REVIEW ARTICLE

# Phytotherapies in inflammatory bowel disease

**Mahboube Ganji-Arjenaki, Mahmoud Rafieian-Kopaei**
Medical Plants Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran

Inflammatory bowel disease (IBD) has been considered as a group of heterogeneous intestinal diseases that affects multiple organs outside of the gastrointestinal tract and is due to an uncontrolled inflammatory response mediated by the immune system. The IBD etiology has not been clearly defined, and it is considered as a multifactorial disease. Due to side effects of some conventional therapies, the consumption of complementary and alternative medicines, and in particular, the herbal therapy, more than before is increasing. Herbal therapy results for management of IBD by various mechanisms including leukotriene B4 inhibition, antioxidant activity, immune system regulation of nuclear factor-kappa B, as well as antiplatelet activity are favorable, and no unfortunate events have been yet reported. In this article, we aimed to review and report the herbal therapies established for management of human IBD or evaluated by animal IBD models. Their possible mechanisms of actions are also discussed.

**Key words:** Herbal medicine, inflammatory bowel disease, medicinal plants, phytotherapy

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## INTRODUCTION

Inflammatory bowel disease (IBD) has been considered as a group of heterogeneous intestinal diseases that affects multiple organs outside of the gastrointestinal (GI) tract and is due to an imbalance in intestinal microbiota and uncontrolled inflammatory response mediated by the immune system.[1,2] Two main types within IBD can be distinguished and are in focus of attention because of their increasing incidence: Crohn's disease (CD) and ulcerative colitis (UC).[3] IBD is clinically designated by abdominal pain and cramps which may be associated with bloody diarrhea. Patients with IBD also have extraintestinal manifestations including arthritis, sacroiliitis, and ankylosing spondylitis. Low body mass index is also usual in these patients.[4-6] The clinical diagnosis of disease is usually supported by histologic, laboratory data, sonography, endoscopy, and radiology.[7]

Clinicians who treat IBD patients should be severely attentive of extraintestinal signs and symptoms to decrease morbidity.[8] Establishment and maintenance of a condition with steroid-free remission should be the main goal of medical therapy.[7] New classes drugs for IBD treatment including janus kinase inhibitors, anti-SMAD7 oligonucleotides, anti-tumor necrosis factor-α (TNF-α), peroxisome proliferator-activated receptor-γ ligand, anti-α four integrins, probiotics, and cell-based therapies are under clinical utilization.[9]

The existing IBD therapies unfortunately are not responsive for a lot of patients. There are serious demands for other therapies with induction and maintenance of remission. Hence, complementary and alternative medicines demands, particularly of herbal therapies, are reported to be higher among patients with IBD (21%–60%), due to their perceived natural effects.[10,11]

Although not all commonly used phytomedicines are safe, most of the herbal products available are fairly safe in comparison to conventional drugs.[12,13] Therefore, investigations on medicinal plants have been resulted in discovery of highly effective drugs such as opiate anesthetics, aspirin, and taxol.[14] Many medicinal plants have been used for thousands of years to treat or prevent

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**Address for correspondence:** Mahmoud Rafieian-Kopaei, Medical Plants Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran. E-mail: rafieian@yahoo.com
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bloody diarrhea. Therefore, in this article, we tried to present the effects of the most important medicinal plants on IBD. In this regards, we searched the herbal therapies for investiture and maintenance of IBD remission in both UC and CD.

## MATERIALS AND METHODS

A search was done on electronic databases such as Google Scholar, PubMed, Web of Science, Cochrane Library, and CINHAL to review the evidence of herbal medicines with IBD Databases. Both *in vivo* and *in vitro* data were collected on major herbal medicines using the search terms of "IBD" combined with the search terms "medicinal plants" or "herbal medicine," in addition to hand searching the literature.

### Pathogenesis of inflammatory bowel disease

The IBD etiopathogenesis is multifactorial and involves a dysregulated, immune-mediated inflammatory response (such as overexpression of multiple inflammatory cytokines and TNF-α), environmental changes, susceptibility gene variants, and an abnormal amount and kind of bowel microbiota.[15,16] CD and UC both have common aspects including symptoms, organic damages, and therapy; however, each one exhibits its own distinct pathophysiological phenomenons.[17] For example, "Immunochip" studies have shown that the UC has maximum genetic association at single-nucleotide polymorphism (SNP) rs6927022 (between DQB1 and DRB1) mapped adjacent to HLA-DQA1 Class II gene, but for CD, no evidence of SNP[18,19] or beta-defensins that is antimicrobial peptide secrete by the epithelium underexpression in CD can be found.[20]

### Mechanism action of herbal medicines

Herbal therapies effective in IBD act through several mechanisms which are discussed below. The propriety of the cells mediating innate immunity including natural killer cells, dendritic cells, neutrophils, and macrophages are altered in IBD. The responses of mucosal T helper cells as well as overexpression of some cytokines including interferon gamma (IFN-γ), TNF-α, interleukin (IL)-1b, IL-6 and IL-12 are determined in IBD patients.[21] TNF-α secretion induces alterations in ion transport and epithelial permeability that may lead to lesions and mucosal inflammation.[22] Therefore, factors the regulating T-cells and pro-inflammatory cytokines have the potential to decrease inflammation scores and then improve the patient's IBD.

