



# Phytotherapy as a Safe Curative Option for Ulcerative Colitis: A Review

Sonal Mamania, Rupa Mazumder\*, Swarupanjali Padhi, Vikas Malik

Noida Institute of Engineering and Technology (Pharmacy Institute), 19 Knowledge Park-2, Institutional Area, Greater Noida, Uttar Pradesh 201306, India.

\*Corresponding Author: Dr. Rupa Mazumder

Noida Institute of Engineering and Technology (Pharmacy Institute) 19, Knowledge Park-2, Institutional Area, Greater Noida, Uttar Pradesh 201306, India.

Email: [rupa\\_mazumder@rediffmail.com](mailto:rupa_mazumder@rediffmail.com)

## ABSTRACT:

Inflammatory bowel disease includes conditions like ulcerative colitis and Crohn's disease, which are chronic inflammatory disorders of the gastrointestinal tract. Bloody diarrhea and extensive inflammation in the large intestine are the hallmarks of ulcerative colitis. Patients can develop the condition at any age; however, the incidence rises in early adulthood. The definite cause for ulcerative colitis is still not well established. Numerous environmental factors act as triggering or preventive factors for ulcerative colitis, with cigarette smoking being the most consistent one. The medical treatment of ulcerative colitis involves corticosteroids, aminosalicylate drugs, immunosuppressive drugs, and TNF monoclonal antibodies. However, these conventional therapies have side effects such as nausea, headache, loss of appetite, dizziness, gas, and fever. Nowadays, the search for therapy that may be a safer alternative has become increasingly important. Various medical conditions are treated using herbal medicine, which is a folk and traditional medical practice that makes use of natural and herbal extracts. Patients with ulcerative colitis in Western and Asian countries, particularly India and China, are increasingly resorting to herbal therapies. Several clinical studies have shown that herbal plants and their bioactive ingredients are promising in terms of their utilization in the treatment of pathological conditions due to their minimal side effects and long-term benefits. This review elaborates on the knowledge of ulcerative colitis covering classification, factors, causes, conventional treatment with potential mechanism and side effects, combination therapy, herbal treatment with potential mechanism and side effects, and novel approaches.

**Keywords:** Bioactive, Colectomy, Herbal, Inflammation, Monoclonal, Ulcerative Colitis.

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## INTRODUCTION

Inflammatory bowel disease (IBD) encompasses a wide range of chronic inflammation-related conditions, including ulcerative colitis (UC) and Crohn's disease (CD). Both UC and CD have many similar characteristics and common symptoms including diarrhea, blood in the stool, weight loss, stomach pain, fever, and fatigue but UC is

described as an unspecified inflammatory condition. As the condition advances from mild to moderate, the patient has additional symptoms such as weariness, weight loss, and lack of appetite, which may result in nutritional shortages, severe rectal bleeding, anemia, fever, and mucus in the stool, as well as other complications. Even though there is a lack of



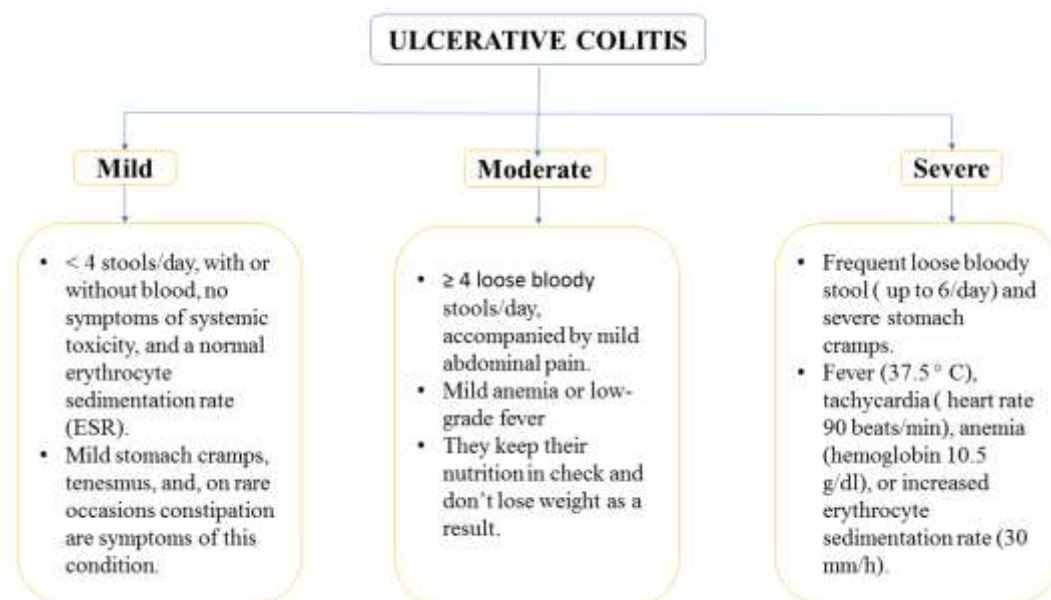
complete understanding of the causes of UC, its high clinical recurrence rate and increased risk of colon cancer in patients suffering from UC have compelled WHO to classify UC as a current refractory disease.<sup>1-4</sup> The risk factors attributed to the development of UC can be genetics, abnormal immune response, environmental factors, and microbiome. In Western nations, the incidence of UC is around 10–20 per 10<sup>5</sup> each year, with an estimated rate of 100–200 per 10<sup>5</sup>. UC can affect the everyday life of a patient and if not treated properly on time leads to colorectal cancer.<sup>5-7</sup> Uncertainty about the cause, high recurrence risk, and bleak outlook of UC has made the treatment challenging.<sup>8</sup> In mild to moderate UC, aminosalicylate drugs are the preferred treatment, whereas flares can be treated with local and systemic steroids. In moderate to severe UC, immune suppressants and biological medicines are employed. Colectomy is required in up to 15% of ulcerative colitis patients.<sup>9</sup> Standard therapies for UC are less effective and might have various adverse effects, hence, it has compelled researchers to find some alternative methods of treatment. To treat UC, herbal therapy has been one of the most popular complementary and

