

A brief overview of medicinal plants to treat Inflammatory Bowel Diseases

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Received: 09-08-2025, Accepted: 31-08-2025, Published online: 01-09-2025



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HOW TO CITE THIS

Rafi IK, Bhuiyan MH. A brief overview of medicinal plants to treat Inflammatory Bowel Diseases. Mediterr J Med Med Sci. [Article number: 8]. 2025; 1(2): 23-31. <https://doi.org/10.5281/zenodo.17014538>

Keywords: IBD, Medicinal plant, PDVLN, ulcerative colitis

Abstract: The term inflammatory bowel disease refers to a group of idiopathic conditions marked by persistent inflammation of the gastrointestinal tract. Individuals who have been diagnosed with inflammatory bowel disease frequently require long-term medication. Due to its ease of use and widespread application, oral administration has become one of the most preferred modes of treatment for inflammatory bowel disease. The effectiveness of oral herbal medical preparations and their extracts as a treatment for inflammatory bowel disease has been examined in recent years. As a result, strong evidence has emerged for their efficacy in treating inflammatory bowel disease. This review focuses on medicinal plants' applications, pharmacological characteristics, and efficacy. The outcomes offer a viable avenue for more study and the creation of plant-based treatments to enhance the treatment of inflammatory bowel disease and improves patient outcomes.

Introduction

Crohn's disease and ulcerative colitis (UC) are examples of inflammatory bowel diseases (IBDs), which are immune-mediated, chronic conditions [1]. Individuals with IBD and colitis-associated cancer are linked to long-term, persistent inflammation [2]. IBD is brought on by aberrant immune responses to intestinal microbes, and the makeup of these bacteria in patients differs from that in healthy people [3]. The gastrointestinal tract is home to the majority of intestinal microbes [4, 5]. Numerous acute and chronic intestinal disorders, including UC, might result from "microbial ecological imbalance," which is a change in the populations of microorganisms' structures or activities [5, 6]. IBD is frequently linked to changes in the makeup of intestinal microorganisms, including the development of facultative anaerobes, particularly when inflammatory and metabolic problems are present [7]. By producing carcinogenic poisons or by regulating the immune system, intestinal microbes contribute to inflammation and carcinogenesis. Because colitis alters the microbial composition of mice, it encourages the growth of tumors [8, 9]. IBD may now be treated with both targeted and non-targeted biological treatments. Glucocorticoids, immunosuppressive drugs, antibiotics, and amino-salicylates are examples of non-targeted therapeutic medicines. It is unclear, therefore, how antibiotics will affect gut microbes in IBD over the long run [10, 11]. While immunosuppressive drugs are only used to sustain remission, corticosteroids are only used to treat active illnesses [12]. Janus kinase signal pathway inhibitors and inflammatory cytokine inhibitors, including anti-TNF antibodies, are examples of targeted biological therapy. However, due to potential damage to healthy organs and allergic responses, biological inhibitors are not appropriate for all IBD patients [13]. Because boiling preserves the active ingredients and

reduces the possibility of adverse effects, herbal medical preparations are frequently made as tonics. Furthermore, they may be readily modified to suit specific demands and symptoms due to their special functions and therapeutic approaches [14]. Furthermore, because of their positive qualities-such as their wide range of applications, strong therapeutic benefits, and minimal side reactions the natural chemicals present in herbal medical products have drawn attention [15-20]. Researchers are becoming more interested in medicinal plants because of their substantial therapeutic potential for IBD. By lowering inflammation, supporting gut health, and easing symptoms while limiting possible side effects, the main goals of using Indian medicinal herbs for IBD therapy are to increase treatment efficacy. It is thought that these plants complement traditional treatments to help people manage their conditions more comprehensively.

Methodology

Scopus, Web of Science, Google Scholar, PubMed, Research Gate, and DOAJ were among the primary sources we used for this investigation. We gathered 109 articles by searching for terms like "inflammatory bowel diseases," "Crohn's disease," "ulcerative colitis," and possible names for therapeutic plants. After that, we arranged them according to publication year, language, topic, and field. In vitro and in vivo researches published in English-language literature were the focus of our review. In general, peer-reviewed scientific literature is seen to be more trustworthy than other kinds of study. The purpose of this thorough research was to investigate and talk about the usage of medicinal plants to treat inflammatory bowel disorders.

