Adjunctive Therapies for Inflammatory Bowel Disease: Beyond Prescriptions

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Introduction

The aims of this article are to summarize the application and discussion of adjunctive therapies for patients with Inflammatory Bowel Disease (IBD). In lieu of conventional therapies, alternative interventions include mind-body techniques, diet, supplements, vitamins, sleep management techniques, and acupuncture. Despite the promise of complementary medicine as an adjunctive treatment for IBD, few studies have been performed to demonstrate efficacy in modulating disease activity. However, gastroenterologists face an overwhelming need to engage with their patients on alternative therapies with increasing adaptation of these non-allopathic interventions.

Dietary interventions and herbal supplementation: The Mediterranean diet

Diet is known to play a profound role in the pathogenesis, etiology, and treatment of IBD. Globally, the burden of IBD is on the rise, with its highest incidence in newly industrialized countries [1]. Emerging data shows a Western-style diet is associated with the rising prevalence of IBD [2]. Conversely, there is an inverse association of IBD rates with the consumption of certain food products characteristic of a Mediterranean-style diet [3]. A Western-style diet is a modern dietary pattern defined as high intake of refined sugar, omega-6 polyunsaturated fats, processed meats, and pre-packaged food items [4]. A Med-
iterranean-style diet is characterized by a high intake of vegeta-
bles, fruits, whole grains, olive oil, fish, and nuts as well as low
amounts of red meat and dairy [5]. Food components that are
characteristic of the Mediterranean Diet (MD) have been asso-
ciated with anti-inflammatory states and reduced risk factors
for disease, with reductions in cardiovascular disease, cancer,
and all-cause mortality [6-8]. The Dietary Guidelines for Ameri-
cans recommends the MD to improve health and to prevent dis-
ease [6]. Consumption of vegetables, fruits, and whole grains is
advised, along with avoidance of red meat, high fructose corn
syrup, trans- and saturated fatty acids.

Many components of the Mediterranean-style diet have been
shown to be beneficial in IBD. Vegetables and seeds con-
tain a high amount of fiber. Additionally, extra virgin olive oil
and nuts contain a high amount of polyunsaturated fatty acids,
and vitamins, as well as a low amount of omega-6 and saturated
fat. These dietary components suppress inflammation by influ-
encing the composition and function of the commensal micro-
bioiome [7,8]. Adherence has also been correlated to a decrease
in inflammatory markers and found to beneficially impact the
metabolome [7,8]. Adherence has also been specifically associ-
ated with a lower risk of later-onset CD in a 20 year study of
83,147 individuals [9]. Non-adherence to the MD conferred an
adjusted population attributable risk of 12% [9]. Several large
clinical studies are underway for the Mediterranean diet, which
will add greatly to our current understanding of the role of diet
in IBD [10,11].

The Trial of Specific Carbohydrate and Mediterranean Di-
ets to Induce Remission of Crohn's Disease (DINE-CD) study
was presented at the 2021 Crohn's and Colitis Congress. The
12-week parallel-group randomized trial included 194 patients
with mild-to-moderate CD; randomization was to the specific
carbohydrate diet (SCD) or the MD [12]. The SCD is a dietary
intervention focused on consumption of specific carbohydrates
(monoand polysaccharides such as glucose, fructose, and galactose).
It excludes disaccharides (sucrose, lactose, and maltose) and
most polysaccharides (starch, wheat, oats, barley, and rice)
which are thought to be proinflammatory, as well as processed
meat because it contains a variety of sugars including molasses
and other sweeteners [13]. The SCD has been demonstrated to
induce and maintain remission in patients with IBD [14]. The
primary clinical end points of the trial were symptomatic remis-
sion, clinical remission, and inflammatory response (defined as
a reduction in fecal calprotectin and C-reactive protein levels).
At 6 weeks, symptomatic remission was observed by 44% in the
MD cohort and 47% in the SCD cohort. Clinical remission was
similar, with 48% for the MD cohort and 49% for the SCD cohort.
At week 12, symptomatic remission rates were 40% and 42%,
and clinical remission rates were 47% and 40%, respectively.
Neither group demonstrated normalization of CRP or fecal cal-
protectin. DINE-CD showed no significant differences in the rate
of symptomatic remission or clinical remission between diets,
which demonstrates either diet as an effective supplement to
current therapy in patients with CD.

