Nutritional, Nutraceutical, and Herbal Supplements in the Treatment of Inflammatory Bowel Disease

Abstract
Complimentary therapies for inflammatory bowel disease are a growing interest, with goals of maintaining remission and reducing the need for more aggressive conventional treatments. Although widely utilized by patients, limited and heterogeneous research has complicated the clinical decision to rely on alternative care for effective disease management. Here we present the most relevant, up to date information regarding the use of herbs, fish oil, probiotics and vitamin D for the treatment of both Crohn’s and Ulcerative Colitis, which will aide clinicians in choosing the most effective collaborative treatment based on their patient’s symptoms and disease state.

Introduction
In Canada, the incidence rate has increased to 10 200 people being diagnosed with inflammatory bowel disease (IBD) each year (Crohn’s and Colitis Foundation of Canada 2013). Crohn’s Disease (CD) and Ulcerative Colitis (UC), two major forms of idiopathic IBD, are characterized by chronic and uncontrolled inflammation within the gastrointestinal tract. Currently, 233 000 Canadians are living with IBD with direct medical costs totaling over $2 billion dollars each year (Rocchi 2012). Conventional therapies such as immunomodulators and 5-aminosalicylic acid (5-ASA) have shown adverse effects (i.e. interstitial nephritis) and have caused patient drop-out rates as high as 22% (Jonkers 2012, Siegel 2005). In addition, approximately 38% of patients treated with 5-ASA are non-responders (Duricova 2010, Gisbert 2002).

Increased recognition of the limitations in conventional medicine has led to growing interests in integrative therapies by patients with IBD (Hilsden 2011). Several studies indicate that supplements are a widely used type of complementary and alternative medicine (CAM) among IBD patients (Hilsden 2011, Sutherland 1994). Limited research and lack of education surrounding the use of CAM makes it difficult for health care professionals to effectively counsel patients regarding the use of supplements in IBD (Hilsden 2011). Given their widespread usage, health care practitioners should be familiar with the potential benefits of nutraceutical supplements for IBD to offer superior care to their patients (Hilsden 2011).

The present paper will investigate the mechanisms of action and clinical effectiveness of several well-documented supplements in managing IBD. The supplements to be examined include Aloe vera, Andrographis paniculata, Bboswellia serrata, Curcuma longa, fish oil, probiotics, and vitamin D.
Mechanism of IBD

The etiology of IBD is unknown. Normally, mucosal immune cells within the intestinal epithelium discriminate commensal from pathogenic bacteria, however those afflicted with IBD are unable to discern between the two (Friedman 2012). Instead, an inappropriate immune reaction is levied against the commensal bacteria leading to elevated levels of pro-inflammatory cytokines and chemokines including tumor necrosis factor-alpha (TNF-α), interferon-gamma (INF-γ), and interleukin-1-beta (IL-1β) (Friedman 2012). For example, compared to healthy controls, there is a significant difference in serum TNF-α concentration in CD and UC patients, resulting in chronic mucosal damage (Avdagic 2013, Friedman 2012). Furthermore, reactive oxygen species produced by activated neutrophils result in the damage of mucosal proteins in patients with IBD (McKenzie 1999).

Mechanisms of Conventional Medicine in IBD

5-ASA is a well-established therapy in the management of UC, but its role in CD is less clear (Criscuoli 2013). The anti-inflammatory and immunosuppressive properties of 5-ASA provide evidence for a multifactorial basis of therapeutic action (Baumgart 2005). A primary target is the nuclear factor kappa beta (NF-κβ) pathway. NF-κβ is normally maintained in an inactive state by inhibitory protein kappa-beta (Iκβ). In patients with IBD, however, the presence of pro-inflammatory cytokines such as TNF-α, phosphorylation of Iκβ activates NF-κβ, initiating the synthesis of more pro-inflammatory cytokines (Jobin 2000). 5-ASA has been shown to inhibit TNF-α-stimulated Iκβ phosphorylation, disrupting a critical signal transduction pathway involved in the onset and progression of chronic inflammation (Fang 1999).

The supplements to be examined target similar pathways as 5-ASA and primarily influence the progression of IBD through reduction of the aforementioned pro-inflammatory cytokines. Thus, their use as alternatives for non-responders to conventional medicine is implicated.

Herbal Medicine

The perceived natural properties of herbal therapies have led to increased use of such therapies by patients with IBD (Hilsden 2011). In the present paper, four notable herbal therapies, namely Aloe vera gel, Andrographis paniculata, Boswellia serrata, and Curcuma longa, will be evaluated.

