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Alternative Medicines as Emerging Therapies for Inflammatory Bowel Diseases

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Abstract

Inflammatory bowel disease (IBD) can be divided into two major categories, ulcerative colitis (UC) and Crohn disease (CD). While the main cause(s) of IBD remain unknown, a number of interventional and preventive strategies have been proposed for use against CD and UC. Many reports have focused on the use of alternative natural medicines as potential therapeutic interventions in IBD patients with minimal side effects. While the use of alternative medicines may be effective in IBD patients that are refractory to corticosteroids or thiopurins, alternative treatment strategies are limited and require extensive clinical testing before being optimized for use in patients.

Keywords

bromelain; Crohn disease (CD); curcumin; inflammation; inflammatory bowel disease (IBD); polyphenols; pomegranate; resveratrol; rutin; ulcerative colitis (UC)

Crohn disease (CD) and ulcerative colitis (UC) are the major chronic inflammatory bowel diseases (IBD) affecting an estimated 1.4 million people in the United States and 2.2 million

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people in Europe [1]. Although the etiology of both CD and UC is unknown, IBD have common complex and multifactorial pathogenesis. During past decades, major insights into pathogenesis of IBD has been achieved, and investigators around the globe agree that factors such as environment, genetic makeup, intestinal microbiota, and, most importantly, a dysregulated immune system are involved in the development of intestinal inflammation that characterizes IBD [2]. Recent evidence has accumulated to demonstrate that IBD-related mucosal inflammation develops in predisposed individuals as result of an inflated mucosal immune response directed against luminal antigens. Both forms of IBD can increase the risk of incidence of gastrointestinal and colon cancer. It has been reported that both CD and UC patients have different pathophysiologies. During IBD progression, tissue damage is mediated by an active cross talk between immune and nonimmune cells and that T cells play a central role in this pathogenic process [3]. It is believed that in CD, the cellular response, with increased activation of CD4⁺ T cells mostly differentiated in T1 subpopulation, increased amounts of cytokines, which has significant impact on the further course of disease progression.

IBD Pathogenesis

IBD diseases have complex and multifactorial pathogenesis. The causes of human IBD are not well known, but the two major forms are defined by their clinical, pathologic, radiologic, and endoscopic characteristics [4]. In a recent study, wide variations in the incidence and prevalence of CD and UC among different populations suggest that genetic factors significantly contribute to susceptibility to IBD. The absolute risk of IBD is approximately 7% among first-degree family members [5]. The nucleotide-binding oligomerization domain containing 2 (NOD2) genes is involved in this increased susceptibility to CD [6]. The NOD2 genes, located on the 16q12 chromosome, encode intracellular proteins activated by both nuclear factor κ B and mitogen-activated protein kinase pathways in response to bacterial cell wall component peptidoglycan [7]. As a result, our increasingly sophisticated knowledge of immune regulation, genetic alterations has been noticed in patients with UC and CD that may have important pathogenic implications [8]. The genetic susceptibility seems to be from regional clusters, because these features are not observed in Asian CD patients. Recently identified CD susceptibility in association with polymorphism in IBD5 locus or interleukin (IL) 23R to European CD counterparts is also not associated with their Asian counterparts [9, 10].

Clinical Features of IBD

During IBD progression, clinical and pathological features solely depend on the genetic background, alteration in immunoregulatory molecules, and susceptibility of the host. There is consensus that abnormalities in T cells are essential for colitis development, which is dependent not solely on excessive immune cell activation but also on the imbalance between proinflammatory and anti-inflammatory responses. These general conclusions strongly support the current assumption that different and independent abnormalities cause IBD and that UC and CD are heterogeneous disorders with multiple pathogenic mechanisms. The inflammatory process in UC is confined to the mucosa and superficial submucosa of the large bowel. The histopathological features of UC include bloody diarrhea, which is one of

the common symptoms of this disease. Nonetheless, it should be recognized that a small number of patients with UC have constipation, even during a period of active disease. The severity of the disease is generally proportional to the extent of bowel involvement and the intensity of inflammation. The extensive disease, particularly pancolitis, rectal prolepses, and bloody diarrhea, is generally associated with severe inflammation, which widely varies from patient to patient.

CD is more variable in its clinical manifestations, reflecting a seemingly more complex inflammatory process in symptoms and clinical features as compared to UC. Active CD is characterized by a huge leukocyte infiltration in which macrophages, neutrophils, and T cells predominate. One of the hallmarks of CD pathogenesis is the granulomas that form due to aggregation of macrophages, leading to the development of CD in approximately 50% of patients. This inflammatory process and accumulation of T cells and macrophages in CD can extend beyond the gastrointestinal tract, e.g., formation of fistulas, rectal prolepses, and sometimes bloody diarrhea [11]. The diverse sites of tissue involvement and varying extent of inflammation give rise to a wide spectrum of clinical manifestations.

