

Therapeutic potential of medicinal plants in Ulcerative Colitis: A Review

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ABSTRACT

Ulcerative colitis (UC) is characterized by abdominal pain, mucopurulent stools and primarily affecting the rectal and colonic mucosa and submucosa. Standard treatments for UC include glucocorticoids, immunosuppressants, antibiotics and biologics, but these have serious long-term side effects. To mitigate these effects, 40 % of UC patients use herbal natural products. However, delivering these treatments precisely to the inflamed colon poses a challenge. This review explores herbal approaches (potential herbal plants, secondary metabolites) used to treat UC and stimuli-responsive nanoparticles for precise drug delivery. These advanced methods could overcome the limitations of traditional delivery systems. Furthermore, *in-vitro* and *in-vivo* studies are crucial to understand the underlying mechanisms of UC and improve treatments. The review emphasizes the potential of integrating herbal plants and novel delivery technologies to treat UC and minimize complications.

Keywords: Anti-ulcer, Herbal approaches, Medicinal plants, Inflammatory Bowel disease, Natural nanoformulations, Ulcerative Colitis

1. INTRODUCTION

Inflammatory bowel disease, (IBD) is a chronic inflammatory disorder with an unknown cause. Ulcerative colitis primarily affects the sigmoid colon and rectum, predominantly involving the submucosal and mucosal layers of the colon, with decreased incidence of muscular layer engagement. It is marked by occasional yet regular relapses. (17). Ulcerative colitis (UC) is a persistent inflammatory condition of the colon, starting in the rectum and possibly spreading to the upper colon. (29,46). The main symptoms of UC include mucous and purulent stools, weight loss, tenesmus, and frequent bowel movements. (28). UC commonly coexists with gastroduodenitis, eosinophilic esophagitis, and inflammation of the upper gastrointestinal tract and can result in colon malignancy (13,42). UC main treatment include microbial agents, biological fecal microbiota transplantation and surgery (15). Pharmaceuticals have various side effects [lupus-like syndrome, heart disease, liver disease, cancer, central nervous system disorders (31)]. Both signaling cascade and cytokines are key factors in assessing the progression of UC and serve as vital targets for treatment (48). Current conventional approaches to manage UC aimed at reducing inflammation and alleviating symptoms. These consist of antibiotics, used to adjust the gut microbiome by targeting intestinal bacteria involved in inflammation, amino-salicylate as Sulfasalazine, releases 5-aminosalicylic acid in the colon, thereby, mitigating inflammation at the affected site. Azathioprine, mercaptopurine and mercaptopurine as Immunosuppressive agents are used for immune system's response, consequently diminishing inflammation (18). However, their adverse effects often restrict their therapeutic use, hence, herbal medicine are used to alleviate side effects. The precise cause of UC is still unidentified as it is influenced by genetic predispositions, infectious agents, oxidative stress, impaired immune regulation, excessive production of prostaglandin (PG) E2 and loss of tolerance intestinal microbiota (5). Oxidative stress is a primary contributor, with the interactions between reactive oxygen species (ROS) and reactive nitrogen species (RNS) affects various physiological functions and colorectal pathological processes. Hence, there is increasing interest in using exogenous antioxidants to treat oxidative gastrointestinal disorders (1). The onset and progression of UC are driven

by the release of inflammatory cytokines by macrophages, B-cells, and T-cells. Among the pro-inflammatory cytokines implicated in the degradation of articular cartilage are tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), IL-6, IL-8, granulocyte-macrophage colony-stimulating factor, and transforming growth factor- β (TGF- β) (10).

2. IBD PATHOPHYSIOLOGY

Inflammatory Bowel Disease (IBD) involves breaches in the intestinal epithelial barrier and mucosal damage due to infectious agents, chemicals, or diet-related metabolic changes. The disease persists due to inadequate treatment of inflammation, potentially worsened by disrupted tolerance to commensal microorganisms or the body's own tissue damage signals.