Medicinal plants to treat IBD: The plant *A. lappa* L. is readily available all year round and has a higher content of polysaccharides and residues than other vegetables. Wu et al. [21] assessed the protective effects of the fruit of *A. lappa*'s ethanol extract, petroleum ether fraction, n-butanol fraction, and water fraction on mice's colitis caused by (Dextran Sodium Sulfate) DSS (3.5%) at dosages ranging from 25.0 to 100 mg/kg (p.o.). They discovered that the active ingredient in this plant's fruit is arctigenin, and the primary active portion is ethyl acetate. According to a prior study, arctigenin polarizes M1 macrophages into M2-like macrophages and inhibits PI3K to provide anti-inflammatory effects [22]. Another study showed that arctigenin reduces the differentiation of Th1 and Th17 cells by inhibiting the mammalian target of rapamycin complex 1 pathway, which is a crucial target for this differentiation. This has a positive effect on colitis [23]. Furthermore, prior research has documented this plant's efficacy in treating experimental colitis. An onopordopicrin-enriched fraction from *A. lappa* leaves, as shown by de Almeida et al. [24], showed an anti-inflammatory effect on colitis caused by 2,4,6-trinitrobenzene sulfonic acid (TNBS). This effect was most likely caused by a decrease in neutrophil function, TNF- α production, and down-regulation of COX-2, in addition to an increase in mucus production. Furthermore, Huang et al. [25] proposed that *A. lappa*'s preventive action against (Dextran Sodium Sulfate) DSS-induced colitis involves inulins and chlorogenic acid. In this investigation, oral *A. lappa* treatment preserved the colon architecture of mice given DSS while reducing body weight loss, the production of inflammatory mediators (IL-6 and TNF- α), and histological scores. It has been demonstrated that several extracts from *B. dracunculifolia* DC have anti-inflammatory and antinociceptive properties [26], protect liver mitochondria from oxidative damage [27], and lessen stomach ulcers in rats. In rats with TNBS-induced colitis, Cestari et al. [28] assessed the intestinal anti-inflammatory properties of an ethyl acetate extract from the aerial portions of *B. dracunculifolia*. Due primarily to the inhibition of MPO activity, decrease in lipid peroxidation, and elevation of endogenous antioxidant defenses in the inflamed colon, such as the GSH level, the administration of doses of 5.0 and 50 mg/kg of this extract decreased the macroscopic colonic damage score and lesion extension. These authors discovered several acid derivatives, including caffeic acid, p-coumaric acid, 3-prenyl-p-coumaric acid (drupanin), 3,5-diprenyl-pcoumaric acid (artepillin C), and 3-prenyl-4-dihydrocinnamoiloxy-cinnamic acid (baccharin), by using HPLC analysis of the ethyl acetate extract of *B. dracunculifolia*. According to other research, the main ingredient in this plant and green propolis is a flavonoid known as artemillin C [29, 30].

