

Challenges and opportunities in the treatment of ulcerative colitis

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Author contributions: Nirmal SA collected data about ulcerative colitis; Gangurde SS contributed to manuscript preparation; Dumbre PS contributed to manuscript preparation and editing data; Pal SC collected data about various plants used for the treatment of ulcerative colitis; Mandal SC collected data about various plants used for the treatment of ulcerative colitis.

Conflict-of-interest: All the authors do not have any conflict of interest.

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Received: November 28, 2014
Peer-review started: November 29, 2014
First decision: January 8, 2015
Revised: January 26, 2015

Accepted: April 8, 2015
Article in press: April 9, 2015
Published online: June 9, 2015

Abstract

Ulcerative colitis (UC) is an inflammatory destructive disease of the large intestine occurred usually in the rectum and lower part of the colon as well as the entire colon. Drug therapy is not the only choice for UC treatment and medical management should be as a comprehensive whole. Many synthetic drugs are available for the treatment of UC like 5-aminosalicylic acid, oral or systemic corticosteroids, immunomodulator, *etc.* but these drugs are associated with many serious side effects after long term use or have certain disadvantage or not suitable for the use in some patients. In short synthetic drugs have many disadvantages and for this reason effective and safe alternative drug treatment for the UC is the challenge. Herbal drugs are found to be very promising results of the treatment of UC and enzymatic level. Researchers explored many herbal drugs for the treatment and even many more may found effective in the treatment of UC. At this point we feel herbal medicine is the better alternative for the treatment of UC.

Key words: Ulcerative colitis; Herbal drugs; Synthetic drugs

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Core tip: Ulcerative colitis (UC) is one of the diseases of gastro intestinal tract having many serious complications. Many synthetic drugs are available for the treatment of UC but they have many serious side effects after long term use. This review presents potential of traditional/

herbal drugs in the treatment of ulcerative colitis. Herbal drugs have great potential with safety which could be better alternative to synthetic drugs.

Nirmal SA, Gangurde SS, Dumbre PS, Pal SC, Mandal SC. Challenges and opportunities in the treatment of ulcerative colitis. *World J Pharmacol* 2015; 4(2): 219-226 Available from: URL: <http://www.wjgnet.com/2220-3192/full/v4/i2/219.htm> DOI: <http://dx.doi.org/10.5497/wjpv.v4.i2.219>

INTRODUCTION

Ulcerative colitis (UC) is chronic idiopathic inflammatory bowel disorders (IBD) in which patients require lifelong treatment^[1]. Corticosteroids, immunosuppressants and antitumour necrosis factor (TNF) antibodies are used in conventional treatment of IBD but due to long term use they are associated with very serious side effects like malignancy^[2,3] and this is the reason nowadays patients prefer complementary and alternative medicine (CAM) as it is more safe compared to synthetic drugs. This is proved by a survey conducted to observe patients preference for CAM drugs^[4]. CAM treatment involves use of herbal medicine, dietary supplementation like probiotics and prebiotics and acupuncture and moxibustion treatments in IBD patients^[5].

SOME FACTS ABOUT UC

Incidence of UC depends on gender, age, and geography^[6,7] but men and women have an equal risk for UC. IBD is more prevalent in young people (10-19 years age), but it can occur at any age. Caucasians have more risk than Africans for the incidence of IBD while Asian and South American have lower incidences. Smokers have lower than incidences of UC than other patients. Study showed that smoking protects against UC. Breast feeding reduces risk of UC. Left-handed people have a significantly higher risk for IBDs than others. Persons with history of depression or anxiety have higher risk of UC because depression alters immunity and makes person more susceptible to UC^[6,8].

SYMPTOMS OF UC

Ulcerative colitis can be diagnosed by symptoms like fever, fever with chills, loss of appetite, weight loss, impaired growth in children, tenesmus, ulcers and fistulae, recurrent diarrhea^[7,9,10], presence of blood is observed in stools, constipation, an ache around the top of the hipbone, or cramps in the middle of the abdomen, bloating, nausea, vomiting, anemia, toxic megacolon, abdominal pain and distention, dehydration, and malnutrition^[6,8,11], colon cancer, arthritis, red eyes, vision impairment and diseases of the liver and bile ducts.

