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Comparing the Efficacy of Cumin Sofouf With Mebeverine on Irritable Bowel Syndrome Severity and Quality of Life: A Double-blind Randomized Clinical Trial

Khadijeh Hatami[1], Amir-Hooman Kazemi-Motlagh[1*], Hossein Ajdarkosh[2], Arman Zargaran[3], Mehrdad Karimi[1], Ahmad Reza Shamshiri[4], Mohammad Reza Ghadir[5]

Abstract

Objectives: The treatment of irritable bowel syndrome (IBS) is not curative and is based on patient symptoms. Some herbal medicines have significant effects on IBS symptoms. The present study aimed to assess the efficacy of a recommended drug from Persian medicine (Cumin Sofouf) on the score of IBS symptom severity and the quality of life as a clinical trial compared with mebeverine, which is a commonly used antispasmodic drug for this disorder.

Materials and Methods: In this double-blind randomized clinical trial, eligible patients were allocated to two groups. One group received 200 mg sustain release mebeverine capsule plus placebo sofouf and another group received the sachets of cumin sofouf plus placebo capsule. Cumin sofouf contains the seed powder of *Bunium persicum, Trachyspermum ammi, Foeniculum vulgare,* and *Pimpinella anisum*. Patients were requested to fill IBS-symptom severity score (IBS-SSS) and IBS-quality of life (IBS-QoL) questionnaires at the base and after 4 weeks of treatment.

Results: Data of 40 patients in each group entered the analysis step. Based on the results, IBS-SSS decreased by 120.13 (SD = 66.04) and 70.75 (SD = 50.75) point after 4 weeks in cumin sofouf and mebeverine groups, respectively. in addition, cumin sofouf was statistically more effective than mebeverine, which was also about IBS-SSS substructures. Further, the IBS-QOL score decreased by 17.40 (SD = 13.66) and 8.55 (SD = 6.88) point in sofouf and mebeverine groups, respectively. Finally, cumin sofouf was significantly more effective than mebeverine.

Conclusions: According to the results, cumin sofouf could be recommended as a supplementary remedy for IBS patients.

Keywords: Herbal medicine, Irritable bowel syndrome, IBS-severity score, IBS-quality of life

Introduction

Irritable bowel syndrome (IBS) is characterized by chronic abdominal discomfort or pain in association with altered bowel habits in the absence of detectable histological or biochemical abnormalities. IBS subtypes are diarrhea-predominant, constipation-predominant, and mixed constipation and diarrhea. (1) In addition, IBS is the most common functional gastrointestinal disorder with global prevalence of 11% (2) Its prevalence rate is about 6%-20% in Iran and imposes a high economic burden on the health system (3,4). This disorder reduces the quality of life (QOL) and can induce serious disability (5). Further, it is known that IBS is a heterogeneous disorder with different pathophysiologic mechanisms (6).

Anti-cholinergic and anti-spasmodic agents are common prescriptions, along with symptom therapy for the abdominal pain of IBS patients (7). Mebeverine is one of the commonly used antispasmodic drugs for the treatment of IBS in Iran. Furthermore, mebeverine hydrochloride is a sodium channel antagonist with a direct effect on the smooth muscle of the gastrointestinal tract, relieving spasm without affecting normal gut motility (8).

There is no complete cure for IBS because of its unknown etiology and current pharmacological treatment only reduces the symptoms and could not remove the basic pathology. (9, 10). Therefore, finding new treatments for IBS is always welcomed. On the other hand, using complementary and alternative medicine as the symptom relief is common among patients who suffer IBS (11).

There are many traditional systems of medicine like Persian medicine, Chinese medicine, Ayurveda, homeopathy, and the like. (12) Among these traditional medicines, Persian medicine is one of the oldest one dating back to at least 7000 years ago. This traditional system of medicine is based on four elements and has a holistic approach to the body and treatment. (13)

Moreover, IBS is completely described in the Persian Medicine books and manuscripts as a disease called "*Maghs*"(14). Cumin sofouf is one of the recommended drugs for *Maghs* in Persian Medicine documents, which