Experimental Models for IBD

During the past decade, the discovery of many new experimental models has enhanced our capabilities to develop the next generation of IBD therapies and to study this complex disease. Many animal models, including genetically engineered mice, congenic mouse strains, chemically induced, and most importantly cell-transfer models, have been established for IBD study [12]. The major agreement on the models is that they exhibit mainly Th1-dominant immune responses, and most of these studies have centered with CD phenotype. In contrast to Th1-mediated models, mouse models that develop Th2-mediated colitis for the study of UC are very limited. The study of UC mouse models mainly depend on chemically induced models. Indeed, during the last decades animal models contributed a lot to our understanding in the mechanisms of IBD development, and have provided new information for development of novel therapies to overcome this disease [13]. A major advancement in the field of IBD has been made after several reports of associated human gene studies that are associated with IBD-associated genes specific for either CD or UC [6, 13–17]. In addition to these models, advances in genetic engineering technology have developed some new molecules for IBD treatment. It has been shown recently that T and B cells deficient in X-box binding protein (XBP1) and T-box transcription factor (T-bet) mice actively participate in innate immune responses and suppresses the development of colitis [18]. Interestingly, Th2 cytokines (e.g., IL-4) have also been shown to exacerbate murine colitis [19]. Another study of the spontaneous development of colitis shows that mice that lack an autophagy gene (Atg) 5, specifically in the thymic epithelial cells, are protected against IBD [20]. It has been shown that several genetically engineered KO mouse strains that lack IBD-associated genes show spontaneous development of chronic inflammation and colitis [14, 21–26]. The overall IBD-associated genes are now classified into at least three groups based on biological function: host defense, IL-23/Th17 axis, and regulatory immunity.

Microbial Induction of IBD and Mucosal Biomarkers

The experimental models of IBD discussed above fail to develop colitis symptoms in a germ-free environment. This gave us enough reason to believe that there is a pathologic interaction between immune cells and commensal enteric bacteria. These interactions provide a strong basis in the development of intestinal inflammatory processes [13, 27, 28]. The pathogenic germ may lead to a state of chronic stimulation of immune responses, a decrease in protective bacteria that induces mucosal permeability that might lead to enhance exposure of bacterial Toll-like receptor (TLR) ligands, and antigens that directly activate pathogenic innate and T-cell immune responses. The dysfunction in regulatory T cells or antigen-presenting cells also leads to decreased tolerance to microbial antigens or to induction of cross reactivity autoimmune responses between host and microbial antigens [29]. The most typical example is *Mycobacterium avium* subsp. *paratuberculosis* (MAP), which is the infectious etiologic agent of Johne disease (JD) [30]. Koch's postulate was fulfilled in 1910, confirming that MAP was the causative agent for JD [31]. Additional interest was developed after a series of reports that showed MAP isolation taken from intestinal biopsies from patients with CD was a causal association between MAP and IBD [32–41]. Similar to this line, IBD patients show increased mucosally associated bacteria [42]. The disease-related genetic polymorphisms in the intracellular bacterial receptor NOD, TLR2, and-4, ATG 16L1, and NCF-4 further support a role for defective immune response against microbial antigens [6, 43–45]. A genetic study also suggests evidence supporting the association of protease (75 coding) and protease inhibitors (7 coding) for the CD and 14 proteases and 4 protease inhibitors for UC, all located on chromosome 3 [46].

The role of mucosal biomarkers associated with tissues in the progression of disease severity has gained momentum in recent years. These mucosal biomarkers include cytokines, chemokines, adhesion molecules, effector immune T cells, nonimmune cells, and markers of activation. The alteration in some cytokines has been shown in patients with active IBD; however, the significance of these studies remains inconclusive as to whether these effects are primary or secondary in the regulation of inflammation [47]. CD is generally associated with a Th1 (IL-12, TNF-, IFN-, IL-23) and T17 cytokine profile, while UC is associated with a Th2 cytokine profile (IL-5 and IL-10) [48–50]. These findings have been complemented with the IL-23/IL-17 axis that is part of effector T-cell response and seems to be involved in IBD [51]. The other chemokine that has received a lot of attention in recent years is CXCL10. While CXCR3 ligands have been shown to be upregulated in IBD, the role that these chemokines play in disease severity, susceptibility, and progression is not certain. We have recently shown that CXCL9, CXCL10, and CXCL11 are upregulated at sites of colitis [52]. CXCL10 has been shown to be upregulated during UC [53], while CD tissues have been shown to express CXCL10 and CXCL9 as well as CXCR3 [54–57]. The inflammatory lymphocytes in the intestinal tract of IBD patients are mediated by the integrins and its specific ligands expressed by endothelial cells.

