hanai H, Tozawa K, et al. Curcumin prevents and ameliorates trinitrobenzene sulfonic acid-induced colitis in mice. *Gastroenterology*. 2002;123(6):1912-1922.
33. Hanai H, Iida T, Takeuchi K, et al. Curcumin maintenance therapy for ulcerative colitis: randomized, multicenter, double-blind, placebo-controlled trial. *Clin Gastroenterol Hepatol*. 2006;4(12):1502-1506.
34. Holt PR. Curcumin for inflammatory bowel disease: a caution. *Clin Gastroenterol Hepatol*. 2016;14(1):168.
35. Schneider A, Hossain I, VanderMolen J, Nicol K. Comparison of remicade to curcumin for the treatment of Crohn's disease: a systematic review. *Complement Ther Med*. 2017;33:32-38.
36. Naftali T, Mechulam R, Lev LB, Konikoff FM. Cannabis for inflammatory bowel disease. *Dig Dis*. 2014;32(4):468-474.
37. Hasenoehrl C, Storr M, Schicho R. Cannabinoids for treating inflammatory bowel diseases: where are we and where do we go? *Expert Rev Gastroenterol Hepatol*. 2017;11(4):329-337.
38. Ahmed W, Katz S. Therapeutic use of cannabis in inflammatory bowel disease. *Gastroenterol Hepatol (N Y)*. 2016;12(11):668-679.
39. Romano B, Borrelli F, Fasolino I, et al. The cannabinoid TRPA1 agonist cannabichromene inhibits nitric oxide production in macrophages and ameliorates murine colitis. *Br J Pharmacol*. 2013;169(1):213-229.
40. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA*. 2015;313(24):2456-2473.
41. Norton C, Czuber-Dochan W, Artom M, Sweeney L, Hart A. Systematic review: interventions for abdominal pain management in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2017;46(2):115-125.
42. Storr M, Devlin S, Kaplan GG, Panaccione R, Andrews CN. Cannabis use provides symptom relief in patients with inflammatory bowel disease but is associated with worse disease prognosis in patients with Crohn's disease. *Inflamm Bowel Dis*. 2014;20(3):472-480.
43. Lal S, Prasad N, Ryan M, et al. Cannabis use amongst patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol*. 2011;23(10):891-896.
44. Lahat A, Lang A, Ben-Horin S. Impact of cannabis treatment on the quality of life, weight and clinical disease activity in inflammatory bowel disease patients: a pilot prospective study. *Digestion*. 2012;85(1):1-8.
45. Naftali T, Lev LB, Yablecovitch D, Half E, Konikoff FM. Treatment of Crohn's disease with cannabis: an observational study. *Isr Med Assoc J*. 2011;13(8):455-458.
46. Naftali T, Bar-Lev Schleider L, Dotan I, et al. Cannabis induces a clinical

response in patients with Crohn's disease: a prospective placebo-controlled study. *Clin Gastroenterol Hepatol*. 2013;11(10):1276-1280.e1.
47. Naftali T, Mechulam R, Marii A, et al. Low-dose cannabidiol is safe but not effective in the treatment for Crohn's disease, a randomized controlled trial. *Dig Dis Sci*. 2017;62(6):1615-1620.
48. Irving PM, Iqbal T, Nwokolo C, et al. A randomized, double-blind, placebo-controlled, parallel-group, pilot study of cannabidiol-rich botanical extract in the symptomatic treatment of ulcerative colitis. *Inflamm Bowel Dis*. 2018;24(4):714-724.
49. Leinwand KL, Gerich ME, Hoffenberg EJ, Collins CB. Manipulation of the endocannabinoid system in colitis: a comprehensive review. *Inflamm Bowel Dis*. 2017;23(2):192-199.
50. Costantini L, Molinari R, Farinon B, Merendino N. Impact of omega-3 fatty acids on the gut microbiota. *Int J Mol Sci*. 2017;18(12):18.
51. Schwanke RC, Marcon R, Bento AF, Calixto JB. EPA- and DHA-derived resolvins' actions in inflammatory bowel disease. *Eur J Pharmacol*. 2016;785:156-164.
52. Feagan BG, Sandborn WJ, Mittmann U, et al. Omega-3 free fatty acids for the maintenance of remission in Crohn disease: the EPIC Randomized Controlled Trials. *JAMA*. 2008;299(14):1690-1697.
