Integrative Treatments (not including food) for IBD – Scientific Studies

Human Studies

Class of Therapy: Herbal Therapy

Name of Therapy: Germinated Barley

Brand Name: N/A

Mechanism of Action: Germinated barley has been shown to inhibit NF-κB by binding to it, preventing it from binding to DNA response elements. This prevents the activation of pro-inflammatory genes, which leads to a diminished inflammatory response (37).

Efficacy: In one study, 21 patients with mild to moderate UC received 20-30 grams of germinated barley for 24 weeks, along with baseline treatments (5-ASA's and/or steroids). After 24 weeks, the patients treated with the germinated barley exhibited a significant decrease in their clinical activity index. Most notably, it was seen that both the degree of visible blood in their stool and the presence of nocturnal diarrhea had decreased (9).

Side Effects: No safety concerns.

Dosage: 20-30 grams/day, for 24 weeks.

Class of Therapy: Herbal Therapy

Name of Therapy: Wheat grass juice

Brand Name: ALO, Now Foods, Amazing Grass, Navitas Natural

Mechanism of Action: Wheat grass juice contains vitamins that may be used in resolving the inflammation, but the mechanism of action for wheat grass juice is currently unclear (36).

Efficacy: A randomized, double-blind, placebo-controlled trial with 23 patients with active distal UC examined the efficacy of wheat grass juice in treating the condition. Out of the 21 patients that completed the study, full information was only available on 19 of them. It was seen that those that received wheat grass juice treatment (100 cc of juice, once a day for 1 month) showed a significant reduction in their CDAI, as well as a decrease in the severity of their rectal bleeding (4).

Side Effects: Nausea.

Dosage: 100 cc/day, for 1 month.

Class of Therapy: Herbal Therapy

Name of Therapy: Aloe vera Gel

Brand Name: Aloecure, Lakewood

Mechanism of Action: It has been demonstrated that aloe vera reduces levels of prostaglandin E2 (PGE2) through its inhibition of the cyclooxygenase pathway (preventing arachidonic acid from being converted to PGE2) (33). PGE2 is involved in the typical signs of inflammation, such as redness, swelling, and pain (34).

Efficacy: There is limited evidence suggesting that aloe vera gel is effective in treating IBD. One randomized, double-blind clinical trial examined the efficacy of aloe vera gel in treating 44 patients with mild to moderate UC. It was seen that in the 30 patients that received aloe vera gel treatment (100 mL, twice per day for 4 weeks), 9 (30%) entered remission, 11 (37%) showed improvement, and 14 (47%) showed a response to the treatment. Out of the 14 placebo patients, 1 (7%) entered remission, 1 (7%) showed improvement, and 2 (14%) showed a response. The researchers also found that the average CDAI decreased significantly in patients being treated with aloe, but not in the placebo (3).

Side Effects: No safety concerns.

Dosage: 100 mL/twice daily, for 4 weeks. For the first three days, patients received 25-50 mL/twice daily, to ensure that they could tolerate the treatment.

Class of Therapy: Herbal Therapy

Name of Therapy: Bovine colostrum enema

Brand Name: New Zealand Pure Health, Surthrival, Symbiotics, NOW

Mechanism of Action: One suspected mechanism of *bovine colostrum* is that it can block the function of TNF-α by preventing it from binding to intestinal epithelial cells, but more studies are required to confirm this activity. It has been seen that *bovine colostrum* is capable of inhibiting the activation of NF-κB in HT29 cells (human colon adenocarcinoma cells) (50).

Efficacy: One study investigated the use of *bovine colostrum* enemas in treating ulcerative proctitis. The first study had 14 patients with mild to moderate UC. This study had the patients receive either albumin or the enema treatment twice daily for 4 weeks. All of the patients also received mesalazine with their treatments. After the 4 weeks had passed, it was seen that the group receiving the enemas was the only one to have a significant reduction in their mean symptom score (19).

Side Effects: No safety concerns.

Dosage: 100 mL/twice a day, for 4 weeks.

Class of Therapy: Herbal Therapy

Name of Therapy: *Andrographis paniculata* extract (HMPL-004)

Brand Name: Swanson, Nature's Way, Vitacost

Mechanism of Action: *Andrographis paniculata* has been shown to inhibit the activity of COX-1 by binding to it, preventing it from converting arachidonic acid into prostaglandins (51). It has also been shown to inhibit the NF-κB pathway by blocking its activation (52).