SIDE EFFECTS OF SYNTHETIC DRUGS

Both medications and surgery have been used for the treatment of UC^[9]. Generally surgery is done for life-threatening complications. As there is no perfect medication for UC, the goals of treatment with synthetic drug is to prevent remissions of UC and to improve the quality of patients life^[12,13]. Table 1 summarizes various drugs used for the treatment of UC with their side effects.

INFLAMMATORY MEDIATORS

Humoral immunity is increased in IBD patients that can be confirmed by increased levels of immune globulins (IgG1)^[21] and autoantibodies^[22,23]. Same thing is evidenced when mucosal plasma cells from UC patients showed increased levels of IgG1^[21]. Anticolon and antineutrophil antibodies are observed in UC patients^[22,23]. Exaggerated Th2 response - elevated interleukin-5 (IL-5) profile is observed in UC patients^[24]. Levels of various cytokines such as IL-1, IL-6, IL-8 and tumor necrosis factor-alpha (TNF- α) are found elevated in IBD^[25,26].

OXIDATIVE STRESS IN ULCERATIVE COLITIS

It is observed that level of oxidative stress is increased in the intestinal mucosa of ulcerative colitis patients. Oxidative DNA damage may occur in IBD patients, which can be evidenced by production of 8-hydroxydeoxyguanosine (8-OHdG). Levels of vitamins A and E are found to reduce in UC patients as compared to normal persons. Mucosal biopsies of UC patients showed increased reactive oxygen intermediates, DNA oxidation products (8-OHdG), and iron in inflamed tissue compared to normal at the same time levels of copper and zinc is found reduced which acts as cofactors for the endogenous antioxidant superoxide dismutase^[27]. Reactive oxygen species (ROS) activate nuclear factor-kappa B (NF- κ B) which increases production of TNF- α and again TNF- α cause production of ROS. In this way a cycle is induced by increased oxidative stress.

ROLE OF GLYCOSAMINOGLYCANS

Glycosaminoglycans (GAGs) is a important substance that affect permeability and immune/inflammatory reactions of the colon. Altered GAG content in the colon of IBD patients is observed. UC patients showed abnormal distribution of GAGs, with significantly greater amounts of total glycosaminoglycans, heparan sulfate, and hyaluronic acid than normal person^[28]. It is hypothesize that change in negatively charged sulfated compounds can affect the passage of substances through the colonic mucosa, leading to leakage of proteins and fluids, thrombosis, and extensive remo-

Table 1 Allopathic drugs used for the treatment of ulcerative colitis and their side effects

