

Evaluating the efficacy of mixture of *Boswellia carterii*, *Zingiber officinale*, and *Achillea millefolium* on severity of symptoms, anxiety, and depression in irritable bowel syndrome patients

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Background: Irritable bowel syndrome (IBS) is the most prevalent functional gastrointestinal disorders (FGIDs) that affects in different aspects of life and patients experienced depression and anxiety more than others. There are several herbal medicines with positive effects in these patients. The aim of this study is to evaluate the effects of mixture of *Boswellia carterii*, *Zingiber officinale*, and *Achillea Millefolium* on severity of symptoms, anxiety, and depression in IBS patients. **Materials and Methods:** This clinical trial study was done in sixty IBS patients (with mild-to-moderate symptoms) divided into two case and control groups. Patients were assessed at the beginning, 1 month, and 3 months after by IBS-severity scoring system (IBS-SSS) and Hospital Anxiety and Depression Scale. IBS-SSS is used for quality of life evaluation too. **Results:** Sixty IBS patients (with mild to moderate symptoms) with a mean age of 38.75 ± 11.74 participated that 55.4% of cases and 72.8% of controls were men. The most prevalent type of IBS was the mixed type of IBS. The mean score of abdominal pain severity and frequency, bloating score, and depression and anxiety score were decreased in patients administered herbal medication, but changes in these variables in controls were not statistically significant. The changes in quality of life score between cases and controls were significant in men ($P = 0.01$) although it was not significant in women. **Conclusion:** A mixture of *B. Carterii*, *Z. officinale*, and *A. millefolium* is effective in eliminating IBS symptoms and its related depression and anxiety and using herbal medicine in IBS treatment is suggested.

Key words: Anxiety, depression, gastrointestinal diseases, herbal medicine, irritable bowel syndrome

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INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most prevalent functional gastrointestinal disorders defined as abdominal pain and alterations in bowel habits.^[1] The prevalence of IBS is 5%–20% worldwide, and it is more prevalent in Western countries and patients younger than 50.^[2]

IBS interacts with different aspects of life including sleep, job, sexual function, and recreations that decreases

the quality of life (QOL) in these patients.^[3] Studies on patients with IBS demonstrated that depression, anxiety, and other psychological disorder are more common in these patients comparison to control groups.^[4] Studies showed that absences in school and job in IBS patients are three times more than non-IBS individuals which showed the effects of this disorder on patients' functions in their life.^[5]

Boswellia carterii is an herbal medication with anti-inflammatory effects without effects in increasing

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acids in gastrointestinal system. The extract of this plant special Boswellic acid had effects in antibody production and cell immunity. It also is a great lipoxygenase inhibitor which inhibits producing leukoterian.^[6] Studies in *B. carterii* reported that this plant has antidepressant effects in addition to its protective effects in Alzheimer's patients.^[6,7] The plant has also positive effects in inflammatory disease including rheumatoid arthritis, allergic reactions, asthma, chronic bronchitis, psoriasis, and multiple sclerosis.^[8]

Z. officinale is a plant from Zingiberaceae family with antioxidant components with antibacterial and anti-fungal effects which stimulates immune system. Recent studies showed that this plant gathers nitrous oxides and free radicals to protect from their damages.^[9] Studies on the effects of this plant demonstrated that methanol extract of *Z. officinale* can decrease depression symptoms and this plant is used in depression treatment as an effective and safe drug.^[10,11]

Achillea millefolium is another herbal medication with glyco-flavonoid components which used in the treatment of arthritis, gastritis, asthma, and hepatic disease in ancient medicine.^[12] Studying this plant in animal models and also patients with anxiety disorders showed that this plant has anxiolytic effects.^[13,14]

Researches on the effects of herbal medicine in eliminating IBS symptoms reported that Chinese formulation with different herbal medications has positive effects in IBS treatment. In a review in herbal medicine, *B. carterii* was useful for IBS treatment and *Z. officinale* significantly eliminated IBS symptoms.^[15-18]

Due to the high prevalence of IBS in society and its impaired effects on patients life and lack of exact treatment for IBS and also the efficacy of herbal medicine in treating IBS in some researches, the aim of this study is to evaluate the effects of mixture of *B. carterii*, *Z. officinale*, and *A. millefolium* on severity of symptoms, QOL, anxiety, and depression in IBS patients.

