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Original Research

Effects of a Traditional Rose-Based Polyherbal Formula on Clinical Symptoms of Patients with Functional Dyspepsia: A Double-Blind Randomized Controlled Trial

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Abstract

Functional dyspepsia (FD) is a common gastroduodenal disorder that can be long-lasting. In the present study, we aimed to investigate the effect of herbal medicine, Ghors-e-Vard (Vard), on clinical symptoms in FD patients. Seventy adult FD patients according to the Rome IV criteria and without *Helicobacter pylori* infection were included. Participants were randomly allocated to either Vard or placebo group for 4 weeks of intervention. Treatments were given orally in a double-blind fashion (500 mg, three times a day, and half an hour after each meal). Patients were evaluated prior to and following 2, 4, and 8 weeks after the intervention, in terms of changes in the total score of gastrointestinal symptoms rating scale (GSRS), Depression Anxiety Stress Scales (DASS-21), scores of various components of the 36-item short-form health survey (SF-36), and any reported side effects. The differences of GSRS and DASS-21 total scores from baseline to the end of intervention were significantly larger in Vard group ($P < 0.001$). Except for reflux, the other subtypes of FD symptoms were decreased with a significantly greater effect in Vard group ($P < 0.05$). Also, changes in the total score of SF-36 at 4 and 8 weeks after the intervention were significantly greater in Vard group ($P < 0.001$). Except for the reflux, improvement of gastrointestinal symptoms, along with depression, stress, and anxiety, as well as the quality of life in Vard group, was significantly superior to the placebo group. These findings suggest that the Vard, as a complementary therapy, may have a promising effect on resolving the FD symptoms.

Keywords: Functional dyspepsia; Gastroenterology; *Glycyrrhiza glabra; Nardostachys jatamansi; Rosa damascena;* Traditional persian medicine

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Introduction

Non-ulcer or functional dyspepsia (FD) is a chronic gastroduodenal condition characterized by upper abdominal symptoms with a structurally normal upper GI endoscopy [1]. FD symptoms include epigastric burning and pain, postprandial fullness, bloating, early satiety, nausea, and belching. Diagnostic symptom-based criteria are defined by Rome IV, if symptoms persist for three months, with onset more than six months, without evidence of another organic, structural, metabolic, or systemic disease [2,3]. Based on symptoms, patients are classified into three subgroups including epigastric pain syndrome (EPS), postprandial distress syndrome (PDS), and patients with the overlap of EPS and PDS [4]. The differential diagnosis of dyspepsia involves acid-related disorders, gastric inflammatory conditions, or less likely, upper abdominal cancer; and when these conditions are excluded by appropriate examinations, the patient is given a diagnosis of FD [5].

The global prevalence of FD is about 20% of the general population [6], which varies depending on geographical location [7,8]. Dyspepsia is estimated to affect up to 29.9% of the Iranian population [3, 9]. Women have a greater prevalence of FD; also smoking, non-steroidal anti-inflammatory drugs (NSAIDs) consumption, and Helicobacter pylori infection are associated with FD [6]. FD patients experience a lower quality of life than the general population, along with less productivity and more health care costs [10]. Pathophysiology of FD comprises various factors including abnormalities in visceral sensory or gastric motility, as well as psychological distress [11]. Also, FD symptoms might be related to lifestyle issues like alcohol consumption, and sleep disorders [12].

As a functional gastrointestinal disorder, FD is caused by a disturbance in the interactions of the gastrointestinal system and the brain [13]. In addition, *H. pylori* eradication is essential for many infected FD patients [14]. However, patients who do not respond to the treatments have challenges with refractory FD [15]. Treatment options for *H. pylori*-negative FD include acid-suppressing medications, central neuromodulators, or prokinetics [1]. Conventional treatments for FD have some adverse effects including renal, cardiovascular, gastrointestinal, autoimmune and neurological adverse reactions associated with proton pump inhibitors (PPIs) [16], diarrhea, abdominal discomfort and nausea related to prokinetics [17], and common side effects of neuromodulators [18].

Several multi-component herbal formulations from different traditional medicine systems have been reported to relieve the symptoms of FD [5]. The combined formulation of caraway oil and L-menthol has been indicated to improve symptoms in patients with epigastric pain syndrome [19]. The herbal medication rikkunshito has also been shown to improve epigastric pain significantly, with a higher rate of improvement in early satiety in comparison with placebo [20]. Vard, is an herbal formulation in Persian medicine recommended for gastric disorders such as gastritis, gastric ulcer and different stomach dystemperaments and some symptoms like epigastric pain [21-23]. It is broadly mentioned in Persian medicine books such as Canon of

medicine (Avicenna) [24], Zakhireh-kharazmshahi (Jorjani) [22], Kholasat-ul-hekma (Aqili khorasani) [21], and Hidayat-al-Mutaallimin fi-al-Tibb (al-Akawayni al-Bokhari) [25]. Based on the concepts of Persian medicine, this drug might improve the function of the stomach by removing harmful humors and moistures in the stomach and also strengthen the stomach tissue [21].