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[1]Department of Traditional Medicine, School of Persian Medicine, Tehran University of Medical Sciences, Tehran, Iran. [2]Gastrointestinal and Liver Disease Research Center, Iran University of Medical Sciences, Tehran, Iran. [3]Department of Traditional Pharmacy, School of Persian Medicine, Tehran University of Medical Sciences, Tehran, Iran. [4]Community Oral Health Department, School of Dentistry, Tehran University of Medical Sciences, Tehran, Iran. [5]Gastroenterology and Hepatology Research Center, Qom University of Medical Sciences, Qom, Iran.
***Corresponding Author:** Amir-Hooman Kazemi-Motlagh, Tel: +9190380168, Email: amirhoomank@yahoo.com

contains *Bunium persicum* (Bioss) B. Fedtch (black cumin), *Trachyspermum ammi* (L.) Sprague (ajwain), *Foeniculum vulgare* Miller (fennel), and *Pimpinella anisum* L. (anise). In this study, this formula was picked up from Qharabadin Salehi, as the last main traditional Persian pharmacopeia that is one of the most well-structured and well-written *Qarabadins* (pharmacopeia) ever in Persian medicine (15). Sofouf is a medication form in Persian medicine which is defined as a mixture of fine crashed parts of one or multiple medicinal plants in the form of powder (16).

Current investigations support the probable effect of the ingredients of cumin sofouf on IBS (17-22). As this historical formulation meets current supports for its probable efficacy on IBS, the current study aimed to prepare and standardize this drug and evaluate its efficacy on symptom severity and the quality of the life of IBS patients in comparison with mebeverine via a double-blind, randomized, controlled trial study.

Materials and Methods

Study Design and Ethical Standards

This double-blind, placebo-controlled, randomized clinical trial was approved by the Ethics Committee of Tehran University of Medical Sciences (No. IR.TUMS.VCR.REC.1396.3756) and was registered in the Iranian Registry of Clinical Trials (registration ID: identifier: IRCT20171127037640N1; https://www.irct.ir/trial/27924). Patients were completely aware of the procedure of this clinical trial and were included in the study after signing written consent forms.

Preparation of Materials

All herbal raw materials were purchased from a traditional herbal shop (*Attari*) in Tehran. The species were identified by an herbalist in the Herbarium Center of the School of Pharmacy at Tehran University of Medical Sciences (Table 1).

According to the protocol, they were powdered and sieved via sieves with a mesh size of 40-70. After mixture, they were packaged as 2.5 grams per sachets. Another group received sustain release mebeverine capsule (200 mg). Additionally, there were placebos for the mebeverine capsule containing 200 mg Avicel in the herbal drug group and sofouf containing 2.5 g Avicel and cumin sofouf 10% W/W and brown color (Iran Essence Company, CODE:FC5220) for blinding in the mebeverine group. Patients in both groups used drugs and placebos with the same pattern.

Standardization of Herbal Formula Via Gas Chromatography Analysis

The product was standardized based on the profile of its volatile components. For this aim, 100 g of the final product was hydrodistillated using a Clevenger apparatus. After 4 hours, 2 mL of essential oil was obtained and analyzed by gas-chromatography/mass spectrometry (GC instrument, Agilent 6890 connected to the mass specific-detector, Agilent 5973N) and 30 m column (BPX5) and the mobile phase of H gas.

Inclusion and Exclusion Criteria

In this study, 16-65 years old patients suffering from moderate to severe IBS according to Rome IV criteria, without red flag symptoms of organic diseases were evaluated for eligibility. The exclusion criteria were suffering from uncontrolled cardiovascular, respiratory, hematological, urinary, along with metabolic and connective tissue diseases, having alcohol or drug abuse, experiencing pregnancy or breastfeeding, suffering from dementia or severe mental diseases and cancer. In addition, other criteria included the recent use of antibiotics (recent month), intolerance or sensitivity to the herbs of Apiaceae family or each component of herbal formula, the consumption of medicine that is effective for gastrointestinal motility. Finally, the history of abdominal surgery except for appendectomy, caesarean section, tubal ligation, and hysterectomy, and inability to fill in the written questionnaire were the other inclusion criteria. The wash-out period for patients to take the antibiotics was one month and for other mentioned drugs was one week. Further, patients were excluded in case of medical conditions, the need for using antibiotics, annoying/severe adverse events, or failure to follow-up regularly.

Randomization: Blinding and Concealment of Allocation

Eligible patients were allocated to A or B treatment groups. One group received a package that contained 90 herbal sachets and the placebo capsule. The other group received sustain release mebeverine capsule (200 mg) and placebo sofouf. One sachet had to be taken after each meal and the capsule was prescribed twice daily 20 minutes before the meal for 4 weeks.