Efficacy: A randomized, double-blind, placebo-controlled trial examined the efficacy of HMPL-004 in treating UC in 224 patients with mild to moderate UC. Patients received either 1200 mg/day, 1800 mg/day, or placebo for 8 weeks. After 8 weeks, it was seen that 45% and 60% of the patients receiving 1200 mg and 1800 mg, respectively, had a clinical response. The response rate of the 1800 mg/day group was significantly different than the placebo group's (40%). However, remission rates between the placebo group and the experimental groups were not significantly different. The remission rates were as follows: the 1200 mg/day group had a remission rate of 34%, the 1800 mg/day group had a remission rate of 38%, and the placebo group had a remission rate of 25% (20).

Side Effects: Diarrhea, rash, abdominal pain, nausea, flatulence, headache.

Dosage: 1200 mg/day or 1800 mg/day, for 8 weeks.

Class of Therapy: Herbal Therapy

Name of Therapy: Xilei-san suppository

Brand Name: N/A

Mechanism of Action: Xilei-san has been shown to reduce infiltration of the intestinal mucosa by inflammatory cells (neutrophils and macrophages) by downregulating the production of IL-1β. Xilei-san has also been shown to increase the expression of colonic MIP-3α, which is involved in mucosal barrier repair (53).

Efficacy: Several Chinese studies have examined the efficacy of the herbal medicine Xilei-san in treating ulcerative proctitis. One study with 35 ulcerative proctitis patients compared the efficacy of Xilel-san and dexamethasone enemas in treating the condition. It was found that that after 12 weeks, both treatments significantly improved the clinical, endoscopic, and histological scores of the patients, compared to their baselines (22). In a double-blind, placebo-controlled study, the efficacy of xilei-san suppositories was investigated in 30 patients with intractable ulcerative proctitis. The patients in this study had already received either topical mesalamine or corticosteroids for at least 4 weeks. This study randomized patients and gave them either xilei-san suppositories (n = 15) or placebo suppositories (n = 15). After 2 weeks, the number of patients that achieved remission in the xilei-san suppositories group was significantly higher than the placebo group. After 180 days, 81.8% of the patients in the suppositories group were without relapse, compared to the 16.7% in the placebo group (23).

Side Effects: No safety concerns.

Dosage: 0.1 g/dose per day, for 180 days.

Class of Therapy: Herbal Therapy

Name of Therapy: Kui Jie Qing enemas

Brand Name: N/A

Mechanism of Action: No studies have determined the mechanism of action for Kui jie Qing enemas.

Efficacy: A randomized controlled trial with 118 UC patients examined the efficacy of the Chinese remedy Kui jie qing enemas in treating the condition. The experimental group (n = 95) received the Kui jie qing enemas 4 times daily while the control group (n = 11) received sulfasalazine, oral prednisolone, and prednisolone enemas. They found that 72% of the patients in the experimental group were cured, while only 9% of the control group was cured. However, the researchers did not clearly define what was classified as "cured" and what was classified as an "improvement" (24).

Side Effects: No safety concerns.

Dosage: Enemas, 4 times daily, for 20 days. Authors did not specify dosages in the enemas.

Class of Therapy: Herbal Therapy

Name of Therapy: Yukui tang tablets

Brand Name: N/A

Mechanism of Action: No studies have determined the mechanism of action for Yukui tang tablets.

Efficacy: One trial examined the efficacy of oral Yukui tang tablets in treating patients with active UC. The experimental group consisted of 118 patients. This group received the tablets and herbal decoction enemas, along with oral prednisolone (15 mg/day), neomycin, and vitamin B. The 86 patients in the control group received low doses of oral prednisolone, neomycin, and vitamin B. The remission rate and response rate in the experimental group was 33% and 51%, respectively. In the control group, the remission rate was 17% and the response rate was 43% (24).

Side Effects: No safety concerns.

Dosage: Authors did not specify dosages.

Class of Therapy: Herbal Therapy

Name of Therapy: *Plantago ovata* seeds

Brand Name: Health Embassy, Starwest Botanicals

Mechanism of Action: *Plantago ovata* seeds have been shown to decrease the levels of colonic leukocyte infiltration. They perform this activity through decreasing intestinal levels of leukotriene B4. It has also been seen that these seeds can downregulate the levels of TNF-α, reducing the levels of colonic inflammation (54).

