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Herbal Medicine as Therapeutic Avenue for Management of Inflammatory Bowel Disease

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Abstract: Conventional treatments for Inflammatory Bowel Disease (IBD) can help alleviate symptoms, but they often come with significant side effects that may diminish the quality of life. Due to these concerns, herbal medicines, which may offer relief with fewer side effects, are growing in popularity. Herbal medicines that show the greatest promise include *Curcumin, Boswellia serrata, Aloe Vera, Bromelain Butyrate, Mentha piperita Glycyrrhizin, Commiphora wightii, Madhuca longifolia, and Ginger*. Natural substances have shown promising results in various animal models of IBD, demonstrating multifaceted therapeutic potential. These compounds exhibit anti-inflammatory, antioxidant, and mucosal healing properties through various mechanisms. They effectively inhibit pro-inflammatory cytokines, including Tumour Necrosis Factor-alpha (TNF-α), and Interleukin-1 beta (IL-1β), while also suppressing the activity of 5-lipoxygenase (5-LOX), a key enzyme in the inflammatory cascade. Additionally, these substances have been observed to reduce oxidative stress markers in the gut, such as malondialdehyde (MDA), and modulate antioxidant factors like glutathione (GSH) and superoxide dismutase (SOD). While these findings highlight the potential of natural compounds as alternative or complementary therapeutic approaches in IBD management, warranting further investigation into their efficacy and mechanisms of action in clinical settings. Additionally, potential interactions with conventional IBD medications and standardization of herbal preparations remain important considerations for their integration into mainstream IBD management.

Keywords: Ulcerative Colitis (UC) • Tumour Necrosis Factor-alpha (TNF-α) • Interleukin (IL) • Nuclear factor kappa B (NF-κB) • Glutathione (GSH) • Mitogen-activated protein kinase (MAPK) • Malondialdehyde (MDA)

Introduction

Inflammatory bowel disease (IBD) is a chronic, relapsing disease that primarily affects the colon mucosa, leading to symptoms such as abdominal pain, diarrhoea, and rectal bleeding. While conventional treatments include corticosteroids, immunosuppressants, and biologics, their long-term use can lead to significant side effects. As a result, there is increasing interest in alternative approaches, including herbal medicine, for managing IBD. This review examines recent data on herbal remedies for IBD, focusing on their efficacy, safety, and underlying mechanisms of action. Various herbal plant-based medicines show a promising effect in both preventing flare-ups and providing effective symptom relief for inflammatory bowel diseases such as ulcerative colitis and Crohn's disease, offering potential complementary or alternative treatment options to conventional therapies (Comar and Kirby 2005) A comprehensive literature review reveals the use of herbal remedies for ulcerative colitis (UC), with the majority of users perceiving these treatments as safe & over 30% of patients asserting that herbal preparations could not possibly be harmful (Langmead and Rampton 2006).

Herbal Plant and Phytoconstituent for IBD

The treatment of IBD, including both UC and Crohn's Disease (CD), has shown promising results through the use of various plants and their bioactive compounds. These natural remedies offer a multi-faceted approach to managing IBD by targeting several key aspects of the condition. They demonstrate anti-inflammatory effects, which help reduce inflammation in the digestive tract, and antioxidant properties that combat oxidative stress. Additionally, these plant-based treatments exhibit immunomodulatory capabilities, allowing them to regulate immune system responses. Furthermore, they promote mucosal

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healing, aiding in the repair of the intestinal lining. This comprehensive approach underscores the potential of plant-derived treatments in effectively managing IBD symptoms and supporting overall gut health.