Curcumin

Curcumin is a plant produced chemical, found in the spice
turmeric, which is a member of the ginger family [15]. The pur-
ported medicinal properties of turmeric have received much in-
terest as it has been shown to be an effective anti-inflammatory
and antioxidant agent [16,17]. Curcumin targets multiple signal-
ing molecules at the cellular level due to potent inhibition of NF-
κB activation and inhibition of TNF-mediated actions [18-20].

In murine colitis models, curcumin inhibits NF-κB activa-
tion and CD4+ T cell infiltration [21]. Curcumin administration
to mice has also been shown to improve gut barrier function
and support a healthy microbiome [22]. Curcumin’s effect on
the microbiome has also been replicated in human studies, and
showed an increase in species diversity [23]. Although curcum-
in’s benefits in molecular studies and animal models has been
well documented, its efficacy in randomized controlled studies
(RCTs) and its side-effect profile are limited.

Curcumin has been shown to induce remission in patients
with active mild-to-moderate UC [24]. Curcumin was given
in combination with mesalamine to 50 patients with mild-to-
moderate UC. Patients were randomly assigned to groups given
mesalamine and curcumin capsules (3 g/day) or an identical
placebo for 1 month. 53.8% of patients who had not responded
to mesalamine treatment achieved clinical remission in the cur-
cumin cohort. Improved clinical remission rates were evident
with curcumin (53.8% versus 0%; P = 0.01), clinical response
(65.3% versus 12.5%; P<.001), and endoscopic remission (38%
versus 0%; P= 0.043). The study demonstrates the efficacy of
curcumin as a synergistic supplement to standard therapy.
These findings were strengthened by a 2020 meta-analysis of
several RCTs [25]. The final analysis included seven studies for
a total of 380 patients and demonstrated that adjunctive use of
curcumin with mesalamine versus placebo increased the odds
of clinical remission by threefold. The study concluded the use
of curcumin as an adjunct to be superior to the use of mesala-
mime alone in the treatment of UC. These findings have not been
demonstrated in CD patients. A recent investigation reported
oral curcumin was no more effective than placebo in preventing
post-operative recurrence of CD [26]. Overall, there is limited
but promising evidence that curcumin as a dietary supplement,
may yield favorable results as a nutraceutical treatment option.

Cannabis sativa

Cannabis sativa, an annual dioecious plant, is indigenous
to Eastern Asia. It has been cultivated throughout history as a
therapeutic, medicinal, and recreational plant [27]. It is com-
prised of several key cannabinoid compounds, including can-
nabinol, cannabidiol, and δ-9-Tetrahydrocannabinol (THC) [28].
Cannabinoid compounds have been on sale in the USA since
1985, although restricted to medicinal use [28]. The therapeutic
potential of cannabis and cannabinoind-based compounds has
been demonstrated throughout history for multiple therapeu-
tic benefits, such as relief of nausea and vomiting [29]. On the
contrary, cannabinoid use has also been non-causally linked
to mood and cognitive disorders, respiratory syndromes, and
cardiovascular complications [30]. On the other hand, new
research highlights potentially promising areas of therapeutic
benefit of cannabis for neurological and psychiatric disorders
[31-33]. This lends itself to the fact that state laws have allowed
marijuana for recreational use (in 17 states, the District of Co-
lumbia, the Northern Mariana Islands, and Guam) and medical
use (in 36 states, District of Columbia, Guam, Puerto Rico and
U.S. Virgin Islands) as of 2021 [34].