Probiotics and IBD

The host immune system is tolerant toward the antigens of commensal gut microbiota believed to be essential for normal healthy gut function. Any deregulation in immune

response toward gut microbiota is thought to be an underlying factor in the pathogenesis of IBD. The hypothesis that intestinal bacterial flora contributes to IBD pathogenesis is supported by several experimental as well as clinical studies. The most affected site of IBD, the terminal ileum and colon, shows the highest bacterial count and antibiotic treatment decreases severity both in UC and CD [58, 59]. In recent years, many attempts have been made to modify the flora with probiotics and it has been reported that some probiotic gut bacteria prevent and or abrogate IBD [60, 61]. Probiotics can be defined as living food supplements that have been shown to have a beneficial effect on human health [62]. There are some criteria for probiotic bacteria to be beneficial, including human origin, acid and bile stability, adherence to intestinal cells, persistence for some time in the gut, and, most important, the ability to modulate immune response [63]. The probiotic activity has been associated mainly with lactobacilli, bifidobacteria, *E. coli*, and *Saccharomyces boulardii* [64]. In experimental colitis, orally or rectally administered lactobacilli reduced established colitis in IL-10^{-/-} mice and in rats [65, 66]. The mechanism involved in anti-inflammatory bacteria may signal through the intestinal epithelium, mucosal regulatory T cells, or dendritic cells, perhaps inducing dendritic cell secretion of IL-10, while at the same time attenuating T-cell production of IFN^γ, via regulation of cytokine transcription factors [64, 67, 68]. The strongest clinical evidence also suggests that probiotics can improve the health condition in UC, pouchitis, and CD patients [69–72]. All of these studies clearly indicate that probiotics show great promise in abatement of IBD, but the current consensus warrants a large number of controlled clinical trials before the use of probiotics as a routine medical treatment for IBD.

Current Available Treatments and Their Limitations

Treatment must begin with accurate diagnosis. The diagnosis of IBD patients depends on clinical history, physical findings, endoscopic, radiologic, and histologic features, as well as the results of routine laboratory tests, disease location, and severity. An expanding number and variety of drugs that target the inflammatory process, either broadly or selectively, are effective in controlling disease in patients and in sustaining symptomatic remission for prolonged periods. However, many patients suffer from the recurrence of IBD, which supports the need for improved treatments without any side effects. Here we describe only few available treatments and their limitations.

Aminosalicylates and Corticosteroids

Topical corticosteroids have been found to be less effective than topical aminosaliclates for remission of distal UC [73]. It has been shown that 5-aminosalicylate was a functionally active moiety of prototypical sulfasalazine congener and may block the production of prostaglandins and leukotrienes, inhibiting bacterial peptide-induced neutrophil chemotaxis, scavenging reactive oxygen metabolites, and inhibiting the activation of nuclear factor- κ B. Topical corticosteroids, in combination with topical salicylates, is often more efficacious than either alone in short-term treatment of distal UC [74]. It has been also shown that methotrexate and cyclosporine are also effective treatments for both UC and CD [75]. There is a consensus that both aminosaliclates and corticosteroids suppress the activation and generation of specific and long-lived T helper cells, which might account for

the prolonged time needed to achieve a therapeutic response and the recurring/relapsing nature for IBD. In a literature-based study, it has been shown that patients with IBD refractory to corticosteroids and thiopurines may respond to alternative anti-inflammatory chemical molecules, but the evidence base for many of these alternatives needs clinical trial before a prudent conclusion can be reached [76].

Tumor Necrosis Factor Blockers

Tumor necrosis factor alpha (TNF- α) is a proinflammatory cytokine with a central role in the pathogenesis of CD [77]. Infliximab is a chimeric monoclonal anti-TNF- α antibody agent, an important advance in the therapy of patients with CD offered in the United States for almost 12 years [78]. Infliximab is a genetically engineered IgG1 murine–human chimeric monoclonal antibody containing approximately 75% human protein and 25% murine protein [79]. TNF- α cytokine is produced by leukocytes that are involved at local sites of inflammation in IBD [80]. TNF- α cytokine also associated with activation of granulocytes and fibroblasts during CD [81]. This cytokine also assists in the development of colitis in certain murine models of colitis [82]. It is also well established that administration of anti-TNF- α antibody or soluble TNF- α receptor, and anti-IFN- α antibody treatment significantly attenuates colitis development in IL-10^{-/-} mice [83]. Apart from infliximab, two additional anti-TNF- α molecules are currently used to treat IBD: adalimumab and certolizumab pegol [84]. To date, evidence for efficacy presented in clinical trials has been more robust for infliximab than for other anti-TNF- α mediators.