Aloe vera gel, an extract of Aloe barbadensis, is a common herbal therapy used in the treatment of IBD (Hilsden 2003, Rahimi 2009). A double-blind, randomized controlled trial (RCT) showed that four weeks of aloe vera gel administration to patients with active UC had greater symptom alleviation than placebo. This difference, however, was not statistically significant (p=0.09) (Langmead 2004).

A. paniculata, namely andrographolide, has been shown to significantly reduce the transcriptional activity of NF-κβ and decrease secretions of pro-inflammatory cytokines including TNF-α and IL-6, both of which have been shown to be elevated in patients with IBD (Chao 2010, Chiou 2000). A double-blind RCT (n=224) reported greater clinical response in UC patients receiving A. paniculata treatment than placebo, which is characterized as a decrease in the total Mayo score of three points and 30% accompanying decrease in rectal bleeding (Sandborn 2013). Similar results were reported in a clinical trial comparing the efficacy of A. paniculata to conventional mesalazine therapy (Tang 2011).

Animal models suggest boswellic acids, the active component of Boswellia serrata, mitigate leukocyte recruitment thereby protecting the intestinal mucosa from the inappropriate immune reaction characteristic of IBD (Anthoni 2006, Hartmann 2012). Two notable studies compared B. serrata extract (BSE), given as 400mg capsules, against placebo in patients with IBD. Madisch (2007) found a statistically significant difference in remission rates between BSE and placebo groups in patients with collagenous colitis was found. However, in a 52 week trial, Holtmeier and colleagues (2011) found that remission rates were not statistically significant between control and treatment groups (p=0.85). Nevertheless, BSE treatment was shown to be well tolerated and demonstrated long term safety as Holtmeier (2011) reported that those treated with BSE experienced less adverse events than those treated with placebo (p=0.087).

Though the aforementioned herbal therapies have yielded greater rates of remission and clinical response compared to placebo in the management of IBD, failure to reach statistical significance warrants additional research to evaluate their effectiveness, perhaps at greater dosages and with larger sample sizes (Langmead 2004, Sandborn 2010, Sandborn 2013).

Historically, Asian countries experience approximately half the incidence rate of IBD seen in North American countries (Lofus 2004). This can be attributed to the prevalence of Curcuma Longa in the traditional diet in Asian countries and has been shown to improve colonic morphology by counteracting the generation of damaging reactive oxidative species (ROS) produced by inflamed colon cells (Irving 2011). Additionally, Curcumin inhibits the secretion of inflammatory cytokines by modulating the activation of NF-κβ, an upregulated in patients with IBD (Atreya 2008). Curcumin suppresses NF-κβ activation by blocking the phosphorylation of inhibitory factor Iκβ kinase, down-regulating the expression of downstream pro-inflammatory eicosanoids (Atreya 2008). Curcumin has also been found to block the action of proinflammatory TNF-α primarily through inhibiting the production of TNF transcription factors leading to transcriptional repression (Aggarwal 2013). In a pilot study of five patients with UC and five with CD, all patients improved over the two month period of Curcumin administration (Holt 2005). For both conditions, diarrhea, abdominal pain, and cramping decreased, and previously elevated serologic indexes of inflammation normalized. However, a major limitation of this study was the absence of a control group. In another multicenter RCT, patients administered with Curcumin in conjunction with 5-ASA saw significantly improved symptoms compared to placebo with 5-ASA. Patients treated with Curcumin also had a lower relapse rate six months post-study (Hanai 2006).
Furthermore, a prospective phase-1 study in adults using a significantly high dose of Curcumin to treat cancer (8 g/day), found no toxic effect (Cheng 2001), validating the safety of the dosage used to treat IBD.

**Fish Oil**

Dietary fat composition affects the immune responsiveness of gut-associated lymphoid tissue (Ruggiero 2009). Eicosanoids, noted mediators of inflammation, are generated from polyunsaturated fatty acids (PUFA) stored as membrane phospholipids (Calder 2006, Ruggiero 2009). Derivatives of n-6 (omega-6) PUFAs act as pro-inflammatory mediators, while N-3 (omega-3) PUFAs found in fish oil, specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), elicit anti-inflammatory effects (Fetterman 2009, Yates 2014). DHA and EPA decrease membrane percent composition of n-6 PUFAs as well as inhibit metabolism of their derivatives, resulting in an alternate series of much less potent eicosanoids (Cabrè 2012, Yates 2014). Other effects include decreased activation of NF-κB, and decreased production of inflammatory cytokines such as TNF-α and IL-1β, known to play a major role in the pathological inflammation associated with IBD (Cabrè 2012, Fetterman 2009, Yates 2014). N-3 PUFAs also lead to the production of pro-resolving mediators such as resolvins and protectins which stimulate and activate endogenous pathways thereby terminating inflammation by reducing TNF-α and INF-γ secretion (Serhan 2008).