Vard formulation is composed of *Rosa × damascena Herrm*. (Vard-e-ahmar; Rose), *Glycyrrhiza glabra* L. (Soos; Licorice) and *Nardostachys jatamansi* (D.Don) DC. (Sonboletib-e-hendi; spikenard). Various pharmacological activities of these herbs indicate the potential effect of Vard in improving the symptoms of FD. The gastroprotective [26], laxative, prokinetic [27], antidepressant [28], as well as antioxidant [29] activities of *R. damascena* have previously been shown in preclinical studies. Also, licorice extract has been indicated to improve gastric emptying along with reducing pro-inflammatory mediators in a rat model of mucosal damage [30]. Moreover, studies have demonstrated the gastroprotective activity [26] of *N. jatamansi* as well as its anxiolytic effect via increasing the levels of monoamine and GABA neurotransmitters in mice [31]. Also, Vard formulation was previously shown to act as a gastroprotective agent in a rat model of ethanol-induced gastric ulcer and it was shown to increase glutathione, heme-oxygenase-1, and catalase activity in stomach homogenates of rats [26].

In addition to therapeutic aspects, traditional medicines should also be considered for safety assessments due to potential toxicities associated with herbs [32-34]. Several studies have pointed out relative safety and potential side effects of *G. glabra* [35]. To avoid the risks of its mineralocorticoid-like activity [36], the standard dose for the rhizome is 1-5 g, three times daily for up to 6 weeks based on phytotherapy resources [37]. The standard dose for rose flowers and spikenard rhizomes are 5-10 g/day and 0.6 to 1.3 g/day, respectively [38,39]. The amounts of these herbs used in Vard formulation are within the recommended dosages.

Vard has been listed in Iran Food and Drug Administration as a traditional medicine product. Nevertheless, no randomized controlled trial has been conducted to investigate the effects of Vard on symptoms of FD. Thus, this study aims to determine the efficacy of Vard as a traditional herbal drug for the treatment of FD.

Methods

Ethical considerations

This study was a double-blind, randomized, parallel placebo-controlled clinical trial of Vard in FD. The study protocol was registered and approved by the Iranian Registry of Clinical Trial with ID: IRCT20200128046291N1. This study was conducted after approval by the ethics committee of Babol University of Medical Sciences, Babol, Iran. Approval date 22 January 2020, Ethics committee reference number: IR.MUBABOL.HRI.REC.1398.319. Before the enrollment, written informed consent was obtained from all the subjects. Both groups in this study received PPIs to avoid any deprivation from the standard treatment.

Plant material and drug preparation

Dry rose petals and rhizomes of licorice and spikenard were purchased from local herbal store of Tehran and authenticated by a botanist. Voucher specimens *Rosa* × *damascena* Herrm.; *Rosaceae*; No: BMS-124, *Glycyrrhiza glabra* L. Var glabra; *Leguminosae*; No: BMS-233 and *Nardostachys jatamansi* (D.Don) DC.; *Caprifoliaceae*; No: BMS-235 were deposited in the phytopharmaceutical laboratory of faculty of traditional medicine, Babol University of Medical Sciences.

Each of the dried herbs was individually milled and powdered. According to the traditional medicine texts [24,40], the weight ratio of 2:1:1 (respectively for *R. damascena, G. glabara*, and *N. jatamansi*) of herb powders was mixed. Then, the powder was briefly moistened and granulated. After drying and decontamination of granules by microwave in three 1 minute steps [41], the granules were re-milled. For placebo preparation, corn starch was mixed with the Vard powder (1%) until the smell was a bit similar.

After microbial control tests, both powders were filled in oral gelatin capsules by a manual capsule-filling machine (Takno fix®) in phytopharmaceutical laboratory, school of traditional medicine, Babol University of Medical Sciences, Babol, Iran. Each Vard capsule contained 500 mg of the powder.

The microbial limit tests (total bacterial count, total mold and yeasts, absence of *E. coli*, and *Salmonella*) were carried out in Professional Center of Analysis, Institute of Medicinal Plants, Karaj, Iran, and were in accordance with the United States pharmacopeia (USP40).

Determination of phenolic compounds

Spectrophotometric analysis of the total phenolic compounds of the dry aqueous extract of Vard powder was performed in Professional Center of Analysis, Institute of Medicinal Plants, Karaj, Iran.