2.1. Innate Immune Cells in the Pathogenesis of IBD

In IBD, the innate immune system is the first responder to PAMPs (Pathogen-Associated Molecular Patterns) and to molecules released from damaged or dying cells, known as DAMPs (Damage-Associated Molecular Patterns). DAMPs and PAMPs activate the innate immune system by interacting with PRRs (Pattern recognition receptors). These patterns can be sensed by several components (granulocytes, neutrophils, monocytes, myeloid-derived suppressor cells, macrophages, and dendritic cells) of the innate immune system. In addition, these patterns can also be recognized by non-immune cells, such as intestinal epithelial cells (IECs) and myofibroblasts.

2.1.1. Neutrophils in Gut Homeostasis: Neutrophils, the most abundant immune cells in human circulation, are rapidly recruited to infection or inflammation sites as the first line of defense. When the intestinal barrier is damaged, they are drawn to the inflamed tissue by chemotactic gradients formed by cytokines (IL-1 β , IL-6, TNF- α), chemokines (CCL8, CXCL10, MIP-2/CXCL2), and growth factors (GM-CSF, G-CSF).

2.1.2. Neutrophils in Gut during IBD: Neutrophil activity increases in IBD patients, associated with TNF- α release and lipopolysaccharides. Factors contributing to NETs production include IL-8 from endothelial cells and elevated protein arginine deiminase 4 (PAD4), which is more abundant in intestinal tissue of UC patients and damaged tissues. PAD4 mediates histone citrullination, crucial for NETosis.

2.1.3 Macrophages in Gut in Steady State Conditions: Host defense macrophages possess microbicidal activity and, when stimulated by interferon (IFN) γ or TNF- α , produce cytokines typically secreted by T cells, natural killer cells, or antigen-presenting cells (APCs). Wound-healing macrophages, activated by IL-4 from T cells or granulocytes, aid in tissue repair. Regulatory macrophages, with an anti-inflammatory role, are generated in response to stimuli such as IL-10, glucocorticoids, and apoptotic cells.

2.1.4 Macrophages in Pathogenesis of IBD: IBD patients have more pro-inflammatory macrophages, including activated mucosal macrophages in pediatric cases. These macrophages express high levels of TNF- α , IL-1 β , IL-6, and iNOS. Ly6Chigh monocytes in IBD upregulate TLR2 and NOD2, increasing sensitivity to bacteria and differentiation

into pro-inflammatory cells. Resident CX3CR1^{high} macrophages maintain an anti-inflammatory phenotype despite the presence of these inflammatory macrophages.

2.1.5 Innate Lymphoid Cells in IBD: In the intestine, innate lymphoid cells (ILCs) are crucial components of the innate immune system. They play essential roles in antimicrobial defence, organ development, tissue protection, regeneration, and maintaining mucosal homeostasis.

3. TREATMENTS FOR ULCERATIVE COLITIS

The primary aims of existing antiulcerogenic drugs is to achieve prompt remission, maintain it over an extended period, prevent disease-related complications, minimize disability, and ultimately enhance patient quality of life and life expectancy (16,32). The selection of treatment varies based on the severity of the condition, including the extent and location of colon involvement. Subsequent therapy decisions depends upon the initial response to induction therapy (36,44). UC therapy involves two key phases: (i). the first step aims to achieve remission and alleviate inflammatory symptoms using induction agents, while the (ii). second step focuses on sustaining remission with maintenance agents (33). The combination of medications, including salicylates (such as olsalazine and mesalazine), immunomodulators (6-mercaptopurine, azathioprine, cyclosporine, and methotrexate), corticosteroids (prednisolone and methylprednisolone) and, tumor necrosis factor signaling inhibitors (infliximab, adalimumab, and golimumab), integrin blockers (vedolizumab, natalizab, and etrolizumab), Janus kinase (JAK) inhibitors (tofacitinib), and interleukin antagonists (mirikizumab and ustekinumab), contribute significantly to treat UC (38).