N-3 PUFAs have been implicated as an intervention for IBD for decades due to their anti-inflammatory properties (Calviello 2013, Ferguson 2010). Despite the vast number of promising preclinical animal studies, as well as human RCTs indicating benefit with minimal side effects, there is a consistent inability to reach statistical significance (Calviello 2013, MacLean 2005). The results of the most recent systematic review are summarized in Table 1. Some sources of heterogeneity include differences in dose, source, placebo selection, and inconsistent reporting on a variety of outcomes (Cabrè 2012, MacLean 2005). The lack of evaluation of patient-related factors such as baseline consumption of PUFAs among other confounders, as well as underpowered sample sizes, may further explain the failure to reach significance (Balk 2007, Cabrè 2012). As a result, no optimal dose or formulation has been ascertained to date (Cabrè 2012, Ferguson 2010). In summary, more well-designed studies which take into account pertinent patient- and treatment-specific variables may be better able to replicate similar positive results in human studies.

**Probiotics**

Probiotics are microorganisms that confer a health benefit to the host (Fedorak 2012). The use of VSL#3 and Escherichia Coli Nissle 1917 (EcN) will be examined due to the existence of substantial evidence supporting their role in the management of UC. VSL#3 is a high-concentration probiotic preparation including eight various bacterial species (Sung 2013). VSL#3 has been shown to improve epithelial barrier function through up regulating anti-inflammatory cytokine pathways, specifically IL-10, as well as reduce the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and INF-γ (Fedorak 2012, Ng 2010, Sood 2009).

EcN is a well-characterized bacterial strain utilized as a probiotic drug (Sung 2013). EcN has an anti-inflammatory effect linked to the production of antimicrobial peptides. For example, EcN has been shown to induce human beta-defensin-2 (hBD-2 peptide) in human enterocytes in vitro. Antimicrobial peptides such as hBD-2 play a key role in enhancing the mucosal barrier to luminal bacteria (Wehkamp 2004). Moreover, EcN modulates expression of intestinal antimicrobial mechanisms by ultimately resulting in the secretion of IL-8, an antimicrobial cytokine. Thus, EcN facilitates the phagocytosis of pathogenic microbes (Lammers 2002, Trebichavsky 2010).

VSL#3 has been shown to be superior to placebo in reducing the disease activity of mild-to-moderate UC. Specifically, significantly more patients exhibited an improvement in their UC disease activity index (DAI) score of at least 50%, which includes rectal bleeding, compared to those who received placebo (Tursi 2010). Another study reported a statistically significant dose response for rectally administered EcN enema with 40mL resulting in clinical remission, defined as a DAI less than or equal to 2 (Matthes 2010). Further well-designed studies, however, are still warranted to support the promising results found for the use of VSL#3 in active UC in addition to the use of EcN in the management of inactive UC (Jonkers 2012).

**Vitamin D**

The main source of vitamin D is endogenous production in the skin upon exposure to ultraviolet radiation (Mouli 2014). It has been demonstrated that the prevalence of IBD increases as one ventures further from the equator (Maitreyi 2011), suggesting that low levels of vitamin D may contribute to disease pathogenesis and severity (Joseph 2009). The functions of vitamin D most central to IBD include tissue barrier formation and immune regulation (Kong 2013). Vitamin D is present in sufficient amounts, it promotes the expression of cell adhesion proteins, stabilizing tight junctions between epithelial cells in the gut (Kong 2013). Since mucosal barrier function is disrupted in IBD, this mechanism is important to ensure mucosal barrier homeostasis (Friedman 2012, Kong 2013). Vitamin D also has an important role in the immune system (Mouli 2014). Upon activation of toll-like receptors on macrophages, vitamin D is converted to the active 1,25-dihydroxyvitamin D3, leading to upregulation of vitamin D receptor (VDR) expression. VDR activation inhibits production of proinflammatory cytokines such as IL-6 and TNF-α ameliorating the disease (Mouli 2014).

