



## Evaluating the effect of Glycyrrhiza glabra, Matricaria chamomilla, and Achillea millefolium on the symptoms of irritable bowel syndrome: Clinical trial

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### Original Article

#### Abstract

**BACKGROUND:** Irritable bowel syndrome (IBS) is a functional disorder of the gastrointestinal (GI) tract that causes multiple and occasionally debilitating symptoms in patients. Given the high prevalence and wide effects of IBS in our society, finding cheap, safe, and effective drugs has a great importance for helping the patients with IBS and helping the community's health economy. The aim of this study was to determine the effect of yarrow, licorice, and chamomile (as a cheap and safe cocktail) on the symptoms of patients with IBS.

**METHODS:** In this double-blinded clinical trial study, 102 patients (referred to Toohid Hospital in Sanandaj City, Kurdistan, Iran, from February 25, 2017 to August 21, 2019) were included in the trial. The diagnosis of IBS was based on clinical findings and Rome-III criteria. Subjects were randomly assigned to intervention and control groups. The intervention group was given a combination of three plants [Glycyrrhiza glabra (G. glabra), Matricaria chamomilla (M. chamomilla), and Achillea millefolium (A. millefolium)] for a month. The control group received a placebo. Outcomes were assessed 2 and 4 weeks later. Data were analyzed using SPSS software.

**RESULTS:** The mean age of the subjects was  $41.2 \pm 11.6$  years (age range: 21-60 years). 42 patients (41.17%) were men, and 60 patients (58.8%) were women. The mean duration of the symptoms was 27.4 [standard deviation (SD) = 24.6] months. Two weeks after the intervention, there was a statistically significant difference between the two groups in terms of some symptoms, including constipation, diarrhea, and mucus excretion. Four weeks after the intervention, there was a statistically significant difference between the two groups in terms of abdominal pain, bloating, constipation, diarrhea, and feeling of incomplete excretion ( $P = 0.001$ ).

**CONCLUSION:** Based on the results of this study, combination of the three plants (G. glabra, M. chamomilla, and A. millefolium) was effective in reducing the symptoms of IBS.

**KEYWORDS:** Glycyrrhiza Glabra; Matricaria Chamomilla; Achillea Millefolium; Irritable Bowel Syndrome

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### Introduction

Irritable bowel syndrome (IBS) is a disorder of

gastrointestinal (GI) tract. The exact cause of the disease is unknown. It has been related to things like food passing through gut too fast or too slow, over-sensitive nerves in gut, stress, and a family history of IBS. Main symptoms of IBS include abdominal pain and discomfort and changes in bowel habits (diarrhea,

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constipation, or both). This syndrome is one of the most common referrals to general and specialized clinics.<sup>1,2</sup> This disorder is the most common functional disease of the GI tract, so that according to the results of various studies, its prevalence in various societies and countries is between 9% and 23%.<sup>3-5</sup> Some research has also been done on the prevalence of IBS in Iran. The studies indicated that the prevalence of IBS in Iran varied from 1.1% to 25%.<sup>6</sup>

Studies have shown that IBS is significantly more prevalent among women than among men. Due to gender differences shown in a variety of physiological and psychological factors, the clinical manifestations of symptoms as well as treatment strategies may be different in men and women with IBS.

Women with IBS have been reported to experience fatigue, depression, anxiety, and lower quality of life (QOL) than men with IBS. In addition, there is evidence of differences in the effectiveness of appropriate treatment for IBS in men and women. However, relatively few men have enrolled in most related clinical trials. Gender differences appear in the prevalence of IBS. In women, IBS occurs most often from late adolescence to the mid-forties. With increasing of age, the incidence of IBS in women is decreased. The prevalence of IBS among men between the ages of 20 and 70 remains constant. With increasing of age around 70, the incidence of IBS is increased. It has been suggested that sex hormones play an important role in these gender differences and in epidemiology, pathophysiology, and treatment of IBS as well. IBS has a high comorbidity with various psychological disorders such as depression and anxiety, especially in adults. This leads to a decrease in QOL. It also increases the economic burden on the individual and family, because these people undergo many diagnostic tests and therapies.<sup>4,7</sup>

Diagnostic criteria for IBS, based on Rome-III criteria, include: intermittent abdominal pain three days a month for three

consecutive months plus two findings from the following three findings that last for 6 months: reduction of pain after excretion, change in bowel habits, and change in the shape and consistency of the stool.<sup>8,9</sup>

