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TOPIC HIGHLIGHT

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Advances in treatment of ulcerative colitis with herbs: From bench to bedside

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Abstract

Ulcerative colitis (UC), an idiopathic inflammatory disorder in the colon, has become a clinical challenge, owing to the increasing incidence and poor prognosis. The conventional treatments for UC including aminosalicylates, corticosteroids, and immunosuppressants, induce remission in only half of patients. Meanwhile, the treatments often come with serious side effects which can be life-threatening. Herbal medicine, one of the most common traditional Chinese medicine modalities, has been introduced for centuries into clinical treatment of many human diseases such as infections and functional disorders. Recently, the potential effectiveness of herbs has been suggested as the treatment of UC, as shown by a variety of clinical trials and experimental studies. The herbs reported in the literature include *aloe vera* gel, butyrate, tormentil extracts, wheat grass juice, and curcumin. In the review, bioactivity of the herbs and their involvement in UC treatment are discussed.

Key words: Inflammatory bowel disease; Herbs; Herb medicine; Ulcerative colitis; Therapy; Safety

Core tip: Herbal medicine has already been used for some diseases including infections and headache in China since the third century BC. Recently, herbs have emerged as a useful treatment for ulcerative colitis as shown by clinical trials. A better understanding of the herbal bioactivities may provide new alternatives to our current treatment for ulcerative colitis.

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INTRODUCTION

Ulcerative colitis (UC), one type of inflammatory bowel disease (IBD), is characterized by uncontrolled inflammation in the colon and rectum. The incidence and prevalence of UC have been reported to be increasing over the past two decades[1]. Due to its unknown etiology, high risk of recurrence, and poor prognosis, UC has become a clinical challenge in terms of treatment. Meanwhile, conventional therapies for UC fail to successfully induce remission and prevent relapse, and also possibly cause various side effects. Therefore, studies exploring the alternative therapies for UC have become a topic of great interest.

In recent years, herbal medicine, the most common modality of alternative and complementary treatment,

has been established for the treatment of UC, and the bioactivities of herbs have been explored by taking a bench-to-bedside approach. Intriguingly, combination treatments with traditional Chinese medicine, especially herbs, have shown to exhibit the preferential effect than single conventional treatment for UC[2], indicating that herb medicine may be a promising alternative treatment for UC in future. In this review, we summarize the potentials of these herbs and their involvement in clinical management of UC.

PATHOGENESIS OF UC

UC is characterized by aberrant innate and adaptive immune responses. Neutrophils, the first line of innate immune cells, are responsible for intestinal tissue damage, through releasing a large amount of toxic components and free radicals upon stimulation, during the progression of UC[3,4]. Meanwhile, atypical T helper cell (Th) type 2 responses is reported in the pathogenesis of UC, including excessive activation of non-classic natural killer T cells and Th2 cells, as well as substantial production of cytokines, *e.g.*, interleukin (IL)-5 and IL-13. Elevated cytokine levels are noted in UC patients, including IL-5, IL-13, and other proinflammatory cytokines such as tumor necrosis factor (TNF). Once released by immune cells, the cytokines act to further trigger immune responses, induce apoptosis of epithelial cells and upregulate claudin-2 expression, which result in impairment of tight junction of intestinal epithelial cells, and herein damage of the epithelial barrier[5-7].

Nuclear factor kappaB (NF-κB) is a transcription factor regulating the expression of a variety of genes, *e.g.*, TNF, in response to extracellular inflammatory stimuli[8]. Since elevated TNF expression is reported in blood[9], stool samples[10], and the mucosa[11] of patients with active UC, it is widely accepted that NF-κB plays a pivotal role in the development of UC. The relevance of NF-κB inhibition in IBD is further demonstrated by treatment of experimental colitis with a NF-κB antisense oligonucleotide, which resulted in amelioration of inflammation in the colon[12].

Intestinal microbiota is also suggested to participate in the progression of UC. A recent study has showed that fecal microbiota composition of UC patients varies significantly from healthy subjects, indicating the potentials of microbial alterations in patients with UC[13]. Intestinal immune cells are tolerant to lumina commensal antigens, but such tolerance is broken as seen in patients with UC and Crohn's disease[14,15]. The current findings suggest that the defective dynamic balance between commensal microbiota and host defense may contribute to the pathogenesis of UC[16].