Chemokines

Chemokines are a group of chemotactic cytokines classified by the position of two cysteine residues in the N-terminal end that are either adjacent (i.e., CC) or separated by another amino acid (i.e., CXC) [85]. The CXC chemokine receptor 3 (CXCR3) has been of particular interest in recent years because it is expressed on a majority of activated Th1 cells, but not on resting or activated TH2 cells. The chemokine CXCR3 ligand CXCL10 has been associated with Th1-dependent immunity and has been observed in many models of inflammatory diseases [86]. CXCR3 ligand expression has been shown to be increased in Alzheimer [87], Hodgkin [88, 89], Graves disease [90], glomerulonephritis [91], multiple sclerosis [92, 93], bronchiolitis [94], skin/mucosal inflammation [95, 96], and IBD [97].

Studies from our laboratories have demonstrated that CXCR3 ligands (CXCL10) blockade abrogated spontaneous colitis in IL-10^{-/-} mice [52], which is mediated predominantly by Th1-type TCR⁺ CXCR3⁺ cells [98]. To further address the cellular mechanism of CXCL10-mediated colitis our laboratories reported that CXCL10 is largely produced by CD4⁺ T cells from the spleen during colitis progression. We noticed that anti-CXCL10 antibody treatment reduced the number of CD4⁺ CXCR3⁺ cells in the mesenteric lymph nodes and similar cells in the LP. The pathologic changes included large multifocal infiltrates in the lamina propria of the colon of control Ab-treated IL-10^{-/-} mice, with the number of these infiltrates being reduced after CXCL10 blockade. These results imply that intestinal inflammation is driven by the presence of CD4⁺ T cells producing CXCL10 and is potentiated mainly by Th1 cytokines. The increase in Th1 cytokines coincides with the increased number of CXCR3⁺

CD4⁺ T cells, which in turn, resulted in the propagation of colitis. Similarly, anti-CXCL10 antibody treatment can mitigate colitis in IL-10^{-/-} mice through decreased trafficking of Th1 cells has been reported by others [99]. Together, these results indicate that chemokine interactions are physiologically and pathologically important for the regulation of colitis and in the future might be developed as a potential therapeutic option for IBD.

Alternative Medicine as Therapeutic Option for IBD Patients

Conventional treatment of colitis can reduce periods of active disease and help to maintain remission, but these treatments often bring marginal results and patients become refractory. As we discussed above, the administration of anti-TNF- α antibody or soluble TNF- α receptor antagonist [81, 82] and anti-IFN- α antibody [83] have been shown to inhibit the progression of colitis. During our previous studies, we have shown that anti-CXCL10, a CXCR3 chemokine ligand, inhibits chronic colitis in IL-10^{-/-} mice [52]. Unfortunately, the side effects associated with these treatments could result in adverse reactions or poor response by the host, which could limit their clinical use [81]. Lack of a cost-effective treatment and a poor refractory period of remission cause many colitis sufferers to turn to unconventional treatments in the hope of abating symptoms of active IBD. It is estimated that 40% of IBD patients use some form of megavitamin therapy or herbal/dietary supplement [100]. The antioxidant effect of many herbal therapies used by patients with IBD received a lot of attention and is an open avenue for more experimentation as well as clinical studies [101]. Here we describe some potent alternative medicine options studied in recent years that mediate IBD (Table 1).

Resveratrol

The polyphenolic phytoalexin resveratrol (3,5,4'-trihydroxy-*trans*-stilbene) is a naturally occurring stilbene found in peanuts, grapes, and red wine that exert several biological activities [102]. Resveratrol has been shown to extend the life span of yeast and mice and regulates tumor growth and oxidation [103]. It also reduces both acute and chronic chemically induced edema [104] and lipopolysaccharide-induced airway inflammation [105]. The anti-inflammatory mechanism of resveratrol is not completely understood, but reductions in the expression and activity of COX-1 and COX-2 have been reported [106]. Resveratrol also modulates early inflammation in colitis [107]. A series of recent studies shows that a natural polyphenol (ellagic acid) protects murine CD, alleviates the oxidative events, and returns proinflammatory protein expression to basal level, probably by MAPK's and NF-B signaling [108]. Similarly, in another recent study, polyphenols were shown to prevent or delay the progression of IBD, especially because they reach higher concentration in the gut than in other tissues [109]. Because of the strong anti-inflammatory and antioxidant properties, we have done extensive studies on resveratrol and colitis and our data indicate that orally administered resveratrol ameliorates both dextran sodium sulfate (DSS) induced and IL-10^{-/-} chronic colitis in mice. Our studies suggest that resveratrol acts as an anti-inflammatory agent by targeting multiple pathways, including the SIRT1 gene, which has not been previously investigated with regard to its association with colitis (Figure 1). Resveratrol treatment suppresses all indicators of inflammation, including cytokines and Th1 cells, as well as expression of COX-2 and activation of NF-B, thereby ameliorating