HPLC quantification of gallic acid and glycyrrhizic acid

Gallic acid, as one of major components of Rose petals, and glycyrrhizic acid as main component of licorice rhizome were analyzed in the prepared dry aqueous extract of Vard powder by HPLC analysis performed in Professional Center of Analysis, Institute of Medicinal Plants, Karaj, Iran.

Inclusion criteria

The trial was conducted on patients ranged from 18 to 65 years old with dyspepsia symptoms diagnosed as FD by gastroenterologists according to Rome IV criteria, with symptoms duration of 3 months, symptom onset ≥ 6 months before the study. The study was conducted from June 2020 to October 2020 in the department of gastroenterology of Omid clinic of Babol University of medical sciences, Babol, Iran.

Exclusion criteria

The absence of organic disorders was confirmed by upper gastrointestinal (GI) endoscopy for all patients (according to the endoscopy performed within the last 3 months prior to intervention for patients younger than 45 years without alarm

features; or using upper GI endoscopy prior to the intervention in cases with alarm features or age over 45 years) [13]. For assessment of *H. pylori* infection status rapid urease test was used; patients with *H. pylori* infection were excluded from this trial. Subjects with the following conditions were excluded: any diagnosed cases of gastric lesions as well as other organic diseases within upper GI; Patients with a diagnosis of irritable bowel syndrome (IBS), erosive gastroesophageal reflux disease (GERD) and severe reflux; patients with biliary motility disorder and any organic gastrointestinal disease, history of GI surgery; systemic diseases such as heart failure, hypertension, hepatic failure, renal failure, asthma, chronic obstructive pulmonary disease, neoplasms and severe psychiatric diseases; addiction to alcohol and opium; use of any medication affecting the intervention for at least 7 days before intervention period including prokinetics, antacids, beta-blockers, (anti) cholinergic drugs, antidepressants, antibiotics and laxatives; pregnant women, women planning pregnancy and breastfeeding women.

Drop out criteria

The drop out criteria included discontinued medication for more than 3 days due to patient non-compliance or adverse drug effects; use of any medication affecting the intervention for at least 7 days during the study. The researchers committed to discontinue medication and exclude patients as soon as the patients reported any complications or exacerbation of symptoms.

Sample size

Considering the effect size of 0.25, power 80%, 95% confidence level using G power software sample size for comparison of two groups over time (repeated measure, within-between interaction) and with considering the 25% dropout rate, 70 people (35 people in each group) were selected.

Intervention

Of all 307 referrals to gastroenterology clinic in the mentioned study period (convenient sampling method), 70 patients were included as cases who matched the inclusion criteria.

After receiving the written informed consent from all listed patients, the patients were randomly allocated into two groups A & B (Vard and placebo respectively). Block randomization were done for the Vard and placebo allocation. Patients training about the drug consumption and the follow up, during the treatment period were performed by a general practitioner, a Ph.D. candidate of traditional medicine, who was a research team investigator and care-provider. The patients were trained to take one capsule three times a day, half an hour after each meal for 1 month. All patients and care-providers were blinded to interventions. All patients were administered PPI (omeprazole: 20 mg orally once a day for 14 days) as standard medication.

Outcome measures

The primary outcome was the change in dyspepsia symptoms severity based on the total score of GSRS at weeks 2, 4 and 8 of the intervention

compared to baseline. Also, for assessment of two cardinal postprandial distress (PD) symptoms including early satiation and postprandial fullness we asked patient's judgment using a 7-point likert scale (like GSRS 7-point likert scale).

Secondary outcomes were the improvement rate in the 5 GI symptoms based on relevant questions of GSRS, as well as alterations in scores of quality of life, depression, anxiety and stress. Also, safety and compliance of the medication as well as the reasons for patient lost to follow up were reported.

GSRS contains 15 questions about the GI symptoms and the questions are scored on a 7-point Likert scale (from "no discomfort at all" to "very severe discomfort"). The questions of GSRS include 5 types of GI symptoms including abdominal pain, reflux, diarrhea, constipation, and indigestion [13]. GSRS questionnaire has previously been translated into Persian and its reliability and validity have been reported in Persian [42].

GSRS questionnaire was filled in by patients at the beginning of the study (for illiterate participants, all forms and questionnaires were filled in the presence of accompanied person or by the main researcher with a present witness), and also at week two of follow up by telephone. Then, in the fourth week, after referring to the gastroenterologist, all patients were followed up in person and GSRS questionnaire was filled in by the main researcher. Patients were followed up again by telephone in the eighth week of the study and GSRS questionnaire was completed for them.