In addition, the randomization process was done by a person who was not involved with the patients through

Table 1. Medicinal Plants Used to Prepare Cumin Sofouf With Their Herbarium Code Obtained From Herbarium Center at Tehran University of Medical Sciences

Persian Name/Common Name	Scientific Name	Used Part	Ratio in Formula	Herbarium Code
Black cumin/Caraway	*Bunium persicum* (Bioss) B. Fedtch	Seed	2	PMP-1616
Zenian/Ajwain	*Trachyspermum ammi* (L.) Sprague	Seed	2	PMP-1617
Razianeh/Fennel	*Foeniculum vulgare* Miller	Seed	3	PMP-1618
Anisun/Anise	*Pimpinella anisum* L.	Seed	3	PMP-1615

using a block-randomization list generated by a computer (block size 4). Furthermore, patients, researchers, and statisticians were blind to treatment groups and drugs and placebos were made in the same shapes, colors, and smells in order to guarantee blindness.

Efficacy and Safety Assessment

The primary objective was a change from baseline in the total IBS-symptom severity score and each item of IBS-SSS within and between treatment groups. Moreover, the IBS-severity score system incorporated severity and frequency, distension, bowel dysfunction, and the QOL (general well-being) as five questions. Each question generated a maximum score of 100 using visual analogue scales. The maximum total possible score was 500 (23).

The secondary objectives included a change from baseline in the total IBS-QOL score and eight IBS-QOL substructures within and between treatment groups. The Irritable Bowel Syndrome Quality of Life (IBS-QOL-34) questionnaire as a 34-items instrument was developed and validated to assess QOL impairment in IBS. It contained eight IBS-QOL subscales such as dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, along with sexual concerns and relationships. Each item obtained a score on a 5-point Likert-type scale within the range of 1-5 indicating options not at all, slightly, moderately, quite a bit, and extremely or a great deal, respectively (24). A Persian translated and validated version of this questionnaire was used in this study (25).

Additionally, it encompassed a change from baseline in associated gastrointestinal symptoms such as gastroesophageal reflux symptoms, recurrent vomiting, drooling and dyspepsia (according to the patient's report as 0 = no change, 1 = partial improvement, and 2 = complete improvement) and the comparison of patient's improvement sense score. Patients were asked the question of *'How do you assess your improvement after 4 weeks of treatment?"*, and they recorded an improvement sense score (1 = not improved, 2= slightly better, 3 = very better, and 4 = complete improvement). Finally, it was attempted to assess drug safety. For safety assessment, all patients receiving at least one dose of study medication were asked to report any possible complications such as pruritus, skin rashes, headache, increased gas, diarrhea, constipation, nausea, and dyspepsia. In addition, they were required to define its severity as mild (easily tolerated signs or symptoms), moderate (enough discomfort to cause interference with usual activity), and severe (incapacitating with inability to work or perform usual activities) by the phone or after the treatment period.

Sample Size

Based on previous studies, 34 patients were required in each group to detect at least a 60-point (SD = 87.6) reduction in the mean IBS severity score for 80% power and 95% confidence. According to the previous study, 40 patients were needed for detecting the minimum treatment changes in the IBS-QOL score in order to have at least an 8-point reduction in the mean total IBS-QOL score (SD = 12.8) for 80% power and 95% confidence. Accordingly, the sample size of at least 40 patients was considered in each group of the study.

Statistical Analysis

For continuous variables, paired-samples *t* test was used to compare the changes before and after interventions in individual groups. Additionally, an independent *t* test was used for comparing the mean changes between the groups. In addition, categorical variables were compared between the groups by the chi-square or Fisher exact test and a $P<0.05$ was considered to be statically significant. Finally, the data were analyzed using SPSS software version 16 (Inc., Chicago, IL, USA). Data related to patients were entered into the analysis after obtaining their post-treatment answer sheets.

Results

Preparing Drug and Placebo and Standardization

Placebos and drugs both in powder and capsule forms were similar in shape, color, and smell. The result of gas-chromatography/mass spectrometry analysis of the cumin sofouf essential oil is shown in Table 2. The

Table 2. GC/MS Analysis of Volatile Components of the Cumin Sofouf

Components[a]	RT[b] (min)	KI[c]	Sample KI[d]	%
α-Thujene	11.84	930	938	0.05
α-Pinene	12.25	939	946	0.16
Sabinene	14.36	975	988	0.12
β-Pinene	14.64	979	993	0.35
Myrcene	15.18	001	1004	0.19
α-Terpinene	16.68	1017	1033	0.07
p-Cymene	17.23	1025	1043	5.00
Limonene	17.37	1029	1046	2.44
γ-Terpinene	18.93	1060	1076	8.09
Fenchone	20.67	1087	1110	3.18
trans-Sabinene hydrate	21.26	1098	1122	0.06
Camphor	23.75	1146	1172	0.04
Terpinene-4-ol	25.31	1177	1203	0.12
α-Terpinol	26.10	1189	1220	0.12
Menthyl chavicol	26.25	1196	1223	1.47
Cumin aldehyde	28.58	1242	1272	4.76
z-Anethol	30.85	1253	1322	44.38
Thymol	30.93	1290	1323	28.60
γ-Himachalene	38.62	1283	1503	0.42
α-Zingiberen	39.12	1494	1515	0.15
Total identified				99.77
Oxygenated monoterpenes				74.75
Monoterpene hydrocarbons				24.45
Sesquiterpene hydrocarbons				0.57