colitis. We have also shown that colitis induction may downregulate SIRT1 and promote both NF- κ B activation and consequently cytokine production in the colon, and that resveratrol may reverse these effects by upregulating SIRT1 [110]. We have also shown that resveratrol reduces tumor incidence and tumor number in DSS-induced colon cancer [111]. Resveratrol also acts as an anti-inflammatory agent by targeting multiple pathways. While many mechanisms of resveratrol-mediated immunosuppression have been identified, our data demonstrated that resveratrol induced immunosuppressive CD11b⁺ Gr-1⁺ cells that express ARG-1, which correlated with reversal of chronic colitis severity. The unique correlation between induction of immunosuppressive CD11b⁺ Gr-1⁺ cells and reversal of chronic colitis can be interpreted to suggest that these cells may also contribute toward reversal of chronic colitis in IL-10^{-/-} mice. These studies also suggested that CD11b⁺ Gr-1⁺ cells (MDSCs) may constitute a novel target for therapeutic intervention in patients with IBD. The overall concept emerges from these studies that resveratrol might be a useful, nontoxic complementary and alternative strategy to abate colitis and potentially colon cancer associated with colitis.

Curcumin

Curcumin, found in plant *Curcuma longa*, is a natural compound used as a spice in curry powder. The perennial herb has multiple ingredients, including curcuminoids, that have medicinal effects. The curcumin major part is turmeric (diferuloylmethane), which possesses both anti-inflammatory and anti-oxidant properties [112–115]. Curcumin effectively inhibits development of skin tumors and proliferation of HT-29 and HCT-15 human colon cancer cell lines [116]. Curcumin has been found to inhibit the activation of various transcription factors that play a role in inflammation, cell survival, and angiogenesis. This includes nuclear factor- κ B (NF- κ B) and catenin [117]. Curcumin also down regulates COX-2 expression and inhibits expression of cytokines, interleukin-1 beta (IL-1), interleukin-6 (IL-6), and tumor necrosis factor- α [118, 119]. Recently, studies of chemopreventive effects of curcumin on colon inflammation have been published in both animal and human models [120–122]. Other pilot studies in humans suggest promising results as patients had lowered CDAI scores and sedimentation rates. In summary, these studies further suggest the need for a large-scale, double-blind clinical trial for any prudent conclusion based on indications that curcumin may pose a less expensive alternative medicine. Due to an advantageous safety profile and low cost, curcumin might be an attractive alternative option for IBD patients.

Pineapple Juice (Bromelain)

Bromelain is a mixture of enzymes typically derived from pineapple plants that has recently been identified by many workers due to its properties that decrease production of cytokines and leukocyte homing to sites of inflammation. Bromelain also shows great promise in reduction of immune-mediated disease, including IBD [123]. Further, it has been shown that the inflammatory condition of two UC patients improved after self-treatment with oral bromelain [124]. In vitro treatment of colon biopsies of human IBD patients with bromelain resulted in decreased production of proinflammatory cytokines and chemokines, suggesting a direct effect at effector sites [124]. These authors also suggested that purified bromelain from pineapple alters leukocyte expression of cell surface molecules CD44, CD62L (L-

selectin), CD45RA, and CD8 and effectively decreases neutrophil migration to the site of inflammation [123, 125]. In a recent study has shown that long-term dietary supplements with fresh pineapple juice decrease inflammation severity and multiplicity of inflammation-associated colonic neoplasia in the IL-10^{-/-} mice model of colitis [126]. These reports focus our attention on bromelain as a natural compound that can be developed as an effective therapy to IBD. In the interim, more study is needed to better understand the mechanism by which bromelain mediates colonic inflammation, including cell signaling pathways. In any case, these studies provide a strong rationale for clinical trials of fresh pineapple juice in human IBD patients.