3.1. HERBAL TREATMENTS OF ULCERATIVE COLITIS

In this review we focus on the Herbal treatment and their formulations. The term "herb" applies to plants whose leaves, stems, or fruits are used as food, medicine, or for their aroma and taste. Herbal medicine encompasses the use of plants and their extracts to treat medical conditions. Herbal medicine is a prevalent aspect of Traditional Chinese Medicine (TCM), with studies suggesting that approximately 28.9 % of adults in the US regularly incorporate one or more TCM therapies into their health regimen, including herbal products. Recent studies have found that approximately 20 % to 26 % adults use Traditional Chinese Medicine (TCM) therapies to manage their gastrointestinal (GI) symptoms. Notably, individuals diagnosed with functional GI disorders or chronic GI conditions use these therapies (45). The adoption of complementary medicine, including herbal therapies, is prevalent among patients diagnosed with IBD, spanning across the Western world and several Asian countries like China and India (11). Worldwide, herbal products are used for their therapeutic potential in treating a variety of conditions. Phytoconstituents (catechins, flavonoids, terpenes, alkaloids, anthocyanins, quinines and anthoxanthins) exhibit anti-inflammatory and antioxidant effects, and have the capacity to modulate the expression of pro-inflammatory signals, making them promising candidates for UC treatment (14).

3.2. HERBAL PLANTS WITH ANTI-ULCER ACTIVITY

The photographs of these Medicinal Plants are given in Figure 1.

