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SMALL INTESTINE (D SACHAR, SECTION EDITOR)

Cannabis and Turmeric as Complementary Treatments for IBD and Other Digestive Diseases

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Abstract

Purpose of Review Complementary therapies for inflammatory bowel disease (IBD) have earned growing interest from patients and investigators alike, with a dynamic landscape of research in this area. In this article, we review results of the most recent studies evaluating the role of cannabis and turmeric for the treatment of IBD and other intestinal illnesses.

Recent Findings Cannabinoids are well-established modulators of gut motility and visceral pain and have demonstrated anti-inflammatory properties. Clinical trials suggest that there may be a therapeutic role for cannabinoid therapy in the treatment of IBD, irritable bowel syndrome (IBS), nausea and vomiting, and GI motility disorders. Recent reports of serious adverse effects from synthetic cannabinoids highlight the need for additional investigation of cannabinoids to establish their efficacy and safety. Turmeric trials have demonstrated some promise as adjuvant treatment for IBD, though not in other GI disease processes.

Summary Evidence suggests that the use of cannabis and turmeric is potentially beneficial in IBD and IBS; however, neither has been compared to standard therapy in IBD, and thus should not be recommended as alternative treatment for IBD. For cannabis in particular, additional investigation regarding appropriate dosing and timing, given known adverse effects of its chronic use, and careful monitoring of potential bleeding complications with synthetic cannabinoids are imperative.

Keywords Inflammatory bowel disease · Complementary therapy · Cannabis · Cannabinoids · Turmeric · Curcumin

Introduction

As the prevalence of inflammatory bowel disease (IBD) continues to increase [1], so has the complexity of medical therapies available to treat both symptoms and underlying pathophysiology. Specifically, IBD which manifests with chronic, relapsing, and remitting inflammatory injury to the digestive tract can sometimes be treated with 5-aminosalicylic acid agents, but often requires immunosuppression to control symptoms and reduce complications generated by untreated or undertreated disease. This risk of poorly treated disease must be weighed against the risks of the therapies themselves, which can result in increased risk of infection, myelosuppression, local reactions, lupus-like reactions, neurologic effects, and malignancy [2]. While these risks are typically rare and are outweighed by the benefits of these therapies, treatment success defined as achieving and maintaining remission remains elusive for some patients [3], and a significant proportion can lose response to these medications over time [4].

Considering these realities with standard therapy, it is not surprising that many patients turn to alternative therapies, with risk/benefit profiles perceived to be more favorable. In many cases, patients are willing to spend significant amounts of money to receive alternative therapies, often without the guidance of a skilled clinician. The 2007 National Health Interview Survey estimated that approximately 38% of adults in the USA use complementary and alternative medicine, and the National Center for Complementary and Integrative Health reports Americans spend over $30 billion out-of-pocket for these therapies (https://nccih.nih.gov/news/camstats/costs/costdatafs.htm). Patients often resist sharing these practices with their provider for fear of disapproval,

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and due to the assumption that their provider is ill informed with regard to these therapies [5]. This is, however, a rapidly evolving area of research and one that is demanding more recognition with sophisticated trials and scientific experimentation, particularly with cannabis and turmeric for the treatment of IBD and other digestive diseases. Among the complementary therapies investigated, cannabis and turmeric have shown the most promise, and in this article, we review the updated literature describing their most recent studies.

Cannabis Therapy

Cannabis sativa, known as the "marijuana plant," is currently widely studied for potential therapeutic purposes in multiple disease processes. Best known for its psychogenic effects, it is now understood that there may be a role for cannabis therapy in the gut. The enteric nervous system contains endogenous cannabinoid receptors, cannabinoid type 1 receptor (CB1) and cannabinoid type 2 receptor (CB2), which have been demonstrated to impact gut motility [6]. In guinea pig and rat models, administration of CB1 receptor agonists resulted in decreased propulsion and transit, while CB1 antagonism produced the opposite effects [7]. *C. sativa* has also been demonstrated to exhibit anti-inflammatory properties in vitro and in vivo [8, 9]. *C. sativa* contains over 60 active phytochemicals known as cannabinoids; the most active and studied cannabinoids are tetrahydrocannabinol (THC) and cannabidiol (CBD). Although THC is well known to produce the psychogenic effect of cannabis, it also produces an anti-inflammatory, anti-oxidant, and analgesic effects [10, 11••]. Patients are aware of this potential benefit, and many have chosen to self-medicate with marijuana, including the pediatric population, where nearly a third of patients surveyed reported using marijuana at some point [12]. The potential effects of cannabinoids on the gut are demonstrated in Fig. 1.