Drug	Use	Dosage form	Disadvantages	Ref.
5-aminosalicylic acid compounds	Treatment of tissue inflammation	Enema or orally	Enema solution cannot reach high enough to treat inflammation in the upper colon and if taken orally, however, the stomach and upper small intestine absorb most of the drug before it reaches the colon	[13]
Sulfasalazine	Decreasing intestinal inflammation and relieving symptoms of abdominal pain, diarrhea, and rectal bleeding	Orally	Nausea, heartburn, headache, anemia, skin rashes, and in rare instances, hepatitis and kidney inflammation. In men, sulfasalazine can reduce the sperm count	[14]
Olsalazine (consists of two 5-ASA molecules linked together)	Decreasing intestinal inflammation and relieving symptoms of abdominal pain, diarrhea, and rectal bleeding	Orally	Secretory diarrhea	[15]
Corticosteroids (prednisone, prednisolone, hydrocortisone, <i>etc.</i>)	Corticosteroids do not require direct contact with inflamed intestinal tissues to be effective. These are potent anti-inflammatory agents	Orally, intravenous	Some patients become corticosteroid dependent and consistently develop symptoms of colitis. Whenever the corticosteroid dose is below a certain level. Common side effects include rounding of the face (moon face), acne, increased body hair, diabetes, weight gain, high blood pressure, cataracts, glaucoma, increased susceptibility to infections, muscle weakness, depression, insomnia, mood swings, personality changes, irritability, and thinning of bones (osteoporosis) with an accompanying increased risk of compression fractures of the spine. Children on corticosteroids can experience stunted growth	[16]
Immunomodulator medications	Immunomodulators decrease tissue inflammation by reducing the population of immune cells and/or by interfering with their production of proteins that promote immune activation and inflammation	Orally	Risks of infection due to weakened immunity	[17]
Azathioprine and 6-Mercaptopurine	These are used mainly in the following situations, UC and CD patients with severe diseases not responding to corticosteroids, patients experiencing undesirable corticosteroid-related side effects, patients dependent on corticosteroids and unable to discontinue them without developing relapses		Increased vulnerability to infections, inflammation of the liver (hepatitis) and pancreas (pancreatitis), and bone marrow toxicity (interfering with the formation of cells that circulate in the blood). 6-MP can reduce the sperm count in men When the partners of male patients on 6-MP conceive, there is a higher incidence of miscarriages and vaginal bleeding. There also are respiratory difficulties in the newborn	[18]
Methotrexate	Helpful in treating patients with moderate to severe CD who neither respond to 6-MP and azathioprine nor tolerate these two medications	Orally or intramuscular	Development of liver cirrhosis when the medication is given over a prolonged period of time (years). Low white blood cell counts and inflammation of the lungs. Methotrexate should not be used in pregnancy	[19]
Cyclosporine	Treatment of severe UC. It is useful in fulminant UC and severely ill patients who do not respond to systemic corticosteroids	Orally as well as intravenously	High blood pressure, renal function impairment, tingling sensations in the extremities, anaphylactic shock and seizures	[20]

5-ASA: 5-aminosalicylic acid; UC: Ulcerative colitis; CD: Crohn's disease.

deling observed in UC and IBD^[29]. These changes leads to the inflammatory process as hyaluronic acid can interact directly with lymphocytes, inhibit macrophage response to cytokines, and increase phagocytosis. GAG content has been associated with alteration in the distribution of macrophages reactive to TNF- α ^[30].

ROLE OF HERBAL MEDICINES IN THE TREATMENT OF ULCERATIVE COLITIS

Herbal medicine means use of folk and/or traditional medicinal practice by using plants and/or plant extracts for the treatment of various diseases or disorders. Eighty percent population from developing country depends on herbal medicines for the treatment of their

diseases. Recent studies showed that about 20%-26% patients use TCM therapies for the treatment of GI symptoms and another observation is that generally patients having chronic GI disorders use or prefer TCM therapies^[31,32]. This use of TCM for the treatment of IBD is spread to Western world and in many Asian countries^[33]. In ancient times Chinese people's are using herbals for the treatment of UC and this is evidenced by Chinese literature. The main intention of using herbals for the treatment of UC was the belief that natural drugs are safe and around 30% peoples think that herbal preparations don't cause any harm or side effects. Herbal drugs contains numerous chemicals and that is the reason its effect is unpredictable^[34]. Today, TCM is most popular way of treatment for UC in Eastern Asian

Table 2 Medicinal plants used for the treatment of ulcerative colitis with their mechanism of action