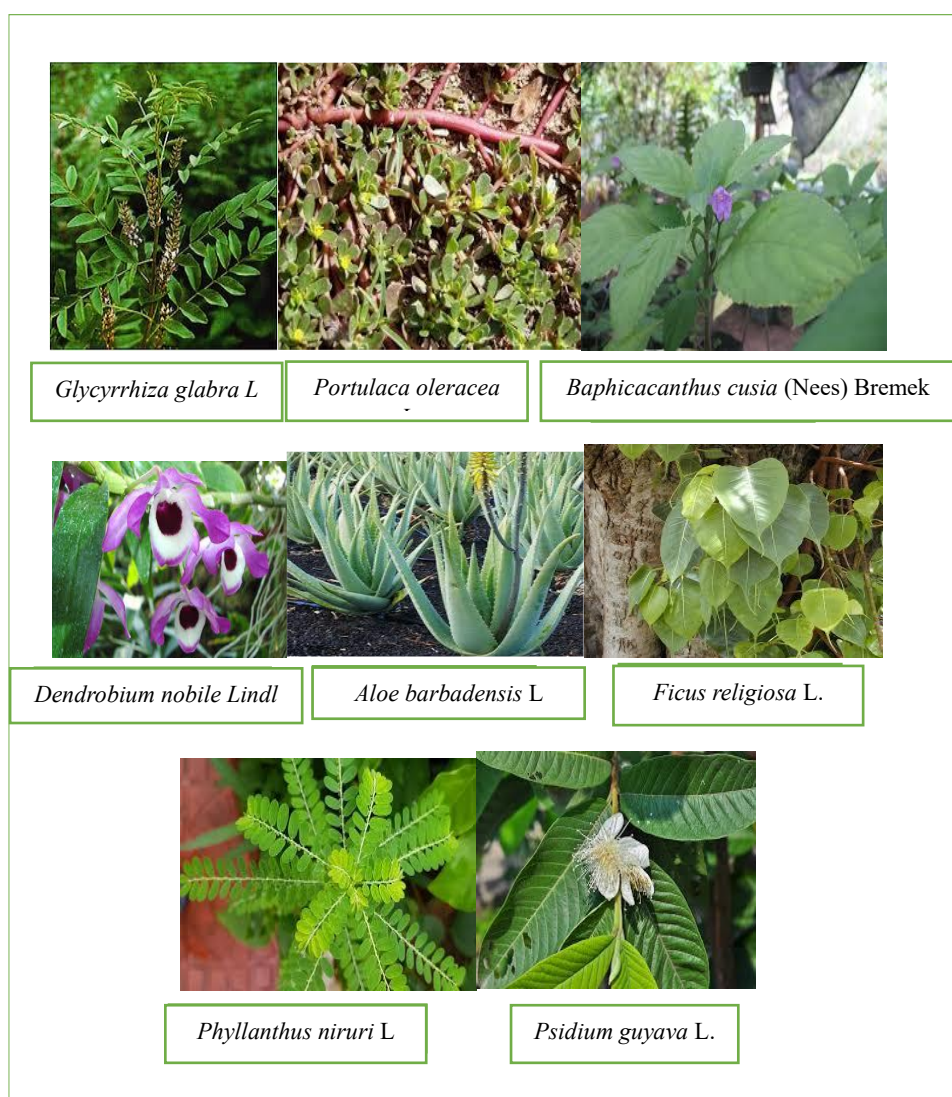


Figure 1. Herbal Plants with Anti-Ulcer Activity

3.2.1. *Glycyrrhiza glabra* L.: It suppresses the NLRP3 inflammasome-mediated immune responses, effectively easing UC symptoms (48). Glycyrrhizic acid decreases the activation of macrophages stimulated by lipopolysaccharide and inhibits the production of pro-inflammatory cytokines IL-6 and IL-1 β . Additionally, glycyrrhiza polysaccharide (GPS) influences both the immune system and gut microbiota of the organism (19).

3.2.2. *Portulaca oleracea* L.: It possesses antibacterial and antioxidant properties, boosts immune function and regulates metabolic processes in the body. Its extract (POE) can alleviate damage to the intestinal mucosal barrier by decreasing the levels of pro-inflammatory cytokines, including IL-1, IL-6, IL-17 and TNF α (3).

3.2.3. *Baphicacanthus cusia* (Nees): It relieves UC by suppressing the stimulation of the TLR4/MyD88/NF- κ B signaling cascade and decreasing the levels of TNF, IL-1 β and IL-6 in serum and tissues (49).

3.2.4. *Dendrobium nobile* Lindl.: *Dendrobium nobile* Lindl., stem reduces the levels of NF- κ B p65, TLR4, and phosphorylated IKK α / β . It additionally suppresses the activation of the TLR4/NF- κ B inflammatory signalling pathway. It restores the expression of tight junction proteins including zonula occludens 1, Occludin, and Claudin-1 to enhance intestinal barrier function. It inhibits the release of pro-inflammatory cytokines like TNF α , IL-1 β and IL-6 (47).

3.2.5. *Aloe barbadensis* L.: *Aloe barbadensis* (Asphodelaceae family) contains compounds viz., Aloin, Barbalin, Isobarbaloin saponins and emodin. Its extracts treats indomethacin-induced g ulcers, exhibiting significant anti-ulcer activity (7).

3.2.6. *Ficus religiosa* L.: *Ficus religiosa* (Moraceae family) active components [caoutchouc (cochtone), tannin, and wax] are found in its bark. It also contains bioactive compounds like flavonoids, saponins and tannins. Its leaves hydroalcoholic extract significantly reduces the ulcer index value than control group (27).

3.2.7. *Phyllanthus niruri* L.: *Phyllanthus niruri* (Phyllanthaceae family) chemical composition includes alkaloids, saponins, tannins, flavonoids, carbohydrates, and glycosides. Key active constituents like alkaloids such as 4-methoxy-securinine, ellagic acid, beta-sitosterol, gallic acid, and hypophyllanthin are noteworthy. The methanolic extract of *P. niruri*'s aerial parts have revealed significant antiulcer activity (40).

3.2.8. *Psidium guyava* L.: *Psidium guyava* (Myrtaceae family) leaves contains resin, cellulose, flavonoids, fat, tannin, volatile oil, chlorophyll and mineral salts. Its methanol leaf extract displays notable anti-ulcer effects against ethanol-induced gastric ulcers (20).

