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Original Article

A double-blind randomized clinical trial of *Dracocephalum kotschyi* Boiss. in the patients with diarrhea-predominant irritable bowel syndrome

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Abstract

Background and purpose: Irritable bowel syndrome (IBS) is a disease that shows its impacts on many populations worldwide. It is known as a functional disorder of the gastrointestinal tract followed by diarrhea and fecal inconsistency. Due to the lack of treatment in the allopathic medicine system for IBS, people in the western world use different herbs as alternative medicine. In the present study, we evaluated the dried extract of *Dracocephalum kotschyi* against IBS.

Experimental approach*:* In a randomized, double-blinded, placebo-controlled clinical trial, 76 diarrhea-predominant IBS patients were randomly assigned to two equal groups: the control group (given the placebo capsule containing 250 mg of dibasic calcium phosphate) and the treatment groups (given the capsule containing 75 mg of the dry extract of *D. kotschyi* and 175 mg of dibasic calcium phosphate as filler). The study was conducted based on Rome III criteria. We studied symptoms included in Rome III criteria and divided the study into the duration of drug administration and four weeks after drug administration. These groups were compared with those of the control group.

Findings/Results*:* Significant improvements were found in the quality of life, temperament, and IBS symptoms throughout the treatment duration. Quality of life, temperature, and IBS symptoms were slightly decreased in the treatment group 4 weeks after stopping the treatment. While concluding the study, we found *D. kotschyi* effective against IBS.

Conclusion and implications*:* Whole extract of *D. kotschyi* modulated symptoms of IBS patients and improved their quality of life.

Keywords: Diarrhea; *Dracocephalum kotschyi;* Irritable bowel syndrome; Persian medicine; Randomized controlled trial; ROME criteria.

INTRODUCTION

Irritable bowel syndrome (IBS) is considered a chronic intestinal disorder. It is clinically associated and characterized by abdominal pain followed by defecation, diarrhea, and constipation due to the absence of biochemical or organic alterations (1). The symptomatic conditions show their adverse effects on the entire gastrointestinal tract, such as recurrent discomfort and abdominal pain.

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Minor alterations are seen in the intestine (2). It affects 10 to 15% of the total population in the western world and is known as one of the most disturbing conditions of the gastrointestinal tract. It is a nosological entity that affects women in their 30 to 39 and 50 to 59 (2). IBS has complex pathophysiology with several responsible factors such as environmental, psychological, and genetic factors. IBS has been adequately identified by having three causes: dysregulation of serotonin, the role of responsible bacterial flora, and visceral hypersensitivity (3). Hypersensitivity of the rectum is identified in 95% of cases of IBS. This hypersensitivity can be due to the affected coliform, lactobacilli, and bifidobacteria (3). These factors play a significant role in increasing the risk of IBS. The variable pathogenic mechanisms of IBS include dysregulation in the axis of bowel-brain, visceral hypertension, food intolerance, dysbiosis, increased permeability of the intestine, intestinal immune activation, and motility disorders. Treatment of IBS focuses on lifestyle modifications and relieving IBS-related symptoms based on the predominant symptoms such as fiber supplements, laxatives, anti-diarrheal medications, anticholinergics medications, pain medications, and antidepressants (1,4). In the present environmental conditions prone to new emerging diseases, effective treatment for IBS is not available in modern medicine. Therefore, 80% of the total affected population in developing countries choose complementary medicines for IBS; they choose herbs to cure IBS (5,6).

In the present study, we used a well-known Iranian herb *Dracocephalum kotschyi* whole plant as our study material. *D. kotschy* named zarrin-giah in Persian from the Lamiaceae family grows wild in elevations in central parts of Iran (7). It is also known as "Dragonhead" and has been traditionally used against several infectious diseases. This plant is well-known for its antifungal, antibacterial, anti-inflammatory (8), analgesic (9), antioxidant (10,11), immunomodulatory, antihyperlipidemic (11), antinociceptive (10), anticancerous (10), and anticholinergic properties (11). Antispasmodic and analgesic effects of *D. kotschyi* were reported on rat ileum contractions (8-11). It has been reported in Iranian traditional medicine for the treatment of intestinal gastrointestinal disorders and as an antispasmodic drug (12). Sadraei and coworkers recently reported the antidiarrhea properties of its hydroalcoholic extract induced by castor oil in mice (12). They also reported its anti-inflammatory properties on acetic acid-induced colitis in rats (13). Another study has shown potent antispasmodic effects on ileum contractions induced by KCl, neural, and acetylcholine in isolated ileum of rats (10). So far, there is no clinical report about *D. kotschyi* extract in gastrointestinal disorders. Therefore, the present study is an endeavor to evaluate the effectiveness of *D. kotschyi* against IBS in patients aged 18 to 50 years in Isfahan city.