Sr. No.	Plant	Mechanism	Ref.
1	<i>Acacia ferruginea</i>	Acacia ferruginea extract significantly resist UC <i>via</i> modulation of oxidant/anti-oxidant balance and inhibition of inflammatory mediators. Extract inhibited the activation and translocation of transcription factors (NF- κ B subunits (p65/p50)	[37]
2	<i>Passiflora edulis</i>	Passiflora edulis peel can significantly resist 2,4,6-trinitrobenzenesulphonic acid-induced ulcerative colitis by modulating microbiota and could be used as a source of fiber and polyphenols in the prevention of oxidative stress through the improvement of serum and tissue antioxidant status	[38]
3	<i>Arnebia euchroma</i>	Effectiveness of a hydroxynaphthoquinone fraction from Arnebia euchroma was evaluated with TNBS-induced UC. The underlying mechanism may be associated with TNF- α inhibition in colonic tissue with the dose of 10 mg/kg	[39]
4	<i>Cannabis</i>	Cannabis had been used successfully to relieve the symptoms associated with IBD by inhalational route	[40]
5	<i>Rhizophora apiculata</i>	R. apiculata significantly resist acetic acid induced colitis in experimental mouse model by increasing anti-oxidant enzymes such as SOD and GSH and reducing LPO, NO and inflammatory mediators such as MPO, LDH, iNOS, COX-2 and TNF- α expressions. And also inhibits the translocation of NF- κ B p65 and p50 subunits	[41]
6	<i>Hymenaea stigonocarpa</i>	Total flavonoid of stem bark extract and fruit pulp flour of Hymenaea stigonocarpa significantly resist TNBS-induced colonic damage in rats. Its mechanism may be related to inhibition of MPO and AP activities, reduction in colon MDA content, and counteraction of GSH depletion induced by inflammatory process	[42]
7	<i>Helicteres angustifolia</i>	Aqueous extract of Helicteres angustifolia significantly resist UC induced by TNBS by keeping balance of inflammatory factors in blood and also by improving increasing expression of IL-10 and decreasing the expressions of IL-6 and TNF- α	[43]
8	<i>Ilex kudingcha</i>	Methanol extracts of Ilex kudingcha increased glutathione and reduced colonic myeloperoxidase and malondialdehyde levels in the colon tissue and prevented edema, mucosal damage and loss of crypts. It also decreased anti-inflammatory effects by decreasing the levels of TNF- α , IL-1 β and IL-6 in the colon tissues on 3% DSS-induced UC in mice	[44]
9	<i>Peony</i>	TGP showed positive effect in 2,4,6-trinitrobenzene sulfonic acid TNBS/ethanol-induced colitis by significant improvements of DAI, CMDI, HPS, and MPO activity. Moreover, administration of TGP (50 or 100 mg/kg per day) decreased the up-regulated levels of serum TNF- α and IL-1 β , and expression of TNF- α and IL-1 β mRNA and protein in colonic tissues, and increased the serum IL-10 and colonic IL-10 mRNA and protein level	[45]
10	<i>Olea europaea</i>	Total phenolic secoiridoid of oleuropein, the major phenolic secoiridoid in Olea europaea significantly resisted dextran sodium sulfate-induced chronic colitis in mice. It decreased inflammatory cell and released the inflammatory cytokines IL-1 β and IL-6 with increased IL-10 levels in colon tissue. The anti-inflammatory mechanism of oleuropein was associated with the suppression of the phosphorylation of p38 mitogen-activated protein kinase and might be mediated by up-regulation of annexin A1	[46]
11	<i>Plumbagin plants</i>	Naphthoquinone constituent of Plumbagin plants significantly resist ulcerative colitis in mice by reducing the levels of proinflammatory cytokines (TNF- α , IFN- γ , and IL-17) but cytokine levels remained unaffected with restoration of goblet cells in colon of mice	[47]
12	<i>Euphorbia granuleta</i>	Alcohol extracts of Euphorbia granuleta (Euphorbiaceae) significantly resist UC by reducing the pro-inflammatory cytokine TNF- α and colonic MDA contents	[48]
13	<i>Amaranthus roxburghianus</i>	Combination of hydroalcoholic extract of roots of A. roxburghianus and piperine showed minimal ulceration, hemorrhage, necrosis and leucocyte infiltration and significantly reduced malondialdehyde and myeloperoxidase levels and increased glutathione levels in blood and tissue	[49]
14	<i>Curcumin</i>	Oral curcumin extract decreases colon injury with decreased inflammatory reactions, lipid peroxidation, apoptotic cell death, and modulating p38- and JNK-MAPK pathways in acetic acid-induced colitis	[50]
15	<i>Bauhinia tomentosa</i>	Extract of Bauhinia tomentosa significantly inhibit colitis by regulating the antioxidant and inflammatory mediators with decreasing myeloperoxidase, tumor necrosis factor and inducible nitric oxide synthase expression on acetic acid induced ulcerative colitis	[51]
16	<i>Cistanche tubulosa</i>	Echinacoside enriched extract of Cistanche tubulosa significantly resist DSS-induced colitis by protecting intestinal epithelium from inflammatory injury and by upregulating TGF- β 1 which enhanced <i>in vitro</i> wound healing activity as well as with an increase in the number of Ki67(+) proliferating cells in diseased colons	[52]
17	<i>Garcinia kola</i>	A natural biflavonoid, kolaviron from the seeds of Garcinia kola significantly increase the inflammatory mediators, IL-1 β and tumour necrosis factor alpha, in the colon of DSS-induced ulcerative colitis in rats. The anti-colitis effect of kolaviron is related to its intrinsic anti-inflammatory and anti-oxidative properties	[53]
18	<i>Marine mangrove Avicennia marina</i>	Marine mangrove Avicennia marina extract significantly decreased the colonic lipid peroxides, glutathione peroxidase, serum nitric oxide and significantly increased the colonic and erythrocyte superoxide dismutase and glutathione levels against acetic acid-induced colitis due to the presence of higher levels of decanoic acid, DEHA, pentanoic acid, pyrrolidine, 4-chlorophenyl, thiazolidinones, and arabinopyranoside (flavonoid)	[54]
19	<i>Soy extract</i>	FSG with standardized isoflavone and stable BBI content exert cumulative or synergistic protection based on protease inhibition and ER-ligand activity in colitic rats. It improved the severity of colitis, by decreasing the TNBS-induced rise in gut permeability, visceral sensitivity, faecal proteolytic activity and PAR-2 expression at all post-TNBS points	[55]