Note. GC/MS: Gas-chromatography/mass spectrometry.
[a] Compounds listed in the order of elution from BPX5 column; [b] Retention time in minutes; [C] Retention indices in the literature; [d] Retention indices of the sample on BPX5 column.

analysis demonstrates the main components of volatile oil, their percentages, retention time, and Kovats index that were obtained from the cumin sofouf. Oxygenated monoterpenes with 74.75% were the most important classes of compounds presented in sofouf. Other major compounds were monoterpene hydrocarbons and sesquiterpene hydrocarbons with 24.45% and 0.57%, respectively.

Study Population

From April 21, 2018 to April 21, 2019, 159 IBS patients referred to the gastroenterology clinic and were assessed for eligibility. Among them, 33 patients did not meet the inclusion criteria and 14 patients were excluded due to their unwillingness to participate in the study. Thus, 112 patients were randomized and allocated to one of the two treatment groups. However, 32 patients were lost during the follow-up, and finally, 80 patients completed the study. In the mebeverine group, 11 patients left the study because of GI upset (n=2), a headache (1), and an unwillingness to continue the study (8). In the cumin group, 21 patients left the study including due to interference with other drugs (n=1), drug side effects (n=6), and an unwillingness to continue the study (n=14). The sampling was continued to have 40 patients in each group. The CONSORT diagram of the study is displayed in Figure 1.

The baseline and demographic data of the two groups are summarized in Table 3. There were no significant differences in age, gender, body mass index, and baseline IBS-SSS and IBS-QOL between the two groups. The mixed-type IBS is the most common type of IBS in both groups.

Primary Objective

Figure 2 illustrates mean changes from baseline in the IBS-SSS total score and each substructure and statistical analysis in each group and between them. There were 120.125 (SD = 66.04) and 70.75 (SD = 50.75) point decreases in the total score in Cumin and mebeverine groups, respectively, demonstrating statistically significant differences between the two groups. It means that Cumin was more effective in decreasing IBS symptoms severity compared to mebeverine. This analysis was correct for the subgroups.

Secondary Objectives

Figure 3 depicts mean changes in the IBS-QOL total score and each substructure, as well as the statistical analysis in each group and between them. There was a 17.40 (SD = 13.66) point decrease in the total score in the cumin group and an 8.55 (SD = 6.88) point decrease in the mebeverine group, which are both statistically significant but cumin sofouf was more effective in improving the IBS quality of life compared to mebeverine. Changes within substructures were also statistically significant except for food avoidance in both groups. In substructure analysis, cumin was significantly more effective than mebeverine except for the substructures of interference with activity, food avoidance, social reaction, and sexual concerns.