MATERIALS AND METHODS

This study is a randomized controlled trial in sixty IBS patients (based on ROME III criteria) in Isfahan, Iran. Participants were selected from IBS patients refer to psychosomatic clinic in Isfahan University of Medical Science (IUMS) in 2015–2016. The inclusion criteria were being older than 18 and having documented diagnosis of IBS. Exclusion criteria were using other treatment for IBS, pregnancy, and unwillingness to participating in this study.

Sixty IBS patients were participated in this study which divided into two groups randomly defined as case and

control groups. In case group, three herbal medications were administrated to patients which contain *B. carterii*, *Z. officinale*, and *A. millefolium*. This capsule was produced in pharmacy school in IUMS, and for this study, we prepared these capsules from starch. In placebo group, placebo similar to herbal medication in shape, color, and size was administered to patients which produced by pharmacy school in IUMS. Each participant received 90 capsules for using in 1 month. Every patient used one capsule in every 8 h. During this 1 month period if participants experienced side effects, came to clinic, and visited by practitioner and necessary advise was explained to patients, and in some cases, they were excluded from the study. Patients were assessed in the beginning of study, 4 and 12 weeks after starting intervention for IBS severity symptom, depression and anxiety, and QOL.

Before intervention, all demographic data about patients such as age, gender, marital status, and educational level and data about their IBS were collected. At the beginning of study, after finishing treatment (1 month) and 2 months after end of using these drugs (3 months after beginning), patients were assessed. In each assessment, two questionnaires were fulfilled by participants including IBS-severity scoring system (IBS-SSS) and Hospital Anxiety and Depression Scale (HADS). HADS questionnaire has seven questions about depression and seven questions about anxiety. Each question has four items and scored from 0 to 3. The questionnaire IBS-SSS was used to evaluate abdominal pain, bloating and their severity, satisfaction of bowel habits, and the effects of IBS in QOL. The questionnaire HADS has 14 questions including 7 questions for evaluating anxiety and 7 for depression. Each question has four items and scored between 0 and 3. Both questionnaires were validated in Persian.^[19,20]

The sample size of this study was estimated according to similar studies. For randomizing patients into two groups, we used random number generators and sampling method was convenience time-based sequential.

For quantitative variables and qualitative variables, we expressed mean \pm standard deviation and proportion in percentage, respectively. To assess differences between two groups in quantitative variables, Student's *t*-test and for qualitative variables Chi-square and Friedman tests were used. For other analysis, repeated measurement analysis was done. All statistical analyses were performed using SPSS version 21 (SPSS corp, Chicago, IL, USA). In all parts, $P < 0.05$ was considered statistically significant. This study was approved by Regional Bioethics Committee of IUMS.

We used starch as our placebo; IBS patients with mild-moderate symptoms how fulfilled our informed

consent were enrolled to this study. This study was approved by Medical Ethics Committee of IUMSs and Iranian Registry of Clinical Trials and the code is IRCT201402089256N3.

RESULTS

Seventy IBS patients were asked to participate in this study that ten of them did not include due to age <18 and unwillingness to participate in this study. Hence, sixty IBS patients were included and then divided into two groups with 30 individuals. In case and control group, six and four patients were excluded because of discontinuing using drugs in the 1st month, respectively, and, in the second follow-up, 8 patients (4 patients in cases and 4 patients in controls) were excluded due to their poor compliance to treatment, and finally data from 22 patients in controls and 20 patients in cases were analyzed [Figure 1]. The side effects were detected in patients: one had nausea, one had skin reaction (itching), and two had diarrhea. However, side effects in these four patients did not exclude them from study (mild symptoms). Side effects are shown in Table 1.

The mean age of participants in case and control group was 36.2 ± 10.88 and 41.3 ± 12.61 years, respectively. Nearly 55.4% of participants in case group and 72.8% in control group were male. Most of the participants in both case and control group had educational level under diploma (50% and 54.3%). The most common type of IBS in case and control groups was IBS-M and IBS-D was the less prevalent type of IBS. Comparing demographic factors between case and control group showed significant differences in

age and gender, and differences in educational level and type of IBS were not statistically significant. All data about demographic factors in both case and control group are shown in Table 2.

