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Efficacy of *Plantago major* seed in management of ulcerative colitis symptoms: A randomized, placebo controlled, clinical trial

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ABSTRACT

Objective: Evaluation of the effect of *Plantago major (P. major)* seed on ulcerative colitis (UC) symptoms.
Methods: In this randomized double-blind clinical trial, 61 subjects received 3600 mg/day roasted *P. major* seed in intervention group (n = 31) and roasted wheat flour in control group (n = 30), for 8 weeks, as a complementary to standard medications. Variables were assessed using the Lichtiger Colitis Activity Index (LCAI) at baseline, week 4, and week 8.
Results: 51 patients completed the trial (n = 28 in *Plantago* and n = 23 in placebo groups). Abdominal tenderness (p = 0.011), gastroesophageal reflux and gastric pain (p = 0.049 for both), were significantly less severe in *P. major* group. Visible blood in stool (p = 0.001), distension (p = 0.001), and anal pain (p = 0.051), decreased significantly in *P. major* group, although no significant difference was observed between the two groups: (p = 0.224), (p = 0.283), and (p = 0.455) respectively.
Conclusion: P. major seems to be effective in complementary management of UC.

1. Introduction

The most common inflammatory bowel disease worldwide, ulcerative colitis (UC), is an idiopathic inflammatory condition of the colon, associated with superficial erosions on the colonic wall, diffuse friability, and bleeding [1]. The main onset, peaks between the ages of 15 and 30 years [2]. UC is characterized by persistent mucosal inflammation that begins in the rectum and spreads to proximal parts [1]. Definitive diagnosis is based on endoscopy and biopsy of intestinal mucosa, which is indicative of chronic colitis. Symptoms include dysentery, abdominal pain, fever (in severe cases), anemia, extreme fatigue, weight loss, and anorexia, as well as developmental disorders in children [3]. The continuous rise in healthcare costs associated with this disease, is in part due to costly therapies [4]. The most widely used drugs for inducing remission in these patients include aminosalicylates and corticosteroids [5]. However, none of the treatment options are effective enough, with 90% of patients still experiencing a relapsing course 25 years after diagnosis [6]. Furthermore, these medications have some important and serious side effects such as acute kidney injury, hemolytic anemia (Heinz bodies), hepatitis, male infertility (with sulfasalazine), pancreatitis, and hyperglycemia (secondary diabetes mellitus) [6]. The importance of paying attention to this disease is clear considering: 1) the increasing rate of colitis (incidence: 1.2 to 20.3 cases per 100,000 persons per year, and prevalence: 7.6 to 245 cases per 100,000 per year) [7], 2) lack of complete remission, which leads to a huge economic burden and is associated with serious complications such as toxic megacolon, stenosis, dysplasia, and colorectal cancer [6], and 3) the side effects of common medications [8]. Therefore, we decided to study a natural medicine that is safe, cheap and accessible, and selected the herb according to Persian Medicine (PM) resources. *Plantago major* L. *(P. major)* (large plantain) is a pharmacological plant, which belongs to the family Plantoginacae. This plant is useful for the treatment of intestinal ulcers and cessation of intestinal diarrhea and bleeding [9]. It contains tannins, coumarins, flavonoids, polyphenols and gluten, which have been shown to have anti-inflammatory, anti-ulcerative, anti-fever, anti-diarrhea, antimicrobial and wound healing properties [10]. The aim of this study was to investigate the effect of *P. major* on clinical symptoms of UC.