MATERIALS AND METHODS

Sample collection and identification of the plant material

Aerial parts of *D. kotschyi* in flowering time were collected in summer from the mountains around Semirom in the Isfahan province of Iran. It was identified and compared with a voucher specimen of the plant (SAM: 1519) deposited in the Samsam-Shariat herbarium of the Faculty of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences. The plant sample was further sent to the Department of Pharmaceutical Sciences Research Centre of Isfahan University of Medical Sciences for drug preparation. Dried plant material (10 kg) was macerated with 40 L of ethanol:water (70:30) for five days, three times at room temperature. Collected extracts were filtered and concentrated at reduced pressure (10 mbar) by a rotary evaporator at 40 °C. A drug assay was done based on the rosmarinic acid (14) as one of the ingredients of *D. kotschyi*, possessing anti-inflammatory properties (14,15). Each capsule containing 75 mg of the dry extract of *D. kotschyi* and 175 mg of dibasic calcium phosphate as filler contained 160.64 ± 9.9.3 μg of rosmarinic acid (Fig. 1).

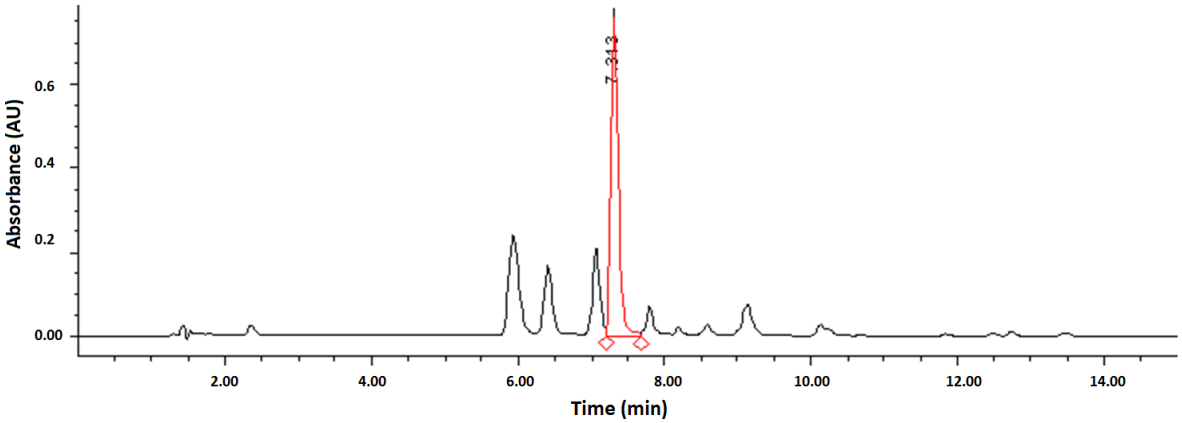

Fig. 1. High-performance liquid chromatogram of capsule formulation containing 75 mg extract of *Dracocephalum kotschyi*. It was taken at 328 nm on a L1 column (150 mm × 3.9 mm, 4 µm) using CH_3CN:H_2O:H_3PO_4 (54.5:445:0.5) as A and CH_3CN:H_2O:H_3PO_4 (345.5:150:0.5) as B started with A:B (100:0) for 2 min, followed with a gradient of 0-100% B in 12 min (40 °C, 1 mL/min). Rosmarinic acid was eluted at 7.313 min.

In the present study, a double-blind clinical randomized trial was conducted. Randomization in the mentioned groups will be conducted according to permuted block randomization based on quaternary blocks. We conducted the study on 76 patients (n = 76), 18-50 years old, with the absence of abnormal colonoscopic examination results admitted to the Gastroenterology Research Center affiliated with Isfahan University of Medical Sciences. According to the criteria of Rome III and the diagnosis of a gastroenterologist, they had moderate to severe IBS. Patients were re-evaluated to participate in the study based on the definition of criterion, history, CBC, CPR, and S/E tests. All the eligible study participants were informed, and their consent was taken. The study protocol received the approval of the Ethical Committee of the Isfahan University of Medical Sciences, Isfahan, Iran (IRCT registration number: IRCT20180823040854N1).