Efficacy: One open label, parallel-group, multicenter, randomized clinical trial with 105 patients examined the efficacy of *Plantago ovata* seeds in preventing relapse in patients with UC. Patients were randomized into three groups: a *Plantago ovata* seed group (received 10 g, twice a day), a mesalamine group (received 500 mg, three times a day), and a combined *Plantago ovata* seed and mesalamine group (same doses as the other groups). After 12 months, the *Plantago ovata* seeds group had a relapse rate of 40% (14/35). The mesalamine group had a relapse rate of 35% (13/37). The group with the combined treatments had a relapse rate of 30% (9/30). The researchers concluded that one treatment was not significantly better than the other. They stated that *Plantago ovata* seeds may be as effective as mesalamine in maintaining remission (25).

Side Effects: Constipation, flatulence, bloating.

Dosage: 10 g/twice a day, for 12 months.

Class of Therapy: Herbal Therapy

Name of Therapy: *Oenothera biennis*

Brand Name: MaxEPA

Mechanism of Action: *Oenothera biennis* contains γ-linolenic acid, which can be metabolized to generate dihomo-γ-linolenic acid (DGLA). DGLA can then be converted by either cyclooxygenase or lipoxygenase to produce anti-inflammatory eicosanoids. These prostaglandins and leukotrienes are involved in resolving the inflammatory response (55).

Efficacy: One placebo-controlled trial with 43 stable UC patients examined the efficacy of MaxEPA, alongside normal treatment, in resolving the condition. This trial had three groups: the MaxEPA group (n = 16), the super evening primrose oil group (n = 19), and an olive oil group (n = 8) as the placebo. These treatments lasted 6 months. It was found that evening primrose oil significantly improved stool consistencies and maintained this difference after treatment was discontinued. The condition did not significantly improve in any of the groups, however (26).

Side Effects: Safety concerns have not been evaluated in pregnant women. Otherwise, no safety concerns.

Dosage: 1 g/capsule. Patients received 12 capsules daily for 1 month, followed by 6 capsules daily for 5 months.

Class of Therapy: Herbal Therapy

Name of Therapy: Wormwood herb (*Artemisia absinthium*)

Brand Name: Health Embassy, Starwest Botanicals, Great Fermentations

Mechanism of Action: Wormwood herb contains cardamonin, which has been shown to inhibit the NF-κB pathway. Wormwood herb also contains artemisin, which is metabolized into artesunate. It was found that artesunate prevented TNF-α from inducing the nuclear translocation of NF-κB and thus its

subsequent DNA binding and transcriptional activity. This interference in the NF-κB pathway results in a decrease in the levels of IL-1β, IL-6, and IL-8 (56).

Efficacy: In a double-blind study with 40 Crohn's disease patients on stable daily doses of steroids, the efficacy of wormwood herb on treating the condition was examined. Patients were randomized and received either wormwood herb or placebo for 10 weeks. It was found that the patients receiving the wormwood herb had a remission rate of 60% (13/20). The placebo group did not have any patients achieve remission (27). Another study with 20 patients with active Crohn's disease also examined the efficacy of wormwood herb in treating the condition. In addition to their existing therapy, patients were given either dried powdered wormwood or placebo. After 6 weeks, 80% (8/10) of wormwood patients achieved clinical remission, while only 20% (2/10) of the placebo patients achieved remission (28).

Side Effects: Muscle aches, vomiting, nausea, insomnia.

Dosage: First study: 500 mg/three times a day, for 10 weeks. Second Study: 750 mg/three times a day, for 6 weeks.

Class of Therapy: Herbal Therapy

Name of Therapy: *Tripterygium wilfordii*

Brand Name: Thunder God Root, NOW

Mechanism of Action: *Tripterygium wilfordii* has been shown to target a multitude of proteins. Pro-inflammatory proteins, such as COX-2 and Nitric oxide synthase area targeted by *Tripterygium wilfordii* and inhibited. Several nuclear receptors are also targeted by components of *Tripterygium wilfordii*, such as progesterone receptors, estrogen receptors, and androgen receptors (57).

Efficacy: There have been two placebo-controlled studies that have examined the efficacy of *Tripterygium wilfordii* (GTW) in preventing the recurrence of postoperative Crohn's disease. The first study contained 45 patients and randomly assigned them to receive either mesalazine or GTW. Both groups had no clinical recurrence after three months. After 6 months, the recurrence rates (18% GTW vs 22% mesalazine) were not significantly different. At 12 months, the recurrence rates (32% GTW vs 39% mesalazine) were not significantly different either (29). The second trial contained 39 patients that had undergone resection for Crohn's disease 2 weeks prior to receiving the treatments in the study. The patients were treated with either GTW (n = 21) or sulfasalazine (n = 18). It was found that the clinical recurrence rate in the GTW group was 6%, compared to the recurrence rate of 25% in the sulfasalazine group. These findings suggested that GTW was more effective than sulfasalazine in preventing recurrence of postoperative CD (30).