Figure 4 displays the rate of accompaniment and

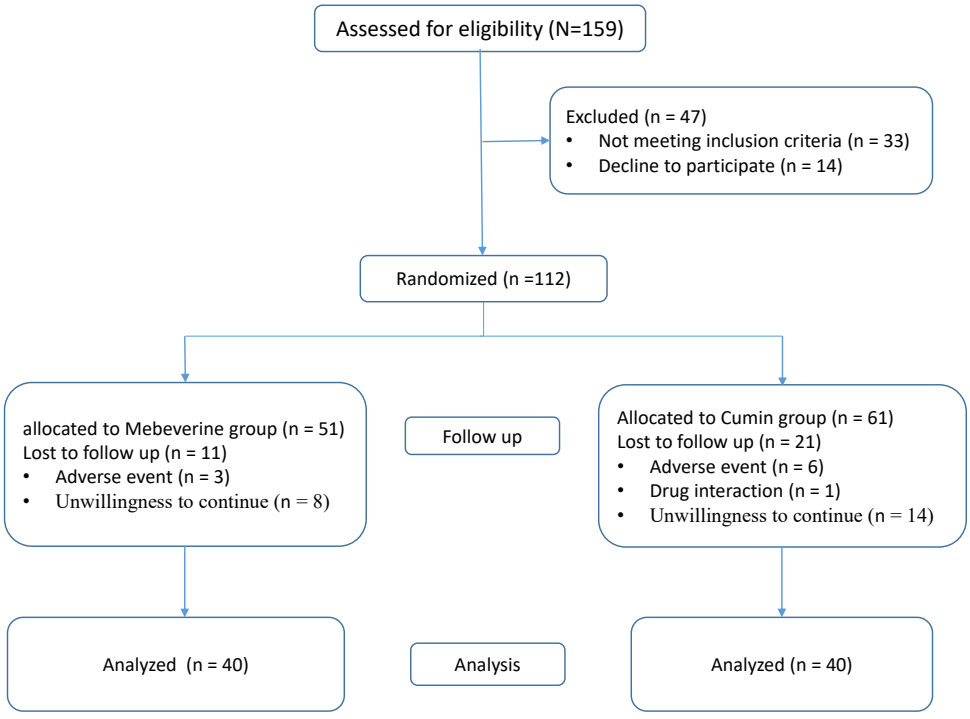

Figure 1. CONSORT Diagram of the Clinical Trial Study Regarding Comparing the Effects of Cumin Sofouf and mebeverine on IBS Severity and QOL.

Table 3. Demographic Table of the Baseline Characteristics of IBS Patients in Each Group

Characteristic	Cumin Sofouf	Mebeverine	*P* Value
Gender, No. (%)			
Female	23 (57.5)	23 (57.5)	
Male	17 (42)	17 (42)	
Age (year), (mean ± SD)	39.13 (11.47)	34.8 (12.10)	0.105
BMI (mean ± SD)	26.05 (5.80)	25.20 (2.84)	0.404
IBS-subgroups, No. (%)			
IBS-C	12 (30.0)	5 (12.5)	
IBS-D	4 (10.0)	9 (22.5)	
IBS-M	24 (60)	26 (65)	
IBS-SSS baseline (mean ± SD)	297.50 (81.35)	276.50 (73.67)	0.230
IBS-QOL baseline (mean ± SD)	94.17 (25.85)	88.35 (30.97)	0.364

Note. SD: Standard deviation; BMI: Body mass index; IBS: Irritable bowel syndrome; IBS-C: Constipation predominant; IBS-D: Diarrhea predominant; IBS-M: Mixed constipation and diarrhea; IBS-SSS: IBS-symptom severity score; QOL: Quality of life.

improvement of associated GI symptoms after treatment. The upper gastroesophageal symptoms are commonly associated with IBS. Except for recurrent vomiting, cumin sofouf was significantly more effective than mebeverine in improving associated gastrointestinal symptoms.

As shown in Table 4, 30% of patients declared significant improvement and 50% reported partial improvements in cumin sofouf. This was 12.5% and 52.5% in the mebeverine group, respectively. Although the improvement sense was reported more in the mebeverine group, it was not statistically significant.

Adverse Drug Effects

The adverse events and their frequency in both groups are shown in Table 5. Cumin sofouf could induce heat-related symptoms in the body. In six cases, adverse events had enough severity to force them to discontinue the study.

Discussion

After four weeks of treatment, both cumin sofouf and mebeverine were found effective in decreasing the severity of IBS symptoms (IBS-SSS) and its subgroups while cumin sofouf was statistically more effective compared to mebeverine. This was related to the IBS-QOL score. The

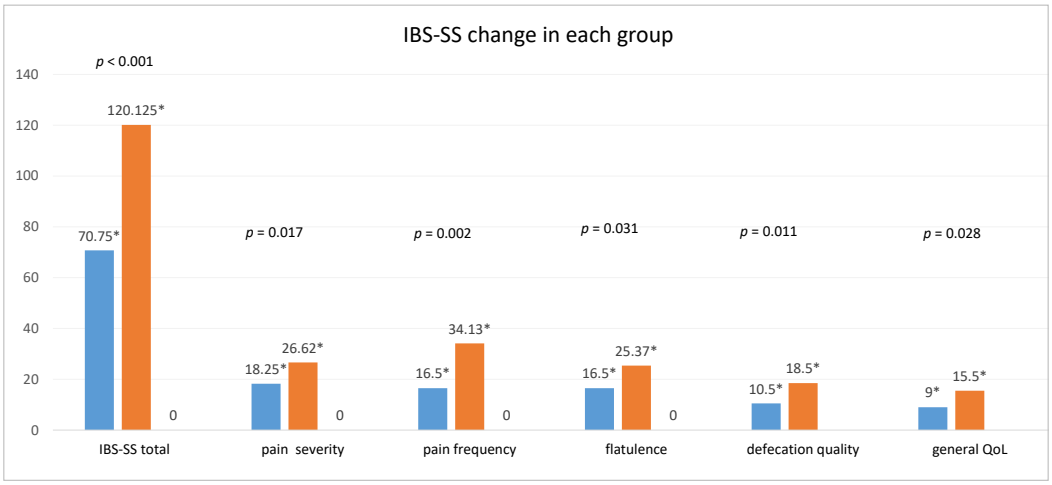

Figure 2. Change From Baseline in Irritable Bowel Syndrome Symptom Severity Score.