Green Tea

Tea is the most popular beverage in the world and is reported to possess remarkable anti-inflammatory and cancer-preventive effects in animal tumors and epidemiological studies [127, 128]. Tea polyphenols, also known as tea catechins, mediate these effects. One of the major polyphenols present in green tea is epigallocatechin-3-gallate (EGCG), which exhibits antioxidant properties and is involved in inhibiting signaling pathways involved in inflammation, including the nuclear factor- κ B (NF- κ B) [129, 130]. Substantial evidence shows that intestinal inflammation is likely to depend at least in part on activation and nuclear translocation of NF- κ B. More importantly, activated NF- κ B has been found in colonic epithelium and macrophages from IBD patients [131, 132]. In light of these pharmacological profiles of green tea, its therapeutic effects on experimental colitis are warranted. Several published reports have evaluated the beneficial effects of green tea on experimental models of colitis [133–137]. All showed protection against colitis by downregulating expression of proinflammatory cytokines, reduction in colonic myeloperoxidase (MPO) production, and, most importantly, downregulation of NF- κ B activity. These studies clearly support a more controlled in-depth study and possible clinical trial on human IBD patient consumption of tea.

Pomegranate

Punica granatum, commonly known as the pomegranate, has been used as a traditional medicine with numerous beneficial effects in many parts of the world. Traditionally, pomegranate has been used extensively for treatment of diarrhea, dysentery, colic ulcer, urinary tract infection, and syphilis. In vivo and in vitro studies have demonstrated antioxidant, anti-inflammatory, and anti-cancer properties of pomegranate. There are reports indicating that pomegranate provides protection from liver fibrosis, prostate cancer, hypoxic–ischemic injury, ultraviolet induced pigmentation, allergic reactions, and rheumatoid arthritis [138–141]. Pomegranate is rich in phenolic compounds and is an important source of ellagitannin or ellagic acid [142, 143]. A recent study has shown that microspheres of ellagic acid were beneficial in treating DSS-induced colitis in rats [144]. Two recent studies that used ellagic acid-rich fractions and metabolites of pomegranate urolithin-A suggest a protective effect against colitis [145, 146]. These results suggest a bright future ahead for pomegranate as an effective treatment of colitis. More systematic and mechanistic studies are needed in terms of identifying the most active compounds and its mechanisms against colitis.

Rutin

Rutin (quercetin-3-rutinoside) is a polyphenolic flavonoid found in citrus fruit, tea, and buckwheat seeds. Rutin has been less studied as compared to other compounds [147]. Reports indicate that rutin has antioxidative and anti-inflammatory properties in rodent models. Rutin anti-inflammatory effects have been reported to act through suppression of proinflammatory cytokines and to inhibit TNF- α and NF- κ B, reducing oxidative stress in various experimental models of colitis [148–150]. A few reports on the effect of rutin on IBD and colorectal carcinogenesis suggest that rutin effectively mediates the amelioration of experimental colitis mainly by attenuation of proinflammatory cytokines [148].

Other Complementary and Alternative Medicine (CAM) Modalities

We want to give a brief overview of some of the other complementary and alternative medicine modalities that are available, but require more thorough study. In a literature survey, fish oil and aloe are identified as the most prevalent types of CAM used by IBD patients. Past reviews conclude that there is benefit from fish oil in treating IBD [151, 152]. In most of these studies, fish oil supplementation in IBD improved outcomes related to clinical score, gut mucosal histology score, induced remission, and relapse [153]. In contrast to this, two studies reported a higher rate of relapse with fish oil as compared to placebo [154, 155]. Thus, despite several favorable studies, there is only weak evidence that fish oil has clinical benefits on IBD. A few studies show that fish oil has an apparent ability to maintain remission in CD patients [156], but this needs further detailed investigation.

There is very limited evidence indicating the efficacy of aloe vera gel and *Boswellia serrata* in IBD. Aloe is widely used in food products and ranked first in health food sales in 2005 in Korea for its biological function of anti-inflammatory activity [157] and acceleration in wound healing [158]. In a recent study, it was clearly shown that aloe components ameliorate inflammatory responses in a DSS-induced ulcerative colitis rat model [159]. Similarly, in a clinical trial aloe vera gel produced more clinical response than placebo in IBD patients [160]. *Boswellia serrata* is a traditional Ayurvedic remedy and a component of incense. Many clinical trials of gum resin from *Boswellia* reported a 70% remission as compared to sulfasalazine [161, 162]. In another clinical trial, 23 patients were given oral wheat grass juice for 4 weeks, which reduced the composite clinical disease activity index and the severity of rectal bleeding without any side effects [163]. However, all of these clinical studies did not get momentum due to lack of promising effects on IBD amelioration.