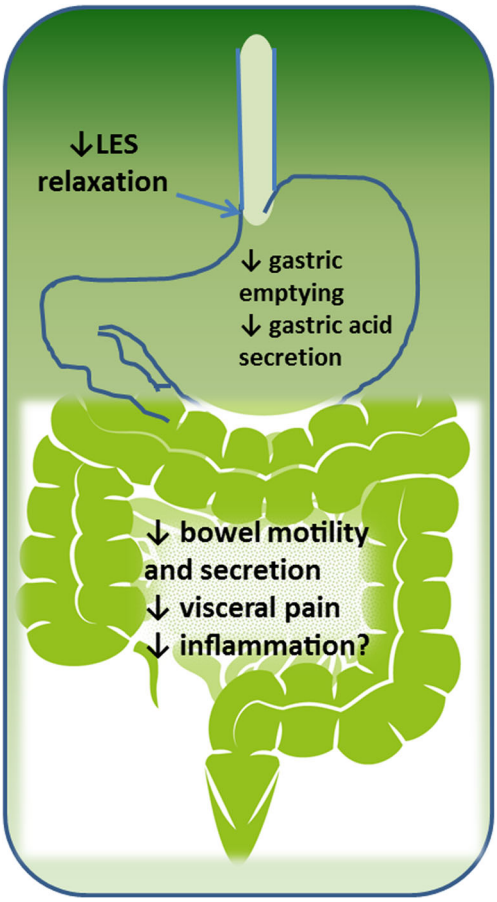

Fig. 1 Cannabinoid effects on the gut. LES, lower esophageal sphincter

Cannabis in IBD

CBD had initially drawn attention with promise of possible immunomodulatory effects without the psychotropic response in mouse models [8, 13], and promising results were described in an observational study investigating the effect of CBD in patients with Crohn's disease, with improvement in clinical symptoms as measured by the Crohn's Disease Activity Index (CDAI), although objective measures of inflammation were not compared [14]. In this landmark placebo-controlled clinical trial observing the efficacy and safety of cannabis in patients with IBD, patients were given two cannabis cigarettes daily with the equivalent of 230 mg THC for 8 weeks, with a 2-week washout period. A statistically significant decline in CDAI scores was seen in the treatment group compared to placement, and the benefit gained was lost after the 2-week washout period. Adverse effects were also monitored in the study, and there were no measured differences between the treatment and placebo groups for nausea, concentration, or memory loss.

More recently, CBD oil was studied by this same group in a randomized clinical trial in patients with moderately active Crohn's disease; CBD oil was found to be safe but not effective in inducing remission [15••]. Participants were given either placebo or 10 mg of oral CBD twice daily for an 8-week period, after which a reduction in CDAI was seen in parallel proportion across the CBD and placebo groups. Similarly, no difference was seen in adverse effects between groups including nausea, headache, sleepiness, or dizziness. It should be noted that among the 20 patients studied, 11 had failed steroids, 14 had failed thiopurines, and 11 had failed anti-TNF therapies, confirming the medically refractory nature of the population studied. Naftali et al. also speculated that the low dose utilized may have undertreated the illness, and thus additional research is warranted.

While clear efficacy of cannabis for Crohn's disease remains to be seen, an abstract presented by Naftali at the 2018 Digestive Diseases Week in Washington, DC demonstrated that cannabis can be used to induce remission in

patients with moderately active ulcerative colitis (UC) [16]. This was the first randomized trial investigating cannabis as treatment for UC, and the administration method differed from prior studies by using THC-rich cannabis cigarettes rather than oil. More importantly, objective inflammatory outcomes were measured including C-reactive protein (CRP), fecal calprotectin, and endoscopic disease activity. Although no statistically significant difference was noted in the reduction of CRP and fecal calprotectin compared to placebo, the Mayo score was reduced significantly from 2 to 1 in the treatment group compared to those who used the placebo cigarettes.

It has been previously noted that the effect of cannabis does not follow a dose-dependent correlation, but rather exhibits a bell curve with respect to dose and efficacy [10]. Similarly, increasing exposure to cannabinoids can cause detrimental gastrointestinal symptoms as demonstrated in a recent study suggesting chronic cannabis use is linked with abdominal pain, heartburn, and vomiting, findings which were corroborated by manometry [17]. This highlights the potential adverse GI effects of cannabis; further, the psychogenic effects, particularly of THC-rich products, should be minimized given their addictive potential. Patients need to be made aware of the potential adverse gastrointestinal and other effects generated by excessive cannabis use.