Side Effects: Upset stomach, diarrhea, skin reactions, vomiting.

Dosage: Authors did not provide dosages.

Class of Therapy: Herbal Therapy

Name of Therapy: *Boswellia serrata*

Brand Name: Pure, Nature's Answer, Piping Rock, Thorne Research

Mechanism of Action: *Boswellia serrata* has been shown to inhibit the formation of leukotrienes through the inhibition of 5-lipoxygenase (59).

Efficacy: In one study, the efficacy of *Boswellia serrata* in treating UC was compared to sulfasalazine. This study had 30 patients with chronically active UC. Of those 30 patients, 20 received 900 mg/day (divided into three doses per day) of gum resin from *Boswellia serrata* and the remaining 10 patients received sulfasalazine (3 grams/day, divided into three doses per day) for 6 weeks. In the *Boswellia serrata* group, 14/20 patients achieved remission, while 4/10 in the sulfasalazine achieved remission. The Boswellia serrata group also saw an improvement in the symptoms of 18/20 patients, while the sulfasalazine group saw improvement in 6/10 patients (21).

Side Effects: Weight loss possible, due to increase thyroid function.

Dosage: 900 mg/day (divided into 3 doses a day), for 6 weeks.

Class of Therapy: Omega 3 fatty acid

Name of Therapy: Fish Oil

Brand Name: Nordic Naturals, GNC, Bronson Vitamins, Nature's Bounty, Sundown Naturals

Mechanism of Action: Omega 3 fatty acids (ω3FA) have been implicated in the synthesis of both inflammatory and anti-inflammatory eicosanoids. One possible mechanism is that the ω3FA, eicosapentaenoic acid, can replace arachidonic acid in the cyclooxygenase and lipoxygenase pathways, preventing its conversion into prostaglandins and leukotrienes. ω3FA have also been shown to be involved in the synthesis of molecules that resolve inflammation, such as resolvins, protectins, and maresins (35).

Efficacy: Fish oil does not appear to provide a substantial benefit to individuals with IBD. There is some improvement in patients with UC, but more research is required (1). In a prospective 12 month randomized trial with 87 UC patients, it was seen that those that received fish oil showed measurable, but not significant clinical benefit. However, patients (n = 53) that entered the trial in relapse had a significant reduction in their requirement for corticosteroids after two months of treatment (2).

Side Effects: Nausea, loose stools, belching, upset stomach, rash.

Dosage: 20 mL/day HiEPA fish oil, for 1 year.

Class of Therapy: Curcuminoids

Name of Therapy: Curcumin

Brand Name: tnvitamins, Piperine, Puritan's Pride, NOW

Mechanism of Action: Curcumin exhibits several inhibitory effects on enzymes and several pro-inflammatory cytokines. It has been seen to inhibit COX-1 and COX-2, which convert arachidonic acid into prostaglandins (6). Curcumin has also been shown to induce apoptosis in neutrophils (38). Beyond that, curcumin has been implicated in the downregulation of pro-inflammatory cytokines through its binding and inactivating of NF-κB (39).

Efficacy: In a small pilot study of 5 patients with Crohn's disease and 5 patients with ulcerative proctitis, it was seen that cucumirin lowered the CDAI in 4 out of 5 patients with Crohn's. It was also seen that all of the proctitis patients showed improvement (5). Another study that had 5 patients with UC and 5 patients with Crohn's examined the efficacy of different curcumin treatment regimes. The UC patients received 550 mg twice a day for one month. The Crohn's patients received 360 mg three times a day for one month, and then 550 mg four times a day for two more months. It was seen that that both sets of patients had an improvement in their symptoms. The Crohn's patients had an average reduction in their CDAI by 55 points (7).

Side Effects: Headache, diarrhea, rash, yellow stool.

Dosage: For UC patients: 550 mg/twice per day, for one month. For Crohn's disease patients: 360 mg/three times a day, for one month. 550 mg/four times a day, for two months.