The first question in IBS-SSS questionnaire was about abdominal pain severity that patients chose a number for their pain severity from 0 to 100. Abdominal pain severity was assessed at the beginning, 1, and 3 months after starting study. The symptom severity was decreased in two periods of study (the first 1 month and the second 2 months) in case groups, significantly ($P < 0.001$), and in control group symptom, severity decreased in first 1 month and increased in second 2 months and both changes were not statistically significant ($P = 0.81$) and also alteration of abdominal pain severity between case and control group was statistically significant ($P = 0.001$). The second question was about abdominal pain frequency in recent 10 days ranged from 0 to 10. The mean symptom frequency was decreased in case group after 1 and 3 months significantly ($P < 0.001$) although it increased in control group but not significantly ($P = 0.61$). Changes in frequency of abdominal pain differ between case and control groups significantly ($P = 0.01$). The third question was about bloating severity ranged from 0 to 100. In case group, the mean score of bloating severity decreased significantly after intervention and 2 months later, and changes in case group were not statistically remarkable ($P < 0.001$ and 1.0) and comparing changes between case and control group were statistically significant ($P = 0.002$). The fourth question in IBS-SSS questionnaire asked participants about satisfaction of bowel

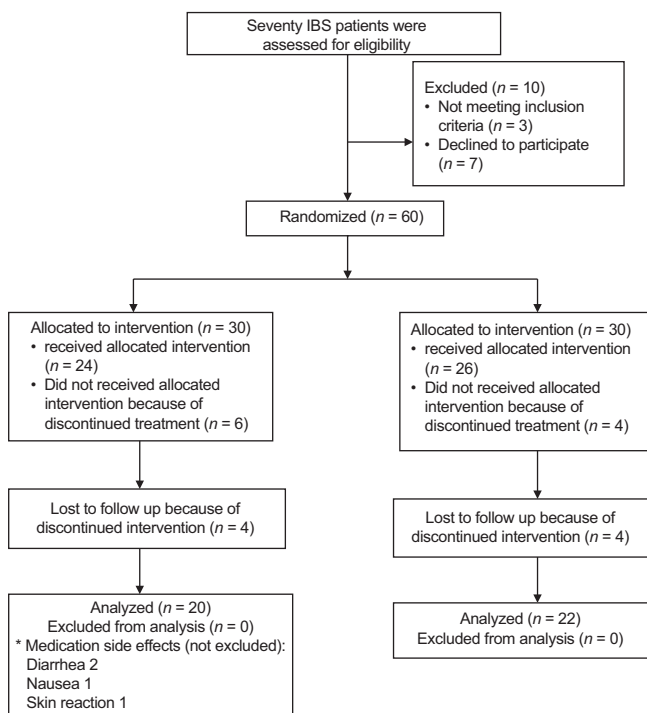


Figure 1: Participants' retention vs. attrition

Table 1: Side effects were detected in patients

Side effects	Number of patients
Diarrhea	2
Nausea	1
Skin reaction	1 (itching)

Table 2: Basic characteristic of study participants

Variables	Case group (%)	Control group (%)	P
Age	36.2±10.88	41.13±12.61	0.01
Sex			
Male	55.4	72.8	0.023
Female	44.6	27.2	
Education			
Under diploma	50	54.3	0.33
Diploma	24.3	21	
Above diploma	16.2	8.6	
Master	9.5	16	
IBS type			
IBS-M	73	67.9	0.51
IBS-C	23	22.2	
IBS-D	4.1	8.6	
IBS-U	0	1.2	

IBS = Irritable bowel syndrome

habits ranged from 0 to 100. In both case and control groups, mean score decreased after intervention and increased 2 months after finishing interventions, but these changes were not statistically significant, but differences between two groups were statistically remarkable ($P = 0.13, 0.16,$ and <0.001). The last question in questionnaire was about the effects of IBS in QOL scored from 0 to 100. The mean score was decreased in case group in both time periods but not significantly although it increased in control group ($P = 0.88$ and 0.66) and differences between case and controls were not statistically significant ($P = 0.29$). The mean score of variables in IBS-SSS questionnaire in case and control groups is shown in Table 3 in details.