HERBAL MEDICINE: THERAPY FOR UC

Herbal medicine is the traditional Chinese clinical practice using plants or/and plant extracts for medical treatment. Due to lack of desirable efficacy and poor tolerance of conventional drugs, more and more populations prefer to accept herb medicine under disease conditions, *e.g.*, headache and infections. Approximately 9.6% to 12.1% of the US adults use one or more forms of herbal products to alleviate disease symptoms, amongst them proximately 10% for digestive symptoms[17]. Recently, herb medicine is employed in clinical trials for UC treatment in many countries including China and India[18].

To study the clinical effect of herbal medicine treatment on UC patients, we searched the controlled clinical trials in PubMed, Google Scholar, and Cochrane Trial Register databases. As a result, a total of 9 controlled studies were included regarding the treatment for UC patients by herb medicine. Among them, 5 were randomized, double-blind, placebo-controlled studies, and one was individually controlled cohort study. These herbs/herb extracts used in the clinical trials included *aloe vera* gel, butyrate, tormentil extracts, wheat grass juice, and curcumin, which are mainly summarized in Table 1.

ALOE VERA GEL

The *aloe vera* plant has been used for skin care as well as medicine for centuries. The leaf of the *aloe vera* plant consists of two main parts: an inner central leaf pulp that stores *aloe vera* gel, the bioactive component, and an outer leaf pulp responsible for transportation of *aloe vera* latex. Aloe vera gel becomes well known due to its anti-inflammatory properties, and is under therapeutic evaluation for UC treatment[19]. For example, *aloe vera* gel inhibits prostaglandin E2 and IL-8 secretion, while having no effect on thromboxane B2 production in the human colorectal mucosa[20]. *Aleo vera* gel has been further reported to inhibit the release of reactive oxygen species (ROS) by PMA-stimulated human neutrophils, and abrogate the ROS-dependent cytotoxicity of neutrophils such as lysis of red blood cells[21]. The anti-inflammatory activities of *aloe vera* gel provide the evidence that it may have a therapeutic effect on IBD.

The clinical value of *aloe vera* gel has been assessed. In a randomized, double-blind, placebo-controlled trial, 44 hospitalized patients with mild or moderate UC received oral *aloe vera* gel treatment or placebo, 200 mL daily for 4 wk[22]. Clinical remission, improvement and response of the disease had been observed in 9 (30%), 11 (37%) and 14 (47%), respectively, of 30 UC patients taking *aloe vera*, compared to one (7%), one (7%), and two (14%), respectively, of 14 UC patients receiving placebo. The clinical colitis activity index and histological scores of the patients decreased significantly during treatment with *aloe vera* ($P = 0.01$ and $P = 0.03$, respectively), but not with placebo. Endoscopic score and laboratory variables displayed no significant differences in both groups of patients with *aloe vera* or placebo treatment. Side events were minimal and similar between *aloe vera* and placebo.

BUTYRATE

Butyrate, a four-carbon short-chain fatty acid, is the main

Table 1 Summary of trials using herbal therapy for patients with ulcerative colitis

Ref.	Herbal medicine	Patient number	Trial design	Treatment method	Duration of treatment	Remission on herb	Remission on placebo
Langmead *et al*[22]	Aloe *vera gel*	44	Randomized, double-blind, placebo-controlled study	Oral	4 wk	30%	7%
Vernia *et al*[34]	Butyrate	25	Randomized, double-blind, placebo-controlled study	Oral	6 wk	58.3%	38.4%
Huber *et al*[39]	Tormentil extracts	16	Individually controlled cohort study	Oral	3 wk	-	-
Ben-Arye *et al*[42]	Wheat grass juice	23	Randomized, double-blind, placebo-controlled study	Oral	4 wk	Not stated, but wheat grass improved symptoms and bleeding more than placebo	Not stated
Singla *et al*[45]	Curcumin	45	Randomized, double-blind, placebo-controlled study	Enema	8 wk	43.4%	22.7%
Hanai *et al*[46]		89	Randomized, double-blind, placebo-controlled study	Oral	6 mo	95.3%	79.5%