53. Seidner DL, Lashner BA, Brzezinski A, et al. An oral supplement enriched with fish oil, soluble fiber, and antioxidants for corticosteroid sparing in ulcerative colitis: a randomized, controlled trial. *Clin Gastroenterol Hepatol*. 2005;3(4):358-369.
54. Middleton SJ, Naylor S, Woolner J, Hunter JO. A double-blind, randomized, placebo-controlled trial of essential fatty acid supplementation in the maintenance of remission of ulcerative colitis. *Aliment Pharmacol Ther*. 2002;16(6):1131-1135.
55. Scaioli E, Sartini A, Bellanova M, et al. Eicosapentaenoic acid reduces fecal levels of calprotectin and prevents relapse in patients with ulcerative colitis [published online January 31, 2018]. *Clin Gastroenterol Hepatol*. doi:10.1016/j.cgh.2018.01.036.
56. Sałaga M, Zatorski H, Sobczak M, Chen C, Fichna J. Chinese herbal medicines in the treatment of IBD and colorectal cancer: a review. *Curr Treat Options Oncol*. 2014;15(3):405-420.
57. Quezada SM, Briscoe J, Cross RK. Complementary and alternative medicine. *Inflamm Bowel Dis*. 2016;22(6):1523-1530.
58. Tang T, Targan SR, Li ZS, Xu C, Byers VS, Sandborn WJ. Randomised clinical trial: herbal extract HMPL-004 in active ulcerative colitis—a double-blind comparison with sustained release mesalazine. *Aliment Pharmacol Ther*. 2011;33(2):194-202.
59. Sandborn WJ, Targan SR, Byers VS, et al. Andrographis paniculata extract (HMPL-004) for active ulcerative colitis. *Am J Gastroenterol*. 2013;108(1):90-98.
60. Naganuma M, Sugimoto S, Mitsuyama K, et al; INDIGO Study Group. Efficacy of *Indigo naturalis* in a multicenter randomized controlled trial of patients with ulcerative colitis. *Gastroenterology*. 2018;154(4):935-947.
61. Sugimoto S, Naganuma M, Kiyohara H, et al. Clinical efficacy and safety of oral Qing-Dai in patients with ulcerative colitis: a single-center open-label prospective study. *Digestion*. 2016;93(3):193-201.
62. Wang Y, Liu L, Guo Y, Mao T, Shi R, Li J. Effects of Indigo naturalis on colonic mucosal injuries and inflammation in rats with dextran sodium sulphate-induced ulcerative colitis. *Exp Ther Med*. 2017;14(2):1327-1336.
63. Cao H, Han M, Li X, et al. Clinical research evidence of cupping therapy in China: a systematic literature review. *BMC Complement Altern Med*. 2010;10:70.
64. Stein DJ. Massage acupuncture, moxibustion, and other forms of complementary and alternative medicine in inflammatory bowel disease. *Gastroenterol Clin North Am*. 2017;46(4):875-880.
65. Bao C, Wang D, Liu P, et al. Effect of electro-acupuncture and moxibustion on brain connectivity in patients with Crohn's disease: a resting-state fMRI study. *Front Hum Neurosci*. 2017;11:559.
66. Zhang D, Ren YB, Wu HG, et al. Effect of different doses of herbal cake-partitioned moxibustion on histopathological changes of colon tissue in ulcerative colitis rats [in Chinese]. *Zhen Ci Yan Jiu*. 2018;43(2):68-74.
67. Bao CH, Zhao JM, Liu HR, et al. Randomized controlled trial: moxibustion and acupuncture for the treatment of Crohn's disease. *World J Gastroenterol*. 2014;20(31):11000-11011.
68. Joos S, Brinkhaus B, Maluche C, et al. Acupuncture and moxibustion in the treatment of active Crohn's disease: a randomized controlled study. *Digestion*. 2004;69(3):131-139.
69. Ji J, Lu Y, Liu H, et al. Acupuncture and moxibustion for inflammatory bowel diseases: a systematic review and meta-analysis of randomized controlled trials. *Evid Based Complement Alternat Med*. 2013;2013:158352.
