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The Efficacy of *Cichorium intybus* L., *Trigonella foenum-graecum* L. and *Foeniculum vulgare* Mill. in Improvement of Ulcerative Colitis Symptoms: A Randomized Clinical Trial

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Abstract

Due to the lack of favorable response to synthetic drugs, the tendency to use traditional medicine to treat inflammatory bowel disease has risen. We aimed to assess the effect of *Cichorium intybus* L., *Trigonella foenum-graecum* L., and *Foeniculum vulgare* L. on the control of recurrent ulcerative colitis (UC) symptoms. This randomized clinical trial was performed on 60 patients suffering from mild-to-moderate UC. Patients were randomly assigned to control and intervention groups. Patients in both groups were treated with a standard dose of oral mesalazine (3 g daily) for eight weeks. In addition, the intervention group was given a mixture of 200 mg *C. intybus*, 350 mg *T. foenum-graecum*, and 1.5 mg *F. vulgare* (three times a day). The disease activity was evaluated before and 60 days after the intervention using a simple clinical colitis activity index (SCCAI). The baseline mean SCCAI score was similar in both groups. Although the SCCAI score significantly reduced in both groups 60 days after the initial assessment, this reduction was significantly higher in the group receiving the herbal combination than in the control group. The intervention-related side effects, such as bloating and dyspepsia, were well tolerated. The use of *C. intybus*, *T. foenum-graecum*, and *F. vulgare* can effectively control UC symptoms and thus, can be used as an effective and safe medication for treating UC.

Keywords: Ulcerative colitis; Complementary medicine; Inflammatory bowel disease; *Cichorium intybus*; *Trigonella foenum-graecum*; *Foeniculum vulgare*

Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease of the large intestine characterized by diffuse superficial inflammation of the intestinal mucosa. The relapse-remission course of the disease is the main characteristic of UC [1]. The disease–related symptoms include abdominal pain, diarrhea, blood in the stool, sometimes fever, and extraintestinal symptoms such as arthritis, uveitis, erythema nodosum, and pyoderma gangrenosume [2]. The extent of colonic involvement varies from the rectum to the cecum and is divided into proctitis (rectal involvement only), left colitis (inflammation extends from the rectum up through the sigmoid and descending colon), and extensive colitis (inflammation starts at the rectum and goes beyond splenic flexure) [3]. Moreover, according to the severity of symptoms and based on clinical, laboratory, and endoscopic manifestations, the disease is divided into mild, moderate, and severe types [4]. The incidence and prevalence of this disease vary according to the geographical area, ethnicity, and race. Current epidemiological data indicates that UC

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is more common in industrialized countries, with an incidence rate of 6.5 to 16.0 percent per thousand people per year and a prevalence of 26 to 214 patients per hundred thousand people [5]. The incidence and prevalence of inflammatory bowel disease (IBD) in less developed countries are estimated at 0.08 to 5.0 and 3.6 to 70.0 patients per hundred thousand per year, respectively [6].

The basis of treatment for mild-to-moderate UC is using mesalamine compounds orally, topically, or in combination [7]. Patients with mild-to-moderate active UC who do not respond to mesalamine compounds usually need corticosteroids or immunomodulatory drugs, but these drugs have numerous and sometimes dangerous side effects [8].

Chicory roots (*Cichorium intybus* L.) of the Asteraceae family contain sugars, inulin, lactosine, lactucopicrin, and minerals (calcium, potassium) [9]. *C. intybus* has various pharmacological properties, including immune response modulation and anti-inflammatory properties [10]. In a study by Karimi et al., murine dendritic cells were treated with ethanolic extract of chicory root. The higher concentrations of the extract inhibited the proliferation of allogeneic T cells, and the lower concentrations regulated the cytokine production toward a Th1 pattern [11]. A phase I clinical trial of chicory extract in patients with osteoarthritis demonstrated its safety and efficacy [12]. Chicory extract significantly reduced colon inflammation in a rat IBD model. Also, no signs of toxicity were observed in a rat toxicity study by doses of chicory up to 1000 mg/kg [13].

Fenugreek seed (*Trigonella foenum-graecum* L.) contains sugars such as starch, galactomannan, vitamin K, vitamin C, phosphorus, sodium, magnesium, manganese, copper, vitamins of saponins such as diogenes, lipids, proteins and nucleoproteins, phosphorite compounds such as lecithin, nitrate compounds such as choline, trigonelline, and nicotine amides [9]. The anti-inflammatory potential of *T. foenum-graecum* has been demonstrated in several experimental models [14-17]. In animal models, the anti-ulcer, anti-stress, and antioxidant effects of methanolic extract of fenugreek leaves against stressful gastric ulcers have been evaluated [18]. Several studies have evaluated the safety and efficacy of *T. foenum-graecum* in humans [19-22].