alternative treatment options in recent years. This approach can be further advanced by studying the various bioactive agents present in the herbs, utilizing a bench-to-bedside methodology [8]. A recent study found that combination therapies with traditional Chinese medicine, particularly herbs had a stronger impact on UC symptoms when compared to the single standard medication implying that herbal therapy could be a better alternative therapeutic option in the management of UC.<sup>10</sup> This review focuses on studies of data available on the potentiality of herbal plants and their bioactive in the prevention and treatment of ulcerative colitis. Data were gathered through a literature review of articles in PubMed, science direct and google scholar from the date of inception to 2021. Keywords such as “ulcerative colitis, inflammatory bowel disease, herbal medicine, and natural products” were used.

**Classification of UC**

European Crohn’s and Colitis Organization, the Japanese Society of Gastroenterology, and the American College of Gastroenterology all use the Truelove–Witts’s criteria to categorize patients who suffer from ulcerative colitis into three severity levels, figure 1:

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**Figure 1: Classification of UC**

Toxic symptoms such as fever and anorexia, as well as an increase in the frequency and severity of the patient’s bowel movements, are all included in the American College of Gastroenterology’s definition of fulminant UC. Colonic dilatation and blood transfusions are common on abdomen plain films. With toxic

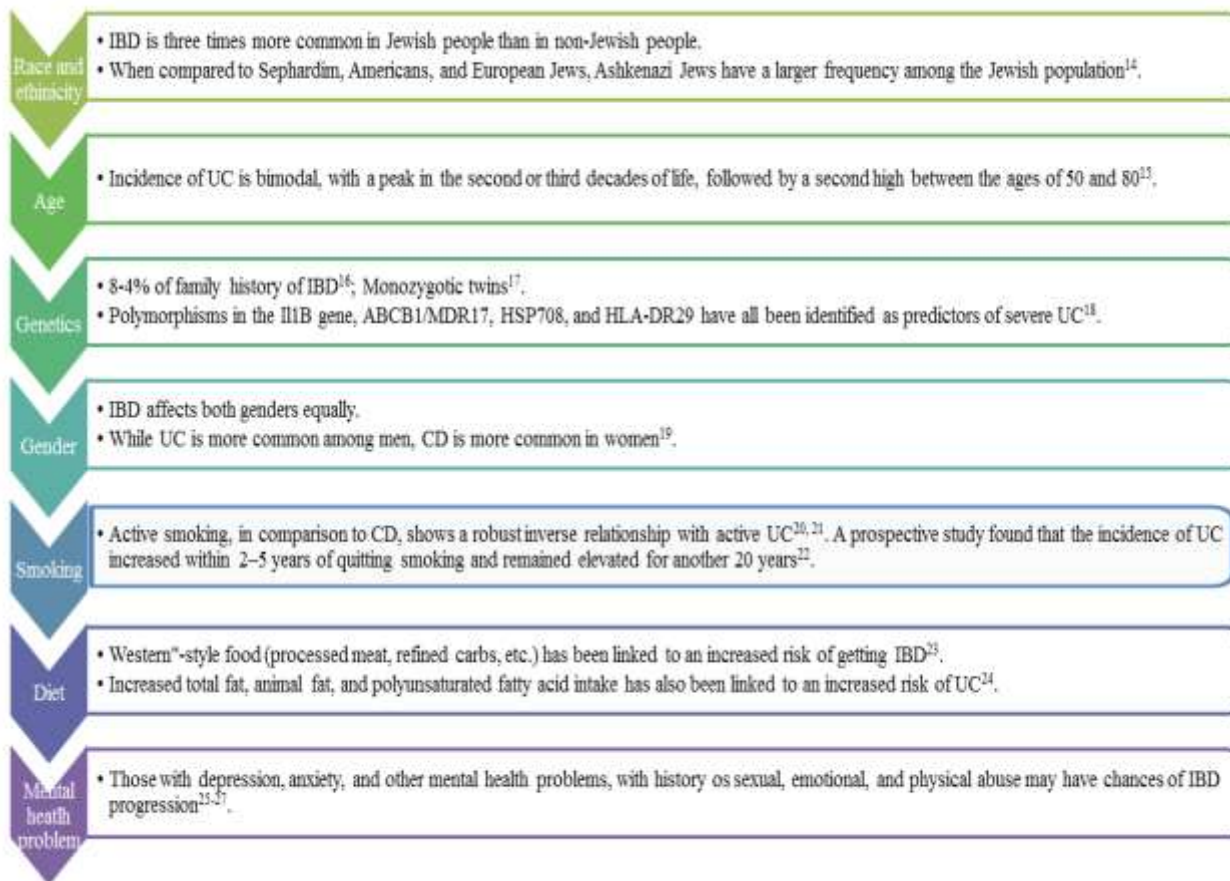
megacolon and perforated intestines, patients have an increased chance of acquiring severe side effects<sup>11-13</sup>.