Aloe vera gel is a rich natural source for human well-being since it includes more than 200 active ingredients that support health. Antioxidants help fight inflammation and free radicals, and imbalances between oxidants and antioxidants may be one of the causes of IBD. SOD enzymes, phenolic antioxidants, and GPx activity are the sources of *A. vera* gel's antioxidant qualities. In two cell-free in vitro systems and inflammatory colorectal tissue, a dose-dependent radical quencher effect was seen. These cell-free techniques assessed the scavenging of peroxyl and superoxide radicals. Additionally, in inflammatory colorectal samples, a 1:50 concentration of *A. vera* gel inhibited prostaglandin E2 synthesis without influencing the release of thromboxane B2 [31]. In rats with AA-triggered colitis, *A. vera* gel (50.0 and 300 mg/kg) showed encouraging preventative and therapeutic benefits by reducing inflammation, ulcer score, and tissue damage in comparison to a water-based control. Furthermore, pre-treatment with sulfasalazine (100 mg/kg) and *A. vera* gel (50.0 and 300 mg/kg) showed comparable therapeutic benefits in reducing fibrosis, lesions, and inflammation [32]. Wistar albino rats with ulcerative colitis (UC) induced by acetic acid (AA) and indomethacin were administered oral doses of *A. marmelos* unripe fruit extract (AMFE). The treatment yielded a dose-dependent reduction in intestinal inflammation, preservation of mast cells, and an increase in antioxidant activity, indicating that the anti-inflammatory properties of AMFE, likely due to its phytochemical components such as flavonoids, phenolic compounds, and steroids, show potential as a protective treatment for IBD [33]. In another investigation, rats with AA-induced colitis received daily doses of 100, 200, and 400 mg/kg of ethanolic extract from dried *A. marmelos* fruit pulp (AME) for 14 days, with the most significant protective effect observed at a 200 mg/kg dosage of AME. Treatment with AME resulted in improved body weight and reduced damage to the colonic mucosa, as well as decreased inflammation, bloody or mucous diarrhea, and stool output in the rats. Furthermore, AME significantly enhanced antioxidant activity, lowered free radicals and myeloperoxidase activity, and exhibited considerable antibacterial properties [34]. When administered orally to rats with colitis induced by TNBS, the 50.0% ethanol extract of AME demonstrated a reduction in colonic damage, inflammation, diarrhea, free radicals, myeloperoxidase levels, and body weight, while promoting an increase in antioxidants within the colon. The antibacterial properties of AME against intestinal pathogens indicate its potential utility in treating TNBS-induced experimental colitis. In terms of efficacy, AME was comparable to the well-established colitis-protective drug sulfasalazine [35].

An extract from the secretory tissues on the bark of the Burseraceae family is known as *Commiphora molmol* (*C. molmol*). A randomized, double-blind, double-dummy study that lasted a year assessed how well mesalazine with myrrh, chamomile, and coffee charcoal maintained remission in individuals with ulcerative colitis. The two groups' mean CAI and recurrence rates were comparable, and the herbal therapy was safe and well-tolerated. 96 UC patients who were not active took part [36]. Rats with ethanol-induced stomach ulcers are more protected and cured by myrrh extract than by *C. molmol* oil. Supplementing with myrrh either prior to or during ethanol-induced gastric ulcers encourages the development and healing of the stomach mucosa. This is because myrrh increases the amount of the stomach antioxidant potential and the transcription factor Nrf2. Because of this, myrrh can successfully lessen the harmful oxidative, inflammatory, and apoptotic processes linked to stomach ulcers brought on by ethanol [37]. According to histopathology results, *C. molmol* oil and extract preserved the integrity of the gastric epithelium, sped up the healing process, and stopped rats from developing gastric ulcers [38].

Green tea is a rich source of the potent antioxidant epigallocatechin-3-gallate (EGCG). It is being researched for potential health benefits, including anti-inflammatory and anti-cancer properties. By lowering reactive oxygen species and peroxides, lowering neutrophil counts, increasing the antioxidant capacity in colonic tissue, lowering IL-8 secretion, and blocking inflammatory signaling pathways, EGCG treatment improved a mouse model of colitis induced by oral DSS administration [39]. When piperine and EGCG were used together in the therapy, this impact was significantly enhanced. The injection of EGCG, sulfasalazine, and green tea polyphenols (GrTP) significantly reduced colonic damage and improved histological scores in mice with UC and CD. The inflammatory markers TNF- α , IL-6, and serum amyloid A, which had been elevated in colitis-

affected mice, significantly decreased as a result of the therapy. Given the serious adverse effects of sulfasalazine, a common IBD drug, this emphasizes the need for safer alternatives like EGCG or GTE. GTE and EGCG are two safer alternatives [40]. In a pilot research, polyphenon E, a green tea extract rich in EGCG (given at 400 mg or 800 mg of total EGCG daily), showed encouraging results for those with mild to moderate UC. Polyphenon E produced a greater response rate (66.7% vs. 0.0%) and active treatment remission rate (53.3% vs. 0.0%) than the placebo. Polyphenon E may be a new treatment option for people with mild to moderately active UC who are not responding to existing drugs since it produced a therapeutic benefit with very few adverse effects [41].