There is a strong relationship between vitamins and minerals and IBD. In IBD, increases in oxidative damage accompanied by production of free oxygen radicals are crucial for progression and severity of the disease. It has been shown that selenium (Se) and vitamin E are two natural antioxidants, which quench reactive oxygen species [164, 165]. In brief, Se, and essential co-factors, may play an important role in binding active sites of glutathione peroxidase, and vitamin E is an effective chain-breaking lipid soluble antioxidant likely to quench oxidants. Recently it has been shown that Se and vitamin E in combination provide protective effects in experimental colitis [166]. Vitamin E and Se may prevent certain types of oxidative damage produced mainly by infiltrating macrophages and neutrophils within

inflamed colon [167]. However, there is a need for more detailed study of Se and vitamin E in experimental colitis.

In pediatric or adolescent CD patients, nutritional therapy is well established as a way to maintain remission of CD [168–170]. It has been shown that exclusive enteral nutrition (EEN) alleviates clinical symptoms, improves quality of life, and rapidly decreases CD activity by influencing the underlying mucosal inflammatory process [171–173]. Furthermore, EEN can be more effective than corticosteroids in inducing remission in children [174]. The meta-analyses of randomized–controlled trial studies have shown that EEN is effective in inducing remission in 50–70% of patients with active CD [175, 176]. Although there is no doubt about the effect of EEN as an induction therapy, the major disadvantage is acceptance of EEN and patient compliance. Recent data indicates that EEN is efficacious as an induction therapy only if given in an exclusive manner and patients require a large volume of formula every day for several weeks by nasogastric tube feeding [177]. Children and adults are sometimes unable or unwilling to accept this form of treatment. In a recent study, it was suggested that fractionated oral nutritional therapy might be efficacious as continuous enteral administration to induce mucosal healing and CD [178]. However, appropriate prospective clinical trials are needed for any valid conclusion.

Chitosan and some of its various synthetic derivatives have attracted great interest in recent years for colon delivery. The systemic delivery of therapeutic protein or peptide may be extremely useful when there is a delay in drug absorption from a therapeutic point of view as in the case of IBD. Chitosan (CH) is a polycationic polysaccharide derived from naturally occurring chitin by alkaline deacetylation. Chitosan rapidly dissolves in the gastric cavity. To prevent this, different strategies have been developed at acidic pH to thus obtain a chitosan-based colon delivery system. Based on this notion, several chitosan coated capsules and microparticles have been reported in the past, as, for example, enteric coated microparticles [179], pH-sensitive based chitosan hydrogel systems [180], chitosan polyelectrolyte complexes [181], and chitosan salt [182]. In a recent study, it was shown that a *N*-succinyl-chitosan system for 5-aminosalicylic acid colon delivery markedly improves efficacy in healing and improvement in the pathology of TNBS-induced colitis in rat [183]. Based on these studies, we can speculate that the future of chitosan coated based targeted delivery would be advantage on overall available strategies to combat IBD.

Conclusion

IBD has a multifactorial etiology that usually requires regular basis of pharmacological cure to maintain remission. The management of IBD patients with conventional therapy is very cost-effective with lots of side effects and remains a clinical challenge. Keeping this in mind, alternative medicine options should be explored when treating patients with refractory IBD. Nearly 50% of the IBD patients have tried some form of alternative medicine. Although a wide range of therapies are available, the reliable mechanistic data about efficacy and safety of most of the remedies are far from clear. As new alternative medicine therapies evolve, there is promise at least in experimental models as well as in few small clinical trials. As patients of IBD increasingly obtain CAM therapies, efforts should be accelerated to assess more dietary compounds toward their therapeutic efficacy and safety.

Data at our disposal on resveratrol clearly suggest that it has great potential to effectively modulate colon inflammation and it is already in clinical trial. With continuation of evolving new CAM therapies and improvement in existing therapies with addition of some form of herbal or dietary supplement, the future for IBD patient management appears promising.

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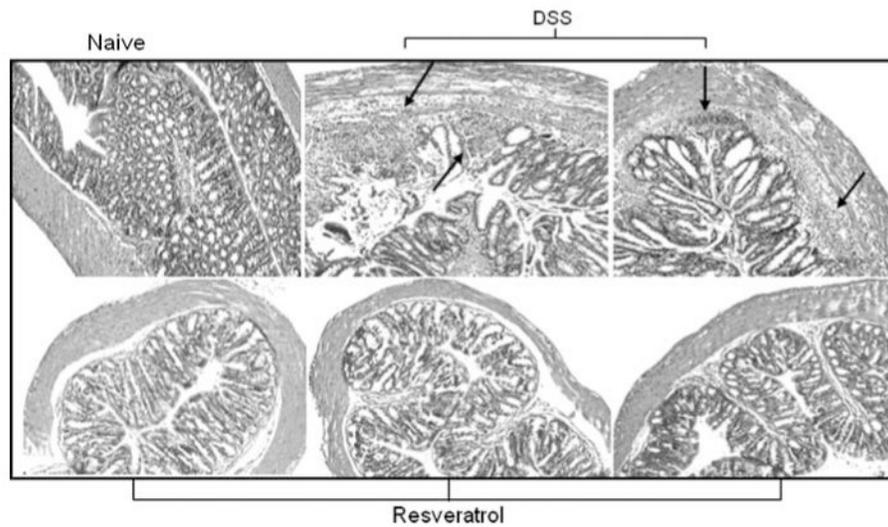


Figure 1.