**Factors affecting UC**

However, UC may be explained by the situations that emerged because of genetic and environmental causes, even if the specific cause is

still unknown. Pathologically, the increase in some pro-inflammatory cytokines, a dysregulated colonic milieu, mucosal content related to glycosaminoglycan (GAG), a decrease in short-chain fat oxidation, an increase in intestinal permeability, oxidative stress, a reduction in methylation as well as the production of sulfur

dioxide all contribute to the development of UC. But initially, no such factors have been identified that trigger the UC, so we can say the combination of these factors may be responsible for the onset of the disorder<sup>14</sup>. Some of the factors associated with ulcerative colitis are mentioned below, fig.2:



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**Figure 2. Factors associated with UC**

**Causes**

As the reason behind the condition is a topic for debate due to its unclearness, the underlying autoimmune condition is also exposed<sup>29,30</sup>. Some people are genetically predisposed, thus their mucosal immune responses to gut flora are dysregulated, resulting in inflammation of the colon<sup>31</sup>.

The most prominent theories concerning the causation of UC can be listed as:

1. **Infection-** Even though ulcerative colitis had been clearly distinguished from contagious forms of diarrhea by the middle of the nineteenth century, many employees refused to believe that it was not infectious until recently. In 1924, Barger developed an effective diplococcus vaccine, but it was only discovered after it was too late. His

allegations were not supported by data that the vaccine was successful in preventing substantial numbers of patients against enterococcal infection<sup>32</sup>. Studies have shown a connection between ulcerative colitis and other microorganisms such as parasites, fungi, and viruses, but there is still a lack of data to substantiate this connection<sup>33-35</sup>.

2. **Mucinase-** When the mucus lining of the colon is destroyed by enzymes (like mucinase), the colon becomes more vulnerable to attack by bacteria and other agents, as Meyer et al. postulated in 1947. Meyer et al. 1947<sup>36</sup> study found that colitic patients had greater levels of lysozyme enzyme in their feces than healthy individuals. But other research report shows that human mucus cannot be digested by lysozyme in vitro, disproving the

theory that the enzyme destroys the mucus lining <sup>37</sup>.

- Allergy-** In 1925 and 1942, Anderson was the one who first raised the possibility that cow's milk was to blame for the development of ulcerative colitis <sup>38,39</sup>. Earlier studies were done by True love and his colleagues from Oxford University, as well as other sources, lend credence to the theory that consumption of cow milk may contribute to the emergence of UC. According to the findings, patients with UC who cut out dairy products from their diets experience remission, but the condition returns when the foods are reintroduced. Antibodies against milk proteins are discovered in considerably higher concentrations in the bowels of colitis patients than in healthy matched controls, and a higher percentage of colitis patients discontinue breastfeeding within the first month after delivery <sup>40-42</sup>.

**Conventional treatment approaches for UC**

To minimize long-term damage, colon cancer, and colectomy, the primary aim of therapy is remission induction and maintenance. Endoscopic healing is typically defined by a mayo score of 0 or 1 (mayo score is a combined histologic and clinical score that can be used to determine the severity of UC and to assess patients' improvement throughout treatment. The score runs from 0 to 12, with a higher number signifying more severity), and remission of clinical manifestation, which is defined as stopping rectal bleeding and improving bowel habits, are two primary goals of remission <sup>43,44</sup>. The endoscopic activity of UC may not coincide with the patient's symptoms or the physician's evaluation <sup>45-47</sup>. Endoscopic recovery

has been found to considerably enhance long-term clinical remission, reduce the risk of surgery, and minimize the usage of corticosteroids, therefore it's crucial to check for mucosal and histological inflammation directly using colonoscopy <sup>48</sup>. The severity and spread of the condition are the two factors that are considered for treatment selection. As the condition progresses and becomes more severe, so does the therapy. A step-up strategy depending on UC severity and treatment response with a frequent examination of intestinal inflammation is recommended for patients. Patients with acute severe UC or steroid-resistant UC who are admitted to the hospital should be evaluated for biological therapy as soon as feasible <sup>44</sup>. To maintain the patient in remission, further medical therapies may be necessary. Suppositories may be effective for people with proctitis, although systemic therapy may be necessary for those with the more extensive condition <sup>49</sup>.

**Medications**

In the case of ulcerative colitis, the most popular therapies include mesalazine, topical or systemic corticosteroids, immunosuppressant drugs, thiopurines, and TNF- monoclonal antibodies. A key part of successful therapy is ensuring that patients comply with their mesalazine regimens, which includes administering the medication correctly, optimizing their doses, using it appropriately (as opposed to initiating it), and optimizing their levels of drug compliance <sup>50</sup>. At present the drug available in the market for the treatment of UC have been enlisted in the Table 1.

**Table 1:** Clinically available drug used in the treatment of UC, their available routes, mechanism involved, and complications.

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Drug category	Drug name	Available routes	Mechanism involved	Complications	Reference
Aminosalicylates	Sulfasalazine Mesalazine Olsalazine Balsalazide	Oral Rectal	Inhibition of Tumor necrosis factor-alpha (TNF-α), Interleukin-1 (IL-1), and platelet-activating factors decreased antibody secretion.	Diarrhea, abdominal pain, nausea, epigastric pain, dizziness, dyspepsia, headache, nausea, and vomiting.	Carter et al. 2004 <sup>51</sup> Feagan et al. 2012 <sup>52</sup> Van Staa et al. 2005 <sup>53</sup> Leighton et al. 2013 <sup>54</sup>
Corticosteroids	Prednisone Methylprednisolone Hydrocortisone	Oral Rectal Intravenous	Arachidonic acid cascade phospholipase A2 inhibition alters prostaglandin-leukotriene	The difficulty of healing, glucose intolerance, full moon face,	Reichel et al. 2010 <sup>55</sup> Leonard et al. 2012 <sup>56</sup>