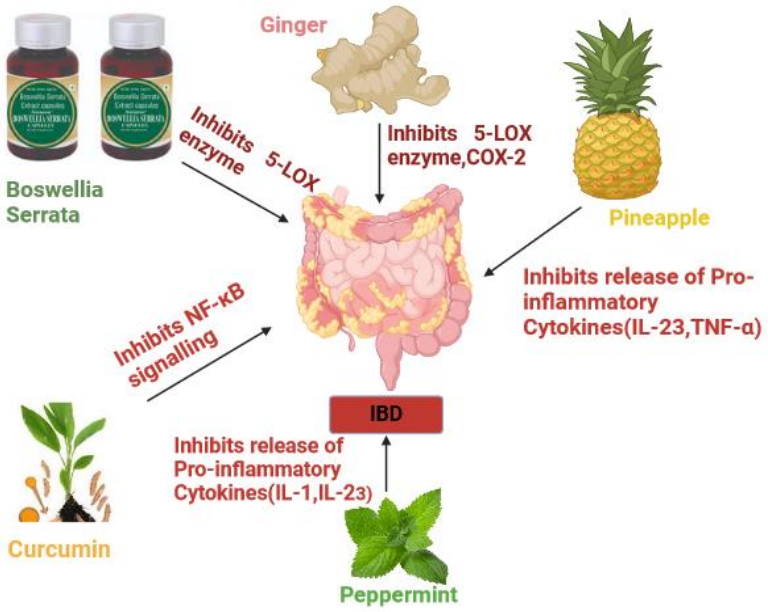

Fig 1. Various Plant and their Extract show anti-inflammatory effects in IBD by inhibiting various inflammatory pathways, enzymes, and mediators

Curcuma longa : Turmeric, derived from the Curcuma longa plant native to Southeast Asia, has garnered significant attention in both culinary and medicinal spheres due to its vibrant yellow colour and potent bioactive compounds. Curcumin, the primary active ingredient in turmeric, has shown promising potential in managing IBD that stems from its multifaceted mechanisms including the suppression of genes linked to oxidative stress, and fibrogenesis (Gupta et.al 2001, Epstein et.al 2010). By modulating crucial signalling cascades such as the PI3K/AKT pathway and inhibiting p38 mitogen-activated protein kinase (MAPK) activation, curcumin helps regulate the inflammatory response in the intestinal environment. One of curcumin's notable actions is its ability to suppress the production and release of pro-inflammatory molecules while simultaneously boosting anti-inflammatory factors. It reduces levels of inflammatory proteins like MIP-2 and IL-1β, and limits neutrophil accumulation at inflammation sites. Conversely, curcumin enhances the production of IL-10, an anti-inflammatory cytokine that helps balance the immune response by counteracting pro-inflammatory agents such as IL-2, TNF-α, and IFN-γ (Epstein et al 2010, Yang et al 2017). Curcumin also downregulates the expression of matrix metalloproteinase-3 (MMP-3), an enzyme involved in tissue remodelling and potentially in IBD progression. Studies using cultured mucosal cells from IBD patients have shown that curcumin significantly dampens inflammatory responses by inhibiting p38MAPK activation and histone acetylation (Dahmen et.al 2010). Similarly, experiments with mouse models of IBD have revealed that curcumin can alleviate intestinal mucosal damage and symptoms by blocking the p38MAPK signalling pathway, thereby reducing the release of TNF-α and other inflammatory cytokines (Krieglstein et.al 2001, Gomaa et.al 2021). These diverse anti-inflammatory properties, combined with its safety profile, position curcumin as a viable and promising therapeutic option for IBD management.

Boswellia serrata: Boswellic acid, the primary active compound in Boswellia can modulate key inflammatory pathways involved in IBD pathogenesis. One of the most significant actions of Boswellic acid is its inhibition of 5-lipoxygenase (5-LOX), an enzyme crucial in the production of leukotriene B4 (LTB4). LTB4 is a potent pro-inflammatory mediator that plays a central role in gut