HADS questionnaire has seven questions about depression and seven questions about anxiety. Each question has four items and scored from 0 to 3. The mean score of depression in cases decreased after two time periods significantly and decreased a little in control group but not significantly and changes in mean score of depression between both case and controls were statistically significant ($P < 0.001, 0.31,$

and <0.001). The mean score of anxiety decreased in cases and increased in controls but not significantly although alteration in anxiety score between case and controls was statistically remarkable ($P = 1.0, 1.0,$ and 0.03). The mean score of depression and anxiety in case and control group is shown in Table 3 in details.

According to the remarkable gender distribution in case and control groups, all variables evaluated in both gender groups separately. The changes in the mean score of abdominal pain severity, alteration of abdominal pain frequency, and mean score of bloating severity were statistically significant in women but not in men (P values in women $< 0.001, <0.001,$ and 0.008 and in men $= 0.27, 0.11,$ and 0.27). The changes in patients' satisfaction of their bowel habits were statistically significant in both men and women between case and control groups ($P < 0.001$ and 0.012). The changes in QOL score between case and controls were significant in men although it was not significant in women ($P = 0.01$ and 0.18). The alteration in mean score of depression between case and controls was statistically significant in women and men ($P < 0.001$ and 0.005) and changes in anxiety score were not statistically significant in both men and women ($P = 0.10$ and 0.62). The mean score of variables in case and control groups in both gender and their P values is shown in Table 4.

Table 3: The mean score of variables in irritable bowel syndrome-severity scoring system questionnaire and anxiety and depression in case and control groups

Variables	Time	Mean score		P
		Case group	Control group	
Abdominal pain severity	At the beginning	54.5±21.18	52.57±17.00	0.001
	After 1 month	32.29±17.56	49.61±12.56	
	After 3 months	29.25±14.53	51.59±13.92	
	P	<0.001	0.81	
Abdominal pain frequency	At the beginning	6.2±2.98	5.42±2.07	0.01
	After 1 month	4.25±2.84	5.80±2.20	
	After 3 months	2.75±2.02	5.68±2.00	
	P	<0.001	0.614	
Bloating severity	At the beginning	61.43±28.7	53.18±15.09	0.002
	After 1 month	40.20±224.20	57.11±17.44	
	After 3 months	24.25±19.28	54.31±17.68	
	P	<0.001	1.0	
Satisfaction of bowel habits	At the beginning	55.16±22.94	43.03±17.36	<0.001
	After 1 month	54.58±26.08	46.15±16.92	
	After 3 months	64.5±19.80	49.31±15.83	
	P	0.13	0.16	
QOL	At the beginning	58.66±23.11	47.96±20.27	0.29
	After 1 month	55.41±24.17	52.69±18.72	
	After 3 months	54.0±27.93	58.18±18.16	
	P	0.88	0.66	
Anxiety	At the beginning	19.36±2.48	18.54±2.69	0.03
	After 1 month	16.5±3.40	18.84±2.73	
	After 3 months	15.55±4.63	18.77±3.13	
	P	>0.99	>0.99	
Depression	At the beginning	17.46±2.62	18.0±3.04	<0.001
	After 1 month	14.41±4.16	18.0±2.09	
	After 3 months	12.5±2.98	17.22±2.50	
	P	<0.001	0.31	

QOL = Quality of life

DISCUSSION

This study was developed in patients with IBS to evaluate the effects of herbal medication on IBS symptom severity, depression, and anxiety. This study showed the positive effects of this herbal medication on IBS symptom severity special in women and on depression and anxiety. This study had a limitation that gender distribution in case and control groups was different that affected our findings. To conquer this problem, we used fixed analysis and evaluated variables in both case and control in different genders.