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2. Materials and methods

2.1. Participants and study setting

This randomized clinical trial was conducted in the gastroenterology clinic of Imam Khomeini Hospital in Urmia city (Iran) between December of 2018 and June 2019. Inclusion criteria comprised men and women aged 15–70 years, and colitis symptoms that were diagnosed as UC and confirmed with colonoscopy. Patients with the following criteria were not included in the trial: massive bleeding, or the need for hospitalization or emergency surgery, symptoms of fulminant colitis, peritonitis, megacolon toxicity, colorectal cancer, stenosis and obstruction, consumption of antibiotics or herbs (in the last 2 weeks) or NSAIDs (in the last 1 week), comorbidities such as liver, kidney, or heart disease, or cancer, smoking, pregnancy or breast-feeding. Exit criteria included: pregnancy during the study, severe complications of the disease or medications during intervention, unwillingness to continue the trial, consumption of other drugs during the study, and changes in medications for any reason. This study was approved by the institutional review Board of Shahed University (approval code: IR. SHAHED. REC.1397.037), and registered at the Iranian Registry of Clinical Trials; https://irct.ir/under the code number of IRCT20181018041375N1.

2.2. Study design

2.2.1. Herbal drug and placebo preparation

Initially, *P. major* seeds were obtained from a reputable local herbal market called *Attari* from Tehran, Iran and the sample was deposited, and thereafter authenticated by the Herbarium of the Faculty of Pharmacy, University of Tehran with voucher specimen No. of PMP-794. Subsequently, *P. major* seeds were roasted in a pan over mild heat and then filled into capsules (600 mg in each capsule), in a pharmacy laboratory. Placebo was prepared by roasting colored wheat flour, granulated to simulate the drug and then filled into similar capsules. Following preparation of the drug and placebo, microbial and fungal tests were performed for both capsules at the Medicinal Plants Research Institute, for which results were acceptable according to the pharmacopeia.

2.2.2. Randomization, blinding, and intervention

An expert in the study center prepared and codified boxes, while the researcher handed over the boxes to patients sequentially based on their codes (simple randomization). The researcher, the gastroenterologist, and participants were blinded to boxes content (drug or placebo) and decoding was performed after data analysis (triple-blind study). All participants read and signed the informed consent form prior to entering the study.

The patients consumed two capsules)600 mg *P. major* seed capsules or placebo (30 min before meals (a total of 3600 mg/day roasted *P. major* seed in intervention group and roasted wheat flour in control group), for 8 weeks. The dose was determined according to PM and modern phytotherapy resources [11] and was administered in two divided of six capsules for more convenience for patients. All patients continued their routine drugs. Both groups received a similar life style modification plan according to PM principles.

2.3. Measurements

Symptoms were assessed at weeks 0, 4 and 8 b y the researcher according to the Lichtiger Colitis Activity Index (LCAI). This index covers eight variables of: diarrhea, nocturnal diarrhea, visible blood in stool, fecal incontinence, abdominal pain/cramping, general well-being, abdominal tenderness, and the need for antidiarrheal drugs, as primary outcomes, with scores ranging from 0 to 21 (Table 1). Based on the study design regarding exit criteria, none of the patients took any other medications, such as antidiarrheal drugs. Therefore, this variable was omitted from the list (Table 2). Clinical remission and disease activity were graded as clinical remission: 3 points or less [12], mildly active disease: 4–8 points; moderately active disease: 9–14 points; and highly active disease: >14 points [13]. Secondary outcomes including: gastroesophageal reflux, gastric pain, distention, constipation, and anal pain were assessed in addition to main symptoms. Possible side effects of the drug were evaluated using a questionnaire for recording drug side effects, at weeks 4 and 8. Drop-outs were contacted by phone calls in order to determine causes of discontinuance (consort diagram).

Table 1
Comparison of demographic data and disease characteristics between the study groups.

Variable		Intervention (N = 28)		Control (N = 23)		*P*-value
Age		40.57	±12.54	35.69	±12.99	0.609
Disease severity index		5.21	±3.91	4.00	±3.81	0.53
Sex	Male	17	60.71	13	56.52	0.49
	Female	11	39.28	10	43.47	
Education	Non-academic	24	85.71	20	86.95	0.45
	Academic	4	14.28	3	13.04	
UC severity	Remission	10	35.71	13	56.52	0.18
	Mild	12	42.85	8	34.72	
	Moderate	6	21.42	1	4.34	
	Severe	0	0	1	4.34	
Other disease	Yes	11	39.28	8	34.78	0.306
	No	17	60.71	15	65.21	
BMI	Low weight	3	10.71	2	8.69	0.37
	Normal	10	35.71	11	47.82	
	Over weight	7	25	7	30.43	
	Obese	8	28.57	3	13.04	

•Data are presented as mean ± standard deviation or number/(%).
•Quantitative variables were analysed by Mann-Whitney.
•Qualitative variables were analysed by Chi-Square.