Medications such as alosetron, eluxadolone, rifaximin, lubiprostone, and linaclotide are the main approved drugs for treatment of IBS. However, these treatments are symptomatic, without addressing the main cause of the disease.<sup>10,11</sup>

According to some descriptive studies and evidence in traditional medicine, *Achillea millefolium* (*A. millefolium*) or yarrow has been suggested as an appetizer and digestive supplement. Its use has been mentioned as a relieving agent for seasonal allergies, antispasmodic for GI spasm, and for treatment of menstrual disorders.<sup>12</sup> *Glycyrrhiza glabra* (*G. glabra*) or licorice is another medicinal plant, which is effective in traditional medicine for cases such as tooth decay, indigestion, abdominal spasm, bloating, headache, cough, and joint pain.<sup>13</sup> *Matricaria chamomilla* (*M. chamomilla*) or chamomile, another medicinal plant, has been suggested in the treatment of gastric ulcer, bloating, intestinal spasm, oral ulcers (especially after tooth extraction), and passing kidney stones.<sup>14</sup>

In a study to determine the effect of glycerin *glabra* (D-reglis tablet) on the pain and defecation of patients with IBS, it was shown that although the pain intensity in both case and control groups had a decreasing trend during 8 weeks of the experiment ( $P < 0.001$ ), no significant difference was observed between the groups at all times ( $P > 0.05$ ). It seems that *G. glabra* has no significant effect on the pain of patients with IBS; however, it may improve the diarrhea or exacerbate the constipation in these patients.

Given the high prevalence and wide effects of IBS in our society and given that the treatment of IBS is symptomatic, finding cheap, safe, and effective drugs has a great importance for

helping the patients with IBS and also helping the community's health economy. The use of herbal medicines has a long history in the treatment of various diseases. The combination of yarrow, licorice, and chamomile plants has been studied in several studies. These three drugs are widely used in herbal medicine and many scientific studies reported their beneficial effects in some patients.<sup>12-16</sup>

In the study of Jenabi and Fereidoony, the effects of *A. millefolium* on relief of primary dysmenorrhea was evaluated. The subjects were randomly divided into two equal groups and were given either placebo or *A. millefolium* in tea bag form for 3 days in 2 menstruation cycles. They graded the severity of their pain using a visual analogue scale (VAS). The severity of pain in the two groups was compared using t-test. The mean change in pain score in the *A. millefolium* group was significantly greater than that in the placebo group in 1 ( $P = 0.001$ ) and 2 ( $P < 0.0001$ ) months after treatment. The results showed that *A. millefolium* was effective in reducing the severity of pain in early menstruation.<sup>17</sup>

In the study of Zakeri et al., the effect of *M. chamomilla* on vulvovaginal candidiasis (VVC) compared to clotrimazole was investigated. This double-blind randomized clinical trial study was conducted on 80 women diagnosed with VVC clinically and by laboratory test; 40 women received vaginal cream clotrimazole 1% and 40 received vaginal cream containing the aqueous extract of *M. chamomilla* for 7 days. The results showed that the vaginal cream containing *M. chamomilla* could reduce the complaints of VVC. However, future studies with larger sample sizes and different doses are recommended to evaluate the results of this new treatment.<sup>18</sup>

In the study of Ayoobi et al., *A. millefolium* was evaluated as an adjunct treatment in patients with multiple sclerosis (MS). The patients were randomized into three groups including placebo and two groups receiving *A.*

*millefolium* with two different doses, i.e., 250 mg/day and 500 mg/day, for 1 year. Observations showed that one-year administration of *A. millefolium* (both doses) decreased the annual relapse rate in patients with MS. The mean volume change of lesions significantly decreased in the 500 mg *A. millefolium* group. The add-on therapy also increased time to first relapse and the Multiple Sclerosis Functional Composite (MSFC) z-score; it decreased the Expanded Disability Status Scale (EDSS) score. *A. millefolium* can be useful as an adjunct in patients with MS.<sup>19</sup>

Given the high prevalence and wide effects of IBS in our society, finding cheap, safe, and effective drugs has a great importance for helping the patients with IBS and helping the community's health economy. The aim of this study was to determine the effect of yarrow, licorice, and chamomile (as a cheap and safe cocktail) on the symptoms of patients with IBS.