Class of Therapy: Acupuncture

Name of Therapy: Acupuncture with moxibustion

Brand Name: N/A

Mechanism of Action: While the mechanism of action is not entirely understood, several anti-inflammatory effects have been observed in rat models. Moxibustion has been shown to significantly reduce the levels of IL-8 and increase the levels of IL-10. It has also been seen that moxibustion inhibits the activation of NF-κB p65. This effect blocks the TLR9 signaling pathway, which is involved in inducing the innate immune response in inflammation (58).

Efficacy: A meta-analysis was performed to determine the efficacy of treating UC with acupuncture and moxibustion. This analysis found 10 trials that compared the efficacy of oral sulfasalazine to acupuncture and/or moxibustion therapy. The analysis concluded that acupuncture and moxibustion therapy demonstrated better efficacy in treating IBD than oral sulfasalazine. However, the authors also stated that definitive conclusions cannot be made because the trials they examined did not provide sufficient evidence (31).

Side Effects: Soreness, bruising, fatigue.

Dosage: Authors stated that 3 types of acupuncture were used across 6 different studies. Did not specify the kinds of acupuncture, however.

Class of Therapy: Exercise

Name of Therapy: Yoga

Brand Name: N/A

Mechanism of Action: Several mechanisms have been proposed for yoga. Physical activity has been shown to lower the levels of inflammatory biomarkers through its effect on adipocytes, as they have been shown to secrete TNF-α and are involved in chronic inflammation. Beyond that, it has been shown that the IL-6 that is released during physical activity has an inhibitory effect on TNF-α production. The IL-6 that is released can also induce IL-10 production, which is involved in resolving inflammation (60).

Efficacy: A trial with 60 ulcerative colitis patients and 40 Crohn's patients examined the efficacy of a yoga intervention during the clinical remission phase. After 8 weeks, it was found that fewer patients reported arthralgia than when the trial began. The number of patients reporting intestinal colic was higher in the control group than it was in the experimental group (32).

Side Effects: Soreness, fatigue.

Dosage: 1 hr/day, for 8 weeks.

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https://www.gastrojournal.org/article/S0016-5085(17)36382-5/fulltext

Class of Therapy: Herbal Therapy

Name of Therapy: Indigo naturalis

Brand Name: Qing-Dai

Mechanism of Action: Indigo naturalis (IN) is a traditional Chinese medicine that contains ligands for the aryl hydrocarbon receptor and promotes regeneration of the mucosa by inducing production of interleukin 22(61). A compound found within, tryptanthrin, was reported to inhibit interferon-γ production by lymphocytes from Peyer's Patches (63).

Efficacy: There is limited evidence suggesting that indigo naturalis is effective in treating IBD (62). In a randomized, placebo-controlled trial of 86 patients with active UC, the study found that 8 weeks of IN (0.5–2.0 g per day) to be effective in inducing a clinical response in patients with UC. Patients who received 0.5, 1.0, or 2.0 g of IN daily exhibited greater improvements in the Mayo score at week 8 compared with patients who received the placebo. Proportions of patients in clinical remission at week 8 were significantly higher in the 1.0 g IN group (55.0%) and the 2.0 g IN group (38.1%) than in the placebo group (4.5%). Proportions of patients with mucosal healing were 13.6% in the placebo group, 56.5% in the 0.5 g IN group, 60.0% in the 1.0 g IN group, and 47.6% in the 2.0 g IN group. The trial was eventually terminated due to an external reason: a report of pulmonary arterial hypertension in a patient who used self-purchased IN for 6 months. The authors of the study noted that IN should not be generally used until additional further evidence is obtained regarding safety. (61)

Side Effects: pulmonary arterial hypertension, mild liver dysfunction, headache, gastrointestinal symptom.

Dosage: .5-2.0 g daily of IN, 8 weeks.

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https://www.gastrojournal.org/article/S0016-5085(18)35278-8/fulltext

Class of Therapy: Therapy

Name of Therapy: Acceptance and commitment therapy (ACT)

Brand Name: N/A

Mechanism of Action: Patients with Crohn's disease or ulcerative colitis have relatively high levels of stress and psychological dysfunction. Acceptance and commitment therapy (ACT) is a psychological intervention that comprises acceptance and mindfulness procedures, along with commitment and behavior change strategies, to increase psychological flexibility and reduce stress. The ACT program consisted of 8 90-minute weekly sessions in groups of 14–16 participants. The course manual was based on contemporary ACT models and tailored toward IBD patients with an emphasis on reducing stress, and all program materials are available in the supplementary materials (64).