Few studies have been performed in humans to assess the effect of vitamin D on IBD pathogenesis and severity. Table 1 illustrates interventional human studies examining the effects of vitamin D supplements on disease activity in CD. The findings suggest that vitamin D supplementation lowers relapse rates and improves Crohn’s DAI scores in patients with CD (Mouli 2014). However, the lack of studies testing the efficacy of vitamin D supplementation remains a significant limitation in the current literature.
D in UC, and the lack of a control group in some of the trials warrants further investigation (Mouli 2014). Patients with IBD should be screened for deficiencies in vitamin D before treatment is administered, thereby tailoring supplementation of vitamin D to individual patients’ needs (Mouli 2014).

**Conclusion**

With the common belief that CAM therapies are safer than conventional therapies, many patients with IBD are turning to integrative interventions to alleviate clinical symptoms and maintain remission. This review analyzed the beneficial effects of alternative therapies in the management of UC and CD. Exploring the mechanism of alternative therapies for IBD provides evidence for therapeutic benefits, since these treatments exert their effects in a similar manner to conventional therapies. The high non-responder rate associated with conventional therapies, warranted the examination of CAM therapies as a safe treatment for IBD.

Curcuma longa, when administered in conjunction with 5-ASA, has been shown to improve symptoms and decrease relapse rates. Vitamin D supplementation has been shown to be clinically effective in patients with CD, however further research is warranted in UC. The probiotics VSL#3 and EcN, have shown promising results in both inactive and active UC to relieve symptoms such as rectal bleeding but have not shown to be effective in CD. A. paniculata extract and B. serrata extract have both shown benefits compared to placebo controls in the management of symptoms and maintenance of remission but failed to reach statistical significance. Likewise, studies investigating the use of fish oil consistently report non-significant results, possibly due to vast heterogeneity across studies. Due to the lack of extensive research with sufficient patient sample size, further research is warranted for these aforementioned CAM therapies.