	Budesonide		ratio, increases lymphocyte death in lamina propria, and inhibits cytokine release.	osteoporosis, acne, subcapsular cataracts, osteonecrosis, myopathy, malaise, intracranial hypertension, sleep, and mood disturbances.	
Thiopurines	Azathioprine 6-mercaptopurine	Oral	Blockage of the <i>de novo</i> purine synthesis pathway.	Leukopenia, elevation in transaminases, nausea, black, tarry stools, vomiting, bone marrow suppression, pancreatitis, hepatitis, and abdominal pain	Bianchi et al. 2007 <sup>57</sup> Ardizzone et al. 2004 <sup>58</sup> Maltzman et al. 2003 <sup>59</sup> Ardizzone et al. 2005 <sup>60</sup> Cox et al. 1988 <sup>61</sup>
Anti-TNF drugs	Infliximab Golimumab Adalimumab	Intravenous Subcutaneous	TNF- $\alpha$ , an inflammatory cytokine, is targeted by monoclonal antibodies.	Infusion/injection site reaction, infections, melanoma, reactivation of latent TB and hepatitis B, headaches, nausea, and abdominal pain.	Järnerot et al. 2005 <sup>62</sup> Rutgeerts et al. 2005 <sup>63</sup> Reinisch et al. 2011 <sup>64</sup> Sandborn et al. 2014 <sup>65</sup>
Anti-interleukin drugs	Ustekinumab	Intravenous (1 <sup>st</sup> dose) Subcutaneous	Limits cell signaling, activation, and cytokine production by binding to the p40 subunit of IL-12 and IL- 23 and preventing them from interacting with the cell surface IL-12R $\beta$ 1 receptor.	Infusion/injection site, headaches, nausea, and diarrhea.	Sands et al. 2019 <sup>66</sup>
Janus-kinase blockers	Tofacitinib	Oral	Inhibition of Janus kinase 1 and 3.	Serious and sometimes fatal infections, nasopharyngitis, arthralgia, and headache.	Hanauer et al. 2019 <sup>67</sup> Sandborn et al. 2014 <sup>68</sup>
Anti-cell adhesion molecule	Vedolizumab	Intravenous	A monoclonal antibody that limits leukocyte migration and the resulting gastrointestinal inflammation by	Headache, nasopharyngitis, abdominal pain, and increased risk of serious	Mozaffari et al. 2014 <sup>69</sup> Feagan et al 2013 <sup>70</sup>

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			inhibiting the adhesion molecule $\alpha 4 \beta 7$ -heterodimer.	infections.	Bosani et al. 2009 <sup>71</sup> Parikh et al. 2012 <sup>72</sup> Danese et al. 2013 <sup>73</sup>
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### Surgery

Surgery is required when haemorrhage, perforation, and colorectal cancer cannot be removed endoscopically. Surgical intervention may be necessary for certain instances of medically inoperable severe acute ulcerative colitis<sup>12,44</sup>. Proctocolectomy and ileal pouch-anal anastomosis (IPAA) are common surgical procedures for UC. When surgery is performed in an emergency, it is usually done in 2 or 3 stages, beginning with a subtotal colectomy and ileostomy (1<sup>st</sup> stage) are performed to minimize postoperative problems, such as anastomotic leakages and pelvic infections<sup>74</sup>. A diverting ileostomy (2<sup>nd</sup> stage) is then used to establish the ileal pouch, which is then anastomosed to the anal canal and removed to restore intestinal continuity (3<sup>rd</sup> stage). IPAA surgical procedures should be performed in high-volume referral facilities with a reduced pouch failure rate<sup>75</sup>.

### Combination therapy

The combination therapy shows the most promising results in the treatment of UC by studying numerous clinical studies.

- The Quyushengxin Formula consists of *Astragalus membranaceus* (Fisch) Bunge, *Pulsatilla chinensis* (Bge.) Regel, *Panax ginseng*, and *Coptis chinensis* Franch. The result of this investigation shows that by utilizing this, patients in the active stage of the UC experience less inflammation and fewer symptoms. In moderate to severe UC conditions, patients may benefit from this medication<sup>76</sup>.
- Panaccione R et al. 2014<sup>77</sup> reported that IFX/AZA combination treatment was shown to be more beneficial for patients when compared to IFX and AZA monotherapies. Compared to monotherapies, combination treatment reduced the risk of hepatotoxicity in patients. As a result, it has been shown that combination treatment produces better

results in terms of lengthening remissions free of steroids.

- Ohkusa T et al. 2010<sup>78</sup> reported that a combination of antibiotics i.e amoxicillin, tetracycline, and metronidazole were more beneficial than a placebo in terms of improvement, steroidal withdrawal, and remission of active UC.
- Shin et al. 2017<sup>79</sup> reported that a combination of medicinal herbs (*Citrus unshiu* + *Bupleuri radix*) and sulphasalazine was compared with sulfasalazine alone. The result of the study revealed that a combination of medicinal herbs and sulfasalazine showed effectiveness in ameliorating the UC induced by DSS in mice.

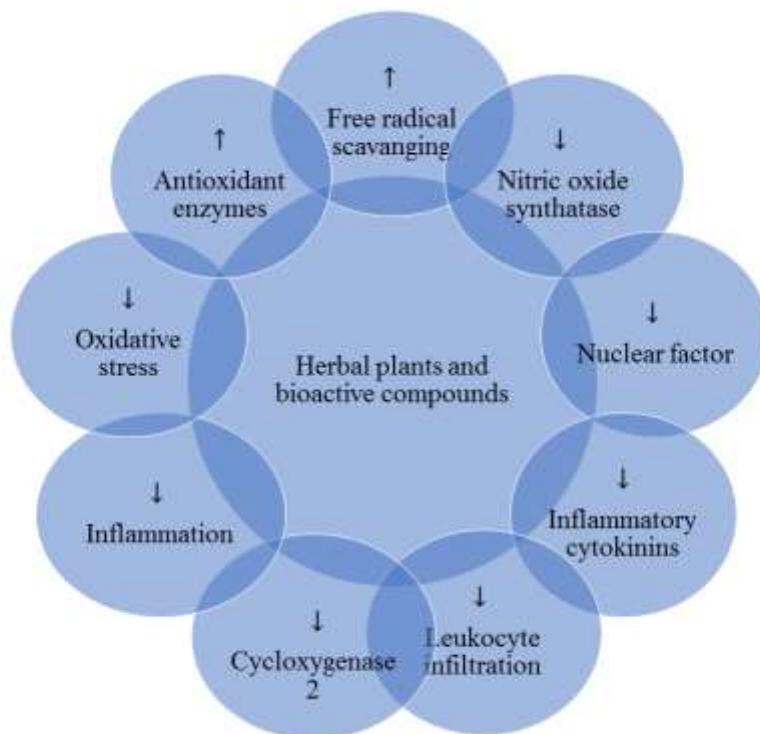
### Herbal approaches for the management of UC