Nearly 15% of patients with IBD report current active use of
marijuana for relief of symptoms [35]. Despite its common use,
objective data on marijuana use, the anti-inflammatory effects
of cannabis, and its therapeutic potential IBD is limited. The lim-
ited literature does indicate cannabis use improves quality of
life measures [36,37]. In one study, patients with active CD on
various therapies were randomized to receive cannabidiol 20
mg/day or placebo [36]. Clinical Disease Activity Index (CDAI)
was measured between groups and no significant difference was noted by the end of the study. These findings were corroborated in a follow up study assessing the safety and tolerability of CBD-rich botanical extract in patients with UC [37]. However, the cannabidiol-rich botanical extract was superior to placebo in improving QOL outcomes, although remission rates at 10 weeks were similar between the 2 groups. Both studies reported cannabinoid use improved IBD symptoms, including pain, nausea, and appetite. It has been postulated that cannabis and its derivatives improve IBD symptoms via endocannabinoid receptors. These effects include lower esophageal sphincter relaxation, a decrease in gastric emptying, improvement in nausea and pain, a decrease in colonic motility, as well as secretions [38]. However, there is no clear evidence that cannabis and its derivatives improve biomarkers, reduce inflammation or improve disease activity. Ultimately, the effect of cannabis use in patients with IBD is inconsistent, with the outlined studies suggesting that cannabis may improve symptoms in patients with IBD, without biological remission or anti-inflammatory effect. Although there is potential for a positive impact on clinical symptoms, it remains challenging to counsel patients as there remains limited guidance on this topic.

**Mindfulness Approaches**

Mindfulness approaches and mind-body therapy incorporate cognitive therapy, mindfulness, yoga, and exercise. They can be utilized in a systematic approach to address the multifaceted aspects of IBD (psychological, cognitive, and psychodynamic factors). In fact, up to 21% of patients with IBD use mindfulness or mind-body therapy techniques such as massage therapy, meditation, yoga, and hypnosis [39].

**Yoga**

Yoga focuses on complex webs of associations between the mind, body, and behavior to promote optimal health. Although psychological therapies like meditation and yoga have shown limited effect on clinical and endoscopic disease markers, their effect on improvement in overall quality of life has been reliably reproduced [40]. Meta-analyses have suggested yoga improves QOL measures as well as pain control [41]. Additionally, the benefits of yoga include improving physical fitness, strength, flexibility, balance, and mobility [42].

Yoga has also been shown to have effects on other physiological systems of the body, including improving immune function [43,44]. In one meta-analysis investigating how yoga and similar practices reduce markers of inflammation, a conglomerate of 34 studies comprising over 2000 participants, reported improvement in inflammatory markers [44]. The study included 7 to 16 weeks of mind-body intervention and demonstrated that there was a moderate effect on reduction of C-reactive protein (effect size ES, 0.58; 95% confidence interval CI, 0.04 to 1.12) [44]. These immunomodulatory effects warrant further investigation as few prospective randomized controlled studies have evaluated the effect of yoga in biomarkers in IBD. However, QOL measures have been investigated. In a RCT investigating how yoga affected patients with UC currently in remission, patients were randomized to a supervised yoga session or self-directed reading over a period of 12 weeks [45]. In the patients practicing yoga, there was a significant increase in disease specific QOL. This finding has been replicated in subsequent studies [46].

**Exercise**

At present, it has been well established that exercise improves well-being, health and quality of life. Exercise is accessible, cost-effective, and a beneficial therapy for a multitude of diseases [47]. On the contrary, intensive training or extreme exercise has been associated with multiple gastrointestinal issues due to reduced blood flow to the gut [48]. Notwithstanding the gastrointestinal effects of extreme exercise, a sedentary lifestyle is an important risk factor for several disease states, including the development of IBD [49]. Further, exercise decreases all-cause mortality by augmenting cardiovascular disease risk [50].