Some trials have revealed that *Curcuma longa* has potential to decrease the pro-inflammatory cytokines such as TNF-α, IFN-γ, IL-1β, and IL-12 [Table 1].[23,24]

Leukotriene B4 (LTB4) is a potent proinflammatory mediator playing an important role in IBD,[32] overexpression of LTB4 has been reported in IBD.[33] Nicotine derived from *Nicotiana tabacum* has been revealed to moderate LTB4 level in dinitrobenzene–sulfonic acid-induced colitis, therefore, it may help to improve IBD.[34]

The microbial content of the GI tract has essential role in the pathogenesis of IBD. It appears that in areas of GI tract that the level of luminal bacteria is more than normal, the possibility of disease progress.[35] Garlic (*Allium sativum*) with the antibacterial properties can help to decrease microbial content then improve IBD.[36]

Overexpression of nuclear factor-kappa B (NF-κB) has been observed in IBD. The NF-κB proteins are eukaryotic transcription factors which usually play crucial roles in regulation of inflammation as well as in inflammatory responses in IBD.[37,38] In response to proinflammatory stimuli, the NF-κB Kinase (IKK) induces transcriptional factor NF-κB.[39] Therefore, the suppressors of IKK and NF-κB can be employed for IBD treatment. Curcumin derived from *C. longa*,[24] a medicinal plant from *Commiphora*,[40] and the

**Table 1: Studies inspecting herbal medicines effects in animal models of colitis**

| Plant | Part | Results | Model | Species | Study |
|---|---|---|---|---|---|
| *Curcuma longa* | Curcumin | ↓ loss of body weight↓Disease in histological colitis scores↓NF-κb↓decrease in activity index | DSS | Mouse | Deguchi *et al*.[25] |
| *Curcuma longa* | Curcumin | ↓ iNOS and Colonic nitrites↓TNF-α ↓COX-2 | TNBS | Rat | Camacho-Barquero *et al*.[26] |
| *Gardenia jasminoides* | Glycoprotein | ↓NO, iNOS↓COX-2↓NF-κbp50 | DSS | Mouse | Oh and Lim[27] |
| *Camellia sinensis* | Theaflavin-3,3×-digallate | ↓NF- κb↓IFN-gamma, TNF-α, and IL12, ↓iNOS | TNBS | Mouse | Ukil *et al*.[28] |
| *Rheum tanguticum* | Polysaccharide | ↓WBC↓Ulcerative area and colon weight | TNBS | Rat | Liu *et al*.[21] |
| *Camellia sinensis* | Thearubigin | ↓Disruption of colonic architecture↓Infiltration of neutrophils↓Lipid peroxidation↓Diarrhea↓Activity of serine protease↓NO, iNOS↓NF- κb | TNBS | Mouse | Maity *et al*.[29] |
| *Polygonum tinctorium* | Tryptanthrin | ↓IL-2 and IFN gamma↓Colon damage | DSS | Mice | Micallef *et al*.[30] |
| *Zingiber zerumbet* | Zerumbone (asesquiterpenoid) | ↓ Colitis suppression↓IL-βb, TNF-α | DSS | Mouse | Murakami *et al*.[31] |

TNF=Tumor necrosis factor; NO=Nitric oxide; IL=Interleukin; NOS=Nitric oxide synthase; COX=Cyclooxygenase; NF=Nuclear factor; WBC=White blood cell; DSS=Dextran sulfate Sodium; TNBS=Trinitrobenzene sulfonic acid; NF-κB= Nuclear factor kappa-light-chain-enhancer of activated B cells; ↓=Decrease

aflavin-3,3′-digallate derived from *Camellia sinensis*[28] can recede IKK and NF-κB. Boswellic acid, derived from *Boswellia* spp. can cause suppression of NF-κB activation and reduction of the proinflammatory cytokines such as IFN-γ, ILs 1, 2, 4, and 6 as well as an enhancement in macrophages phagocytosis.[41,42]

Nitric oxide (NO) as well as inducible isoform of NO synthase (iNOS in IBD is increased.[43-45] Some herbal remedies, including a glycoside derived from *Polygonum multiflorum*,[46] a glycoprotein derived from *Gardenia jasminoides*,[27] theaflavin-3,3′-digallate derived from *Clonorchis sinensis*,[28] and curcumin,[23] are effective against IBD by decreasing the levels of NO and iNOS [Table 1].