Moreover, fennel essential oil (*Foeniculum vulgare* Mill.) belongs to the family Apiaceae and has diverse pharmacological properties [23]. It reduces acetic acid-induced colitis by inhibiting nuclear factor (NF)-κB expression and inflammatory cascade in the colon and thus, can be effective in improving UC [24].

The anti-inflammatory properties of *C. intybus*, *T. foenum-graecum*, and *F. vulgare* could positively affect UC. In the current study, we aimed to assess the effect of these traditional medicines on the control of UC symptoms.

Material and Methods

The present parallel clinical trial was performed on 60 patients suffering from mild-to-moderate UC referred to the gastroenterology clinic of Rasool-Akram Hospital, Tehran, in 2020. The sample size was calculated to be 30 participants in each group, based on formula for the comparison of two independent means in a clinical trial [25], with a significance level, power, and effect size of 0.05, 0.8 and 0.7, respectively.

All methods were performed in accordance with the Declaration of Helsinki and the relevant regulations. The study was approved by the Research Ethics Committee of Iran University of Medical Sciences (Code No: IR.IUMS.REC.1397.1188). The details of the trial were explained to all patients and a written consent was obtained from them before entering the study. This study was registered in the Iranian Clinical Trial Registration System (IRCT) in 30/12/2019 (IRCT20190712044182N2).

Diagnosis of UC was previously established in participants based on the conventional clinical, colonoscopy, radiologic, and histological criteria. In addition, participants had to fulfill the following criteria: consent to participate, a history of UC more than six months, age of 18-80 years old, mild-to-moderate severity of the UC based on American Gastroenterological Association (AGA) guidelines [26].

The exclusion criteria included severe colitis, patients who were admitted to hospital for their disease at the time, other comorbidities, history of receiving herbal medicine for their disease, sensitivity to the plant compounds used in this study, pregnant and lactating women, and patients aged under 18 years.

After obtaining informed consent from all participants, a questionnaire related to demographic and clinical information, which includes criteria for assessing the disease severity, was completed, and patients with mild-to-moderate degrees of disease were identified.

The severity of the disease was determined based on the criteria of simple clinical colitis activity index (SCCAI) as follows: 1) If the frequency of defecation was 4-6 times a day, 7-9 times and more than nine times a day, the scores one, two and three were given, respectively. If the patient had defecation 1-3 times a night, score one, and if it was more than that, score two was given. The urgency in defecation was divided into three categories: immediate, hurry, and incontinence, and the scores of one, two, and three were given, respectively. Regarding the general condition of the patients, if the illness was mild, moderate, severe, and very severe according to the doctor's judgment, scores from one to four were given, respectively. One point was also specified for each extraintestinal symptom

(arthritis, erythema nodosum, pyoderma gangrenosum, and uveitis). In sum, the maximum score was 19, and patients who got 5-11 points were considered to have mild-to-moderate UC.

After the initial assessment, patients were randomly assigned into control and intervention groups by Excel's RANDBETWEEN function. Patients in both groups were given a standard dose of oral mesalazine (3 g in 24 hours) for eight weeks. The intervention group was assigned to take three Chicoridin tablets daily. Chicoridin tablets are commercial herbal products developed from 200 mg *C. intybus* root extract, 350 mg T. foenum-graceum seeds, and 0.3 mg *F. vulgare* oil, and standardized to 4 mg total polyohenols based on pyrogallol. Since no previous human experience was performed to assess the effect of Chicoridin on UC, the dose and duration of use was arbitrarily selected based on Chicoridin administration instruction for the purpose of appetite stimulation [27]. The control group received placebo drug in the same form and shape of Chicoridin tablets. The patients and the physician were blind to the patients' assigned groups. Then the disease activity was re-evaluated based on the mentioned criteria, and the results were compared between the two groups.

Finally, the data were analyzed by SPSS software. The results were reported as mean and standard deviation (mean ± SD) for quantitative variables and as a percentage for categorical variables. Comparisons between quantitative variables were performed by t-test or in case of abnormal distribution by Mann-Whitney test. The Chi-square test or Fisher's exact test was used to compare the categorical variables. The significance level for all tests was considered 0.05 with a 95% confidence interval. The statistical software SPSS version 26.0 for windows (IBM, Armonk, New York) was used.