The patients provided their basic details, such as their age, gender, marital status, and education. Later, they were asked to fill out the Rome III-based IBS questionnaire. The information collected from all the study participants was categorized based on IBS symptoms. They were placed next to each other to minimize the probability of all kinds of errors. All participants included in the study complained of having diarrhea of moderate severity of IBS (mean score based on the IBS severity index: 17.5-30).

Inclusion and exclusion criteria

Patients included in the study had IBS based on Rome III criteria. All the participants were diagnosed and confirmed by a gastroenterologist. They had severe IBS and predominant diarrhea and had a routine colonoscopy with clinical and paraclinical evidence of a complete absence of bowel cancer and another differential diagnosis. They were psychologically fit. These patients were not taking any other medicine for the treatment of IBS. Patients who were incapable of following the prescription, those diagnosed with any mental disorder during the study, those who became pregnant, and those reluctant to continue reading were excluded from the study.

Sampling method

in the present study, consecutive or sequential sampling was done. The subject selection was conducted among the patients referred to the outpatient department (OPD) of the Gastroenterology Research Centre in Isfahan. All the patients were diagnosed and confirmed to have IBS.

Data collection method

In the present study, data collection was done based on the questionnaire. The tools provided in the questionnaire focus on the quality of life of the IBS patient (IBS-QOL) (14), a severity index based on the symptoms of IBS, and a temperament checklist. A demographic questionnaire was based on essential information such as gender, age, education, marital status, and disease prognosis. The IBS-QOL questionnaire, IBS

severity index, and temperament checklist of the patients were assessed at baseline and at the end of weeks 4 and 8. The IBS-QOL questionnaire contains 34 items with a 5-point Likert scale belonging to eight specific areas related to the study, such as boredom, activity interference, body image, concern with the health of the patient, avoidance, eating habits of the participants, their social reactions, sexual issues faced by them, and communication issues (16). Studied items were scored from 0 to 100 in 10 min, and the participants did the scoring. The participants were from three different countries France, Italy, and the UK. Based on the culture and lifestyles of different countries, minute changes were made to the standard questionnaire, followed by internal validation (17). The first part of the questionnaire was generalized, whereas the second part was focused on the IBS-SS severity index. The questionnaire consists of defecation, pain, bloating, the effect of IBS on daily life, and extraintestinal symptoms with the IBS-SS severity index. Scoring was done from 0 to 10 points, where the total score was 50. Points were categorized into three different ranges mild, moderate, and severe. A mild IBS was scored between 7.5 to 17.5, moderate was scored from 17.5 to 30, and severe was scored with more than 30 points (17).

Capsule formulation preparation

A capsule formulation containing plant extract was prepared by wet granulation. The *D. kotschyi* was placed in 250-mg capsules containing 75 mg of the dry extract of the herb and 175 mg of dibasic calcium phosphate as filler. The placebo contained only 250 mg of dibasic calcium phosphate and was placed in similar capsules. Dibasic calcium phosphate is an inert filler usually suggested in placebo formulations. Their packages of capsules were identical in shape, colour, size, and fragrance. The patients consumed a capsule three times per day (before breakfast, lunch, and dinner) for four weeks and were followed up until the end of eight weeks.

Statistical analysis

An independent T-test and a Chi-square were used to ensure the similarity of the study groups due to random allocation. To evaluate the effects of group and time in the present study, a repeated measures analysis of variance (ANOVA) was used. M-Box tests were used to evaluate the homogeneity of the variance. For the analysis, SPSS software version 24 was used (SPSS crop, Chicago, IL, USA). Besides, descriptive statistics were used to answer the questions, and also, ANOVA tests with repetition of observations were used to test the study hypotheses.

RESULTS

In total, 137 patients who attended the clinic were assessed for eligibility, and 101 of them were randomized to receive either the *D. kotschyi* (52 patients) or placebo (49 patients). Twenty-five patients dropped out during the four-week study duration; fourteen and eleven patients were withdrawn from the study in the intervention and control groups, respectively. Among the total studied patients, the drop rate was 20%. After excluding the dropped patients, the total number of patients was divided into two equal groups of 38 each (Fig. 2).

No significant differences were seen in any demographic characteristics between the two groups (Table 1).

