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### KEY TAKEAWAYS

- Complementary and Alternative Medicine (CAM) use is common among individuals living with inflammatory bowel disease (IBD)
- Most evidence-based consensus guidelines do not recommend the clinical use of CAM, including FMT, probiotics, cannabis, Curcumin, and PUFAs
- Recent advances in CAM research suggest a potential role for some forms of CAM, such as probiotics in preventing pouchitis or fecal microbiota transplant for induction of remission in ulcerative colitis
- More research, specifically well-designed randomized control studies, are required in this field before results can be applied to the clinical treatment of IBD

# RECENT ADVANCES IN COMPLEMENTARY AND ALTERNATIVE THERAPIES FOR INFLAMMATORY BOWEL DISEASE

## Introduction

Inflammatory bowel disease (IBD) is a chronic relapsing-remitting inflammatory condition of the

gastrointestinal (GI) tract, primarily comprised of 2 major types: Crohn's disease (CD) and ulcerative colitis (UC).<sup>1</sup> The pathogenesis of IBD is not fully elucidated but is thought to be multifactorial involving genetic,

environmental, and immunological contributors.<sup>2</sup> The incidence of IBD has been rising worldwide, particularly in developed nations. Canada, in particular, has one of the highest prevalence rates of IBD globally, with recent data indicating that over 320,000 Canadians are living with IBD, making it a significant public health concern.<sup>3,4</sup>

The chronic nature of IBD, along with the severity of its symptoms, and the adverse effects occasionally attributed to management (e.g. immunosuppression, corticosteroids, surgical complications) can significantly reduce the quality of life for those affected.<sup>5</sup> As such, many patients with IBD use complementary and alternative medicine (CAM) due to safety concerns of conventional therapy and a sense of greater control over their disease.<sup>6</sup> CAM refers to a broad range of healthcare practices, such as herbal medicine, acupuncture, homeopathy, fecal microbiota transplants, and probiotics, which are not typically considered part of conventional western medicine.<sup>7</sup> The use of CAM among patients with IBD is high, with current or past use of CAM ranging from 21-60% of IBD patients.<sup>6</sup> Given the propensity of patients with IBD to seek CAM and the unfamiliarity that many medical practitioners have with the evidence of benefit/harm from these practices, this review seeks to summarize recent advances in clinical research on CAM use for IBD.

## Probiotics

Probiotics are living microorganisms that can be ingested to confer a health advantage to the host. They have been an attractive target in the treatment of IBD given that patients with this condition have been demonstrated to have less diverse/changed GI microbiota (dysbiosis). However, the science and clinical implications of probiotics in IBD treatment continues to be explored.<sup>8,9</sup> The 2019 Canadian Association of Gastroenterology (CAG) clinical practice guidelines for CD strongly recommend against the use of probiotics to induce or maintain symptomatic remission in CD, citing a lack of evidence at that time.<sup>10</sup> The 2015 CAG clinical practice guidelines for the management of UC also recommend against probiotics to induce or maintain remission.<sup>11</sup> More recently, the 2019 British Society of Gastroenterology (BSG) consensus guidelines on the management of IBD is in agreement with previous guidelines regarding the use of probiotics in CD, but states that there may be modest benefit for UC, specifically in maintaining remission, although routine use of probiotics is not recommended.<sup>12</sup> An important limitation of the literature evaluating probiotics is the variation of bacterial strain combinations (most often *Lactobacillus GG*, *Lactobacillus johnsonii*, *Escherichia coli* strain Nissle 1917, or *Saccharomyces boulardii*) used in studies, which makes pooled analyses challenging. Additionally, the studies exhibit wide inter-study variability as well as small sample sizes.<sup>10</sup> These limitations have led to the consensus among most gastroenterology providers

that more research is required into the use of probiotics as a therapeutic option for IBD at the time.

Research in probiotics for IBD has continued since the publication of the above-mentioned guidelines. A recent meta-analysis of 13 studies (N=930 patients),<sup>13</sup> reported no statistical difference between probiotic and placebo groups in the rates of inducing remission in UC patients. No statistical difference was observed in the maintenance of clinical remission, clinical course, change in the Ulcerative Colitis Disease Activity Index (UCDAI) scores, or mucosal healing outcomes between the 2 groups. Interestingly, for UC patients, the probiotic group showed a statistically significant decrease in relapse rates (OR 0.34; 95% CI 0.14–0.79; P=0.01). Importantly, there were no statistically significant differences in adverse events between the 2 groups. Additionally, Estevinho et al. conducted a systematic review and updated meta-analysis of randomized controlled trials (RCTs) that analyzed data from 22 systematic reviews and 45 RCTs, making it the largest meta-analysis performed on probiotics in IBD to date.<sup>14</sup> The findings indicated that the effects of probiotics were positive for induction of clinical remission in patients with UC (OR 2.00; 95% CI 1.28–3.11; I<sub>2</sub> = 57%), but the effect was not significant in CD (OR 1.61, 95% CI 0.21–12.50, I<sup>2</sup> = 65%). With regards to maintenance, the study found that probiotics had a protective effect against relapsing pouchitis (OR 0.03; 95% CI 0.00–0.25) and exhibited a tendency to maintain remission in UC (OR 0.65; 95% CI 0.42–1.01), but not in CD. Subgroup analysis determined that the most efficacious use of probiotics occurred with multi-strain formulations. Further, combining 5-aminosalicylic acid (5-ASA) and probiotics vs 5-ASA alone was superior for the induction of remission. However, this analysis was limited by significant heterogeneity. Importantly, this study also found that the likelihood of experiencing adverse events was comparable to that of the placebo group.