20	<i>Aegle marmelos</i>	Effect of <i>Aegle marmelos</i> unripe fruit extract was studied on acetic acid induced ulcerative colitis and indomethacin-induced enterocolitis in Wistar albino rats. Its mechanism is related with protection in mast cell degranulation by significantly decreasing the MDA levels and increased SOD activity. Extract produced anti-inflammatory, antioxidant, and mast cell stabilizing effects demonstrating protective effect in inflammatory bowel disease	[56]
21	<i>Andrographis paniculata</i>	<i>A. paniculata</i> extract at a dose of 1800 mg daily were found to be effective in the treatment of ulcerative colitis	[57]
22	<i>Terminalia chebula</i>	Fruit pulp of <i>Terminalia chebula</i> TCE (600 mg/kg) shows healing effect against acetic acid induced colitis in rats. TCE showed antibacterial activity and both TCE and SS enhanced the antioxidants, but decreased free radicals and myeloperoxidase activities affected in acetic acid-induced colitis	[58]
23	<i>American ginseng</i>	HAG cause apoptosis and suppress mouse colitis through a p53-mediated mechanism. HAG might be very effective in targeting the inflammatory cells and cancer cells since it induces apoptosis of inflammatory cells and cell cycle arrest in both p53 ^{-/-} and WT p53 colon cancer cells	[59]
24	<i>Vaccinium myrtillus</i>	Anthocyanins from <i>Vaccinium myrtillus</i> were shown to have antioxidative and anti-inflammatory effects are useful in the treatment of UC	[60]
25	<i>Moringa oleifera</i> and <i>Citrus sinensis</i>	Results show that a combination of <i>Moringa oleifera</i> root extracts with <i>Citrus sinensis</i> fruit rind extract is effective in the treatment of UC and results are comparable with the standard drug prednisolone. The combination reduced the levels of MPO and MDA in blood and tissue	[61]
26	<i>Lavandula intermedia</i>	<i>Lavandula intermedia</i> protected acute colitis in a mouse model of caused by <i>Citrobacter rodentium</i> . It reduced intestinal tissue damage, and decreased infiltration of neutrophils and macrophages, with reduced levels of TNF- α , IFN- γ , IL-22, macrophage inflammatory protein-2 α , and inducible nitric oxide synthase expression	[62]
27	<i>Chelidonium majus</i>	The CA, a constituent of <i>Chelidonium majus</i> L., has protective effects against DSS-induced UC. CA was found to regulate levels of IL-6 and tumor necrosis factor- α in serum. In colonic tissues, prostaglandin E(2) production levels and COX-2 and HIF-1 α expression levels were increased by DSS, but CA attenuated increases in COX-2 and HIF-1 α levels	[63]
28	<i>Boswellia serrata</i>	Extracts of the plant <i>Boswellia serrata</i> showed significant reduction in lipid peroxidation and SOD level and GPx glutathione level increased significantly. The activity might be due to presence of antioxidant substances	[64]
29	<i>Apple polyphenol extract</i>	Apple extract treatment reduced the severity of colitis. Apple polyphenols reduced the degradation of tissue transglutaminase protein occurring through calpain action. The efficacy of apple extract is mediated by its effects on COX-2 and TNF- α . The unbalance between calpain and tissue transglutaminase may play a role in colonic damage and future therapeutic interventions in ulcerative colitis can target this mechanisms	[65]
30	<i>Cordia dichotoma</i>	The bark of <i>Cordia dichotoma</i> f. (Boraginaceae) was used in the treatment of ulcerative colitis. Apigenin (5 mg/kg, <i>p.o.</i>) isolated from methanol extract of <i>C. dichotoma</i> bark showed significant healing and reduction in inflammatory enzymes when screened for UC	[66,67]
31	<i>Vitex negundo</i>	Ethanol extract of <i>Vitex negundo</i> Linn. (Verbenaceae) root is effective in the treatment of UC. Extract reduced MPO and MDA levels in blood and tissue	[68]