Table 1. Characteristics of individuals

Variables	Drug group	Control group	*P*-values
Age (year, mean ± SD)	38 ± 11	36 ± 7	0.195
Sex (frequency%)			
Male	16 (42.1)	18 (47.4)	0.645
Female	22 (57.9)	20 (52.6)	
Education (frequency%)			
Low education	4 (10.5)	0	0.008
Educated	34 (87.2)	38 (100)	
Marital status (frequency%)			
Single	11 (28.9)	15 (39.5)	
Married	27 (71.1)	19 (50)	0.104
Divorced	0	3 (7.9)	
Widow	0	1 (2.6)	

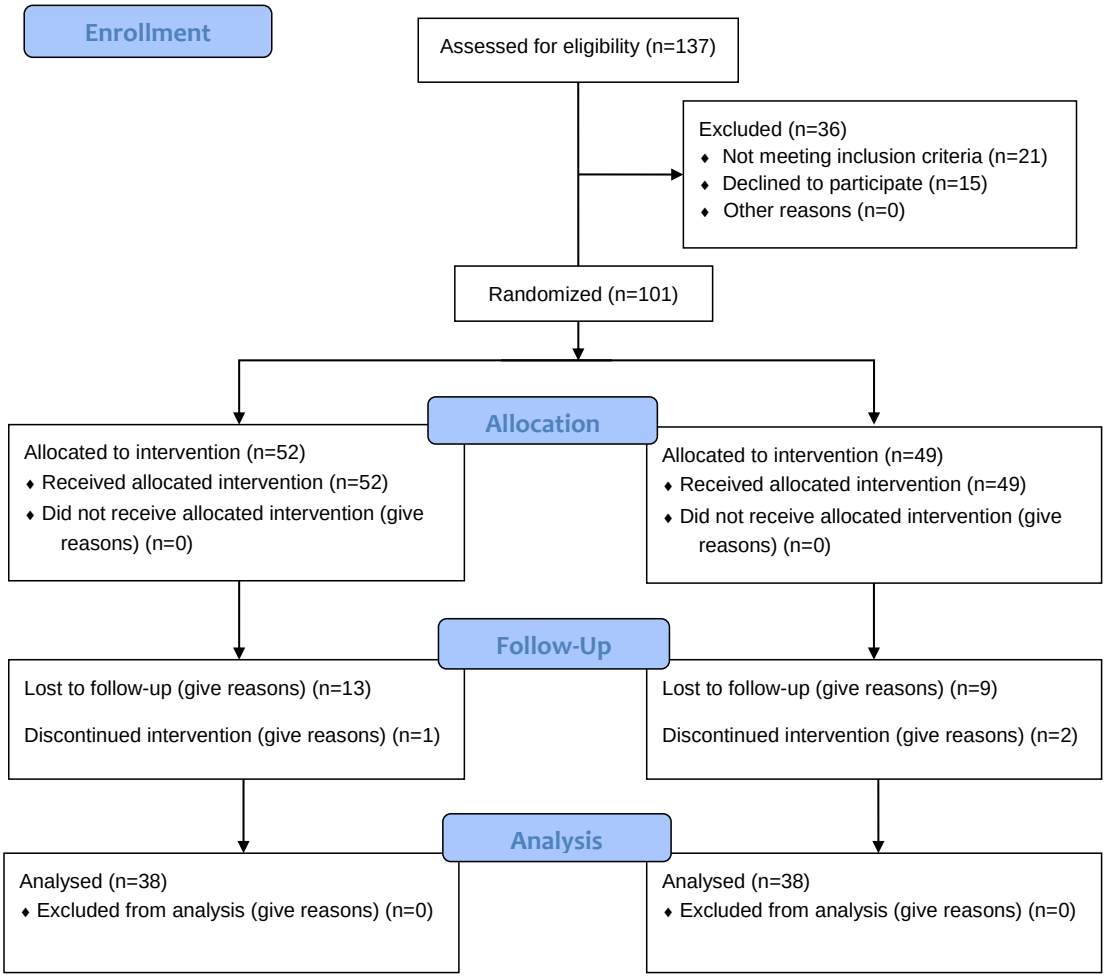

Fig. 2. CONSORT flowchart of study presenting a general scheme of the trail, number of recruited patients, dropouts, and accomplished cases

The test on intergroup analysis to evaluate the effect of "group (drug)" showed that there is a difference between the two groups in terms of the mean score of QOL in none of the areas of boredom, body image, health concerns, avoidance of eating, or social reaction (Table 2). There are no communication issues and the average QOL score (Fig. 3).