2.4. Data analysis

Statistics analysis was performed via SPSS (ver. 16, Chicago, IL, USA). Quantitative and qualitative variables were presented as mean ± SD and frequency (percent), respectively. Mann-Whitney and Chi-Square were used for statistics analysis. Moreover, GEE regression and GEE logistic regression was performed to assess the combination of the studied tests. Significant differences were shown as $p < 0/05$ between study groups.

3. . Results

3.1. Participants characteristics

A total of 75 patients with mild, moderate and severe ulcerative colitis were recruited, of which 14 had one of the exclusion criteria and thus, 61 were included and randomized in two groups. During the 8 weeks of study, 10 patients dropped-out (three in *P. major* group and seven in placebo group). Ultimately, 51 patients completed the study and were analysed (28 patients in *P. major* group and 23 patients in the placebo group) (Fig. 1). The baseline variables did not significantly differ between the two groups ($P > 0.05$) (Table 1).

3.2. Effects of intervention on clinical symptoms of LCAI

Clinical treatment response was better and statistically significant, in *P. major* group compared with placebo group in terms of abdominal tenderness ($p = 0.011$). Although there was no significant difference between the two groups regarding visible blood in stool ($p = 0.224$), the *P. major* group, experienced a significant decrease in this symptom after 8 weeks of treatment ($p = 0.001$), ($p = 0.331$ for placebo group) (Table 2).

Table 2
Comparison of the clinical symptoms of LCAI between the study groups.

Variable	*Plantago major* groupn (%)			placebo groupn (%)			*P*-value
	baseline	Week 4	Weak 8	baseline	Week 4	Weak 8	
Diarrhea	11(39)	9(32)	9(32)	10(44)	8(35)	5(22)	0.251
Nocturnal diarrhea	4(14)	2(7)	1(4)	6(26)	3(13)	2(9)	0.885
Visible blood in stool	15(54)	7(25)	5(18)	4(17)	3(13)	2(9)	0.224
Fecal incontinence	1(4)	1(4)	0(0)	2(9)	3(13)	1(4)	NA
Abdominal pain	19(68)	10(36)	13(46)	11(48)	8(35)	8(35)	0.506
Abdominal tenderness	12(43)	4(14)	3(11)	6(26)	4(17)	4(17)	0.011
Poor to terrible General well-being	2(7)	2(7)	1(4)	1(4)	2(9)	0(0)	NA
Severity point(Mean ± SD)	5.21 ± 3.91	2.68 ± 2.78	2.43 ± 2.71	4.00 ± 3.81	2.83 ± 3.30	2.09 ± 3.01	0.282

•GEE regression and GEE logistic regression was performed to assess the p.value of severity point and qualitative variables respectively.
• NA: Not Applicable.