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inflammation. This mechanism has been demonstrated in both laboratory studies and animal models (Majeed et.al 2021, Gomaa et.al 2021, Catanzaro et.al 2015). Boswellic acid has been shown to inhibit the phosphorylation and activation of NF-κB and prevent NF-κB from translocating to the cell nucleus and initiating the transcription of pro-inflammatory genes. By interfering with this pathway, Boswellic acid helps reduce the overall inflammatory response in the colon, potentially alleviating symptoms of UC and other forms of IBD. In a clinical study by Gupta et al., 30 patients with chronic UC were treated with either Boswellia gum extract (900 mg daily, divided into 3 doses for 6 weeks) or sulfasalazine (3 g daily, divided into 3 doses for 6 weeks). Results showed that 14 out of 20 patients treated with Boswellia achieved remission, while 18 experienced improvements in one or more metrics. These outcomes led the researchers to conclude that Boswellia is an effective treatment for IBD (Chauhan et.al 2021, Siddiqui et.al 2011). While more extensive clinical trials are needed to fully establish its efficacy and optimal dosing regimens, the current evidence suggests that Boswellic acid could offer a valuable addition to the therapeutic arsenal against IBD.

***Aloe Vera* :** *Aloe Vera* has also been shown to be effective against anti-inflammatory, SARS-CoV-2 (Catalano et.al 2020), analgesic (Budai et.al 2013), immunomodulatory (Montoya et.al 2022), antioxidant (Wagan et al 2022), anti-ulcerogenic, anti-irritant, antimicrobial, anticancer, aphrodisiac & antiviral (Hęś et.al (2019), Danish et.al (2020), Gao et.al (2019), Erhabor et.al (2017), Catalano et.al (2020), Mahboubi et.al (2024), Sousa et.al (2022), Maiuolo et.al (2022), Alesci et.al (2022), Al-Salman et.al 2023). Additionally, it is well-known for its ability to heal a variety of illnesses, particularly gastrointestinal issues. The anti-inflammatory properties of Aloe vera are largely attributed to its bioactive compounds, such as flavonoids and anthraquinones, which inhibit nitric oxide production and modulate key inflammatory pathways. These compounds suggest that Aloe vera could be effective in alleviating inflammation associated with conditions like UC. In a clinical trial conducted by Langmead *et al*., Aloe vera gel was tested on 30 patients with mild to moderate UC. The results showed that 30% of patients treated with Aloe vera achieved remission, and 37% showed improvement, compared to only 7% remission and 7% improvement in the placebo group. These findings underscore Aloe vera's potential as a treatment for UC. Additionally, in vitro studies demonstrated that Aloe vera inhibited inflammatory markers, further supporting its anti-inflammatory properties (Al-Salman et.al 2023). Moreover, research has also explored the regulation of inflammation-mediator gene expression in UC, highlighting Aloe vera's potential to influence gene pathways involved in inflammation (Tornero et.al (2022), Paul et.al (2021).

Ananas comosus: Bromelain, a proteolytic enzyme derived from pineapples, has shown promise as an anti-inflammatory agent for treating UC and other forms of IBD (Salibay et.al 2021). Its anti-inflammatory effects are primarily attributed to its proteolytic activity, which influences T-cell activation and cytokine release in both *in vitro* and *in vivo* IBD murine models (Hale et.al (2002), Varilla et.al 2021). While the exact mechanisms are not fully understood, bromelain exhibits immunomodulatory and hormone-like effects by affecting intracellular signalling pathways (Akkol et.al 2020). Studies have demonstrated that bromelain reduces the expression of key pro-inflammatory mediators such as TNF-α, IL-1β, and IL-6, which are heavily involved in the inflammatory processes of IBD. This reduction in inflammatory mediators helps decrease inflammation in the intestines (Chakraborty and Gupta et.al 2021). Additionally, bromelain influences immune responses by modulating the activity of various immune cells. Notably, it decreases CD4+ T-cell activation and reduces CD25 expression, which is related to T-cell activation (Manhart et.al (2002), Kumar et.al (2023). Bromelain also modulates the release of cytokines and chemokines, further altering the inflammatory response (Manhart et.al (2002), Kumar et.al 2023). These multiple anti-inflammatory properties make bromelain a promising supplement for managing IBD, especially UC. However, further research is needed to fully elucidate its mechanisms of action and optimize its therapeutic potential in treating inflammatory conditions.