The mean score of these indicators was the same in both the intervention groups (*D. kotschyi* extract) and the control group. However, there was a significant difference between the two groups in the mean score of the severity of irritable bowel symptoms and QOL in the areas of interference with activity and sexual issues (Table 3). The mean score of activity interference in the drug group was lower than in the control group (Table 3).

The mean score of sexual problems in the drug group was 4.5, and in the control group, it was 5.6. Also, the mean score of the variable severity of irritable bowel symptoms was lower in the drug group than in the control group (Fig. 3). This means that interference with activity, sexual problems, and the severity of irritable bowel symptoms are significantly lower in the drug group (*D. kotschyi* extract) than in the control group.

The results of the intragroup analysis to examine the changes in mean indicators at different times of measurement (baseline and at the end of weeks 4 and 8) showed that the mean score of temperament variables, the severity of symptoms of IBS, QOL in general, and in all areas between measurement times was significantly different (Table 2).

Table 2. Mean quality of life score in all areas at the time of measurement in the intervention and control groups.

Variable	Time	Treatment group (Mean ± SD)	Control group (Mean ± SD)	*P*-value (Intra-group)	*P*-value (Inter-group)	Drug group *P*-value (Intra-group)	drug group *P*-value (Inter-group)
Dysphoria	Before treatment	23 ± 6	22 ± 4	< 0.001	0.110	< 0.001	0.018
	4 weeks after treatment	17 ± 5	22 ± 6				
	4 weeks after stopping the drug	22 ± 5	23 ± 5				
Interference with activity	Before treatment	22 ± 5	23 ± 4	< 0.001	0.011	< 0.001	0.001
	4 weeks after treatment	17 ± 5	22 ± 4				
	4 weeks after stopping the drug	20 ± 5	23 ± 5				
Body image	Before treatment	11 ± 3	10 ± 3	< 0.001	0.084*	< 0.001	0.014
	4 weeks after treatment	8 ± 2	10 ± 2				
	4 weeks after stopping the drug	11 ± 3	11 ± 3				
Health worry	Before treatment	10 ± 3	10 ± 2	< 0.001	0.124	< 0.001	0.965
	4 weeks after treatment	8 ± 2	10 ± 2				
	4 weeks after stopping the drug	10 ± 3	10 ± 2				
Food avoidance	Before treatment	8 ± 2	7 ± 1	< 0.001	0.099	< 0.001	0.016
	4 weeks after treatment	6 ± 2	7 ± 1				
	4 weeks after stopping the drug	7 ± 2	7 ± 1				
Social reaction	Before treatment	10 ± 3	9 ± 3	0.001	0.958	< 0.001	0.091
	4 weeks after treatment	9 ± 3	10 ± 3				
	4 weeks after stopping the drug	10 ± 3	10 ± 3				
Sexual concerns	Before treatment	5 ± 2	6 ± 2	< 0.001	0.01	< 0.001	0.091
	4 weeks after treatment	4 ± 2	5 ± 2				
	4 weeks after stopping the drug	5 ± 2	6 ± 2				
Relationships issues	Before treatment	12 ± 3	11 ± 2	< 0.001	0.543	< 0.001	0.059
	4 weeks after treatment	9 ± 2	11 ± 2				
	4 weeks after stopping the drug	11 ± 3	11 ± 2				
Quality of Life	Before treatment	101 ± 20	98 ± 15	< 0.001	0.056*	< 0.001	0.022
	4 weeks after treatment	78 ± 17	96 ± 17				
	4 weeks after stopping the drug	95 ± 19	103 ± 17				
Temperament	Before treatment	65 ± 9	64 ± 7	< 0.001	0.472	< 0.001	0.001
	4 weeks after treatment	59.6 ± 8.5	63.8 ± 7.9				
	4 weeks after stopping the drug	66.4 ± 9.2	67.3 ± 7.9				
Irritable bowel syndrome	Before treatment	375 ± 81	390 ± 75	< 0.001	< 0.001	< 0.001	0.001
	4 weeks after treatment	282 ± 71	394 ± 86				
	4 weeks after stopping the drug	336 ± 68	407 ± 78				