Rosemary, or *Rosmarinus officinalis* L., is a Mediterranean-originated medicinal plant that has long been used as a natural remedy for digestive issues. The administration of *R. officinalis* leaves' hydroalcoholic extract or essential oil prevented the changes brought on by TNBS in rats, as shown by Minaian et al. [42]. Treatment with dosages of 400 mg/kg of extract and 400 µL/kg of essential oil decreased weight/length ratio, ulcer area and severity, inflammation severity and extension, and crypt damage.

C. oblonga is recognized as a significant food source and has been traditionally utilized as a gastric tonic, antidiarrheal, antiulcer, anti-inflammatory, antiemetic, and astringent, as well as for managing uterine and hemorrhoidal bleeding. Minaian et al. [43] explored the effects of quince (the fruit of *C. oblonga*) juice and quince hydroalcoholic extract on UC induced by TNBS in rats. When administered orally, both quince juice (400 and 800 mg/kg) and quince extract (200-800 mg/kg) led to a reduction in ulcer lesions, the colon weight-to-length ratio, and various histopathological parameters. Similar results were observed with the intraperitoneal administration of quince extract (500 mg/kg), although quince juice did not produce the same effects. These benefits appear to be associated with the phenolic compounds found in quince. Earlier research identified chlorogenic acid as the primary phenolic component, along with rutin, quercetin, and kaempferol present in the quince fruit [44].

Applications of herbal medicines in human clinical settings for IBD: There is currently little clinical data showing that cannabis use improves enteritis symptoms in patients; most of this data comes from research and a small number of clinical studies [45]. It's crucial to remember that a lot of these trials lack enough incentive and control. However, these studies indicate that cannabis may have unique therapeutic potential for patients, providing relief from symptoms including diarrhea, cramps, and stomach discomfort [46]. But it's essential to make sure patients are aware of the possible negative consequences of cannabis use. The primary ingredient in cannabis, cannabidiol (CBD), has been demonstrated to have anti-inflammatory and immunomodulatory effects and a minimal potential for addiction [47]. CBD (at doses of 100 and 500 mg/day) was shown to be helpful in 10 weeks of a placebo-controlled randomized controlled trial (RCT) with 60 UC patients. The experiment's objective was to evaluate the safety, effectiveness, and tolerability of CBD in UC patients. The patient's quality of life has improved and their Mayo score has decreased, according to the experiment. The safety and effectiveness of Qing Dai (QD) in UC patients were examined in a medical experiment that involved a placebo-controlled RCT with 86 UC patients. It was found that QD at doses of 0.5, 1.0, and 2.0 g/day facilitates intestinal epithelium repair in 8 weeks and encourages intestinal mucosa regeneration. Additionally, it raises IL-22 levels, which helps to lessen UC symptoms. An investigation on the safety and effectiveness of HMPL-004, an aqueous ethanol extract of *Andrographis paniculata*, was conducted over the course of eight weeks in 120 individuals with mild to moderately active UC. When compared to the placebo group, the clinical response rate is higher at the suggested minimum dose of 1800 mg of HMPL-004 (**Table 1**). A placebo-controlled RCT with 21 UC patients was conducted to evaluate the effectiveness of *Triticum aestivum* juice. The results showed that 100 mL of the juice per day significantly relieves abdominal and rectal bleeding symptoms and lowers the DAI scores in UC patients after four weeks. Interestingly, *Triticum aestivum* has amazing therapeutic benefits, especially for individuals with active restrictive left colon UC. It has also been shown to be safe with few adverse effects (**Table 1**).