metabolite in the colon derived from bacterial fermentation, and also an important energy source of intestinal epithelial cells. Depletion in butyrate-producing microbial communities has been reported in colon mucosal samples from UC patients, attributing to deficiency of butyrate production and exhaustion of energy supplies to intestinal epithelial cells[23,24]. Nevertheless, oral supplement of butyrate exhibits anti-inflammation functions, and ameliorates murine colitis, *via* reduction of neutrophil infiltration and attenuation of intestinal inflammation[25]. Currently, functions of butyrate have been linked with regulation of innate immune responses. For example, butyrate down-regulates lipopolysaccharide-induced expression of proinflammatory mediators by macrophages and neutrophils, including nitric oxide, IL-6, and IL-12, through inhibition of NF-κB activation and histone deacetylase activities[26-29]. Butyrate has also emerged as a modulator of adaptive responses, owing to its multiple bio-functions, *i.e.*, restoring transforming growth factor beta and IL-10 production in the colon mucosa, inducing T cell apoptosis and dampening interferon-γ (IFN-γ) secretion[30].

Clinical trials have shown the effectiveness of butyrate monotherapy or/and in combination with conventional treatment in patients with UC, di-version colitis, as well as acute radiation proctitis[31-33].

A randomized, double-blind, placebo-controlled pilot study on UC patients was conducted to evaluate the safety and efficacy of oral sodium butyrate tablets, coated with a pH-dependent soluble polymer[34]. Administration of butyrate (4 gram daily) in combination with mesalazine significantly improved the disease activity score in 25 patients with active UC, in comparison with mesalazine treatment alone. The combined treatments other than mesalazine alone decreased disease activity index score, and significantly improved disease outcomes *vs* baseline values ($P < 0.05$). Meanwhile, the histological and endoscopic scores improved after treatment in both groups ($P < 0.05$). The similar observations were reported in other non-controlled clinical trials using oral administration or enemas of butyrate[32,35,36].

TORMENTIL EXTRACTS

Tormentil is a member of the rose family that grows wild over Europe. Tormentil extracts contain a high content of tannins which displays potent superoxide-scavenging effects, suggesting tannins as an anti-inflammatory agent. Tormentil has also been shown to be effective in treatment of diarrhea or intestinal inflammation[37,38]. *In vitro* studies have further confirmed the anti-inflammatory, anti-oxidative, and bacterial growth regulatory effects of tormentil extracts[37].

Positive results of tormentil extract treatment have been observed in individual patients with UC[39]. Sixteen patients with active disease took oral tormentil extracts in escalating doses of 1200, 1800, 2400, and 3000 mg every day for three weeks each. Every treatment phase was followed by a 4-wk washout phase. During treatment with 2400 mg of tormentil extracts per day, the clinical activity index, and C-reactive protein levels decreased from 8 mg/L (range: 6-10.75 mg/L) and 8 mg/L (range: 3-17.75 mg/L) at baseline to 4.5 mg/L (range: 1.75-6 mg/L) and 3 mg/L (range: 3-6 mg/L), respectively. During treatment, the clinical activity index improved in all patients, but it turned to increase during the washout phase. There were no apparent side effects with tormentil extract treatment observed during the study.

WHEAT GRASS JUICE

Wheat grass juice is the extract from the pulp of wheat grass and has been used for the treatment of various intestinal diseases and thalassemia for several years. By radical scavenging in correlation with phenolic and flavonoid contents inside, wheatgrass extracts exhibited an antioxidant activity[40]. In particular, pigenin, the main constituent in wheat grass, was shown to inhibit the production of proinflammatory cytokines, *e.g.*, IL-1β, IL-8, and TNF in LPS-stimulated human and mouse macrophages, by inactivating NF-κB through suppression of p65 phosphorylation[41].

The clinical usage of wheat grass juice in UC treat-

ment has been reported[42]. In a randomized double-blind placebo-controlled trial, 23 patients with active UC were randomly grouped to receive either 100 mL of wheat grass juice, or the same volume of placebo, daily for 1 mo. Efficacy of treatment was evaluated by disease activity index, bleeding feces, number of bowel movements, sigmoidoscopic evaluation, and global assessment. The patients treated with wheat grass juice showed significant reductions in disease activity index ($P = 0.031$) and severity of rectal bleeding ($P = 0.025$), in contrast to those receiving placebo. No adverse effects of wheat grass juice were observed.