Butyrate: Butyrate, a key energy source for intestinal epithelial cells, plays a crucial role in maintaining colonic homeostasis and is used as a treatment for UC. Research suggests that topical administration of butyrate may help reduce colon inflammation in UC. According to Nancey et al., elevated levels of TNF-α in UC patients can impair the breakdown of butyrate, contributing to the inflammatory process (Nancey et.al 2005). Various *in vitro* and *in vivo* studies have established the anti-inflammatory properties of butyrate, primarily

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through the suppression of NF-κB. This suppression results in reduced levels of inflammatory markers such as myeloperoxidase, cyclooxygenase-2 (COX-2), adhesion molecules, and cytokines (Segain et.al (2000), Song et.al 2006). Patients with active UC have been shown to have a decreased ability of the intestinal mucosa to oxidize butyrate (Kato et.al (2007), Simpson et.al 2000). In clinical settings, the administration of enteric-coated tablets containing 4 g of butyrate daily, in combination with mesalamine, significantly improved disease activity scores in patients with mild-to-moderate UC compared to treatment with mesalamine alone. This highlights butyrate's potential as an effective adjunct therapy in managing UC (Rahimi et.al ;2012).

Mentha piperita: Peppermint (*Mentha piperita*) and its primary active compound, menthol, have emerged as promising natural agents for treating gastrointestinal disorders, including IBD (Rahimi et.al ;2012). Their therapeutic potential is particularly evident in addressing the oxidative stress and inflammation associated with IBD. Menthol is reported to significantly lower malondialdehyde (MDA) levels, a marker of lipid peroxidation, while simultaneously increasing glutathione (GSH), a crucial antioxidant, thereby restoring the balance of oxidative stress in the intestinal mucosa, which is often disrupted in IBD patients. Moreover, it has been observed to improve both macroscopic and microscopic ulcer scores in the colon, indicating its potential not only in reducing inflammation but also in promoting the healing of ulcerated tissues (Khanna et.al 2014). The anti-inflammatory properties of menthol are further highlighted by its ability to significantly reduce levels of pro-inflammatory cytokines, including IL-1, 23, and TNF-α, potentially leading to symptom relief and enhanced mucosal healing. These multifaceted actions position peppermint and menthol as promising natural therapeutic options for IBD, offering a holistic approach to managing this complex disease (Khanna et.al 2014).

Glycyrrhizin: The efficacy of Glycyrrhizin and its active component glycyrrhizic acid in experimental models of induced colitis has been explored in numerous studies. Both oral administration and combinations with other anti-inflammatory substances have been shown to mitigate the inflammatory process in the colonic mucosa, reduce oxidative tissue damage, and promote epithelial healing (Yuan et.al (2006), Sun et.al (2009), Kudo et.al; (2011), Sethuraman et.al 2015). In an early study by Yuan *et al*. on acetic acid-induced colitis, the glycyrrhizinate extract was found to inhibit NF-κB and TNF-α in the colonic mucosa, demonstrating its anti-inflammatory properties. Sun *et al.* later investigated glycyrrhizinate in a TNBS-induced colitis model in mice, administering oral doses of 10, 20, and 30 mg/kg over 10 days. Results showed a dose-dependent reduction in inflammation, as evidenced by lower myeloperoxidase (MPO) activity and improved inflammatory scores. Glycyrrhizinate also downregulated pro-inflammatory cytokines such as TNF-α, IL-12, IFN-α, and IL-17, while increasing the anti-inflammatory cytokine IL-10 in the colon. Further studies assessed the topical administration of glycyrrhizinate in DSS-induced colitis in rats with UC. Glycyrrhizinate significantly reduced the severity of colitis by decreasing pro-inflammatory cytokines and chemokines, including IL-1β, IL-6, TNF-α, CXCL2, and CCL2, in the inflamed mucosa. It also lowered MPO activity and improved colitis symptoms (Kudo et.al; (2011), Sethuraman et.al 2015). Combining glycyrrhizinate with other treatments enhanced its therapeutic effects, resulting in reduced MPO levels, fewer macroscopic and microscopic lesions, and downregulation of TNF-α and PPARγ expression (Jeon et.al 2016).