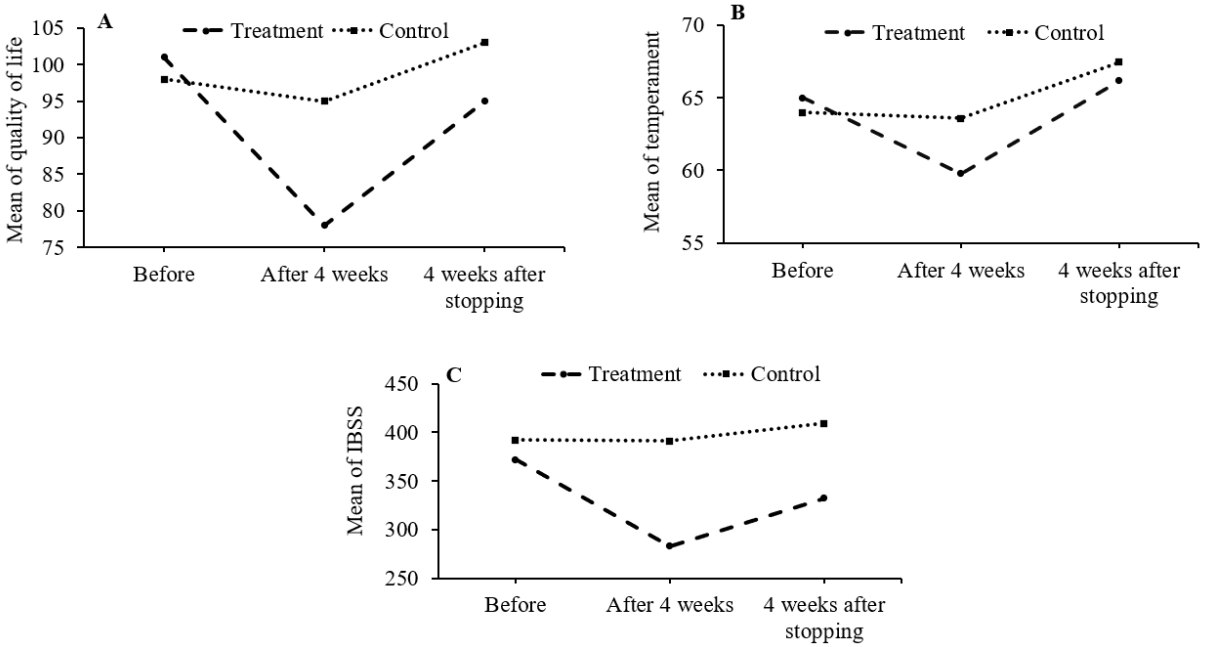

Fig. 3. (A) Score of irritable bowel syndrome quality of life; (B) temperament score; and (C) IBSSS syndrome with activity among the control and treatment group before treatment, after 4 weeks of the treatment, and 4 weeks after stopping the treatment. IBSSS, Irritable bowel symptom severity scale.

Table 3. The difference in the mean score of quality of life in all areas between the measurement times.

Variable	Time	Treatment group	Control group	Treatment group changes (%)	Control group changes (%)	Difference changes	*P*-value
Dysphoria	Before treatment 4 weeks after treatment	6 ± 1.3	0 ± 1.2	26%	0%	26%	< 0.001
Interference with activity	Before treatment 4 weeks after treatment	3 ± 0.58	1 ± 0.93	23%	4%	19%	< 0.001
Body image	Before treatment 4 weeks after treatment	5 ± 1.1	2±0.59	27%	0%	27%	< 0.001
Health worry	Before treatment 4 weeks after treatment	2 ± 0.58	0 ± 0.46	20%	0%	20%	< 0.001
Food avoidance	Before treatment 4 weeks after treatment	2 ± 0.45	0 ± 0.23	25%	0%	25%	<0.001
Social reaction	Before treatment 4 weeks after treatment	1 ± 0.68	-1 ± 0.70	10%	11%	-1%	< 0.001
Sexual concerns	Before treatment 4 weeks after treatment	1 ± 0.45	1 ± 0.46	20%	17%	3%	0.017
Relationships issues	Before treatment 4 weeks after treatment	3 ± 0.58	0 ± 0.46	25%	0%	25%	< 0.001
Quality of life	Before treatment 4 weeks after treatment	23 ± 4.2	2 ± 3.7	23%	2%	21%	< 0.001
Temperament	Before treatment 4 weeks after treatment	5.4 ± 2	1.7 ± 0.2	8%	0%	8%	< 0.001
Irritable bowel syndrome	Before treatment 4 weeks after treatment	93 ± 17.2	18.8 ± 4	25%	1%	24%	< 0.001

The results showed that the mean scores of temperament variables, the severity of symptoms of IBS, and QOL scores in all areas were significantly different between times one and two (i.e., before treatment and four weeks after treatment). It was observed at time 3 (i.e., four weeks after receiving treatment and four weeks after stopping treatment) (Table 2).