Pouchitis, a phenotype of IBD, is an area where probiotics have perhaps been better studied and are more commonly used in clinical practice. Alphonso et al. conducted a systematic review of 20 RCTs investigating medical therapy for the treatment and prevention of pouchitis.<sup>15</sup> In regards to probiotics, they pooled 2 studies (N=20) that used the De Simone Formulation (a specific multispecies probiotic combination that consists of a mixture of 8 strains of bacteria). They found that 90% (18/20) of participants using the De Simone Formulation did not develop pouchitis compared with 60% (12/20) of placebo participants (RR 1.50; 95% CI 1.02–2.21). Thus, there are signals in the literature that suggest probiotics may play a role in specific subtypes of IBD, particularly UC and pouchitis, but more study is needed before these therapies can be recommended.

## Fecal Microbiota Transplant

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Fecal microbiota transplant (FMT) is the transplantation of feces, and the microbiome present within, from a healthy donor to the recipient via enema or nasogastric tube. The advantages of FMT over probiotic supplementation for restoring a healthy colonic microbiome include a vastly higher number of administered organisms, greater heterogeneity of the bacterial species, and the elimination of concerns over probiotic bacterial strains adapting to an ex-vivo environment.<sup>16</sup>

The current recommendations from the CAG clinical practice guidelines for UC advise against the use of FMT to induce or maintain complete remission outside the setting of clinical trials, citing insufficient data.<sup>11</sup> The recently published BSG consensus guidelines on managing IBD in adults comments that the initial data on FMT is promising, citing evidence of improved remission in UC, but recommends it only as an investigational treatment at this time.<sup>12</sup> Among the larger trials used to inform these recommendations includes a RCT by Moayyedi et al., which found that patients with UC treated with FMT were significantly more likely to achieve induction of remission compared to placebo.<sup>17</sup>

More recent evidence since the publishing of these guidelines include a meta-analysis by Tan et al. of 14 trials using FMT in UC.<sup>18</sup> The authors noted that FMT had a statistically significant increase in inducing remission compared with placebo (RR 1.44; 95% CI 1.03–2.02;  $I^2 = 38\%$ ,  $P = 0.03$ ), with minimal study heterogeneity. Additionally, FMT resulted in a statistically significant clinical response (most commonly defined as a reduction in the Mayo score and improved endoscopic findings) compared with placebo (RR 1.34; 95% CI 0.9–1.94;  $I^2 = 51\%$ ;  $P = 0.12$ ) with moderate study heterogeneity. Regarding safety, symptoms of gastrointestinal distress were the most common adverse events, however all were self-limiting, no major adverse events were attributed to FMT. While these results are promising and the mechanism of action of FMT is an area of significant interest in elucidating the pathogenesis of IBD, it is generally not performed outside of research studies. The nature of researching FMT is challenging given the difficulty standardizing aspects of therapy, such as the microbiome of the donor and dosing, which can contribute to significant variability. Larger studies will be required with control over factors such as route of administration, timing, preceding antibiotics, and number of administrations to better define the optimal role of FMT in patients with IBD.

## Cannabis

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Cannabis, typically from the *Cannabis sativa* plant, contains cannabinoids, such as tetrahydrocannabinol (THC) and cannabidiol (CBD). These compounds interact with the body's

endocannabinoid system and are theorized to have beneficial effects on inflammation, appetite, and pain, making them an attractive therapeutic option under investigation for IBD.<sup>19</sup>

The current recommendations from the CAG consensus on clinical practice guidelines for CD recommend against the use of cannabis for inducing or maintaining symptomatic remission, citing the poor quality of evidence available at the time of publication.<sup>10</sup> The BSG consensus guidelines on managing IBD in adults recommend further research into the effects of cannabis extracts in IBD. They acknowledge that literature to date has demonstrated a positive influence on self-reported symptomology but lacks statistical significance in the under-powered blinded studies that are available.<sup>12</sup>

Since the publishing of these guidelines, Doeve et al. conducted a meta-analysis including 15 nonrandomized clinical trials and 5 RCTs.<sup>20</sup> They found that cannabinoids were not effective at inducing remission (RR 1.56; 95% CI 0.99–2.46), and that they had no effect on inflammatory biomarkers. However, in keeping with pre-existing research, they did find that clinical symptoms (abdominal pain, general well-being, nausea, diarrhea, and poor appetite) all improved with cannabinoids.