3.3. SECONDARY METABOLITES WITH ANTIULCEROGENIC ACTIVITY

Table 1. Alkaloids with anti-ulcerogenic activity

Botanical name, Family	Common name	Main Phytoconstituent	Role in Treatment of UC	Reference
<i>Capsicum annuum</i> L. (Solanaceae)	Bell pepper	Capsaicin	Diminish the levels of pro-inflammatory cytokines including Interleukins IL-6, Tumor necrosis factor TNF- α , and IL-1 β . Alleviate oxidative stress in the colon.	24
<i>Papaver somniferum</i> L. (Papaveraceae)	Opium poppy	Morphine	Block the secretion of neurotransmitters implicated in pain signaling, like substance P and glutamate.	43

Table 2. Terpenoids with anti-ulcerogenic activity

Botanical name, Family	Common name	Main Phytoconstituent	Role in Treatment of UC	Reference
<i>Fabiana imbricate</i> (Solanaceae)	Pichi	11-hydroxy-4-amorphen-15-oic acid	Suppress the production of pro-inflammatory cytokines such as Interleukins IL-6, IL-1 β , and Tumor Necrosis factor TNF- α . Decrease oxidative stress levels.	37
<i>Prumnopitys andina</i> (Podocarpaceae)	Chilean Plum yew	ferruginol	The existence of antioxidants aids in diminishing oxidative stress, a contributing factor to UC's development. Antioxidants counteract free radicals, safeguarding cells against harm and alleviating inflammation.	5
<i>Xanthium cavanillesii</i> Cass. (Asteraceae)	Cocklebur	Dehydroleucodine	Xanthium species have been discovered to regulate immune responses, providing potential advantages in autoimmune disorders like UC.	5
<i>Zingiber officinale</i> Roscoe (Zingiberaceae)	Ginger	b-sesquiphellandrene, b-bisabolene and zingiberene	Prevents the activity of enzymes such as cyclooxygenase (COX) and lipoxygenase (LOX), which contribute to producing pro-inflammatory prostaglandins and leukotrienes. Also, hinders the activation of nuclear factor-kappa B (NF- κ B).	22

Table 3. Phenolics with anti-ulcerogenic activity

Botanical name, Family	Common name	Main Phytoconstituent	Role in Treatment of UC	Reference
<i>Mangifera indica</i> L. (Anacardiaceae)	Mango	Mangiferin	Sustaining equilibrium between Helper cell type1 and type 2(Th1 and Th2 cells), essential for a controlled immune reaction. Prevent the activation of nuclear factor-kappa B (NF-κB).	39

Table 4. Flavonoids with anti-ulcerogenic activity

Botanical name, Family	Common name	Main Phytoconstituent	Role in Treatment of UC	Reference
<i>Camellia sinensis</i> Nung (Theaceae)	Tea	Flavonols and dihydroflavonols	Decreases inflammatory factors while increasing Trefoil factor 3 (TFF3) levels.	35
<i>Origanum vulgare hirtum</i> L. (Lamiaceae)	Greek Oregano	Flavanones	Upregulates occludin, Junctional adhesion molecule (JAM-A), claudin-3 and claudin-7. Elevates Inter Leukins IL-17A. Decreases IFN-γ, TNF-α, IL-6 and IL-1β	8

Table 5. Saponins with anti-ulcerogenic activity

Botanical name, Family	Common name	Main Phytoconstituent	Role in the Treatment of UC	Reference
<i>Aralia elata</i> Miq (Araliaceae)	Angelica tree	Araloside	It has the potential to block the nuclear factor-kappa B (NF-κB) pathway, which serves as a significant regulator of inflammation. By adjusting this pathway, the plant could potentially alleviate chronic inflammation in the colon.	25
<i>Aesculus hippocastanum</i> L. (Sapindaceae)	Common Horse Chestnut	Aescin	Aescin has demonstrated significant anti-ulcer properties by inhibiting the release and activity of inflammatory mediators such as prostaglandins and leukotrienes, which are pivotal in the inflammation associated with UC.	26
<i>Glycyrrhiza glabra</i> L. (Fabaceae)	Licorice	Glycyrrhizic acid	Glycyrrhizin demonstrates potent anti-ulcer characteristics by inhibiting enzymes engaged in the inflammatory process, like cyclooxygenase (COX) and lipoxygenase (LOX). Additionally, it	4

			modulates the activity of nuclear factor-kappa B (NF- κ B), a crucial transcription factor in inflammation.	
<i>Panax ginseng</i> L. (Araliaceae)	Korean ginseng	GinsenosideRb1	Ginseng has the ability to boost the effectiveness of intrinsic antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase, offering extra defense against oxidative harm.	21

3.4. NATURAL NANO-BASED FORMULATIONS TO TREAT ULCERATIVE

COLITIS: Nanoparticles from the natural origins have less toxicity and enhanced safety than synthetic nanoparticles (41).