## Methods

In this double-blind clinical trial study, 102 patients (referred to Toohid Hospital in Sanandaj City, Kurdistan, Iran, from February 25, 2017 to August 21, 2019) with IBS were randomly divided into two groups of 51 patients. Patients were selected based on Rome-III criteria when diagnosed with IBS by a specialist physician.<sup>20</sup> Informed consent of all patients to participate in the study was obtained by the researcher. Patients who had a history of abdominal surgery or had high blood pressure, high erythrocyte sedimentation rate (ESR), and positive findings in colonoscopy were excluded from the study. Patients with a diagnosis of IBS based on Rome-III criteria and also the absence of bleeding, weight loss, malabsorption, anemia, and absence of blood or leukocytes in stool were included in the study. Patients with other GI symptoms and taking drugs such as omeprazole, clidinium, dimethicone, and maburin stopped taking these drugs one week before the beginning of the study with the doctor's opinion and patient satisfaction. Then the patients were

randomly assigned to the intervention and control groups (with block randomization). During the treatment, the patient and the treating physician were unaware of the received drug (main treatment or placebo).

The intervention group received a combination of three plants of yarrow (165 mg), licorice (110 mg), and chamomile (55 mg) every eight hours. The plants were dried, powdered, and prepared as capsules. The physician prescribed the medicine and the members of the research team presented the medicine and placebo to the people based on the grouping. The placebo group received capsules similar to those of intervention group, which did not have drugs every eight hours. The time of treatment for both groups was 28 days. The placebo drug used in this study was similar to the main capsule in terms of shape, size, and color, as well as the box and label. The patients and the person completing the information did not know about the patients being assigned to which group. Patients in two groups were evaluated simultaneously in terms of abdominal pain, bloating,

constipation, diarrhea, incomplete excretion, and mucus excretion in three stages: before the intervention, two weeks after the intervention, and four weeks after the intervention. The data were recorded and collected in a checklist. Data analysis was performed using SPSS software (version 22, IBM Corporation, Armonk, NY, USA). Chi-square test was used to examine the qualitative variables between the two groups. Significance level in this test was considered as  $P < 0.05$ . There were no confounding factors.

This clinical trial was also registered on Iranian Registry of Clinical Trials (IRCT) website with the registration code IRCT2013093014827N1. This study was the result of a research project that was approved by the Ethics Committee of Kurdistan University of Medical Sciences, Sanandaj, with the code number IR.MUK.REC.229/14.

## Results

Among the 114 patients, four were excluded from the study because of withdrawing from participation, and eight were excluded from the study because of not meeting inclusion criteria (Figure 1).

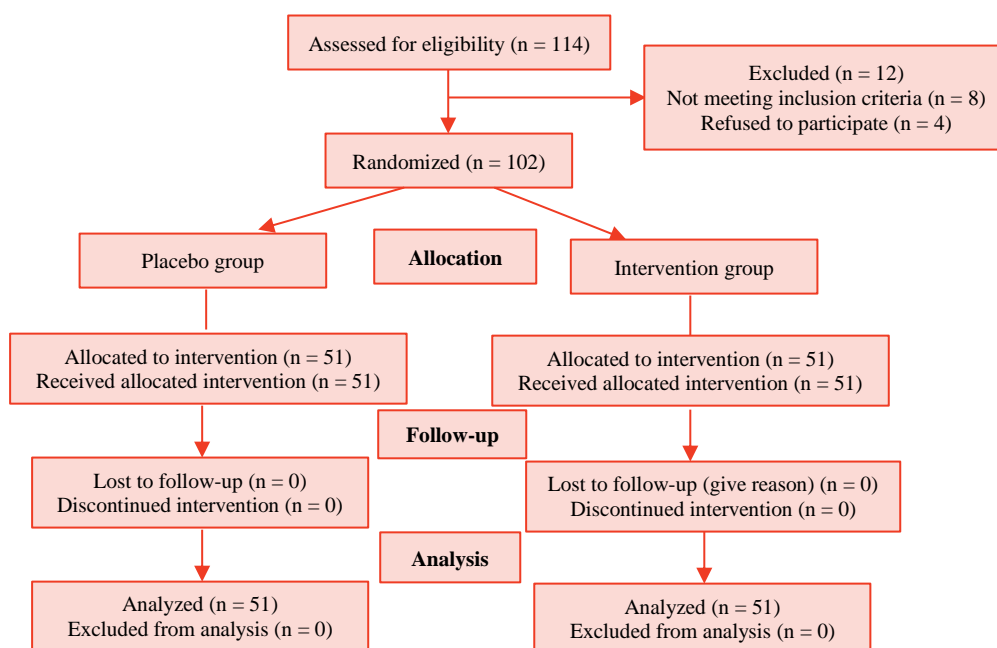


Figure 1. Consort flowchart

42 patients (41.17%) were men and 60 patients (58.8%) were women. There were 32 women (62.7%) and 19 men (37.3%) in the intervention group, and 28 women (54.9%) and 23 men (45.1%) in the control group. The mean age of the subjects was  $41.2 \pm 11.6$  years (age range: 21-60 years). The mean duration of the symptoms was 27.4 [standard deviation (SD) = 24.6] months (range: 6-84 months).