Our finding in this study demonstrated that herbal medication can decrease the severity of IBS symptoms in patients with IBS. Compare to control group which administered placebo, using herbal medication had positive effects in abdominal pain severity and frequency, bloating, and satisfaction of bowel habits. It also showed that this drug increased QOL in patients, but it was not statistically significant. It may be due to this fact that participants did not really understand the exact meaning of QOL and it is better to explain QOL and all aspects of it for patients in further researches. The herbal medication contains *B. carterii*, *Z. officinale*, and *A. millefolium* that each one had effect in IBS symptoms. Studies reported that *A. millefolium* is one of the plants used in folk medicine for gastrointestinal disorders.^[21,22] In Brazil, the main indication

Table 4: The mean score of variables in case and control groups in both gender and their P-values

Variables	Gender	Time	Case group	Control group	P
Abdominal pain severity	Male	At the beginning	70.31±14.07	49.79±15.28	0.27
		After 1 month	40.35±17.59	49.21±11.75	
		After 3 months	29.54±15.24	51.25±14.08	
		P	<0.001	0.77	
	Female	At the beginning	36.42±10.60	60.00±20.00	<0.001
		After 3 months	28.88±14.52	52.50±14.74	
Abdominal pain frequency	Male	At the beginning	8.62±1.36	5.58±2.16	0.11
		After 1 month	5.64±2.92	5.68±2.28	
		After 3 months	3.36±2.57	6.0±2.19	
		P	<0.001	0.56	
	Female	At the beginning	3.57±1.74	5.0±1.87	<0.001
		After 3 months	2.0±0.5	4.8±1.16	
Bloating severity	Male	At the beginning	70.18±30.50	53.12±12.66	0.27
		After 1 month	47.5±27.57	57.63±15.66	
		After 3 months	29.54±21.90	52.81±15.8	
		P	<0.001	0.86	
	Female	At the beginning	51.42±23.73	53.33±23.45	0.008
		After 3 months	17.77±13.94	58.33±23.16	
Satisfaction of bowel habits	Male	At the beginning	64.68±23.69	46.45±16.84	<0.001
		After 1 month	63.57±23.48	45.52±17.86	
		After 3 months	66.36±19.11	50.31±13.35	
		P	0.83	0.42	
	Female	At the beginning	44.28±16.96	33.88±16.15	0.012
		After 3 months	62.22±21.66	46.66±22.50	
QOL	Male	At the beginning	63.12±24.07	45.54±17.70	0.01
		After 1 month	63.21±21.44	46.84±15.38	
		After 3 months	57.72±30.11	51.56±14.68	
		P	0.67	0.24	
	Female	At the beginning	53.57±21.69	54.44±26.03	0.18
		After 3 months	49.44±26.03	75.83±14.97	
Anxiety	Male	At the beginning	19.43±2.06	18.66±2.76	0.10
		After 1 month	17.0±3.92	19.21±2.93	
		After 3 months	15.54±5.04	19.43±2.92	
		P	0.027	1.0	
	Female	At the beginning	19.28±2.97	18.22±2.63	0.62
		After 3 months	15.55±4.39	17±3.22	
Depression	Male	At the beginning	18.62±2.55	18.25±3.11	0.005
		After 1 month	15.14±4.84	17.78±2.25	
		After 3 months	12.54±3.67	17.5±2.63	
		P	<0.001	0.41	
	Female	At the beginning	16.14±2.07	17.33±2.91	<0.001
		After 3 months	12.44±2.06	16.5±2.16	
		P	0.072	0.40	