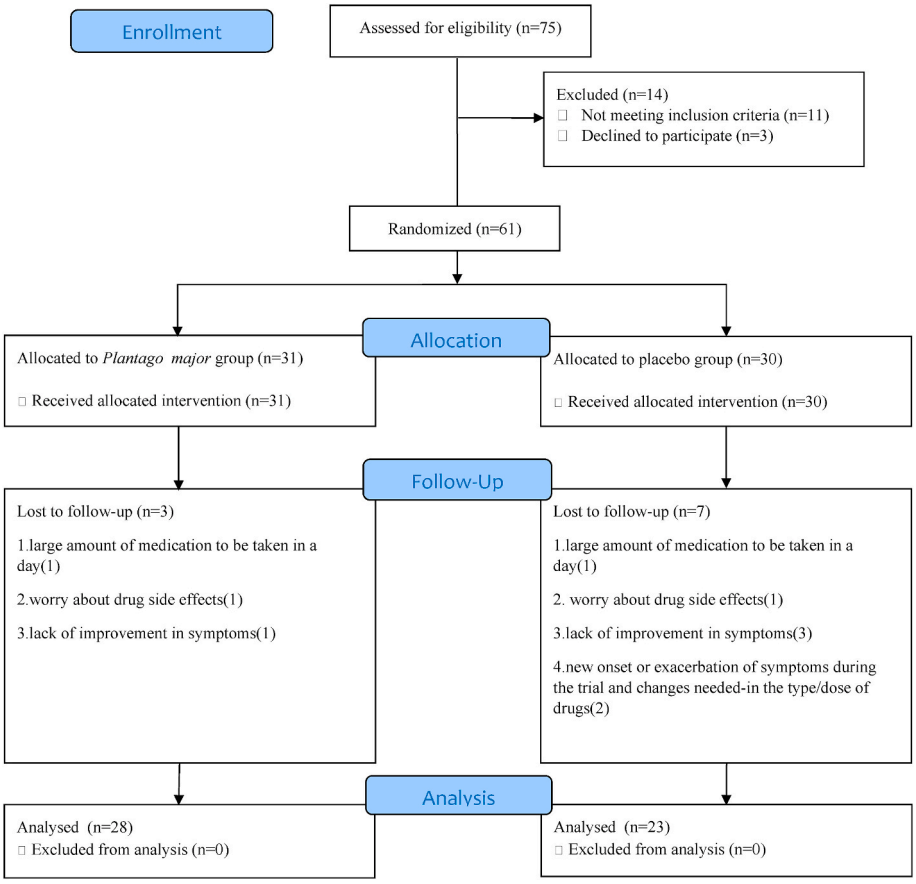

Fig. 1. Consort diagram.

3.3. Effects of intervention on secondary outcomes

In the present study, symptoms of gastroesophageal reflux and gastric pain improved significantly in *P. major* group compared with placebo group (p = 0.049 for both). Although there was no significant difference between the two groups regarding symptoms of distention (p = 0.283) and anal pain (p = 0.455), both variables significantly decreased in the *P. major* group at the end of the 8th week compared

Table 3
Comparison of secondary outcomes between the study groups.

Variable	*Plantago major* groupn (%)			placebo groupn (%)			*P*-value
	baseline	Week 4	Weak 8	baseline	Week 4	Weak 8	
Gastroesophageal reflux	9(32)	5(18)	3(11)	6(26)	6(26)	5(22)	0.049
Gastric pain	8(29)	4(14)	2(7)	2(26)	7(30)	4(17)	0.049
Distention	22(79)	16(57)	12(43)	14(61)	11(48)	9(39)	0.283
Constipation	6(21)	4(14)	3(11)	3(13)	1(4)	1(4)	0.66
Anal pain	7(25)	2(7)	2(7)	4(17)	1(4)	2(9)	0.455

•The p.value was calculated by GEE logistic regression.

with baseline ($p = 0.001$ and $p = 0.051$ respectively), ($p = 0.124$ and $p = 0.186$ respectively for placebo group) (Table 3).

3.4. Side effects

No side effects such as fever, headache, nausea, vomiting, dyspepsia, abdominal pain, skin rashes, and etc. were detected in any of the groups throughout the study.

4. Discussion

The aim of this study was to compare the efficacy of *P. major* seed with placebo for UC symptom management. Our results showed that abdominal tenderness improved significantly in *Plantago* group compared with placebo ($p = 0.011$). Visible blood in stool decreased significantly in *Plantago* group at the 8th week ($p = 0.001$), although no significant difference was observed between the two groups ($p = 0.224$). Secondary outcomes including gastroesophageal reflux and gastric pain improved significantly in *Plantago* group compared with placebo ($p = 0.049$ for both). These results support the hypothesis of the therapeutic effects of *P. major* on UC symptoms.