To date, recreational marijuana is legal in nine states, and medical marijuana use is legal in 29 states and in Washington, DC. That said, despite multiple proposals to remove marijuana from Schedule I of the Controlled Substances Act, marijuana remains a Schedule I drug restricting its research to areas outside the USA. Marijuana has known potential adverse effects such as decreased memory in children and adolescents [18, 19], dependency, psychiatric effects [20], and pulmonary disease [21, 22]; however, as the number of those exposed to synthetic medical marijuana increases, it is anticipated that other adverse effects will emerge. Synthetic marijuana has been linked to cases of severe bleeding complications, severe cyclical nausea and vomiting, and 3 deaths (https://www.washingtonpost.com/news/to-your-health/wp/2018/04/03/synthetic-marijuana-leaves-two-dead-and-dozens-with-severe-bleeding/?noredirect=on&utm_term=.ed84fd7771cd, https://abcnews.go.com/US/dead-100-severe-bleeding-synthetic-pot-illinois-health/story?id=54362392) (see Table 1).

Cyclic vomiting syndrome (CVS) is a functional disorder defined by Rome III criteria as 6 months or greater of incapacitating nausea and vomiting episodes lasting less than 1 week and occurring at least three times in 1 year, with symptom-free intervals [25]. While a direct causal relationship between cannabis and CVS has not been established, marijuana use was associated with approximately half of CVS patients in an extensive literature review [26]. A better understanding of these risks must be clarified before cannabis can be recommended as a therapy for IBD.

Cannabis in IBS and Other GI Diseases

In vivo studies confirm the ability of cannabinoids to reduce GI motility [27]; thus, the potential role for cannabis in diarrhea-predominant IBS has also been investigated, although rigorously designed trials are scarce. A 2017 randomized, placebo-controlled trial studying the effect of THC in IBS demonstrated mixed results, with an improvement in the total number of weekly stools and Bristol scale after 4 weeks of therapy compared to the placebo group, but no difference in quality of life [28]. Additional placebo-controlled trials are needed to clarify the role of cannabis in IBS treatment. Another important symptom in patients with IBS is abdominal pain, and cannabinoids have shown analgesic effects at the spinal and peripheral nerve levels and can be effective treatment for visceral pain [29]. The use of cannabis as an analgesic is limited by its psychotropic effects, and additional research is needed to identify a mechanism to utilize the analgesic effect without inducing these psychotropic consequences.

Cannabinoid receptors are clearly also found in the brain [30], and cannabinoids have been well studied as treatment for nausea and vomiting. While cannabinoid receptors are not found in the

Table 1 Potential adverse effects of marijuana and synthetic cannabinoids

Adverse effects of marijuana	Adverse effects of synthetic cannabinoids
Impaired brain development and cognitive function, especially in those with initial use in adolescence	Psychosis
	Respiratory depression
	Cardiac events
	Nephrotoxicity
Impaired memory	Hyperemesis[a]
Impaired motor coordination	Rhabdomyolysis
Impaired judgment	Hyperthermia
Psychosis disorders (including paranoia and schizophrenia)	Acute cerebral ischemia
	Seizures
	Bleeding complications

[a] It should be noted that these effects can be seen either in the setting of intoxication or withdrawal [23, 24]

chemoreceptor trigger zone (CTZ), the brain center responsible for the act of vomiting, they are located on dopaminergic and noradrenergic neurons along the pathway that stimulates the CTZ and elicits this response [31]. Thus, cannabis has produced beneficial results for patients who experience nausea and vomiting due to multiple causes, such as in those with chemotherapy-induced nausea and vomiting. A randomized trial confirmed that THC delayed gastric emptying when used as a prophylactic agent for patients with chemotherapy-induced nausea and vomiting [32]. There currently are two synthetic cannabinoid compounds that are FDA-approved for the treatment of nausea and vomiting caused by chemotherapy: dronabinol (e.g., Marinol®) and nabilone (Cesamet®) (https://nccih.nih.gov/news/camstats/costs/costdatafs.htm).

Turmeric Therapy

Turmeric is a spice known for its bright yellow hue and citrus flavor; however, it has gained significant popularity as a natural anti-inflammatory ingredient, and patients add it in large quantities to their diet. Turmeric originates from the *Curcuma longa* plant, producing the naturally occurring phytochemical curcumin [33•], which is recognized to have anti-inflammatory, anti-tumor, and anti-oxidant effects [34•]. As a result, the phytochemical curcumin has been studied in multiple disease processes, including but not limited to IBD, IBS, pancreatic and colorectal cancer (among other cancers), diabetes, and psoriasis [35].