Table 1: Clinical trials with herbal traditional medicine preparations for inflammatory bowel disease

Herbal product	Study design	Dose	Results	References
Aloe vera gel	Placebo-controlled RCT	200 mL/day orally for 4 weeks	Clinical response (CR) ↑, improvement and response ↑, activity Index ↓, histological scores ↓	[48, 49]
Curcumin	Placebo-controlled RCT	2.0 g/day orally for 24 weeks	Clinical activity index (CAI) ↓, endoscopic index (EI) ↓, recurrence rates ↓	[50, 51]
Cannabidiol	Placebo-controlled RCT	100 mg/day, escalated in the first 2 weeks to the maximum tolerated dose up to 500 mg/day, orally for 8 weeks	Mayo scores ↓, physician's global assessment of illness severity ↓, patient-reported quality-of-life ↑	[52]
Triticum aestivum juice	Placebo-controlled RCT	100 mL/day orally for 4 weeks	Diffuse Axonal Injury ↓, rectal bleeding ↓, physician global assessment (PGA) ↑	[53]

Plant-derived vesicle-like nanoparticles: Because of their immunomodulatory, antioxidant, and drug delivery properties, plant-derived vesicle-like nanoparticles (PDVLNs) have shown promise in the treatment of IBD and colitis-associated cancer. PDVLNs have the ability to control gut microbiota and alter macrophage polarization, which affects inflammation. Additionally, they serve as drug transporters, which enhances medication stability and may help combat drug resistance (**Table 2**). PDVLNs are naturally occurring nanocarriers that may enter mammalian cells and control cellular activity. They include lipids, proteins, DNA, and microRNA (miRNA). PDVLNs offer a great deal of promise for immunomodulating macrophages, controlling intestinal microbes, exhibiting beneficial antioxidant action, and combating medication resistance [54].

Table 2: PDVLNs derived from plant sources for inflammatory bowel disease

Plant source	Cell target	Mechanism	Study type	References
Ginger	RAW 264.7 macrophages	Induce the expression of the HO-1 and IL-10	In vitro	[55]
Turmeric	DSS-treated ICR mice	Decrease the secretion of IL-1b, MCP-1, TNF-a, IL-6, IL-12p70, IFN-b	In vivo	[56]
Tea flower	BALB/C Mice lung metastasis model of breast cancer	Boost intestinal bacteria diversity and abundance in the community	In vivo	[57]

Plant-based alkaloid against IBD: Alkaloids are secondary metabolites that plants make in response to biotic or abiotic stressors and environmental modulations. This gives alkaloids a variety of structural variations and important biological functions [58]. Because of these characteristics, alkaloids are becoming more and more popular among scientists as possible candidates for future medication development. Alkaloids are often categorized as indole-, isoquinoline-, and pyridine-like alkaloids based on their carbon skeletons. However, based on their molecular antecedents, they can also be categorized as tryptophan originated alkaloids, lysine, tyrosine, and ornithine [59]. Alkaloids are useful in treating intestinal inflammatory diseases, according to a growing body of current research, which gives promise for the development of new IBD medications [60, 61].

Conclusion: Herbal medicinal preparations have proven been to enhance a number of parameters in preclinical studies in colitis-affected, plus lower DAI scores, decreased pathology scores, decreased pro-inflammatory factors, increased anti-inflammatory factors, and reduce colitis by maintaining intestinal flora, promoting antioxidants, and shielding the intestinal barrier. Herbal medicines are effective in treating inflammatory bowel disease, and have been demonstrated that medications increase the rates of clinical remission, improve colonoscopy indices, encourage mucosal healing, and help lower histopathological and Mayo scores. Thus, herbal remedies provide encouraging substitute approaches to treating inflammatory bowel disease.

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Author contribution: Both authors conceived and designed the study, and collected the data. IKF performed analysis and interoperated data. Both authors drafted the manuscript, and approved the final version of the manuscript and agreed to be accountable for its contents.

Conflict of interest: The authors declare the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical issues: The authors completely observed ethical issues including plagiarism, informed consent, data fabrication or falsification, and double publication or submission.

Data availability statement: The raw data that support the findings of this article are available from the corresponding author upon reasonable request.

Author declarations: The authors confirm that they have followed all relevant ethical guidelines and obtained any necessary IRB and/or ethics committee approvals.