Two isoforms of cyclooxygenase, i.e., Cox-1 and Cox-2 catalyze the synthesis of prostaglandins. Prostaglandins produced through Cox-1 play an important role in GI homeostasis maintenance such as blood flow and gastric cytoprotection. Prostaglandins synthesized through Cox-2 moderate inflammatory responses.[47,48] Some trials have revealed that curcumin and *G. jasminoides* are able to reduce Cox-2 level.[6,23,24,27]

Patients with IBD exacerbations have shown an enhancement in platelet numbers.[49] Platelets have several important roles such as modulatory role for the activity of other inflammatory cells, release of inflammatory mediators, recruitment, and chemotaxis.[50] Therefore, herbal antiplatelet drugs such as *Angelica sinensis* can suppress platelet activation, moderate the injury of endothelial cells, and improve microtransmission in IBD patients.[51,52]

## CLINICAL TRIALS

The clinical trials on the effects of herbal medicines for IBD patients are promising. Clinical remission and positive responses were detected in more number of UC patients who used gel of *Aloe vera* in comparison to placebo group. Components of the gel, mainly used for control of intestinal inflammatory process, are anthraquinones (aloe-emodin), aloesin, and aloin which were able to decrease myeloperoxidase (MPO), LTB4, pro-inflammatory cytokines such as TNF-α and IL-1β activities that their effects are blockage of the activation of the NF-κB pathway, and downexpression of TNF-α gene. Therefore, they greatly reduce the index of clinical colitis, activities, progression, and histological scores of these patients.[53-57]

Distribution of the capsules containing components of cardamonin and wormwood decreased TNF-α serum level and pro-inflammatory cytokines such as IL-1β or IL-6, NF-κB, PGE2, COX-2 expression, iNOS, and NO. In CD patients, the symptoms were completely remitted in 65% of the patients in comparison to placebo group.[58-61]

The diterpene lactone, andrographolide from *Andrographis paniculata* and *A. paniculata* reduced the cytokines of multiple pro-inflammation, including NF-κB, cysteine 62 of p50 subunit, inducible NO synthase (iNOS), TNF-α, IL-1β, IL-2 release and ERK1/2 phosphorylation following modulation of PKC-pathway, and reduction in the levels of several genes expressions such as TNF-α, p35, p40, IL-12, IL-16, and IL-12.[62-69] The results revealed a significant reduction in the CD Activity Index in the patients who treated with the extract of the plant in comparison to placebo group.[70,71] Table 2 demonstrates detailed data of clinical trials from the use of herbal medicines in IBD patients.

Histopathology and scanning in electron microscopy have shown improvement in most of the parameters such as stool properties in UC patients that treated by *Boswellia serrata* extract for 6 weeks.[76] Boswellic acid component reduces lipid peroxidation, NF-κB activation, block the 5-lipoxygenase pathway, and increase the levels of superoxide dismutase in intestinal inflammation.[79-81]

Curcumin (the active component of *C. longa*) is effective in modification of signaling pathways such as MAPK and ERK, in expression of cascade, such as MPO, COX-2, iNOS, and LOX, and in decreasing the expression of TNFα, IL-1β, IL-12, or IFNγ, and NF-κB, but it is able to increasing the expression of anti-inflammatory cytokines.[82-86] Potential of curcumin in modulating the NF-κB activity may hinder inflammatory responses and prevent the colonic mucosa damage.

Two clinical trials investigated the effects of *Tripterygium wilfordii* on prevention of postoperative recurrence in CD patients. In this trial, 45 CD patients received *T. wilfordii* extract. No recurrence was occurred during 3 months with no significant difference in relapse during 6–12 months of trial.[87] In the second trial, the CD patients were subjected to *T. wilfordii* extract 2 weeks after operation. The clinical recurrence was reported in 6%, however, endoscopic recurrence in these patients was 22%.[88]

Grass juice derived from *Triticum aestivum* improved the index of total disease activity and the severity of bowel bleeding of UC patients.[89]

The marijuana plant *Cannabis sativa* use in human IBD; there are very few controlled trials. In a study that cannabis was used in 291 patients with IBD, the pain and diarrhea were improved in CD patients [Table 2].[90,91]