Data analysis showed that there was no statistically significant difference between the two groups regarding these factors ( $P > 0.05$ ). In this study, there was no statistically significant difference between the subjects in terms of symptoms of abdominal pain, bloating, constipation, diarrhea, incomplete excretion, and mucus excretion before the intervention (Table 1).

Two weeks after the intervention, a statistically significant difference between the two groups was observed in some clinical findings, so that constipation was lower in the intervention group compared to the control group ( $P = 0.001$ ). In addition, less diarrhea was observed in the intervention group compared to the control group ( $P = 0.006$ ). There was a statistically significant difference between the two groups in terms of mucus excretion ( $P = 0.02$ ). Four weeks after the

intervention, there was a statistically significant difference between the two groups in terms of abdominal pain ( $P < 0.001$ ), bloating ( $P < 0.001$ ), incomplete excretion ( $P = 0.047$ ), and mucus excretion ( $P = 0.001$ ). A summary of the study data is shown in table 2.

## Discussion

Given the high prevalence and widespread effects of IBS in our society, it is important to find cheap, safe, and effective drugs to help patients with IBS as well as to help the community's health economy.

The results of this study showed that the yarrow, licorice, and chamomile combination on the symptoms of IBS in two weeks and four weeks after the intervention was effective on abdominal pain, bloating, constipation, incomplete excretion, and mucus excretion. In a study conducted by Rahimian et al., with the aim of the effect of licorice on the defecation status of patients with IBS, the positive effect of licorice was confirmed. Additionally, the abdominal pain reduced significantly in the intervention group.<sup>21</sup> The results of another study conducted by Agah et al. showed that chamomile (as oral drops) effectively reduced the symptoms of patients with IBS.<sup>22</sup>

**Table 1. Basic information of patients with irritable bowel syndrome (IBS) in the experimental and control groups at baseline**

Characteristics	Category	Case	Control	P
Age (year) (mean $\pm$ SD)		42.0 $\pm$ 11.3	40.4 $\pm$ 11.8	0.487
Duration of IBS (month) (mean $\pm$ SD)		25.6 $\pm$ 21.6	30.1 $\pm$ 26.6	0.353
Sex [n (%)]	Male	19 (37.3)	23 (45.1)	0.546
	Female	32 (62.7)	28 (54.9)	
Abdominal pain [n (%)]	Mild	17 (51.5)	16 (48.5)	0.546
	Moderate	18 (43.9)	23 (56.1)	
	Severe	16 (57.1)	12 (42.9)	
Constipation [n (%)]	No	11 (52.4)	10 (47.6)	0.807
	Yes	40 (49.4)	41 (50.6)	
Diarrhea [n (%)]	No	17 (41.5)	24 (58.5)	0.225
	Yes	34 (55.7)	27 (44.3)	
Incomplete excretion [n (%)]	No	22 (44.9)	27 (55.1)	0.428
	Yes	29 (54.7)	24 (45.3)	
Mucus excretion [n (%)]	No	28 (48.3)	30 (51.7)	0.842
	Yes	23 (52.3)	21 (47.7)	