Effect of resveratrol on the histopathology in mice after DSS-induced colitis. Histological evaluation of colon section from DSS and resveratrol-treated as well as naïve mice were evaluated 14 days after colitis induction. In the upper panels, the arrow indicates the area of cellular infiltrates enlarged epithelial and distorted crypts. The lower panel reveals lower cellular infiltrates as well as some normal crypts. Representative sections from three separate experiments (20× magnification) are shown, with each group containing 6 mice.

Table 1
Current available alternative medicine treatments and their effect on IBD

Medicine	Disease	Effects	Remission	References
Aloe vera gel	UC	Improved histological score	30%	Langmead L, et al. <i>Aliment Pharmacol Ther.</i> 2004;19:739-47
Wheat grass juice	UC/distal	Improved symptoms	90%	Ben-Arye E, et al. <i>Scand J Gastroenterol.</i> 2002;37:444-49.
Germinated barley	UC	Improved diarrhea	—	Kanauchi O, et al. <i>J Gastroenterol.</i> 2002;37: 67-72
Curcumin	UC/CD	Lowered CDAI scores and sedimentation rates	90%	Holt PR et al. <i>Dig Dis Sci.</i> 2005;50:2191-3
Curcumin	UC/CD	Reduced histological sign of inflammation	—	Katia N, et al. <i>Br J Nutr.</i> 2009;101:169-181.
Rutin	UC	Ameliorates DSS induced colitis	—	Ki Han K, et al. <i>Biochem Pharmacol.</i> 2005;69:395-406.
Fresh pineapple juice	UC/CD	Ameliorates colitis and colonic neoplasia	—	Hale LP, et al. <i>Inflamm Bowel Dis.</i> 2010;16: 2012-2021
Pomegranate	UC	Ameliorates DSS induced colitis	—	Singh K, et al. <i>Phytother Res.</i> 2009;23: 1565-1574.
Pomegranate/metabolite	UC	Reduced DSS inflammation	—	Larorosa M, et al. <i>J Nutritional Biochem.</i> 2010;21: 717-725
Epigallocatechin-3-Gallate	UC/CD	Beneficial in colitis	—	Abboud PA, et al. <i>Eur J Phramacol.</i> 2008;579:411-417
Green tea polyphenols	UC	Protect against DSS induced colitis	—	Oz HS, et al. <i>J Nutr Biochem.</i> 2005;16(5):297-304
Green tea polyphenols	UC/CD	Attenuates colon injury and inflammation	—	Mazzon E, et al. <i>Free Radic Res.</i> 2005;39:1017-1025.
Green tea polyphenols	UC/CD	Attenuates colitis	—	Varilek GW, et al. <i>J Nutr.</i> 2001;131(7): 2034-9
Resveratrol	UC/CD	Ameliorates CD	—	Singh UP, et al. <i>Brain Behav Immun.</i> 2012; 26(1):72-82.
Resveratrol	UC	Protect from DSS induced UC	—	Singh UP, et al. <i>J Pharmacol Exp Ther.</i> 2010;332:829-839
Resveratrol	UC/CD	Attenuates colonic inflammation	—	Sanchez-Fadalgo S, et al. <i>Eur J Pharmacol.</i> 2010;633: 78-84
Resveratrol	UC in Rat	Attenuates colonic inflammation	—	Martin AR, et al. <i>Biochem Pharmacol.</i> 2004;67(7): 1399-1410.
Cinnamon extract	UC/CD	Suppress experimental colitis	—	Kwon HK, et al. <i>World J Gastroenterol.</i> 2011;17: 976-986
Freeze-dried black raspberry powder	UC	Potent anti-inflammatory effects	—	Montrose DC, et al. <i>Carcinogenesis.</i> 2011;32: 343-50
American ginseng	UC	Suppress colon cancer associated colitis	—	Cui X, et al. <i>Carcinogenesis.</i> 2010;32: 1734-1741
Ginger extract	UC/rat	Improved inflammation	—	El-Abhar HS, et al. <i>J Ethnopharmacol.</i> 2008;118(3): 367-372