Commiphora wightii: Guggulsterone, a plant steroid derived from the resin of *Commiphora wightii*, has shown potential in both the prevention and treatment of T-cell-induced colitis (Cheon et.al 2006). It works by suppressing key inflammatory pathways, including inhibiting IKK activity, preventing IκB phosphorylation and degradation, and reducing NF-κB DNA binding. Additionally, it inhibits LPS- or IL-1β-induced ICAM-1 expression in intestinal epithelial cells. In a DSS-induced mouse colitis model, guggulsterone was found to downregulate IκB and IKK expression, further demonstrating its anti-inflammatory effects (Kim et.al 2010). Its derivative, GG-52, shows therapeutic and preventive effects on colon inflammation, suggesting potential for IBD treatment (Cheon et.al 2006). In experimental mice with DSS-induced UC, Kim et al. studied the effects of guggulsterone isomer (200 mg/kg q.d.) and found a significant reduction in the severity of the disease as measured by the Disease Activity Index (DAI), colon length, and histology (Priya et.al 2022). It caused a noticeable and significant histological reduction of acute colitis and significantly decreased both the clinical and macroscopic inflammatory indices. A comparable result was observed in the treatment model as well, where GGS (100 mg/kg

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Q.D.) dramatically reduced clinical indices in the mice, including body weight change, colon length, and DAI (Kim et.al 2010).

Madhuca longifolia : *Madhuca longifolia* an Indian evergreen tree, is used for treating UC, its effectiveness stems from anti-inflammatory, antioxidant, and gastroprotective properties (Simon et.al 2021) .Recent studies showed that its aqueous leaf extract reduces oxidative stress and inflammation in colitis models. The plant's bioactive compounds, including flavonoids and triterpenoid saponins, decrease pro-inflammatory cytokines and promote mucosal healing by forming a protective barrier on the intestinal lining (Jamtsho et.al 2024). Research has shown that administering *Madhuca longifolia* bark extracts to animal models of colitis can reduce inflammatory markers, suggesting that the plant may have anti-inflammatory properties for the intestinal lining. Tissue damage will worsen due to the oxidative stress linked to ulcerative colitis. Strong antioxidant qualities found in *Madhuca longifolia* are known to help scavenge free radicals and lessen oxidative damage in the gastrointestinal tract. This protective action may be essential for preserving gut health and averting more UC problems (Jamtsho et.al 2024).

Zingiber officinale : Ginger and its active component gingerol showed encouraging therapeutic effects in treating diseases. The anti-inflammatory, antioxidant, and gut-modulating qualities of ginger's bioactive substances, especially its polysaccharides, help reduce symptoms and encourage the healing of inflammatory bowel diseases (Hao et.al 2022). Ginger polysaccharides were also observed to inhibit pro-inflammatory cytokines TNF-α and IL-1β, which are key mediators of the IBD inflammatory cascade. Ginger helps to heal the intestinal tract by reducing mucosal damage and modulating the inflammatory response. Studies have demonstrated that ginger polysaccharides can regulate the composition and function of gut microbiomes in colitis mice, specifically by increasing positive bacteria while decreasing negative expression which will help to re-balance the gut microbial and bolster intestinal barrier function (Wang et.al 2022).

Conclusion

Herbal plants and their phytoconstituents present a viable adjunct therapy for IBD, potentially improving patient outcomes and quality of life. As research progresses, these natural remedies could become integral components of a holistic approach to IBD treatment, complementing existing therapies and offering new hope to those affected by these chronic conditions. Further investigation in clinical and pre-clinical are necessary to further validate the effectiveness of these plant.

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