UC: Ulcerative colitis; TNBS: 2,4,6-trinitrobenzene sulfonic acid; IBD: Inflammatory bowel disorders; SOD: Superoxide dismutase; GSH: Glutathione; LPO: Lipid peroxides; NO: Nitric oxide; MPO: Myeloperoxidase; LDH: Lactate dehydrogenase; iNOS: Nitric oxide synthase; COX-2: Cyclooxygenase-2; TNF- α : Tumor necrosis factor- α ; AP: Alkaline phosphatase; MDA: Malondialdehyde; DSS: Dextran sulfate sodium; TGP: Total glucosides of peony; CMDI: Colon macroscopic damage index; DAI: Disease activity index; HPS: Histopathological score; IL: Interleukin; TGF: Transforming growth factor; DEHA: Diethylhydroxylamine; FSG: Fermented soy germ extract; BBI: Bowman-birk inhibitors; ER: Estrogen receptor; HAG: Hexane fraction of American ginseng; CA: Chelidonic acid; HIF-1 α : Hypoxia induced factor-1 α ; GPx: Glutathione peroxidase.

countries. Slippery elm, fenugreek, devil's claw, Mexican yam, tormentil, and Wei tong ning (a TCM) are some of the herbal remedies for the treatment of IBD^[34,35]. Chen *et al.*^[36] compared TCM and synthetic drugs for the management of UC and result showed that 118 cases of UC patients were treated with integration of TCM and 86 cases of UC were treated with prednisone as controls (Table 2).

CONCLUSION

Ulcerative colitis is a chronic disease condition in which patients need to be treated with medicines throughout their lives to either to prevent relapse or to reduce other threats. This is the way by which quality of life of patients suffering from UC can be improved. Many synthetic drugs prescribed for the treatment of UC are associated with large side effects. Large number

of herbal medicines is available with promising results for the treatment of UC. Now it is proved that herbal medicines and TCM can treat conditions of ulcerative colitis. We feel it is the duty of physicians to guide UC patients to inform them regarding availability of TCM treatment which is more effective and safe. These herbal medicines have opened new avenues for the treatment of UC. Thus we feel that herbal medicines are better option for the treatment of UC.

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S- Editor: Tian YL **L- Editor:** A **E- Editor:** Wu HL





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