Efficacy: Stress, anxiety, and depression place a significant burden on IBD patients and, although the link between stress and IBD has been contentious,10 recent data indicate that psychological dysfunction may be causally associated with both onset and subsequent IBD activity. Overall, 79 participants were included in the complete case intention-to-treat analysis. There were 39% and 45% reductions in stress in the treatment group from baseline to 8 and 20 weeks, respectively, compared with 8% and 11% in the control group. ACT was associated with reduced perceived stress (P = .036) and depression (P = .010), but not anxiety (P = .388), compared with control individuals. In the intention-to-treat analysis, changes in all 4 quality-of-life domains over time were similar in the ACT and control groups. In the per-protocol analysis, the overall well-being quality-of-life domain improved in the ACT group compared with the control group (P = .009). Subjective and objective disease activity measurements were similar between groups over the study period. Hair cortisol concentrations correlated with stress (rs = 0.205, P = .050) and anxiety (rs = 0.208, P = .046) at baseline but did not change significantly in the ACT group over the study period compared with the control group (P = .831) (64).

Side Effects: confusion and drowsiness (65).

Dosage: 8 90-minute weekly sessions in groups of 14–16 participants (64).

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https://journals.lww.com/md-journal/Fulltext/2018/11160/Efficacy_of_vitamin_D_in_treatment_of_inflammatory.4.aspx

Class of Therapy: Vitamin therapy

Name of Therapy: Vitamin D

Brand Name: N/A

Mechanism of Action: Vitamin D (VitD) deficiency is prevalent in patient with inflammatory bowel disease (IBD). Recent studies have found that VitD can induce and maintain IBD remission through

antibiosis, anti-inflammatory, and repair of intestinal mucosal barriers, thus improving the patient's disease activity and quality-of-life. The purpose of this meta-analysis is to evaluate the therapeutic effect and safety of VitD in the treatment of IBD (66).

Efficacy: Eighteen Random controlled trials involving 908 patients were meta-analyzed. The results from the trials showed that VitD improved the 25(OH)D3 levels more significantly than the control group, and compared with lower doses, there were significant differences increasing 25(OH)D3 levels in high-dose VitD treatment while there was no significant difference in the adverse events between 2 groups. This study also showed that adjuvant therapy with VitD can reduce the relapse rate of IBD by 64%, but there are not significantly different in reducing the recurrence rate of the disease between high-dose and low-dose VitD, which is, on the one hand, related to the large difference in the specific dose and method of VitD used between the different trials. The erythrocyte sedimentation rate (ESR) and high-sensitivity C-reactive protein (hsCRP) of the VitD and the control group showed no statistically significant difference (66).

Side Effects: unusual fatigue or weakness, and mild gastrointestinal events (66).

Dosage: between 800 and 7000 IU/d.

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https://www.cghjournal.org/article/S1542-3565(18)30751-1/abstract

Class of Therapy: Fecal microbiota transplant

Name of Therapy: FMT

Brand Name: N/A

Mechanism of Action: FMT is a procedure in which fecal or stool matter is collected from a healthy donor and placed into a patients' GI tract to correct the dysbiosis and to restore healthy conditions (68). FMT has already been successfully used for the treatment of recurrent *Clostridium difficile* infection (rCDI) resistant to conventional antibiotic therapies with an efficacy >90% (69).

Efficacy: It appears that FMT does have the potential to induce remission in UC, but unknowns remain with respect to donor selection, optimal dosing frequency, role of anti-biotic preconditioning, as well as safety and efficacy as a maintenance treatment. In a study conducted with the Academic Medical Center in Amsterdam, researchers administered FMT via a nasoduodenal tube at times zero and 3 weeks vs autologous stool, but found no significant difference in response. However, in another study from McMaster University, administered weekly FMT enemas for 6weeks vs tap water enemas and found that 9 of 38(24%) in the FMT group vs 2 of 37 (5%) in the placebo group achieved remission. The authors of the MacMaster study noted that 7 of 9 responders received FMT from the same single donor, suggesting that donor selection is important in FMT therapy of IBD. Additional standardized trials should be conducted to fully assess the efficacy of FMT (67).

Side Effects: mild fever and mild GI symptoms (abdominal discomfort, flatulence, diarrhea, constipation, and vomiting).

Dosage: Varies.