At this time, evidence for cannabis and the use of cannabinoids in the treatment of IBD remains underpowered and lacking validity in dose, extract, and formulation, but is consistent in that it has not been found to induce remission or prevent relapse. Some studies do point towards symptomatic benefit, although this may be in part due to the un-maskable psychotropic effects of the treatment, making blinded studies difficult to facilitate.

## Polyunsaturated Fatty Acids

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Polyunsaturated fatty acids (PUFAs), including omega-3 and omega-6 fatty acids are natural compounds often found in fish oil and plant oils.<sup>21</sup> They are theorized to have anti-inflammatory properties, and although clear mechanistic evidence in this regard is lacking, their proposed benefit to the inflammatory nature of IBD has long been of interest. The current recommendations from the CAG consensus on clinical practice guidelines for CD recommend against using omega-3 fatty acids for inducing or maintaining symptomatic remission, citing 2 key systematic reviews that concluded that omega-3 fatty acids (primarily as monotherapy) were likely no more effective than placebo for maintenance therapy in CD.<sup>10</sup> The BSG consensus guidelines on managing IBD in adults reiterates the same message, citing that the most comprehensive study at the time, published by Feagan et al., did not demonstrate any benefit of omega-3 fatty acid supplementation in CD.<sup>12,22</sup>

Recent advances in the research on PUFA supplementation for treating IBD includes the largest and most comprehensive meta-analysis of RCTs

to date by Ajabnoor et al., which included 83 RCTs with 41,751 participants.<sup>21</sup> In this analysis, omega-3 fatty acid supplementation showed a trend toward improvement in the risk of IBD relapse (RR 0.85; 95% CI 0.72–1.01), however, it did not reach statistical significance. In addition, the outcomes for other PUFAs, such as omega-6 fatty acid and alpha-linolenic acid, were not statistically significant.

## Natural Compounds

Curcumin is a substance found in the rhizomes of the plant *Curcuma longa* (Aka. turmeric) as well as other *Curcuma* species, which has been used for centuries in Asia, both in traditional medicine and in cooking due to its vibrant yellow colour.<sup>23</sup> It contains natural compounds termed curcuminoids, thought to have anti-inflammatory properties.<sup>24</sup> Current guidelines regarding the therapeutic use of curcumin in IBD is lacking in Canadian guidelines, however the BSG consensus guidelines on IBD comment that no recommendations can be made due to lack of sufficient high-quality evidence regarding efficacy and dose and larger studies are needed, but that there have been some promising signals from pilot studies.<sup>12</sup> QingDai (QD), also known as Indigo naturalis, is a natural compound isolated from plants such as *Strobilanthes cusia* and *Isatis tinctoria*, which contains natural ingredients such as indigo, indirubin, isoindigotin, and nimbosterol.<sup>25</sup> Originally used as a natural blue dye since ancient times, it has been used to treat various inflammatory disorders including UC, primarily in China.<sup>26</sup> QD is not mentioned in Canadian or British IBD guidelines, however preexisting evidence for its use in IBD includes a small Japanese trial demonstrating dose dependant clinical response and an American dose-escalation study without a placebo group and with patients (N=11) patients demonstrating clinical response.<sup>26, 27</sup>

Recent evidence for natural compounds includes a double-blind RCT by Ben-Horin et al. In part 2 of the trial they randomized patients (n=42) with moderate-severe UC to receive enteric coded Curcumin-QD (1.5 g of each compound) combination therapy vs placebo, with the primary outcome being induction of remission, defined by a clinical response (reduction in the Simple Clinical Colitis Activity Index of  $\geq 3$  points) and an objective response (Mayo endoscopic subscore improvement of  $\geq 1$  or a 50% fecal calprotectin reduction). Here, they found that the curcumin-QD arm had a statistically significant increase in achieving remission, with 12 of 28 patient (43%) in the treatment arm vs 1 of 13 patients (8%) in the placebo arm meeting this primary outcome ( $P = .033$ ; RR, 1.62; 95% CI, 1.13–2.31).<sup>28</sup>

Ultimately, although there are promising signals towards the treatment of UC, sample sizes remain small and standardization of the proposed therapeutic compounds within these herbal compounds remains

elusive. More research will be required before results can be applied to the clinical treatment of IBD.

## Conclusion

In summary, most forms of CAM lack consistent moderate or high-quality evidence to support their routine use in the induction and maintenance of IBD. However, some subtypes of IBD show stronger signals of benefit from CAM, such as probiotics in preventing pouchitis or FMT for induction of remission in UC. More research is needed to define the role of these therapies. Nonetheless, patients are increasingly using CAM, and providers should familiarize themselves with the various forms of CAM. Moreover, providers should make a point to ask about CAM use, as patients may not volunteer this information. Ultimately, research into CAM will require large-scale RCT data before their specific role can be better defined. This remains a key area of research given the high use of CAM among patients with IBD.

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