70. Mizrahi MC, Reicher-Atir R, Levy S, et al. Effects of guided imagery with relaxation training on anxiety and quality of life among patients with inflammatory bowel disease. *Psychol Health*. 2012;27(12):1463-1479.
71. Bernstein CN, Singh S, Graff LA, Walker JR, Miller N, Cheang M. A prospective population-based study of triggers of symptomatic flares in IBD. *Am J Gastroenterol*. 2010;105(9):1994-2002.
72. Oxelmark L, Lindberg A, Löfberg R, et al; SOIBD, the Swedish Organization for the Study of Inflammatory Bowel Disease. Use of complementary and alternative medicine in Swedish patients with inflammatory bowel disease: a controlled study. *Eur J Gastroenterol Hepatol*. 2016;28(11):1320-1328.
73. Bennebroek Evertsz' F, Sprangers MAG, Sitnikova K, et al. Effectiveness of cognitive-behavioral therapy on quality of life, anxiety, and depressive symptoms among patients with inflammatory bowel disease: a multicenter randomized controlled trial. *J Consult Clin Psychol*. 2017;85(9):918-925.
74. Mikocka-Walus A, Bampton P, Hetzel D, Hughes P, Esterman A, Andrews JM. Cognitive-behavioural therapy for inflammatory bowel disease: 24-month data from a randomised controlled trial. *Int J Behav Med*. 2017;24(1):127-135.
75. Gracie DJ, Irvine AJ, Sood R, Mikocka-Walus A, Hamlin PJ, Ford AC. Effect of psychological therapy on disease activity, psychological comorbidity, and quality of life in inflammatory bowel disease: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2017;2(3):189-199.
76. Neilson K, Ftanou M, Monshat K, et al. A controlled study of a group mindfulness intervention for individuals living with inflammatory bowel disease. *Inflamm Bowel Dis*. 2016;22(3):694-701.
77. Jedel S, Hoffman A, Merriman P, et al. A randomized controlled trial of mindfulness-based stress reduction to prevent flare-up in patients with inactive ulcerative colitis. *Digestion*. 2014;89(2):142-155.
78. Keefer L, Taft TH, Kiebles JL, Martinovich Z, Barrett TA, Palsson OS. Gut-directed hypnotherapy significantly augments clinical remission in quiescent ulcerative colitis. *Aliment Pharmacol Ther*. 2013;38(7):761-771.
79. Peters SL, Muir JG, Gibson PR. Review article: gut-directed hypnotherapy in the management of irritable bowel syndrome and inflammatory bowel disease. *Aliment Pharmacol Ther*. 2015;41(11):1104-1115.
80. Ballou S, Keefer L. Psychological interventions for irritable bowel syndrome and inflammatory bowel diseases. *Clin Transl Gastroenterol*. 2017;8(1):e214.
81. Cramer H, Schäfer M, Schöls M, et al. Randomised clinical trial: yoga vs written self-care advice for ulcerative colitis. *Aliment Pharmacol Ther*. 2017;45(11):1379-1389.
82. Sharma P, Poojary G, Dwivedi SN, Deepak KK. Effect of yoga-based intervention in patients with inflammatory bowel disease. *Int J Yoga Therap*. 2015;25(1):101-112.
83. Klare P, Nigg J, Nold J, et al. The impact of a ten-week physical exercise program on health-related quality of life in patients with inflammatory bowel disease: a prospective randomized controlled trial. *Digestion*. 2015;91(3):239-247.
84. Robinson RJ, Krzywicki T, Almond L, et al. Effect of a low-impact exercise program on bone mineral density in Crohn's disease: a randomized controlled trial. *Gastroenterology*. 1998;115(1):36-41.
85. Engels M, Cross RK, Long MD. Exercise in patients with inflammatory bowel diseases: current perspectives. *Clin Exp Gastroenterol*. 2017;11:1-11.
86. Jones PD, Kappelman MD, Martin CF, Chen W, Sandler RS, Long MD. Exercise decreases risk of future active disease in patients with inflammatory bowel disease in remission. *Inflamm Bowel Dis*. 2015;21(5):1063-1071.
87. Ellingsgaard H, Hauselmann I, Schuler B, et al. Interleukin-6 enhances insulin secretion by increasing glucagon-like peptide-1 secretion from L cells and alpha cells. *Nat Med*. 2011;17(11):1481-1489.