Results

As demonstrated in the CONSORT flow chart (Figure 1), 76 patients were assessed for eligibility in the present study. However, three patients were excluded due to unwillingness to participate, five declining the drug, and eight due to severe stage of UC. Ultimately, 30 patients in each group entered the trial. The baseline characteristics of the study population are

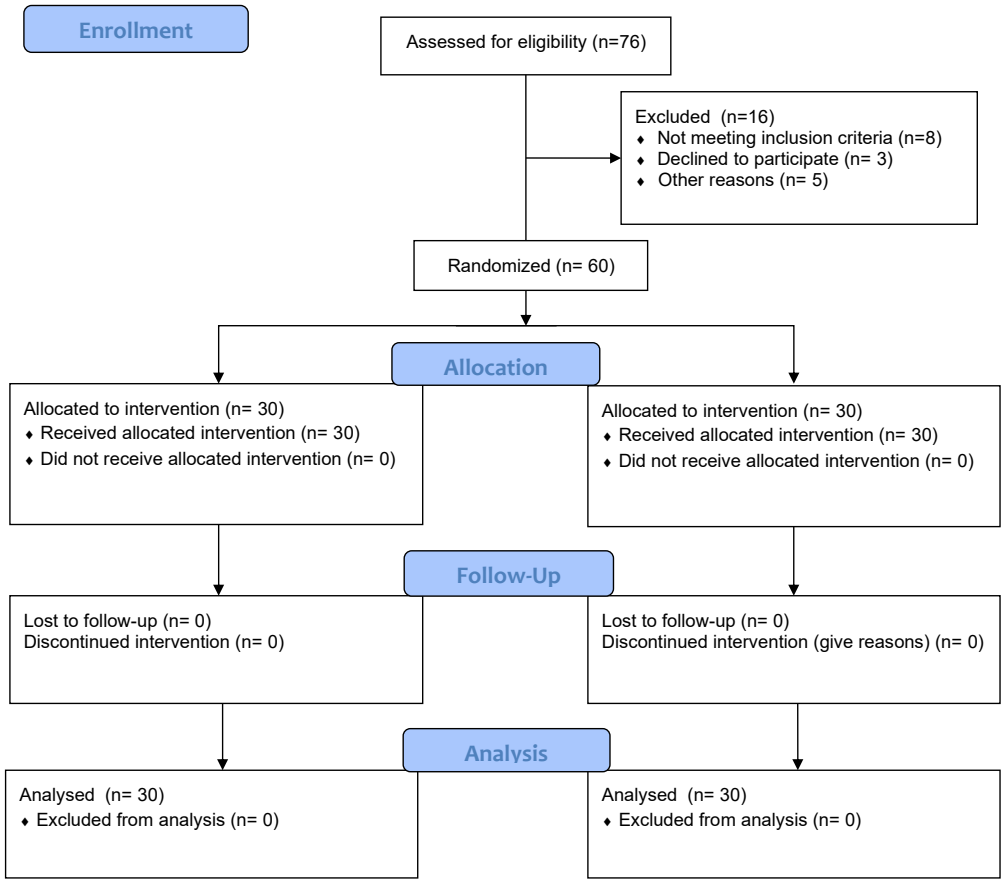

Figure 1. The CONSORT diagram

Table 1. Baseline characteristics of the study population.

Baseline Characteristics	Intervention Group	Control Group	P value
Male Gender, n (%)	18 (54.5)	15 (45.5)	0.436
Extent of Bowel Involvement, n (%)			
Proctitis	3 (30.0)	7 (80.0)	0.383
Left Colon Involvement	14 (53.8)	12 (46.2)	
Full Colon Involvement	13 (54.2)	11 (45.8)	
Age, year (mean ± SD)	38.17 ± 12.45	41.77 ± 15.55	0.371
Disease Duration, month (mean ± SD)	64.04 ± 45.53	30.09 ± 27.64	0.005
Oral Medications, n (%)			
Sulfasalazine	2 (50.0)	2 (50.0)	0.694
Azathioprine	9 (81.8)	2 (18.2)	0.020
Mesalazine	21 (55.3)	17 (44.7)	0.284
Prednisolone	7 (77.8)	2 (22.2)	0.071
Folic Acid	10 (43.5)	13 (56.5)	0.426

Table 2. The change in SCCAI score in the intervention and control groups.

SCCAI Score	Intervention Group	Control Group	P value
Before Intervention	4.83 ± 1.76	5.10 ± 2.17	0.604
60 Days After	0.87 ± 1.47	2.00 ± 1.98	0.020
P value	< 0.001	< 0.001	

Data presented as mean ± SD; SSCAI: simple clinical colitis activity index
Regarding intervention-related side-effects, three patients experienced bloating, and two patients had dyspepsia, which was all well-tolerated.

summarized in table 1. The two groups were matched for baseline parameters, except for disease duration and Azathioprine consumption. The mean overall age of participants was 39.97 ± 14.07 years, and 55% of participants were male. Full colon involvement was found in 40.0%, and the mean disease duration was 48.15 ± 41.51 months.