Herbal medicine is a folk and traditional medical approach that uses natural and herbal extracts to treat medical conditions. According to recent studies, 20% to 26% of adults use herbal therapy to ease gastrointestinal symptoms, with patients with acute or chronic GI conditions being more prone to do so<sup>80,81</sup>. UC sufferers in Western and Asian nations, including India and China, are increasingly turning to herbal remedies<sup>82</sup>. The number of randomized research on the effectiveness and safety of these bioactive substances is still limited, but it is growing. Secondary metabolites found in the plants give rise to a wide variety of actions. However, it is important to consider the possibility of cross-contamination in the locations where the pollutants are grown, transported, or marketed, as well as their impacts and side effects<sup>83</sup>. The role of various herbal plants and bioactive in the management of UC have been depicted in table 2 and 3.

### Mechanism

The general mechanism on which numerous herbal plants and bioactive compounds work and resulted due to their efficacy is expressed in the below diagram (Figure 3):

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**Figure 3.** Targeting effected by various plants and their bioactive compounds to prevent UC  
 ↑: Increase; ↓: Decrease

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**Table 2:** Bioactive with anti-ulcerogenic activity

Bioactive	Cellular, molecular, and systemic effects	Complications	Activity	Reference
Curcumin	IL-10, IL-4, PGE2 increase activity. Suppression of CD4 (+) T-cell infiltration and NF-κB activation. INF-γ, MAPK, IL-1, IL-4, IL-5, IL-6, IL-12, TNF-α, MPO, LPO, iNOS, COX-2, TLR-4 decrease activity.	Some people may experience nausea, dizziness, or diarrhea.	Patients with quiescent UC may benefit from taking curcumin by improving the clinical activity index & the endoscopic index, which seems to be a viable and safe treatment option. Curcumin exhibited protective action against TNBS-induced colitis by the suppression of pro-inflammatory mediator messenger RNA gene expression level in the colon.	Hanai et al. 2009 <sup>84</sup> Larmonier et al. 2011 <sup>85</sup> Singla et al. 2014 <sup>86</sup> Hanai et al. 2006 <sup>87</sup> Sugimoto et al. 2002 <sup>88</sup> Akshaya et al. 2019 <sup>89</sup>

Boswellic acid	Inhibition of the 5-LOX enzyme. Inflammation-fighting properties. Direct suppression of intestinal motility.	Lose weight via increasing thyroid activity, retrosternal burning, nausea, diarrhea, or constipation, postprandial fullness, burning of hands and feet, numbness, abdominal pain, drug rash, agranulocytosis, and thrombocytopenia.	Boswellic acid has beneficial anti-inflammatory and antioxidant properties in colitis induced by acetic acid. BA significantly lowered the LPO, NO, and iNOS levels as well as showed improvement in the injury of tissue. In another study boswellic acid was found to be effective in the treatment of chronic UC with minimal side effects.	Dahmen et al. 2001 <sup>90</sup> Gupta et al. 2001 <sup>91</sup> Hartmann et al. 2014 <sup>92</sup>
Resveratrol	Activation of NF-κB induced by TNF-α and endogenous NF-κB activity inhibited. Inhibition of I kappa B kinase-mediated NF-κB activation. TNF- α, IL-8, COX-2, iNOS, & IFN- γ level reduced. Decrease MDA and MPO activity. IL- 10 increasing activity.	A rumbling tummy, pain in the abdomen, nausea, vomiting, irritation of the skin, dizziness, fever, and/or headache.	Patients with UC may benefit from resveratrol's ability to reduce inflammation and hence their quality of life and illness clinical colitis activity. Resveratrol supplement diet ameliorates DSS-induced colitis in mice by lowering the pro-inflammatory cytokines and increasing the anti-inflammatory cytokine, as well as reducing various gene expression levels in the colonic mucosa.	Rahal et al. 2012 <sup>93</sup> Yao et al. 2010 <sup>94</sup> Abdallah et al. 2011 <sup>95</sup> Samsami-Kor et al. 2015 <sup>96</sup> Sánchez-Fidalgo et al. 2010 <sup>97</sup>
Guggulsterone	Inhibition of LPS or IL-1b-induced expression of the intracellular adhesion molecule-1 gene, and NF-κB transcriptional activity. Phosphorylation/degradation of I kappa B kinase (IKK). In intestinal epithelial cells, NF-κB DNA binding transcriptional activity.	Diarrhea, vomiting with a headache, overly loose stools, vomiting due to nausea, and upset stomach.	Guggulsterone ameliorates ulcerative colitis induced by DSS by targeting the I kappa B kinase (IKK) complex in the IEC, it may be beneficial for the treatment of IBD.	Mencarelli et al. 2009 <sup>98</sup> Cheon et al. 2006 <sup>99</sup> Kim et al. 2010 <sup>100</sup>