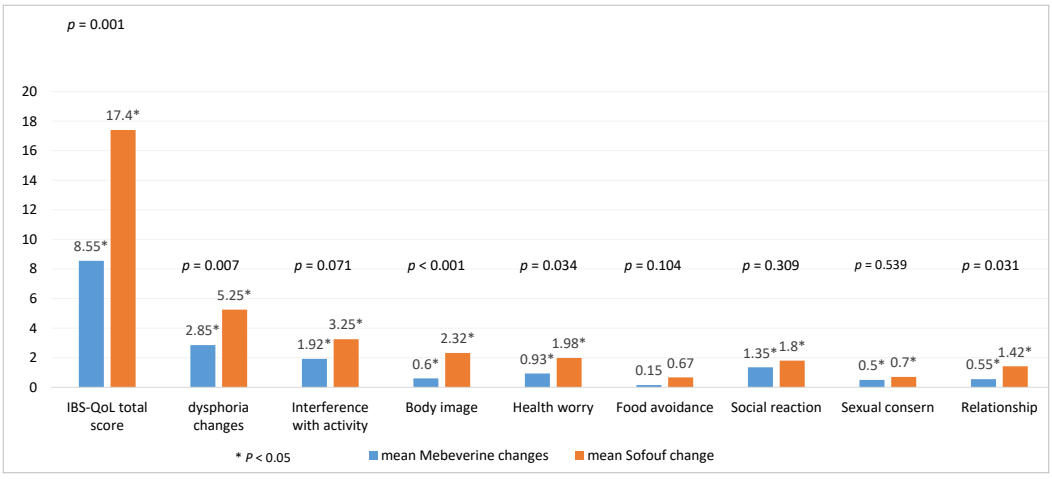

Figure 3. Change From Baseline in Irritable Bowel Syndrome Quality of Life.

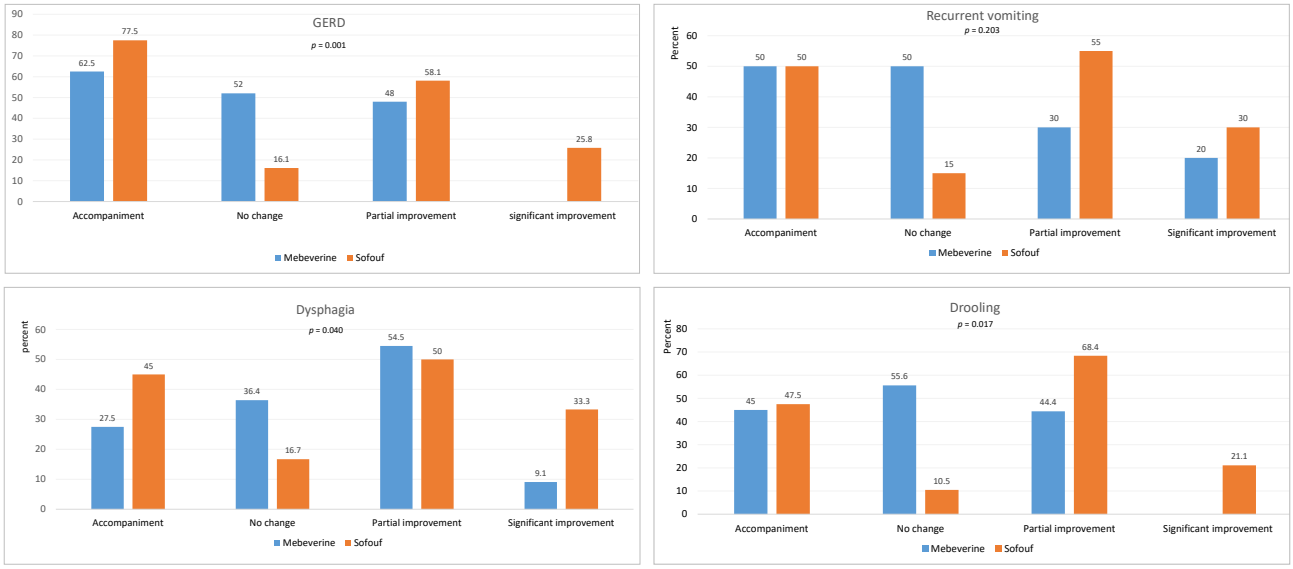

Figure 4. The Rate of Accompaniment and Improvement of Associated GI Symptom After Treatment.