In gastrointestinal disease states, exercise has been shown to decrease risk of constipation, diverticular disease, and cholelithiasis [51]. Further, moderate exercise may reduce risk of colorectal cancer [51]. Studies in murine models of chronic intestinal inflammation have demonstrated that exercise attenuates expression of pro-inflammatory cytokines [52]. The mucosal barrier integrity is challenged in stress-induced states, exacerbating dysfunction in the gut and mucosal biome. These findings have not been directly replicated in the IBD population as few studies have examined the effect of exercise on disease outcomes in human trials. Further, the studies that have been conducted vary greatly in their primary outcome but have included measures such as bone mineral density and oral-cecal transit time [52-55]. Given the large variability in the study outcomes, results have been mixed. For instance, a yearlong exercise intervention increased BMD [54], which is beneficial in IBD patients, whereas a subsequent study found that exercise worsened disease outcomes [55]. The study showed exercise had no significant effect on multiple parameters, including transit time, intestinal permeability and lipoperoxidation [55]. However, larger follow up studies have established that exercise has been shown to be an effective intervention when part of a multifaceted approach, even decreasing the risk of relapse for both CD and UC [56]. As part of a combined approach, stress management, exercise, and a Mediterranean diet was shown to have a significant increase in QOL scores [57].

**Acupuncture**

Acupuncture is a 3000-year-old therapy of traditional Chinese medicine. More Americans have adopted acupuncture with recent estimates approaching 14 million [58]. This recent trend can be observed in major hospital systems across the United States as now many offer and promote acupuncture services and recommend acupuncture therapy for treating pain. Another therapeutic modality of Chinese medicine is combining acupuncture with moxibustion, this involves burning dried mugwort (moxa) on acupuncture points [59]. These therapies offer an attractive option for IBD as a recent meta-analysis comparing the overall efficacy of acupuncture and acupuncture combined with moxibustion, concluded that either therapy was greater than the efficacy of oral sulfasalazine monotherapy for the treatment of UC [60]. The current literature to date suggests mindfulness approaches and mind-body therapies are safe complements to our conventional therapies. Regular participation in these techniques may help improve quality of life for people with IBD as well as immune function. Clearly more studies are needed to determine their clinical significance as objective data on disease markers is limited.

**Sleep**

Disruption of environmental factors, such as diet and sleep, is linked to impaired nutrient metabolism and systemic inflammatory response that is associated with IBD [61,62]. A large component of this effect is through alteration of the composi-
tion of the commensal microbiome [62-65]. Disordered sleep is common in modern society, and contributes to dysbiosis, gastrointestinal symptoms, and pathogenesis through inflammatory cascades [61,66,67]. Sleep deprivation, restriction, and fragmentation has been associated with cytokine expression [68-72]. The inflammatory cascade and impaired epithelial barrier function leads to bacterial translocation and further inflammation [73-76].

In addition to gut translocation, circadian dysrhythmia is associated with dysbiosis, changes in bacterial taxonomic composition that may promote progression to inflammatory disease, and this effect has been noted to be inducible in animal models [77,78]. Specific changes noted in disordered sleep include phylum-level changes, including increase in Firmicutes to Bacteroidetes ratio, and this effect has been noted to be inducible in animal models [68]. Changes in this composition can compromise the integrity of the intestinal epithelial barrier, immune response, as well as metabolic function [61].

While sleep dysfunction is associated with IBD pathogenesis, conversely, those affected by IBD also experience disordered sleep as a consequence of their disease. Over 50% of IBD patients experience abnormal sleep and this effect is associated with increasing severity of disease [79,80]. While there is some literature evaluating the effect of sleep interventions on fatigue and sleep quality in IBD patients, there is a paucity of literature on sleep interventions as a method to mitigate disease severity [81].

Melatonin

Melatonin is a neurohormone produced by the pineal gland that is responsible for regulating sleep-wake cycles. It is also produced by enterochromaffin cells in the gastrointestinal tract in approximately 400 times greater concentration than the pineal gland [82,83].