Table 4. The comparison among the number and proportion of the patients reveals an improvement of 50 points from their initial scores.

Name	Points	Treatment group		Control group		*P*-value
		Number	**Number% (95%CI)**	**Number**	**Number% (95%CI)**	
IBS-SSS	< 50	9	24.3 (12.8-39.7)	28	75.7 (60.3-87.2)	< 0.001
	≥ 50	28	77.8 (62.4-88.9)	8	22.2 (11.1-37.6)	

IBSSS, Irritable bowel symptom severity scale.

Table 5. The comparison among the number and proportion of the patients with lower severity rates.

IBSSS class	**Control group Number** (%)	**Treatment group Number** (%)	***P*-value**
IBSSS class decrement	3 (8.3)	17 (45.9)	< 0.001
IBSSS class non-decrement	33 (91.7)	20 (54.1)	

IBSSS, Irritable bowel symptom severity scale.

Considering the significance of the effect of group and time, it can be said that the score changes of these indicators over time depend on the type of group. By looking at the averages and graphs, it can be seen that the QOL score in all areas before receiving treatment in both drug and control groups was the same, with only one point difference. However, the scores of these indicators decreased significantly four weeks after receiving treatment in the drug group, but in the control group did not differ from the time before receiving treatment.

Also, the QOL score in all areas increased again in the intervention group (*D. kotschyi* extract) four weeks after cessation of treatment in the control group, which was either unchanged or significantly increased. The QOL score in all areas had the highest decrease at four weeks after receiving treatment in the intervention group (*D. kotschyi* extract).

The above graph reveals the effect of the *D. kotschyi* drug on the treatment group, which showed a rapid decrease in IBS symptoms after four weeks of treatment compared to the control group (Fig. 3). Rapid changes were seen in QOL. Before and after treatment, the patients did not affect their QOL in the control group. While decreased QOL was seen in the treatment group after four weeks of stopping the drug, it was comparatively less than in the control group, before and after treatment (Fig. 3B). The temperament remains unaltered in the control group. While the increased temperament was seen in the treatment group after four weeks of stopping the drug, it was comparatively less than in the control group before and after treatment (Fig. 3C); a slight treatment increment was seen in the control group. While decreased IBS symptoms were observed in the treatment group after four weeks of stopping the drug, they were comparatively less than in the control group.

As shown in Table 4, the comparison between the number and proportion of the patients reveals an improvement of 50 points from their initial scores. Also, the comparison between the numbers and proportions of the patients with lower severity rates is shown in Table 5.

DISCUSSION

We evaluated *D. kotschyi* extract against general and specific IBS symptoms in the present study. This study is an endeavor to explore the medicinal properties of *D. kotschyi* because of its anti-inflammatory, antibacterial, antioxidant, and anticholinergic properties. From earlier researchers, it has been reported that IBS does not have any perfect treatment; Iranians use herbal remedies for its treatment. Hence, considering the traditional use of *D. kotschyi* this study aimed to investigate the effect of *D. kotschyi* on relieving symptoms in patients with diarrhea-predominant IBS (18). Plants are commonly used as medicine due to empirical experiments by several ethical groups using common sense; they are used as phytotherapeutics and for designing new drugs (18). These complementary medicines are not considered part of allopathic medicine. Few herbal drugs have potential activity against IBS. It is considered that these alternative medicines

provide 7-15% medicinal benefits in the case of IBS. In Western countries, it has been observed that people are more interested in alternative medicines in place of allopathic medicines for the treatment of IBS (19). A few studies have been published on medicinal herbs for IBS treatment in recent years. For example, the leaf extract of *Cynara scolymus* was studied on 208 patients for two months with IBS. 26.4% of patients showed a reduction in symptoms and intensity of IBS (20).