SCCAI criteria were calculated at the beginning of the study and 60 days after the initial intervention. As shown in table 2, the mean SCCAI score was similar in both groups at baseline. Although the SCCAI score significantly reduced in both groups 60 days after the initial assessment, this reduction was significantly higher in the intervention group than in the control group.

Discussion

In this study, we compared the SCCAI score between the intervention and control group and observed that there was no significant difference in the baseline score; however, after 60 days of intervention, the intervention group had a significantly lower SCCAI score and thus experienced greater improvement in clinical symptoms. Reviewing the literature shows different mechanisms for such improvement.

In 2006, Shishodia et al. showed that fenugreek contains a substance called diosgenin, which can inhibit allergic reactions and inflammation of the gut and ultimately reduce diarrhea. It also increases goblet cells in the duodenum of an animal model. Another role of diosgenin is to inhibit the activation of NF-κB by reducing tumor necrosis factor (TNF) and causing anti-inflammatory effects, inhibiting abnormal cell growth, and inducing apoptosis and anti-cancer effects [28]. In 2001, Langmed et al. evaluated the impact of six plants, including fenugreek, in IBD treatment. For this purpose, they compared these six compounds with 5-ASA compounds and measured and compared the production of free radicals using fluorimetry. They found that plants such as fenugreek played an influential role in reducing the number of free radicals in the intestines of patients with IBD [29]. In a study published in 2014, fenugreek extract (*T. foenum-graecum*) was shown to have several properties, including antidiabetic properties, increasing milk production, reducing cholesterol and blood lipids, antioxidant, anti-inflammatory, anticancer, antibacterial, and antifungal effects. In addition, fenugreek compounds

can reduce digestive problems such as reflux, gastritis, and duodenal ulcers [14]. Furthermore, Pandian et al. demonstrated that *T. foenum-graecum* granules had a more significant effect on ethanol-induced gastric ulcers than omeprazole in rats. It was attributed to the anti-secretory properties of fenugreek, and its effect on mucosal glycoproteins. In addition, the antioxidant properties of *T. foenum-graecum* seeds have a tremendous effect on the prevention and treatment of gastric ulcer lesions against omeprazole [30]. In 2004, Choi et al. investigated fennel extract's anti-inflammatory and analgesic effects. They showed that fennel extract suppresses acute and subacute inflammatory and type IV allergic reactions and has a central analgesic effect. Additionally, this plant substance improved the activity of superoxide dismutase and catalase and increased high-density lipoprotein cholesterol levels. In contrast, the activity of lipid peroxidation enzymes was significantly suppressed [31]. In another study conducted in 2017 by Rezayat et al., they examined fennel oil's protective effect on acetic acid-induced intestinal inflammation in mice. It was found that injection of fennel oil in the colon of mice reduced microscopic and macroscopic inflammation and inhibited the NF-κB pathway by inhibiting MPO enzyme activity and TNF expression in immune cells [24].

Chicory root contains various substances such as inulin and sesquiterpene lactones (SLs). The primary source of SL in nature is chicory root which has multiple biological effects. In 2020, Matos et al. found that SL compounds could play an essential role in intestinal barrier permeability and regulating immune responses via the NFAT pathway. Moreover, chicory root contains various phenolic compounds, including anthocyanins. In a study by D'evoli et al., the effects of these anthocyanin compounds on intestinal immunity and cells were evaluated. It was demonstrated that these compounds have antioxidant, anti-cell growth, and cell-specific properties. Also, these properties are seen more in the red leaves of the chicory plant, which have higher amounts of phenolic and anthocyanin compounds [32].

No study has specifically addressed the effect of *C. intybus*, *T. foenum-graecum*, *F. vulgare* on improving the clinical symptoms in patients with UC so far. According to our results, this drug combination significantly reduces UC clinical symptoms 60 days after treatment and thus, can be considered a safe treatment option for improving IBD symptoms.

The limitations of the present study include the small sample size and lack of data on laboratory findings and imaging studies, which could provide us with helpful information about the effect of *C. intybus*, *T. foenum-graecum*, *F. vulgare* on UC.

Conclusions

In conclusion, *C. intybus*, *T. foenum-graecum*, *F. vulgare* can effectively control UC symptoms and thus can be used as an effective and safe supplementary treatment option in UC. However, further studies with long-term follow-up need to be conducted to reveal its long-term efficacy.

List of Abbreviations

UC: Ulcerative Colitis; IBD: Inflammatory Bowel Disease; SCCAI: Simple Clinical Colitis Activity Index; SL: Sesquiterpene Lactone

Conflict of Interests

None.

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