QOL = Quality of life

for using this plant is having pain, ulcer, inflammation, and gastrointestinal complications.^[23,24] Studies on IBS patients showed that there are levels of immune system activation in IBS patients without considering type of IBS or recurrent infections.^[25] Components which target immune system are a favorable item for treating some parts of gastrointestinal pathologies.^[16,26] Chinese studies demonstrated that herbal medicine, which has positive effects on IBS symptoms, had anti-inflammatory effects on innate immune cells and inhibits cytokine production stimulated by inflammatory mediators.^[16] The intestine has some parts of immune system, and mucus is the first part contact with pathogenic organisms, and immune dysregulation causes inflammatory pathogenesis although intestine homeostasis is under controlled.^[27,28] Other studies reported that, in IBS patients, getting biopsy from their intestine mucus showed the increasing in pro-inflammatory agents and decreasing in anti-inflammatory cytokines in their biopsies and also in peripheral blood mononuclear cell and circulation.^[26,29] In addition, in other studies increasing in immune cell infiltration and abnormal activity of B-cell and T-cell was seen in IBS patients.^[30,31] *A. millefolium* had anti-inflammatory effects and also antibacterial effects, and some similar studies showed the anti-inflammatory effects of this plant in acute phase of inflammations.^[32,33] *A. millefolium* had anti-inflammatory, anti-pain, and antioxidative effects in acute phase of inflammations^[34] which showed may be this component had positive effects in IBS because of inflammatory pathology of IBS. *Z. officinale* is another component of MemoGut capsules that have antioxidant agents.^[35,36] Studies on this plant showed the anti-inflammatory and antibacterial and antifungal effects for *Z. officinale* which activated immune systems.^[37,38] *In vitro* studies demonstrated that this plant is an agent for gathering peroxynitrite and adjusting pathologic situation causes by oxidation productions and it also can inhibit free radicals action during inflammation.^[39,40] *B. carterii* is the last component of herbal medication which has anti-inflammatory and anti-pain effects and it also is effective in elimination inflammatory pains.^[41] In animal studies, *B. carterii* had anti-inflammatory and antihyperalgesia effects.^[42] Other studies showed that this plant inhibits production of groups of leukoterian in inflammatory process of disease, and in gastrointestinal studies, *B. carterii* decreased gastrointestinal symptoms in IBS patients' special bloating.^[43] Due to some inflammatory parts in IBS pathogenesis, the effects of herbal medication in IBS symptom in this study are explainable. Herbal medication has three components which all of them had anti-inflammatory effects, and due to the inflammatory pathogenesis of IBS, these components had positive effects in eliminating IBS symptom severity. For further researches, it is better to evaluate IBS patients with greater sample size and using these plants separately to identify the exact effects

of each herbal medication. The effects of herbal medication in most of IBS symptom severity were higher in women than men in this study. Maybe it is because of the higher prevalence of IBS in women and also higher severity of symptom in women than men.^[44] For further researches, it is better to evaluate women and men in separate groups with similar sample size and controlling other factors influencing study.

Our findings in this study showed that using herbal medication can improve depression and anxiety in patients with IBS. Comparing the effects of this drug on anxiety and depression in men and women separately showed that, in men and women, this drug has significant effects in mean depression scores and changing in anxiety based on gender was not statistically significant. The effects of herbal medication on depression and anxiety are due to its components. Studies showed that using decoction of aerial part of *A. millefolium* used for calmness.^[45] In another animal studies, this plant had anxiolytic effects that activating by nonbenzodiazepine gamma-aminobutyric acid (GABA) mechanism which showed the differences of this plant with benzodiazepine drugs. This study also showed that the extract of this plant did not cause intolerance after frequent uses.^[13] In other studies in diabetic mice, using *Z. officinale* decreased depression symptoms.^[46] Studies showed that, in depressed patients, the level of GABA in 10% lower than healthy individuals and the concentration of it in cerebrospinal fluid have an inverse relationship with depression severity.^[47] Studies showed that *Z. officinale* increased releasing of serotonin, norepinephrine and GABA which caused decreasing depression symptoms.^[48] The effects of herbal medication decreasing depression and anxiety are maybe to the effects of herbal medication components, and it is also due to the placebo effects in depressed and anxious patients. For further researches, it is better to evaluate the effects of these components separately on depression and anxiety symptoms.

CONCLUSION

According to the findings, the pathophysiology of IBS is multifactorial including visceral hypersensitivity, abnormal gut motility, intestinal microbiota, inflammatory and immune disturbance, psychosocial factors, intestinal infections, central nervous system, and serotonin.^[18] This disorder has different types of treatment, but involvement of different factors in pathophysiology of IBS makes its treatment more complex.^[49] This research project was the first study, in which our triple herbal formula was used and we cannot compare our findings with other studies. Due to the disappointed results in treatment of IBS symptoms with conventional treatment, using alternative and complementary medicine is a favorable choice for

decreasing IBS symptom severity and improving depression and anxiety in IBS patients.

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Conflicts of interest

There are no conflicts of interest.

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