In 11 patients, thrice a day for 30 days, the arrowroot was potently effective against diarrhea and abdominal pain. In 1990, Ramarao and Bhargava studied ginseng against IBS symptoms (21). For treating IBS symptoms, a mill extract of *Aloe barbadensis* is used (22). *Cumin* extract was studied for IBS treatment and found effective in decreasing IBS symptoms (23). Bordbar *et al.* found the combination of *Trachyspermum ammi* L. (TA), *Zataria multiflora* Boiss (ZM), and *Anethum graveolens* L. (AG) effective in relieving IBS symptoms (24). *Hypericum perforatum* extract was studied on rats against IBS. They incorporated 150, 300, and 450 mg/kg body weight of *Hypericum perforatum* extract into the rat model and found that it minimizes the emptying of the stomach by controlling the factors responsible for IBS. They also reported that this extract diminishes the tumor necrosis factor alpha and inflammatory cells in a dose-dependent manner and affects myeloperoxidase activity; it increases the antioxidant potential of the colon (25). Use of *Zataria multiflora* Boiss in patients suffering from IBS found this herb effective in its treatment (26). Negative results were published. They reported a randomized clinical trial using *Lactobacillus plantarum* 299v on IBS symptoms, and they found it non-effective on the IBS symptoms, including abdominal pain and bloating (27). A placebo control study on IBS symptoms found *Aloe vera* effective in reducing the IBS symptoms and improving QOL (28). Combining Korean herbal medicine Gwakhyangjeonggisan with the combinations of probiotics and found it effective in IBS (29). A review article published by Rahimi and Abdollahi in 2012 provided details of several plants and their doses used against symptoms of IBS (30). They used *Curcuma longa* for eight weeks, *Curcuma xanthorrhiza* for 18 weeks, *Cynara scolymus* leaf extract for six weeks, *Funaria officinalis* whole plants extract for 18 weeks, *Iberis amara* whole plants extract for four weeks, *Maranta arundinaceae* root extract for one month, *Mentha piperata* essence for four weeks, *Paeonia lactiflora* root extract in just a single dose and *Plantago psyllium* seeds for 12 weeks.

Aller *et al.* studied the effect of dietary fibers on IBS symptoms and found that the intake of moderate edible fibers in the diet helps reduce IBS symptoms (31). Another similar study by Bundy *et al.* reported the use of artichoke leaf extract in patients suffering from IBS; they found the extract reduced IBS symptoms (20). At the same time, Daley *et al.* reported that regular exercise effectively reduces the symptoms of IBS (32).

The present study has a few limitations, such as its dependency on Rome III criteria. The Rome III criteria are based on a self-assessment by the participants included in the study. Therefore, follow-up and the proper diagnosis were difficult. The Rome III criteria have few limitations. The Rome IV criteria were designed in 2016 to overcome these limitations, 10 years after the Rome III criteria. The Rome IV criteria are more specific with a meaningful diagnosis of diarrhea-predominant IBS and mixed type IBS, identifying the physiological subgroups meaningfully (28). The Rome IV criteria are based on therapeutic and diagnostic IBS biomarkers designed explicitly for clinical studies (33). Studies based on Rome IV criteria showed severe gastrointestinal symptoms, including lower QOL and increased abdominal pain. Rome IV criteria also work on alterations in fecal incontinence or functional diarrhea, which can't be studied *via* Rome III criteria. A few psychological and gastrointestinal symptoms overlap functional constipation while discussing Rome III criteria and functional diarrhea, whereas these factors can be easily studied in Rome IV criteria. Hence more studies are required on IBS symptoms to explore herbal medicines based on Rome IV criteria.

The present study examined the effects of the herbal drug *D. kotschyi* on patients suffering from IBS. We conducted a randomized, double-

blind clinical trial on 76 patients aged 18 to 50, following Rome III criteria. We asked the participants to fill out the IBS questionnaire, and we divided the participants into the placebo and treatment groups. In the present study, we prepared the capsule from the herbal extract and studied several symptoms of IBS. We evaluated the IBS symptoms such as interference with activity, and sexual problems, and the severity of irritable bowel symptoms was significantly lower in the drug or placebo group. At the same time, QOL was improved in the participants after four weeks of drug administration.

CONCLUSION

D. kotschyi whole plant extract was effective and tolerable in relieving the symptoms of IBS and improving the QOL of patients with IBS. Many of these effects were maintained even 4 weeks after discontinuation of *D. kotschyi* administration.

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Conflicts of interest statement

The authors declared no conflicts of interest in the present study.

Authors' contribution

All authors contributed equally to this work. The final version of the manuscript was approved by all authors.

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