IBS: Irritable bowel syndrome; SD: Standard deviation

**Table 2. Comparison of the groups 2 weeks and 4 weeks after the intervention**

Factors	Status	2 weeks after intervention			4 weeks after intervention		
		Intervention group [n (%)]	Control group [n (%)]	P	Intervention group [n (%)]	Control group [n (%)]	P
Abdominal pain	Mild	23 (45.1)	18 (35.3)	0.595	36 (70.6)	10 (19.6)	0.001
	Moderate	14 (27.5)	17 (33.3)		7 (13.7)	15 (29.4)	
	Severe	14 (27.5)	16 (31.4)		8 (15.7)	26 (51.0)	
Bloating	No	19 (37.3)	13 (25.5)	0.200	35 (68.6)	14 (27.5)	0.001
	Yes	32 (62.7)	38 (74.5)		16 (31.4)	37 (72.5)	
Constipation	No	31 (60.8)	15 (29.4)	0.001	32 (62.7)	15 (27.0)	0.001
	Yes	20 (39.2)	36 (70.6)		19 (37.3)	36 (73.0)	
Diarrhea	No	41 (80.4)	28 (54.9)	0.006	44 (86.3)	26 (51.0)	0.001
	Yes	10 (19.6)	23 (45.1)		7 (13.7)	25 (49.0)	
Incomplete excretion	No	32 (62.7)	25 (49.0)	0.160	33 (64.7)	23 (35.0)	0.047
	Yes	19 (37.3)	26 (51.0)		18 (35.3)	28 (55.0)	
Mucus excretion	No	45 (88.2)	36 (70.6)	0.020	47 (92.2)	34 (66.7)	0.001
	Yes	6 (11.8)	15 (29.4)		4 (7.8)	17 (33.3)	

The results of these two studies were consistent with the results of our study.

In the study of Raveendra et al., the effects of extract of *G. glabra* on the symptoms of functional dyspepsia was evaluated. The patients received *G. glabra* for 30 days. Effectiveness was assessed for changes in symptom severity, global effectiveness evaluation, and QOL using the Nepean Dyspepsia Index (NDI). *G. glabra* group showed a significant decrease ( $P \leq 0.05$ ) in total symptom scores on days 15 and 30. Similarly, GutGard showed a significant improvement in global efficacy evaluation compared with placebo. The GutGard group also showed a significant decrease ( $P \leq 0.05$ ) in the NDI on days 15 and 30.<sup>23</sup>

In a study, the effect of *M. chamomilla* on intestinal disorders in children and adolescents was investigated. Evidence has shown that *M. chamomilla* reduces abdominal pain and frequency and severity of pain in children suffering from undifferentiated functional abdominal pain. Evidence was found for the effectiveness of *M. chamomilla* in the treatment of children with neonatal colic.<sup>24</sup>

In the study of Kazemian et al., the effects of *Boswellia carteri*, *Zingiber officinale*, and *A. millefolium* on the symptoms of patients with IBS was evaluated after 3 months. They

reported that the intensity and duration of abdominal pain was reduced due to the treatments. Additionally, some clinical trials mentioned positive effects of licorice on IBS.<sup>25</sup>

The reason for the effect of licorice on the symptoms of patients with IBS is probably due to its antispasmodic effects, which reduce bowel movements and most of the symptoms of these patients are alleviated.<sup>23,26,27</sup>

In the study of Derakhshande et al., efficacy and safety of *Achillea wilhelmsii* capsules on the severity of symptoms and QOL in patients with IBS were evaluated. Patients were randomly divided into two groups of 45 patients. Patients' QOL and severity of symptoms were assessed at the beginning and end of treatment using Irritable Bowel Syndrome Quality of Life (IBS-QOL) questionnaire and IBS severity index. The result indicated that although the severity of symptoms and QOL in both groups improved compared to before the intervention, there was no significant difference between the two groups.<sup>28</sup>

There are studies available that have examined the effect of chamomile and ginger on the symptoms of patients with IBS. These studies were performed especially in Iran and China. One of the reasons that can justify the role of these drugs and their effect on the

clinical symptoms of patients with this common GI disorder is probably the anti-inflammatory effects of these substances. There is no doubt that the role of the immune and inflammatory systems in the development of GI dysfunction in IBS is pivotal. Thus, it is possible that these herbal remedies can alleviate the symptoms of patients with IBS by modulating the immune system.<sup>26,27,29</sup>

The main limitation of this study was related to the lack of para-clinical assessments, which was due to the lack of appropriate diagnostic tests for IBS. Indeed, there is no available routine para-clinical test for IBS. This leads to failing in precise statistical evaluations. The lack of para-clinical test for IBS also leads to a higher rate of misdiagnosis. Thus, it is strongly recommended for future studies to investigate new biomarkers and indices for evaluating the severity of IBS quantitatively.

### Conclusion

The use of medicinal plants has a very long history. If we can use these drugs in the treatment of patients who usually do not manifest serious complications, also for the patients that do not have standard and decisive treatment, we have done a great help to this group of patients. The results of our study showed that using a combination of yarrow, licorice, and chamomile could reduce the symptoms of IBS and open a new window in the treatment of these patients with low cost and complications.

### Conflict of Interests

Authors have no conflict of interests.

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