Animal Studies

Class of Therapy: Herbal Therapy

Name of Therapy: Rutin

Brand Name: Thompson, Vitacost, Country Life, Freeda

Mechanism of Action: It has been shown that certain flavonoids can inhibit both the cyclooxygenase and lipoxygenase pathways. This would prevent the conversion of arachidonic acid to prostaglandins and leukotrienes, which are involved in propagating an inflammatory response (40).

Efficacy: Studies involving the oral administration of rutin to rats with acid-induced colitis have shown that this treatment can diminish inflammation in the colon. However, more research is required to examine its efficacy in treating humans (8).

Side Effects: Headache, dizziness, blurred vision, redness.

Class of Therapy: Herbal Therapy

Name of Therapy: Bromelain (pineapple juice)

Brand Name: Puritan's Pride, Jarrow Formulas, Bronson, GNC, Vitamin Shoppe

Mechanism of Action: Bromelain partially inhibits the synthesis of PGE2, decreasing the total amounts of pro-inflammatory prostaglandins that are circulating. This shifts the ratio of circulating prostaglandins from favoring pro-inflammatory prostaglandins to favoring anti-inflammatory prostaglandins. This leads to the anti-inflammatory prostaglandins binding more readily to the receptor sites that they share with the pro-inflammatory prostaglandins, diminishing the inflammatory response (41).

Efficacy: A study examined the efficacy of bromelain in treating colitis in mice with proxicam-induced colitis. The experimental mice were divided into two groups. One group received fresh pineapple juice for 6 months, while the other received boiled pineapple juice for 6 months (to inactivate the enzymes). The mice that consumed the fresh pineapple juice survived significantly longer than the boiled juice group did. It was also seen that the fresh pineapple juice group had a decrease in their mean histologic colon inflammation scores, as well as a lower incidence of inflammation associated colonic neoplasia (10).

Side Effects: Diarrhea, nausea, flatulence.

Class of Therapy: Herbal Therapy

Name of Therapy: Pomegranate

Brand Name: N/A

Mechanism of Action: Pomegranate byproducts have been shown to inhibit the growth of pathogenic gut bacteria and increase the growth of certain beneficial bacteria, such as *Bifidobacterium breve* and *Bifidobacterium infantis* (42). These byproducts have also been shown to activate peroxisome proliferator-activated receptors (PPARs). PPARs can inhibit pro-inflammatory molecules, such as NF-κB, from binding to DNA, thus diminishing the overall inflammatory response (43).

Efficacy: One study investigated the efficacy of pomegranate (*Punica granatum*) in treating UC and inflammation in mice. In this study, the researchers induced ulcerative colitis in mice using 2% dextran sulfate sodium. These mice were then treated with *Punica granatum* (100 mg/kg) and it was seen that there was a significant decrease in the colonic inflammation (11). Both *in vivo* and *in vitro* studies have demonstrated that pomegranate exhibits anti-cancer and anti-inflammatory effects (1). However, these effects need to be further examined in human models to determine their efficacy in treating UC and/or Crohn's.

Side Effects: Possible allergic reactions involve: itching, swelling, runny nose, and difficulty breathing.

Class of Therapy: Herbal Therapy

Name of Therapy: Green Tea Polyphenols

Brand Name: Puritan's Pride, Nature's Bounty

Mechanism of Action: Green tea polyphenolic compounds have been shown to exhibit anti-inflammatory and anti-cancer effects. Epigallocatechin gallate (EGCG) and epicatechin gallate (ECG) are two compounds that are found in green tea and can induce apoptosis in monocytes at concentrations between 10 and 50 uM. Several cancer cell lines are also inhibited by green tea polyphenols through their inhibition of DNA synthesis and their generation of peroxyl radicals in cancer cells (44).

Efficacy: In a study with mice that had experimentally-induced colitis, researchers found that those treated with green tea extract showed an improvement in their disease symptoms (attenuation of diarrhea and weight loss). They also noted a significant reduction in the levels of colonic myeloperoxidase and TNF-α in the colon (12).

Side Effects: Upset stomach, constipation.

Class of Therapy: Herbal Therapy

Name of Therapy: Resveratrol

Brand Name: ResVitále, Puritan's Pride, Pure Synergy, Genex Formulas

Mechanism of Action: Resveratrol has been shown to bind to and inhibit COX-1 and COX-2, as well as activate peroxisome proliferator-activated receptors (PPARs). The direct binding to the COX enzymes

reduces the amount of prostaglandins that are generated. Resveratrol has also been shown to downregulate the expression of COX-2 (45).