meaningful clinical response for the IBS-QOL measure is an increase of at least 14 and minimal important response is an increase of 10.2 (26). Thus, sofouf could induce acceptable changes in IBS-QOL and was more effective than mebeverine. The results showed that patients in the sofouf group declared more significant and partial improvement in comparison with the mebeverine group. In addition, cumin sofouf was statistically more effective than mebeverine in the upper GI symptom relief.

Symptom-based pharmacologic therapy is recommended for IBS patients with mild to moderate symptoms without response to lifestyle and dietary modification or moderate to severe symptoms with impaired quality of life. Antispasmodics are used for the abdominal pain of IBS patients. Further, drugs with antimuscarinic or anticholinergic properties could not be used for the long term because of their side effects. Mebeverine and pinaverine directly affect intestinal smooth muscle relaxation and reduce postprandial abdominal pain, fecal urgency, and bloating with modest efficacy and the least side effects (7,27,28). Mebeverine is a safe and accessible antispasmodic drug in our country.

Some herbal products are used with good efficacy in IBS. Peppermint oil is a calcium channel antagonist with direct antispasmodic effects on the smooth muscle of the gastrointestinal tract (29). A compound drug containing *Menthe longifolia*, *Cyperus rotundus*, and *Zingiber officinalis* was effective in reducing IBS symptoms comparable with mebeverine (30). In addition, the red pepper in the capsule form was more effective than a placebo in reducing the abdominal pain and flatulence of IBS patients (31).

In Persian medicine, it is believed that each substance

Table 4. Patients' Improvement Sense After Treatment

Patients Improvement Sense			
Changes after treatment	**Mebeverine (%)**	**Cumin Sofouf (%)**	***P* value***
No change	14 (35)	8 (20)	0.104
Slight improvement	21 (52.5)	20 (50)	
Significant improvement	5 (12.5)	12 (30)	

* Pearson chi-square test.

Table 5. Incidence of Adverse Events Between Two Groups of IBS Patients

Treatment Group	Adverse Events	Frequency (n)	Grade = (n)	Study Dropout (n)
Cumin group	Increased appetite	2	Grade 1*=2	
	Increased menstrual bleeding	2	Grade 1=1 Grade 2**=1	1
	Premature ejaculation	1	Grade 1=1	
	Urticaria	1	Grade 1=1	Managed with chicory sweat
	Flushing	2	Grade 1=1 Grade 2=1	1
	Pruritus	2	Grade 2=2	2
	Head ache and vomiting	1	Grade 2=1	1
	Diarrhea	1	Grade 2=1	1
Mebeverine	GI upset	2	Grade 2=2	2
	Headache	1	Grade 2=1	1

Note. GI: Gastrointestinal; *Grade 1 Mild: Asymptomatic or mild symptoms, clinical or diagnostic observations only, the lack of intervention indicated. **Grade 2 Moderate: minimal, local, or noninvasive intervention indicated.

(e.g., humors and body organs) has a natural temper that is suitable for its function. Humors are derived from consumed foods and drinks. The accumulation of humors in excess amount or bad quality adjacent to the body organs within its lumen or its tissue changes their natural temper and result in their distemperment and dysfunction and even could induce inflammation and pain. Furthermore, the exposure of body organs to the cold or warm weather or condition could lead to simple organ distemperment without humor excess. (32,33)

Moreover, it is believed that *Maghs* (most compatible with IBS definition) is a heterogeneous disorder due to different gastrointestinal distemperments, and treatments are designed to return the balance of the organs. The accumulation of phlegm (wet and cold) is the most prevalent etiology of GI distemperment. Additionally, the coldness and different distemperament of bowels and the stomach could induce maldigestion, flatulence, diarrhea, constipation, and pain (34-38).

Cumin sofouf is traditionally used in some parts of our country for gastrointestinal problems. However, the prolonged use of one herbal drug is not recommended in Persian medicine. A compound drug is frequently used for reducing the side effects of compound drug by decreasing the amount of each component or adding the components that could balance the temper of the drug and have a more potent drug because of their additive or synergistic effects by acting via different mechanisms of action. All cumin sofouf ingredients have the warm and dry temperament. Similarly, they have digestive, carminative, and analgesic effects and could remove phlegm from the GI system and strengthen it (16).