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Aloe vera gel	Inhibition of the secretion of PGE2 and IL-8. Inhibits the release of ROS and SOD by PMA stimulated human neutrophils.	Hypoglycemia, pain, and cramping in the stomach (high doses), urinary tract infections (UTIs), low potassium, muscular weakness, and weight loss for long-term use at high doses.	A 4-week course of oral aloe vera reduced histological disease activity and seemed to be a safe therapeutic option in the treatment of UC. Aloe vera preparation has a protective effect against UC induced by acetic acid on rats by improving the symptoms of the disease, as well as preventing people who are prone to the disease.	Langmead et al. 2004 <sup>101</sup> 't Hart et al. 1990 <sup>102</sup> Langmead et al. 2004 <sup>103</sup> Bahrami et al. 2020 <sup>104</sup>
Glycyrrhizin	Reduce pro-inflammatory cytokines and chemokines such as IL-1, IL-6, TNF- $\alpha$ , cytokine-induced neutrophil chemoattractant-2, and monocyte chemoattractant protein-1 in inflamed mucosa. Inhibit the oxidative activity of mucosal and purified MPO.	Missing a menstrual cycle, diabetic cardiomyopathy, loss of sexual arousal (libido), inability to ejaculate, inflammation of the lungs and accumulation of fluid (pulmonary edema), retention of fluids and sodium, headache, blood pressure is too high.	Experimental colitis in rats may be treated with the GL-p enema, which seemed to be a potential therapeutic option in the treatment of UC.	Asl et al. 2008 <sup>105</sup> Liu et al. 2011 <sup>106</sup> Kudo et al. 2011 <sup>107</sup> Yuan et al. 2006 <sup>108</sup>
6- Gingerol	Inhibit the level of IL-6, IL-17, and mRNA. Inhibits the increase of IL-10 level. Reduce the level of IL-1 $\beta$ and TNF- $\alpha$ Reduce oxidative damage in the colon by enhancing the activity of the antioxidant enzyme.	Heartburn, diarrhea, burping, general stomach discomfort.	6-gingerol suppresses DSS-induced colitis by lowering the level of pro-inflammatory cytokines and improving weight loss. Experimental colitis in mice treated with 6-gingerol may have a protective effect in the treatment of UC. 6-gingerols suppress pro-inflammatory cytokines and chemokines as well as restore the histopathological damages.	Haniadka et al. 2013 <sup>109</sup> Ajayi et al. 2015 <sup>110</sup> Zhang et al. 2016 <sup>111</sup> Zhang et al. 2018 <sup>112</sup> Sheng et al. 2020 <sup>113</sup> Ajayi et al. 2018 <sup>114</sup> Akshaya et al. 2019 <sup>89</sup>

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Bromelain	Decrease secretion of IFN- $\gamma$ , & TNF- $\alpha$ .	Diarrhea, vomiting, rapid heartbeat, heavy menstrual periods.	In Animal model of gastrointestinal inflammation, bromelain has also been shown to diminish CD4+ T-cell infiltrations, which are important effectors. In a mouse colitis model, researchers discovered that bromelain was beneficial in reducing the degree of colonic inflammation, both clinically and histologically, in IL-10-deficient animals.	Hale et al. 2005 <sup>115</sup> Kane et al. 2000 <sup>116</sup>
Quercetin	Inhibits LPS-induced TNF- $\alpha$ production in macrophages and LPS-induced IL-8 production, increasing colonic microbial diversity and reducing the severity of colitis.	A loss of protein function, headache, upset stomach.	Quercetin (1 and 5 mg/kg) may relieve symptoms of TNBS-induced colitis when given early on (24 hours). When tested using biochemical endpoints, the flavonoids reduced colonic MDA levels and suppressed the activity of both iNOS and alkaline phosphatase, but they did not affect the visible damage.	Stayric B 1994 <sup>117</sup> Guazelli et al. 2013 <sup>118</sup> Sánchez de Medina et al. 2002 <sup>119</sup>
Rutoside or rutin	Decrease TNF- $\alpha$ , expression of intercellular adhesion molecules, and pro-inflammatory cytokines (iNOS, COX-2, master transcription factors (NF- $\kappa$ B), and ROS).	Stomach upset, headache, skin rashes with a reddish hue, The rate of one's heart increases when one is anxious, muscular stiffness due to a build-up of fluid in the knees, excessive levels of white blood cells in the blood.	0.1 percent rutin-containing diet, but not quercetin, reduced the weight of ICR mice by 5% and improved the histology of colitis. A reduction in proinflammatory gene expression in the colonic mucosa was seen following two weeks of rutin therapy or four days of therapeutic post-treatment, commencing three days after DSS delivery.	Chen et al. 2003 <sup>120</sup> Cruz et al. 1998 <sup>121</sup> Kwon et al. 2005 <sup>122</sup>

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Abbreviations: IL= Interleukin, INF- $\gamma$ = Interferon- $\gamma$ , TNF- $\alpha$ = Tumor necrosis factor- $\alpha$ , MAPK= Mitogen-activated protein kinase, MPO= Myeloperoxidase, LPO= Lipid peroxidase activity, iNOS= Inducible nitric oxide synthase, COX-2= Cyclooxygenase-2, TLR= Toll-like receptor, NF- $\kappa$ B= Nuclear factor- $\kappa$ B, TNBS= 2,4,6-trinitrobenzene sulfonic acid, RNA= Ribonucleic acid, LOX= Lipoxygenase, NO= Nitric oxide, MDA= Malondialdehyde, DSS= Dextran sulfate sodium, LPS= Lipopolysaccharide, ROS= Reactive oxygen species, PGE<sub>2</sub>= Prostaglandin E<sub>2</sub>, SOD= Superoxide dismutase, PMA= Phorbol myristate acetate.