Efficacy: In mice models, resveratrol has been seen to suppress colitis-induced inflammatory molecules (TNF-α, IL-6, COX-2) (13). A human trial assessing the effects of resveratrol on inflammation found that individuals treated with 40 mg/day had significant reductions of plasma TNF-α and C-reactive protein in their blood plasma levels (IBD was not the focus of this study) (14).

Side Effects: No safety concerns.

Class of Therapy: Herbal Therapy

Name of Therapy: Cinnamon Extract

Brand Name: Watkins, McCormick, Natrol

Mechanism of Action: Studies of *C. cassia* bark have shown that it exhibits an inhibitory effect on the production of nitric oxide through inhibiting the activation of the transcription factor NF-κB. Compounds in *C. ramulus* extract have been shown to suppress the expression of COX-2 and nitric oxide as well (46).

Efficacy: In colitis-induced mouse models, it has been seen that cinnamon extract ameliorates the experimentally-induced condition. Mice were orally fed either PBS (phosphate buffer solution) or cinnamon extract (50 μg/g body weight) for 20 days. Following colitis induction, both groups of mice exhibited weight loss after the second day. The mice that were treated with the cinnamon extract had a 95% survival rate, compared to the 50% survival rate in the PBS group. It was also seen that there was a significant reduction in the colonic inflammation in the cinnamon extract group (15).

Side Effects: No safety concerns.

Class of Therapy: Herbal Therapy

Name of Therapy: Freeze-dried Black Raspberry Powder (BRB)

Brand Name: Berrihealth, Eclectic Institute, Virgin Extracts

Mechanism of Action: It is believed that BRB inhibits the phosphorylation of IκBα. Normally, the phosphorylation of this target marks it for ubiquitinylation and proteasomal degradation. The degradation of IκBα allows NF-κB to enter the nucleus and activate its target genes, leading to the production of pro-inflammatory molecules. By preventing the phosphorylation of IκBα, the target genes are not activated, which leads to reduced levels of COX-2, TNF, and IL-1B (16).

Efficacy: In experimental UC mice models, freeze-dried black raspberry powder has been shown to significantly reduce injury and inflammation in the colon. Two groups of mice were studied for 14 days; one group (n = 10) received the freeze-dried powder treatment while the control group (n=10) received plain drinking water. There was a noticeable maintenance of the body mass in the experimental group, as well as reductions in colonic shortening and ulceration (16).

Side Effects: No safety concerns.

Class of Therapy: Herbal Therapy

Name of Therapy: American Ginseng

Brand Name: Puritan's Pride, NOW, Prince of Peace

Mechanism of Action: Ginseng has been shown to target and inhibit several molecules involved in the inflammatory response. Ginseng can directly target and inhibit NF-κB, as well as reduce the expression of COX-2. Ginseng has also been shown to inhibit the inflammatory cytokines that are produced by NF-κB activation (47).

Efficacy: One study examined how effective American ginseng was in suppressing colon cancer associated with colitis in mice. The researchers used azoxymethane and dextran sulfate sodium to induce colitis in the mice. In the experimental group, several proteins involved in colon cancer associated with colitis were present in lower levels than when compared to the control group. The findings from this study suggest that American ginseng offers protection from colon cancer associated with colitis (17).

Side Effects: Diarrhea, itching, headache, insomnia.

Class of Therapy: Herbal Therapy

Name of Therapy: Ginger Extract

Brand Name: NOW, Puritan's Pride, OliveNation

Mechanism of Action: Ginger extract has been shown to inhibit LPS-induced COX-2 expression, leading to reduced levels of PGE2 (48). Ginger extract also appears to have an inhibitory effect on the NF-κB pathway, although it is unclear at which step. It has been seen that ginger extract results in diminished levels of NF-κB in rats (49).

Efficacy: One study examined the efficacy of ginger extract in treating rats with induced UC. The condition was induced through intra-rectal acetic acid administration. Three days before the induction of the condition, the rats received 3 different doses of either ginger extract, sulfasalazine, or vehicle. The rats continued to be treated for seven days after the induction. Afterwards, inflammatory responses were determined by measuring levels of TNF-α, prostaglandin E2, and myeloperoxidase. It was found that the group receiving ginger extract produced comparable results to the group receiving sulfasalazine treatment (18).

Side Effects: Abdominal pain, diarrhea, burning feeling in mouth/throat.

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