CURCUMIN

Curcumin is an active phytochemical substance in turmeric, and exhibits pharmacologic activities that might benefit patients with UC. A large number of publications have reported the promising pharmacologic effects of curcumin, *i.e.*, inhibition of expression of a variety of inflammatory genes, including cyclooxygenase (COX)-1, COX-2, lipoxygenase, TNF, IFN-γ, inducible nitric oxide synthase, as well as abrogation of NF-κB activation[43]. Recently, curcumin has been shown to attenuate colonic inflammation through direct inhibition of neutrophil chemotaxis and chemokinesis, and partly through inhibition of the chemokine expression[44].

Clinical trials have evaluated the therapeutic effect of curcumin in patients with mild-to-moderate UC. In a randomized, double-blind, single-centre pilot study, 45 patients received oral 5-aminosalicylic acid in combination with either curcumin preparation (140 mg in 20 mL water) or placebo enema. The patients receiving additional curcumin preparation treatment showed improvements in disease activity, compared with those patients with placebo enema[45]. Another group also showed the similar efficacy of combination treatment of curcumin (2 g daily) and sulfasalazine or mesalamine in maintenance therapy for 89 patients with quiescent UC, indicating that curcumin may confer additional therapeutic advantages when used in combination with conventional anti-inflammatory medications in UC[46].

SAFETY OF HERB MEDICINE

So far, it remains unclear about the safety of herb medicine. Butyrate, the most common treatment used for UC patients, has been shown to be relatively safe for UC patients. Hallert *et al*[47] reported that supplement of dietary fiber elevated the fecal butyrate level, and kept UC patients in remission, without increment in gastrointestinal complaints during the trial. Recently, a meta-analysis evaluated the efficacy and tolerance of herbal medicines in patients with IBD. With the results from seven placebo-controlled clinical trials, the analysis has showed that herbal medicines can induce clinical response and remission in IBD patients, without serious side events[48].

Due to limitation of human studies, animal models become alternatives to explore the safety of herbs. Acute toxicity of Tormentil rhizomes was assessed in rats and mice, with a single dose administration by gavage of 2.5 and 6.8 g/kg (body weight), respectively[49]. No apparent toxic effects have been recorded at two weeks after the administration of Tormentil rhizomes. Nevertheless, some researchers questioned the safety of herbs with the evidence that fatal hepatic and irreversible renal failure occurred with some herb preparations, and that interactions of herbs with conventional drugs were potentially detrimental[50]. Meanwhile, a recent study has reported the increased incidences of mucosa hyperplasia and goblet cell hyperplasia in the colon of rats and mice at 13 wk after exposure to drinking water containing *aloe vera*[51]. Thus, the safety and long-term benefits of herb medicine need to be intensively investigated before it can be applied for patients.

CONCLUSION

Because of the relatively natural and multiple biological properties, herbs have emerged as the alternative for current treatment of inflammatory disorders, including UC. Clinical trials have indicated the promising possibility of herb medicine for UC treatment. However, there have some concerns to be clarified before herb medicine can be securely introduced into UC patients. So far, the clinical trials with herb medicine treatment were conducted in a small number of UC patients, and large case-controlled studies and reliable data about the detailed mechanism of the herbs are still lacking. Meanwhile, herbal preparations are the mixture containing a huge range of biological compounds, other than purified single component. It might not be known which component in the herbs provides the exact pharmacological effects, even in some cases the herb mixtures exhibit clinical benefits. Thus, determination of herb components, dosage and course of herb treatment becomes a challenge for clinical employment. In addition, the safety of herb medicine remains to be further investigated, especially under long term treatment.

Overall, herb medicine treatment becomes widespread and prevalent, with encouraging results from clinical trials. Further evidence about the components of herbs and their bio-functions will shed light on clinical administrations of herb medicine in future. With discerned safety of herbs, herb medicine itself or in combination with conventional therapies would largely benefit patients with UC and other immune disorders.

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