**Table 3:** Herbal plants used in the treatment of UC

Herbal plants	Activity	Reference
Cannabis	IBD symptoms have been successfully treated with cannabis inhalation.	Storr et al. 2014 <sup>123</sup>
Peony	In TNBS/ethanol-induced colitis, treatment with total glycosides of peony (TGP) dramatically lowered DAI, CMDI, and HPS levels, as well as MPO activity, in the presence of TGP. Furthermore, TGP therapy reduced blood TNF- $\alpha$ and IL-1 elevation, as well as TNF- $\alpha$ and IL-1 mRNA expression in	Zhang et al. 2014 <sup>124</sup>



	colonic tissues, while increasing blood and intestine IL-10 mRNA levels.	
<i>Euphorbia granulata</i>	<i>Euphorbia granulata</i> alcohol extracts reduce the levels of pro-inflammatory mediator TNF- $\alpha$ & MDA content in the intestine.	Awaad et al. 2013 <sup>125</sup>
<i>Piper nigrum</i>	In acetic acid-induced colitis rats, <i>Piper nigrum</i> shows potent therapeutic effect against various histopathological changes occurred by acetic acid. Plant extract form layer a layer over damaged colonic mucosa and decrease the local inflammatory mechanism by affecting inflammatory mediators.	Samyuktha et al. 2019 <sup>126</sup>
<i>Terminalia chebula</i>	In rats with acetic acid-induced colitis, <i>Terminalia chebula</i> fruit pulp (600 mg/kg) decreased the score of damage in the colon and weight. Both TCE and sulfasalazine boosted antioxidants but decreased free radicals and myeloperoxidase activity in acetic acid-induced colitis rats.	Gautam et al. 2013 <sup>127</sup>
<i>Moringa oleifera</i> and <i>Citrus sinensis</i>	The mixture of <i>Moringa oleifera</i> root extract and <i>Citrus sinensis</i> Linn fruit extract exhibited a therapeutic effect in treating UC when compared to prednisolone. The combination of both lowered the MPO and MDA levels in tissues and blood.	Gholap et al. 2012 <sup>128</sup>
<i>Andrographis paniculata</i>	<i>Andrographis paniculata</i> extract was seemed to be beneficial in the treatment of mild to moderate UC at a daily dosage of 1800 mg. A. paniculata decreased the level of TNF- $\alpha$ , NF- $\kappa$ B, and IL-1 $\beta$ . It is found to be as effective as mesalamine.	Sandborn et al. 2013 <sup>129</sup>
Apple polyphenol extract	The severity of colitis was reduced in TNBS induced UC rats when treated with rectal administration of apple polyphenol extract for 14 days. Apple polyphenols decreased the calpain-mediated degradation of tissue transglutaminase protein. The effects of apple extract on COX-2 and TNF- $\alpha$ influence its efficacy.	D'Argenio et al. 2012 <sup>130</sup>
<i>American ginseng</i>	Murine colitis is reduced by HAG-induced apoptosis via a p53-mediated pathway. p53-/- and WT colon cancer cells may benefit from HAG's ability to target inflammatory and malignant cells.	Poudyal et al. 2012 <sup>131</sup>
<i>Passiflora edulis</i>	In the TNBS-induced colitis model, <i>P. edulis</i> peels boosted blood antioxidant status, decreased LPO, reduced the number of aerobic bacteria, and improved acetic and butyric acid levels in the feces. As it contains fiber and polyphenols that may use for the prevention of oxidative stress by enhancing blood and tissue antioxidant status.	Cazarin et al. 2014 <sup>132</sup>
<i>Lavandula intermedia</i>	The <i>Lavandula intermedia</i> plant showed a therapeutic effect against <i>Citrobacter rodentium</i> -induced colitis. With lowered levels of TNF- $\alpha$ , IFN- $\gamma$ , IL-22, macrophage inflammatory protein-2, and iNOS expression, it reduced tissue damage in the intestine and neutrophil and macrophage infiltration.	Baker et al. 2012 <sup>133</sup>
<i>Aegle marmelos</i>	Wistar albino rats were used to test the effects of unripe fruit extract of <i>Aegle marmelos</i> on UC and enterocolitis induced by acetic acid and indomethacin, respectively. Its mechanism is linked to mast cell degranulation inhibition by drastically lowering MDA levels and increasing SOD activity. The extract's anti-inflammatory, antioxidant, and mast cell stabilizing properties may aid individuals with inflammatory bowel disease.	Behera et al. 2012 <sup>134</sup>
<i>Rhizophora apiculata</i>	<i>R. apiculata</i> ameliorates acetic acid-induced UC by reducing iNOS, NO, COX-2, LPO, and TNF- $\alpha$ levels which are achieved by enhancing antioxidant enzymes like SOD and GSH, which are found in <i>R. apiculata</i> . NF- $\kappa$ B subunits p65 and p50 are also prevented from migrating across the cell.	Prabhu et al. 2014 <sup>135</sup>
<i>Chelidonium majus</i>	The chelidonic acid found in <i>Chelidonium majus</i> L. protects against ulcerative colitis induced by DSS. CA has been proven to influence IL-6 and TNF- $\alpha$ . DSS raised the expression of COX-2 and HIF-1 in colonic tissues,	Kim et al. 2012 <sup>136</sup>

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	while CA decreased the expression of these genes.	
Plumbagin plants	Mice and humans showed substantial reductions in the levels of proinflammatory cytokines after taking naphthoquinone from plumbagin plants. In mice, regenerating goblet cells in the colon did not affect the amount of IFN- $\gamma$ , IL-17, and TNF- $\alpha$ .	Pile et al. 2013 <sup>137</sup>

Abbreviations: MPO= Myeloperoxidase, TNBS= 2,4,6-trinitrobenzene sulfonic acid, IL= Interleukin, MDA= Malondialdehyde, TNF- $\alpha$ = Tumor necrosis factor-  $\alpha$ , IBD= Inflammatory bowel disease, ED= Erectile dysfunction, FSG= Fermentation of soy germ extract, BBIs= Bowman-birk inhibitors, HAG= Hexane portions of American ginseng, COX-2= Cyclooxygenase-2, iNOS= Inducible nitric oxide synthase, SOD= Superoxide dismutase, LPOs= Lipid peroxidation, NO= Nitric oxide, LDH= lactate dehydrogenase, HIF-1= Hypoxia-induced factor-1.