Turmeric for IBD

In IBD, this potential therapy has been investigated in an ex vivo study, a small observational pilot study, and a randomized trial. In the ex vivo study, curcumin treatment added to colonic biopsies from patients with IBD exhibited dose-dependent suppression of inflammatory mediators, suggesting its ability to interrupt the inflammatory cascade [36]. The small pilot investigation studied the effect of oral curcumin given to patients with active CD or UC proctitis or proctosigmoiditis, previously treated with 5-ASA. All patients experienced a reduction in frequency and an improvement in consistency of stools, 4 patients were able to discontinue or decrease their baseline 5-ASA, and overall sedimentation rates declined 10 mm/h after treatment [33•]. In the double blind, randomized trial, 89 UC patients with quiescent disease received either curcumin 2 g/day or placebo in addition to 5-ASA for 6 months [34•]. Those patients who received curcumin demonstrated a statistically significant reduction in relapse rates and endoscopic activity compared to placebo. Adverse effects reported included nausea, abdominal bulging, transient increase in stool frequency, and transient hypertension; however, no patients discontinued participation due to these adverse effects.

Turmeric for IBS and Other GI Diseases

A pilot study evaluating IBS symptom response to two different doses (once weekly versus twice weekly) of oral turmeric in patients with IBS resulted in a 53% (once weekly) and 60% (twice weekly) drop in IBS symptoms in both groups after an 8-week period [37]. No placebo group was included in this study, which is critically important as high placebo response rates have been observed in both IBD and IBS trials. Thus, placebo-controlled trials are needed to more clearly gauge the efficacy and safety of turmeric in the IBS population.

Turmeric was one of three key ingredients in an Ayurvedic-combined herbal supplement studied in a placebo-controlled crossover trial testing the effect of a turmeric/curry/pomegranate compound in patients with diarrhea-predominant IBS [38]. The compound was not found to be more effective than placebo; in fact, the placebo group fared better than the treatment group with a mild reduction in symptoms. Despite the placebo-controlled trial design, given turmeric's combined administration with other compounds, the efficacy of turmeric for the treatment of IBS still warrants further investigation.

Curcumin compounds have also been tested as anti-cancer agents, and in vitro studies exhibit their ability to induce autophagy and apoptosis, downregulate the cell cycle, and optimize cellular response to chemotherapeutic agents such as gemcitabine in pancreatic cancer cells [39–41]. Similarly, curcumin appears to have beneficial effects on colon cancer cells, reducing the oncogenicity and inducing cell cycle arrest [42, 43]. These results have been limited to the in vitro setting for both conditions thus far, but given the early positive findings, clinical trials assessing its impact on GI malignancy as adjuvant therapy are likely to follow.

Conclusion

Cannabis and turmeric are purported to have value beyond recreation use, with in vitro and in vivo studies demonstrating their ability to modify GI function and pathophysiology at the cellular and molecular levels. Among all complementary therapies studied in GI diseases, cannabis and turmeric have demonstrated the most promise in observational studies and small randomized, controlled clinical trials. Additional research is warranted to further reveal their potential efficacy as well as adverse effects. Given their increasing popularity, clinicians must remain updated with the ever-evolving literature in this area to best advise patients, not only with regard to potential efficacy but also with emerging adverse effects associated with their use. This is particularly important in patients with IBD, as patients perceive that cannabis has beneficial effects in treating the disease. This can result in patients withdrawing conventional therapy with worsening of the underlying disease process. Further, patients may delay

initiation of conventional therapy to initiate alternative treatment with therapies such as cannabis and curcumin. This can result in a poor response to medical treatment, development of complications, and the need for surgery. Furthermore, patients often view alternative therapies as "harmless." However, particularly with cannabis, numerous adverse events exist with serious emerging adverse effects such as cyclical nausea and vomiting syndrome. Discussion, particularly of the use of cannabis, is also a highly controversial, with both patients and providers having strong opinions on its use. It is clear that further research is needed to investigate the efficacy and safety of these agents in the treatment of digestive and other diseases. Unfortunately, unless cannabis is removed as a Schedule I drug, research will be restricted outside of the USA. In the meantime, providers need to be aware of the widespread use of alternative and complementary therapies. Providers need to establish a strong therapeutic relationship with patients to foster trust so that patients will disclose the use of alternative therapies. Providers need to emphasize the potential safety concerns with the use of alternative agents, particularly with cannabis, to patients and they should discourage the use of alternative therapies as sole therapy for disease control. There is probably a subset of patients with digestive diseases that will benefit from adjunctive treatment with cannabis or turmeric, namely IBD patients with chronic abdominal or other pain not related to active inflammation or complications and not responsive to conventional supportive treatments (i.e., antidepressant use and non-narcotic analgesics). Likewise, patients with IBS may benefit from alternative treatment to treat both diarrhea and abdominal pain.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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