As previously mentioned, gut hypersensitivity, brain-gut axis disorder, dysbiosis, infection, inflammation, diet and the like has been proposed as important pathophysiologic factors in different groups of IBS patients (6). Cumin sofouf ingredients could treat IBS with a different mechanism that is reviewed in the following sections.

Different studies on aniseeds represent its antiemetic, antimicrobial, antioxidant, analgesic, and anti-inflammatory properties. Furthermore, in-vivo studies demonstrated its antispasmodic and relaxant effects on the anococcygeus smooth muscle of the rat (39). A human study indicated that the enteric-coated capsules of the anise oil were superior to placebo and Colpermin in reducing IBS symptom severity and the quality of life (20). Moreover, the aniseed and fennel extract was effective against gastric ulcer in animal studies (40, 41). A clinical trial also confirmed the laxative properties of *Pimpinella anisum* and *Foeniculum vulgare* (fennel) (42). Additionally, the essential oil of fennel is effective on spastic gastrointestinal disturbances and functional dyspepsia by reducing intestinal gas and regulating gastrointestinal motility (43). Moreover, curcumin and fennel essential oils improved IBS symptom severity and IBS-QOL more than placebo in a clinical trial (21). The fennel seed oil contains anethole that has relaxant effects on the intestinal smooth muscle and could decrease the severity of colicky abdominal pain (22). In addition, the valuable phytochemical constituents of *Foeniculum vulgare* Miller (fennel) such as volatile oil, flavonoids, phenolic compounds, fatty acids, and amino acids lead to its antimicrobial, anti-inflammatory and antispasmodic, anxiolytic and antinociceptive properties. Thus, fennel could be an effective drug for IBS by different mechanisms (44).

Current investigations show that hot caraway oil poultices were effective and safe in decreasing the symptom severity of IBS (19). *Bunium persicum* (caraway) is a potent drug for IBS considering its antibacterial (on Gram-positive and -negative bacteria and *Helicobacter pylori*), antidiarrheal, anticholinergic, antioxidant, antinociceptive, and anti-inflammatory effects (18, 45).

In an *in-vivo* study, it was shown that the hydro-alcoholic extract of the fruits of *T. ammi* can reduce the severity of stress-induced IBS and possesses anti-oxidative and anticholinergic effects. (17).

Further, the active phytochemical components of *T. ammi* (ajwain), mainly tannins, glycosides, phenolic compounds, saponins, and the volatile oil (i.e., thymol, γ-terpinene, para-cymene, and α- and β-pinene), are responsible for its different medicinal properties such as antimicrobial, anti-inflammatory, antispasmodic, gastroprotective, carminative, and digestive stimulant effects (46).

The adverse effect of the drug was more prevalent in the sofouf group. There were three cases (6%) of adverse effects in the mebeverine group. In the cumin group, 6 patients had grade 1 and 6 patients had grade 2 adverse events, leading to the drop out of 6 patients. It means that about 20% of the cumin group experienced the adverse effects of the drug and 10% of cases had enough severity to cut off the drug. This is because of grade-two warm and dry temperament of sofouf that causes warm and dry distemperment of the other organs such as the liver and causes pruritus, urticaria, and the like (16). Although sofouf was effective and satisfactory for improving the symptoms in some patients, this rate of side effects decreases its application. In this condition, it is suggested that the drug temperament should be balanced with adding cold tempered herbs that have similar effects. For example, adding *Coriandrum sativum* (Coriander) seed or mixing it with candy powder and decreasing the amount of cumin powder in each meal could be useful solutions in this regard. Another reason for missing the follow-up is the form of the drug that is unpleasant for some people. Therefore, it is suggested to use drug essence or oil in different pharmaceutical forms such as soft gels or capsules.

Other limitations of this study were small sample size,

a large amount of missed follow-ups, the short period of trial, and the lack of follow-up period after drug discontinuation. To the best of our knowledge, this is the first randomized clinical trial for assessing the therapeutic and side effects of cumin sofouf on IBS. Thus, it is suggested to modify the drug temperament with the above proposed methods and include larger sample sizes with longer periods of follow-up in future investigations.

Conclusions

The findings of this study showed that cumin sofouf is an effective drug in the treatment of IBS patients. Thus, future studies are recommended with large sample sizes and small changes in their pharmaceutical forms and formula to be applicable for most patients that seek an effective and cheap complementary medication for their functional gastrointestinal disorders such as IBS and dyspepsia.

Conflict of Interests

Authors have no conflict of interests.

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