**Table 1. Clinical trials.**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Intervention</th>
<th>Trial Design (study length)</th>
<th>Dose</th>
<th>Subjects (n)</th>
<th>Findings</th>
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</thead>
<tbody>
<tr>
<td>Sandborn 2010</td>
<td>HMPL-004 (A Paniculata extract)</td>
<td>Randomized, double blind, placebo controlled (8 weeks)</td>
<td>1200 mg daily</td>
<td>Moderately active CD (n=101)</td>
<td>Remission rate (CDAI &lt; 150): HMPL-004 29.4%, placebo 14% (p=0.069)</td>
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<tr>
<td>Sandborn 2013</td>
<td>HMPL-004 (A Paniculata extract)</td>
<td>Randomized, double blind, placebo controlled (8 weeks)</td>
<td>1200mg or 1800mg daily</td>
<td>Mild-moderate UC (n=224)</td>
<td>Clinical response: HMPL-004 52%, placebo 40% (p=0.092) Clinical remission: HMPL-004 36%, placebo 25% (p=0.1173)</td>
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<tr>
<td>Tang 2010</td>
<td>HMPL-004 (A Paniculata extract)</td>
<td>Randomized, double blind vs 500mg mesalazine (8 weeks)</td>
<td>1200 mg daily</td>
<td>Mild-moderate UC (n=120)</td>
<td>Remission rate: HMPL-004 21%, mesalazine 16% (p&lt;0.05) Adverse event: HMPL-004 13%, mesalazine 27%</td>
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<td>Gupta 1997</td>
<td>Boswellia serrata gum resin extract (BSE)</td>
<td>Controlled trial vs 3g sulfasalazine (6 weeks)</td>
<td>1050 mg daily</td>
<td>Mild-moderate UC (n=30)</td>
<td>Remission rate: BSE 82%, sulfasalazine 75% (p&lt;0.05)</td>
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<tr>
<td>Madisch 2007</td>
<td>Boswellia serrata gum resin extract (BSE)</td>
<td>Randomized, double blind, placebo controlled (6 weeks)</td>
<td>1200mg daily</td>
<td>Collagenous colitis (n=31)</td>
<td>Remission rate: BSE 63.6%, placebo 26.7% (p=0.04)</td>
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<td>Holtmeier 2011</td>
<td>Boswellia serrata extract (Boswelan)</td>
<td>Randomized, double blind, placebo controlled (52 weeks)</td>
<td>2400mg daily</td>
<td>Inactive CD (n=82)</td>
<td>Maintenance of remission: Boswel 59.9%, placebo 55.3% (p=0.85)</td>
</tr>
<tr>
<td>Holt 2005</td>
<td>Curcuma Longa (Turmeric)</td>
<td>Pilot study (2 months)</td>
<td>550mg twice daily for 1 month and then 550mg three times daily another month</td>
<td>5 patients with UC and CD</td>
<td>9/10 IBD patients returned to the normalized levels of inflammatory indicator and other serologic indexes of inflammation</td>
</tr>
<tr>
<td>Hanai 2006</td>
<td>Curcuma Longa (Turmeric)</td>
<td>Randomized, multicenter, double blind, placebo control trial</td>
<td>45 patients received 1 g of curcumin twice daily while controls received a placebo</td>
<td>89 patients with quiescent UC</td>
<td>Clinical activity index and endoscopic index reduced in treatment group (P= 0.049) Relapse rate lower in treatment group (4.65%) compared to placebo (20.51%) (p= 0.04)</td>
</tr>
<tr>
<td>Author</td>
<td>Treatment/Supplement</td>
<td>Study Design</td>
<td>Outcome Measures</td>
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<td>Cabré 2012</td>
<td>Fish Oil (n-3 PUFAs)</td>
<td>Systematic review of 19 RCTs; 7 for active UC; 4 for inactive UC; 2 for active CD; 6 for inactive CD (Range: 6-24 months)</td>
<td>EPA dose range: 1.2-5.1g; DHA dose range: 0.6-2.4g; or unclear  Both active and inactive UC and CD. Active UC: 3/7 statistically significant improvement in clinical score, 3/7 non-significant results, 1/7 endoscopic improvement with clinical symptomatic worsening. Inactive UC, active CD, and inactive CD: All non-significant or inconclusive results.</td>
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<td>Miheller 2009</td>
<td>Vitamin D (active vs inactive VD)</td>
<td>Open label (6 weeks)</td>
<td>0.5 mcg daily</td>
<td>Inactive CD (n=37)</td>
<td>Active VD: CDAI decrease from 69 to 57 (p&lt;0.05)  Inactive VD: No difference</td>
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<tr>
<td>Jorgenses 2010</td>
<td>Vitamin D3</td>
<td>Randomized, double blind, placebo controlled (12 months)</td>
<td>1200 IU Vitamin D3 daily</td>
<td>CD patients in clinical remission (n=104)</td>
<td>Relapse rate lower with VD3 (13%) compared to placebo (29%) (p=0.06)</td>
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<tr>
<td>Yang 2013</td>
<td>Vitamin D3</td>
<td>Open label (24 weeks)</td>
<td>Started at 1000 IU daily. Increased until serum reached 40 ng/mL.</td>
<td>Mild to moderate CD (n=18)</td>
<td>CDAI scores decrease from 230 to 118 (p&lt;0.0001). Improved HRQOL.</td>
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<td>Sood 2009</td>
<td>VSL#3</td>
<td>Multicenter, randomized, double-blind, placebo-controlled trial (12 weeks)</td>
<td>3.6 x 10^12 CFU twice daily</td>
<td>Mild to moderately active UC (n=147)</td>
<td>&gt; 50% improved disease activity at wk 6 in 32.5% vs 10% of patients (p=0.001)</td>
</tr>
<tr>
<td>Tursi 2010</td>
<td>VSL#3</td>
<td>Randomized, placebo-controlled trial (8 weeks)</td>
<td>3.6 x 10^12 CFU daily</td>
<td>Mild to moderately active UC (n=144)</td>
<td>Improvement in UCDAI score in treatment (41(63.1%)) vs. control (29(40.8%)) groups (P&lt;0.05)</td>
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<tr>
<td>Shen 2014</td>
<td>VSL#3</td>
<td>Meta-analysis of randomized controlled trials</td>
<td></td>
<td></td>
<td>Remission rate higher with VSL #3 compared to placebo (P=0.004). No difference between treatment and control group with adverse events (P=0.94).</td>
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<tr>
<td>Matthes 2010</td>
<td>Escherichia Coli Nissle 1917 (EcN)</td>
<td>Randomized, placebo controlled trial (8 weeks)</td>
<td>Escherichia Coli 1917 enema (4 x 10^9) vs (2X10^9) vs (10^9) daily vs Placebo</td>
<td>Mild to moderately active UC (n=90)</td>
<td>Remission rates dose-dependent and statistically significant. EcN 40 ml (9/17 (52.9%)), 20 ml (8/18 (44.4%)), 10 ml (3/11 (27.3%)), and placebo (2/11 (18.2%)).</td>
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</table>

References


Kong J, Zhang Z, Musch MW. Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier. Am J Physiol Gastrointest Liver Physiol 2008; 294:G208-16.