**Table 4:** Novel formulations available for the treatment of UC

Herbal agent	Novel approach	Remark	Reference
Resveratrol	Ca-pectinate beads	Colonic bacteria may break down the Ca-pectinate beads formulation, resulting in significant improvements in oxazolone-induced colitis and cancer risk.	Abdin et al. 2013 <sup>138</sup>
Rutin	Coated pellets	The chitosan and sodium alginate-coated rutin pellets decreased neutrophil infiltration, inflammatory response, and improved clinical activity in TNBS-induced rats.	Rabišková et al. 2012 <sup>139</sup>
Ginger	Nanoparticles derived from ginger	Pro-inflammatory mediators were decreased, and anti-inflammatory mediators were raised in the DSS-induced colitis in mice after oral administration of GDNPs.	Zhang et al. 2016 <sup>111</sup>
Curcumin	Microsponges	Curcumin-loaded microsponges reduced edema, necrosis, and hemorrhage in the colon by preventing premature release in the upper GIT and releasing the medication exclusively at colonic pH.	Sareen et al. 2014 <sup>140</sup>
Rutin	Hydrogel	Using a DSS-induced rat model of colitis, the rutin-loaded pH-sensitive polyhydrogels provided maximal release when pH climbed from 6.8 to 7.7 in the colon and prevented mucosal damage.	Abdel et al. 2016 <sup>141</sup>
Silybin	Nanoparticles	Nanoparticles loaded with silybin reduced inflammation produced by acetic acid to a greater extent by when compared to dexamethasone.	Varshosaz et al. 2015 <sup>142</sup>
Icariin	Microspheres	Microspheres loaded with icariin lowered mucosal damage index in the colon and reduced inflammation responses in the simulated colonic fluid.	Wang et al. 2016 <sup>143</sup>
Berberine	SNEDDS	As the SNEDDS increased the concentration of Berberine in the targeted area, it helped to restore the mucosal damage in the colon and enhance the crypt structure.	Pund et al. 2014 <sup>144</sup>
Andrographolide (AG)	Nanoemulsion	Lowered ulcer index and histological damage score in mice with indomethacin-induced histological damage by andrographolide nanoemulsion. It also improved the relative bioavailability.	Yen et al. 2018 <sup>145</sup>
Epigallocatechin 3-gallate (EGCG)	Ovalbumin nanoparticles	When it comes to suppressing pro-inflammatory factors and increasing the synthesis of anti-inflammatory ones, EGCG nanoparticles have a remarkable ability.	Gou et al. 2018 <sup>146</sup>
Curcumin & celecoxib	pH-Sensitive nanoparticles	Cur-Cel loaded nanoparticles controlled the release of encapsulated drug at stomach pH, while selectively releasing it in the colon.	Gugulothu et al. 2014 <sup>147</sup>

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Curcumin & 5-ASA	Microparticles	Microparticles loaded with 5-ASA and curcumin were transported to the colon through pH-sensitive and mucoadhesive microparticles, and they significantly reduced inflammation in the colonic mucosa of colitis rats.	Duan et al. 2016 <sup>148</sup>
Curcumin & piperine	SMEDDS	Using retention enema delivery, Curcumin & piperine SMEDDS may reach the damaged epithelium of the colon in DSS-induced colitis, reducing DAI and histological lesions while decreasing inflammatory mediators including MPO activity, MDA content, and TNF- $\alpha$ and IL-6 concentrations.	Li et al. 2015 <sup>149</sup>

Abbreviations: TNBS= 2,4,6-trinitrobenzene sulfonic acid, DSS= Dextran Sulfate Sodium, GDNPs= Ginger derived nanoparticles, GIT= Gastrointestinal tract, SNEDDS= Self-nanoemulsifying drug delivery systems, 5-ASA= 5-aminosalicylic acid, SMEDDS= Self-microemulsifying drug delivery system, DAI= Disease activity index, MPO= Myeloperoxidase, MDA= Malondialdehyde, TNF- $\alpha$ = Tumor necrosis factor- $\alpha$ , IL-6= Interleukin-6.

**Conclusion**

Ulcerative colitis affects a large number of individuals in Western countries, yet the cause is still a mystery. A great deal of work has gone into finding the most effective treatments while causing the least amount of harm. WHO found that 80-85% of the world's population utilizes herbal treatments for the treatment of various disorders and that nutritional supplements are used as a part of daily life. Medical experts are becoming more interested in herbal plants and the bioactive compounds they contain, owing to the health benefits they provide and the reduced likelihood of adverse responses. However, there have some concerns to be clarified before herb medicine can be securely introduced to UC patients. Clinical studies with herbal treatment have only been done on a small number of UC patients so far, and more case-control studies and accurate data on the exact mechanism of the herb are still unavailable. Somore investigation into their molecular processes as well as the safety profile of these compounds is required before they can be demonstrated to be useful in human people.

**Conflicts of Interest**

The authors have reported no conflict of interest.

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**Author's Declaration**

The authors hereby declare that this review is original and that any liability for claims relating to the contents will be borne by them.

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