## CONCLUSION

Side effects and acceptable safety of conventional therapies have caused an increased interest in herbal therapies

**Table 2: Clinical trials on the effects of herbal treatments in patients having inflammatory bowel disease**

| Plant name | Plant part | Study design | Number of patients | Duration of treatment | Results | Type of IBD | Study |
|---|---|---|---|---|---|---|---|
| *Artemisia absinthium* | Powder | Placebo-controlled, double-blind trial | 40 | 10 weeks | Complete remission in 65% of plants group in comparison to no remission in placebo group | CD | Micallef *et al*.[30] |
| *Aloe vera* | Gel | Placebo-controlled, double-blind trial | 44 | 4 weeks | Clinical remission in 9, improvement in 11, and good response in 14 patients on aloe group in comparison to 1, 1 and 2 patients in placebo group, respectively. Also significant improvement in histological scores and index of clinical colitis activity in aloe group | UC | Langmead *et al*.[72] |
| *Triticum aestivum* | Grass juice | Placebo-controlled, double-blind trial | 23 | 4 weeks | Significant improvement in severity of rectal bleeding and disease activity index. No serious side effects | UC | Ben-Arye *et al*.[73] |
| *Andrographis paniculata* | Extract | Placebo-controlled, double-blind trial | 101 | 8 weeks | Significant reduction in the mean CRP level in 8th week in patients who received extract in comparison to placebo group | CD | Sandborn *et al*.[74] |
| *Plantago Ovata* | Seed | Open-label, parallel group, randomized | 105 | 12 months | Same as mesalamine in maintenance of remission | UC | Rodríguez-Cabezas *et al*.[75] |
| *Boswellia serrata* | Powder | Open-label, parallel group, randomized | 30 | 6 weeks | Improvement in more than one parameter such as stool properties in Boswellia group | UC | Gupta *et al*.[76] |
| *Oenothera biennis* | Oil | Placebo-controlled | 43 | 6 months | Stool consistency improved and also was maintained even when the treatment discontinued | UC | Greenfield *et al*.[77] |
| *Curcuma longa* | Extract | Placebo-controlled, double-blind trial | 89 | 6 months | A marked decrease in endoscopic index and the index of disease-associated clinical activity | UC | Algieri *et al*.[78] |

CD=Crohn's disease; UC=Ulcerative colitis; IBD=Inflammatory bowel disease

for the management of IBD and other diseases. Herbal remedies have been shown to decrease histological damage, increase the disease activity index as well as the level of clinical response, improve the remission and decrease the relapse rates, improve stool consistency, and ameliorate rectal bleeding in IBD patients. Oxidative stress, allergy, psychological factors, platelets, LTB4, iNOS, and NF-κB are involved in pathogenesis of IBD.[92-95] Herbal medicines have shown to improve these parameters by several mechanisms, including antioxidant activity, inhibition of IKK or NF-κB, suppression of LTB4, inhibition of platelets, and iNOS activities.

In UC patients, the extract of *A. paniculata*, gel of *Aloe vera*, powder of curcumin, and juice of wheat grass (*T. aestivum*) in comparison to placebo significantly increased the remission maintenance or response. Seeds of *Plantago ovata* and gum resin of *Boswellia serrata* showed efficacy the same as mesalazine, whereas in UC therapy, the oil of evening primrose (*Oenothera biennis*) had the relapse rate the same as omega-3 fatty acids. In CD therapy, *T. wilfordii* and *Artemisia absinthium* both were superior to placebo group in induction of remission, as well as in clinical recurrence prevention of postoperative CD.

Although some herbal remedies have been used for treatment of IBD patients were effective, there is no strong evidence for recommendation of these drugs in IBD as a single effective treatment. It must be emphasized that the role of phytotherapies is limited to supplementary component. The most IBD patients have good response to conventional therapy. The problem is refractory and complicated cases that almost always excluded in the herbal treatment research. Lack of reproducibility, the licensing requirements, lack of scientific knowledge of indications for the products of medicinal plants, are some problems in the use of herbal medicines in IBD.[53] Furthermore, because of ethical issues in these studies patients with low or moderate activity index have been selected. Moreover, in many of these researches, the effect of herbal drugs has been compared with placebo. There is a lack of studies with large sample size and head to head comparison of phytotherapy and conventional drug therapy for IBD. Other problem is that most studies have been performed in animal models and clinical trials, as mentioned in the manuscript, are limited with low sample size. Therefore, more clinical studies are suggested to obtain reliable results for the use of medicinal plants in IBD. It also should be emphasized that these herbal drugs have not magic effect in treatment of IBD and there is no significant effect as a single therapy.

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## Conflicts of interest

There are no conflicts of interest.

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