3.4.1. Formulation – Curcumin NPs

Isolated Compound- Curcumin extracted from the rhizome of turmeric (*Curcuma longa* L.), is a hydrophobic polyphenolic compound with numerous biological and pharmacological properties, including anti-inflammatory, antioxidant, and anticarcinogenic effects (12).

Mechanism: Curcumin nanoparticles significantly inhibit nuclear factor κ B (NF- κ B) in colonic epithelial cells (34).

3.4.2. Formulation – Silymarin and Nano-Se

Isolated Compound Silymarin, derived from *Silybum marianum*, is a combination of flavanolignans with promising intracellular antioxidant properties.

Mechanism: Reduced the NF- κ B activity, oxidative stress biomarkers and levels of pro-inflammatory cytokines (30).

3.4.3. Formulation – GDLVs

Isolated Compound- 6-gingerol and 6-shogaol, sourced from the rhizome of *Zingiber officinale* Roscoe, has anti-inflammatory, antioxidant and anticancer effects.

Mechanism: Lowered the levels of TNF- α , IL-6, and IL-1 β cytokines, while increasing the anti-inflammatory cytokines IL-10 and IL-1 β (50).

3.4.4. Formulation – GELNs

Isolated Compound- Grape juice (*Vitis* spp): It is a beverage from *Vitis* sp genus, mainly *V. labrusca*, *V. vinifera* and *V. rotundifolia* species. It is very rich source of polyphenols, containing flavonoids, anthocyanins, proanthocyanidins tannins and resveratrol.

Mechanism: By targeting intestinal stem cells, the generates Lgr5+ stem cells by inhibiting the β -catenin signalling pathway in cells receiving GELNs (23).

3.4.5. Formulation – Embelin-loaded lipid nanospheres

Isolated Compound- Embelin also known as 2,5-dihydroxy-3-undecyl-1,4-benzoquinone, is a natural compound from *Embelia ribes* Burm.f (9).

Mechanism: Reduced levels of LDH, MPO, and LPO, along with an increase in GSH levels, indicate improved treatment efficacy for UC (6).

4. CONCLUSIONS

Ulcerative colitis (UC) is a chronic medical condition often requiring lifelong medication to prevent recurrence, lower the risk of colorectal cancer, and enhance quality of life. Typically, glucocorticoids and immunosuppressants are prescribed for UC treatment, but these have numerous side effects. Herbal approaches play a significant role in UC prevention and treatment, effectively addressing a wide range of acute and chronic gastrointestinal disorders, including UC. In some cases, diseases necessitate targeted delivery, leading to the use of herbal nano-formulations for precise drug delivery. Nanoparticles enhance the bioavailability of natural compounds. Nano-formulation combines all the benefits of efficient delivery with a unique formulation. The herbal nano-formulations used in UC treatment, highlighted their importance.

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AUTHOR'S CONTRIBUTION

In the present review, Disha Gupta and Monika analysed the herbs, phytochemicals, and nanoparticles used for the treatment of obesity and was the primary contributor in making the manuscript. The systematic evaluation was carried out by Saumya Das and Avijit Mazumder. The final manuscript was read and approved by all authors.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

DECLARATION

We declare that all authors of this Ms. have made substantial contributions. We did not exclude any author who substantially contributed to this Ms. We have followed our ethical norms established by our respective institutions.

ETHICAL STATEMENT

This is to inform you that in this study, we have not been involved in any animal and human studies.

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