Given the fact that both groups received a similar lifestyle modification plan according to PM principles and that all benefited from its positive effects, an overall improvement in symptoms was observed and intervention results were not significantly different between the two groups.

PM literature have specified: anti-infective, anti-hemorrhagic, wound healing, anti-inflammatory, astringent, and hemostatic actions for *P. major*, some of which having been confirmed in recent researches [9]. Bioactive components such as flavonoids, polysaccharides, terpenoids, phenolic compounds (caffeic acid derivatives), alkaloids, and vitamins are present in nearly all parts of *P. major* [10]. The seeds of this plant contain gluten, holoside plantose, succinic acid, adenine, tannins, coumarins such as ascoltin, flavonoids including apigenin, and zinc and potassium salts [14]. Flavonoid and phenolic compounds are effective anti-oxidant sources [15]. Studies have shown that secondary metabolites such as alkaloids, polysaccharides, saponins, terpenes, and especially phenolic compounds, show wound healing effects [16]. Biological properties of the plant extract include wound healing, anti-inflammatory, analgesic, antioxidant, weak antibiotic, immunomodulating and antiulcerogenic activities [14]. *P. major* seed is demulcent and its cold infusion is used in dysentery and in arresting fluxes and griping pain in the bowels [17].

The main pathophysiological characteristics of UC include inflammation, oxidative stress and increased immune activity, all of which lead to injury and ulceration of intestinal mucosa. High levels of pro-inflammatory cytokines and lowered levels of anti-inflammatory cytokines and proteins, lead to oxidative stress, inflammation, and also concomitant decrease in antioxidants. Ultimately, cell inflammation, and infiltration of immune cells, especially neutrophils result, which cause epithelial cell damage and colonic barrier dysfunction [18]. Therefore, consumption of agents with anti-inflammatory, immunomodulatory, antiulcerogenic, and antioxidant effects, could be helpful in improvement of this disease. Considering the therapeutic properties of *P. major*, this medicinal herb seems to be a suitable option for relieving symptoms in patients suffering from UC.

4.1. Limitations

UC is an idiopathic and chronic disease with multiple genetic and environmental risk factors. The multifactorial nature of the disease impedes control and maintenance of remission periods. Any change in patient routines, can lead to disease flare-up, making medical intervention and longtime follow up difficult. On the other hand, many patients avoid consuming more drugs, due to taking multiple medications and fear of probable side effects.

In our study, low sample size, short intervention period, time limitations that prevented follow-up, and consumption of routine drugs that had a role in relieving the symptoms, could be the causes of reaching trivial results and lack of significant difference between the two groups in main LCAI symptoms, such as bleeding and diarrhea.

Furthermore, despite the primary intention to include UC patients regardless of disease severity, most participants had no severe and significant symptoms (26% moderate and 4% severe). This prevented analysis of the real effect of *P. major* seed.

On the other hand, the "visible blood in stool" variable was significantly different between the two groups at the beginning of the study ($p = 0.008$). Thus, despite the fact that the drug was able to reduce the number of patients with bleeding ($p = 0.001$), there was no significant difference between the two groups at the end of the study.

5. Conclusion

P. major seeds effectively improve abdominal tenderness, gastroesophageal reflux, and gastric pain in UC compared with placebo, and may be considered for complementary management of UC. Further studies with larger sample size, longer intervention, follow-up, and inclusion of more cases of severe disease is suggested.

Author contribution

AB generated the study idea and participated in designing the study, acquisition of data, analysis and interpretation of data, and drafting the article. As the statistical consultant, AD participated in study design, and analysis and interpretation of data. AJH participated in clinical assessment and acquisition of data. FE and JA participated in designing the study and drafting the article. All authors participated in writing parts of the manuscript draft, revised the whole manuscript critically, and approved the final submitted version.

Declaration of competing interest

The authors have no conflict of interests to declare.

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