Precursors and biosynthesis

Biosynthesis of melatonin occurs through a pathway that starts with L-tryptophan (Trp) conversion to serotonin, and subsequent serotonin conversion to melatonin [84]. Intake of dietary Trp is associated with improved sleep, likely through this synthetic pathway [85]. Luminal Trp can be consumed by gut flora, directly affecting availability for melatonin synthesis, and in-turn affecting the sleep-wake cycle. Trp itself has also been implicated as a modulator of gut immune activity by inhibiting Angiotensin I Converting Enzyme 2 (ACE2)-dependent decreases in epithelial barrier function and progression to colitis, as well as through microbial metabolites [86,87]. This is demonstrated by literature suggesting that tryptophan deficiency is associated with IBD activity, though it is unclear if this is a precursor or consequence of IBD [88]. Serotonin is a neurohormonal intermediate in melatonin synthesis that has also been demonstrated to have anti-inflammatory and sleep effects. Medications affecting serotonin uptake including selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors have been demonstrated to decrease disease activity in CD and UC [89].

Gastrointestinal Effects

Melatonin acts as a modulator of several gut functions, including circadian fluctuation of microbial composition, direct antioxidant effects, and immunomodulatory effects [90,91]. Melatonin potentiates anti-inflammatory signaling cascades and oxidative stress [91]. The antioxidant effects of melatonin as a therapeutic intervention have been studied in several inflammatory disease states [92]. Melatonin improved disease severity in rat models with trinitrobenzenesulfonic acid (TNBS)-induced colitis [93]. The improvement in rat models was attributed to blocking transcription factors such as NF-kB and reducing free radical formation, which can cause intestinal mucosal barrier damage [94,95]. Melatonin has been demonstrated to decrease ulceration in animal models through decreased intestinal permeability and influx of bacterial toxins [93,96].

Therapeutic potential

Given the significant effects on gut-microbe interactions and anti-inflammatory effects, melatonin supplementation is a reasonable therapeutic target to optimize gastrointestinal physiological function and improve disease states such as IBD. In animal models, melatonin has been demonstrated to alleviate circadian dysrhythmia-related colitis, as well as sleep deprivation-related colitis through reduction in pro-inflammatory cytokines [97,98]. However, clinical trials investigating melatonin supplementation and their correlations with disease severity are lacking. Melatonin supplementation in combination with traditional therapy has been demonstrated to have both improved UC remission as well as decreased mucosal infiltrate when compared to traditional therapy alone in CD and UC [99,100]. A randomized, placebo-controlled clinical trial was designed but terminated prior to data analysis [101]. Controlled investigation of the therapeutic potential of melatonin on sleep and IBD disease activity is needed.

Conclusion

The treatment for IBD traditionally targets biologic or immunosuppressant medications. Recognizably however, there is increasing evidence that ancillary interventions through diet, sleep, exercise as well as some other homeopathic approaches may be beneficial and further enhance outcomes. Use of these approaches helps empower the patient to have a more active role in disease management and thereby transform approaches from global disease “en bloc” treatment to more patient-specific targeted interventions. Recognizably a cardinal “rule of medicine” is to do no harm, but these adjunctive therapies beyond prescriptions seemingly offer translational opportunities to improve patient outcomes. Open minded care providers need to integrate these possibilities with good clinical judgement!

References


11. Department of Gastroenterology and Liver Diseases Tel Aviv Sourasky Medical Center. Mediterranean Diet as an add-on Therapy for Induction of Remission in Patients with Active Crohn’s Disease - Full Text View - ClinicalTrials.gov. 2019.


13. Parrish CR, Rdn MS. The Specific Carbohydrate Diet in Inflammatory Bowel Disease: The Evidence and Execution.


34. State Medical Marijuana Laws. 2021.


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79. Ananthakrishnan AN, Long MD, Martin CF, Sandler RS, Kappelman MD. Sleep disturbance and risk of active disease in patients


81. Hashash JG, Knisely MR, Germain A. Brief Behavioral Therapy and Bupropion for Sleep and Fatigue in Young Adults with Crohn’s Disease: An Exploratory Open Trial Study. Clin Gastroenterol Hepatol. Published online September 2020.