The effects of Vard on depression, anxiety, and stress as well as quality of life were assessed by using DASS-21 and SF-36 questionnaires on weeks 4 and 8 of intervention compared to baseline. DASS-21 and SF-36 questionnaires were filled in by patients at the beginning of the study. Then, in the fourth week, after referring to the gastroenterologist, all patients were followed up in person and both DASS-21 and SF-36 questionnaires were filled in by the main researcher. Patients were followed up again by telephone in the eighth week of the study, and then questionnaires were completed for them. DASS-21 assesses three negative affective states: (1) depression (DASS-D), (2) anxiety (DASS-A), and (3) stress (DASS-S) using a 4-point likert scale for all questions (No discomfort at all 0; Mild discomfort 1; Moderate discomfort 2; Severe discomfort 3). Its Persian version has been published with approved reliability and validity in Iran [43].

SF-36 questionnaire (in Persian) contains 36 items in 2 general groups score contain Mental Component Summary (MCS) and Physical Component Summary (PCS) and eight subgroups consist of mental health (MH), vitality (VT), role emotional (RE), social functioning (SF), general health (GH), bodily pain (BP), role physical (RP) and physical functioning (PF) [44].

Safety and compliance

Subjects were asked for potential adverse events to evaluate the safety of the treatment. If there were severe adverse events, the treatment was discontinued. If patients had taken more

than 80%, 60-80% and less than 60% of the prescribed medications by the end of the study, acceptance rates were considered full, good, and poor, respectively. The lower limit of medication compliance was 80% and patients with compliance less than 80% were considered as non-compliance group and excluded from the study [45].

Randomization and concealment

The subjects were randomly allocated (1:1) to either Vard or a placebo groups via the permuted blocks. Random sequence generation and allocation were carried out by an independent researcher. The allocation was concealed from the researchers, and patients were informed that they would either be allocated to Vard or placebo groups.

Blinding

The drug and placebo were both prepared in identical non-transparent capsules and in completely similar containers and packages and coded according to the random number table. None of the participants, principal investigator, health care personnel (physicians, nurses, etc.) responsible for patient care and data collectors were aware of the content of the packages and the coding.

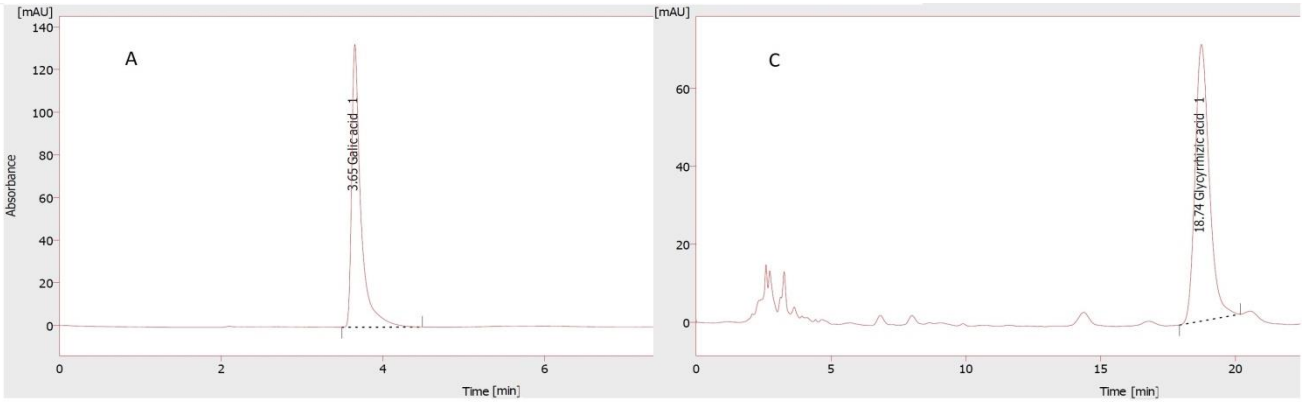
Statistical analysis

Data are shown as mean and standard deviation (SD) for continuous variable and n (%) for the categorical variable. For evaluation of the difference between groups at baseline independent T-test and chi-squared were used. Between groups changes were measured using repeated measure analysis. For sensitivity analysis, per-protocol (PP) and intention to treat (ITT) were used. Statistical significance was defined by P value < 0.05. Statistical analyses were done using SPSS version 22.0.

Results

Phytochemical analysis

The obtained amount of total phenol was 50.65 ± 5.21 mg/g (equivalent as gallic acid) in dry extract. Amounts of glycyrrhizic acid and gallic acid were 11.3 mg/g and 3.95 ± 0.15 mg/g, respectively. HPLC chromatograms are shown in figure 1(A-D).



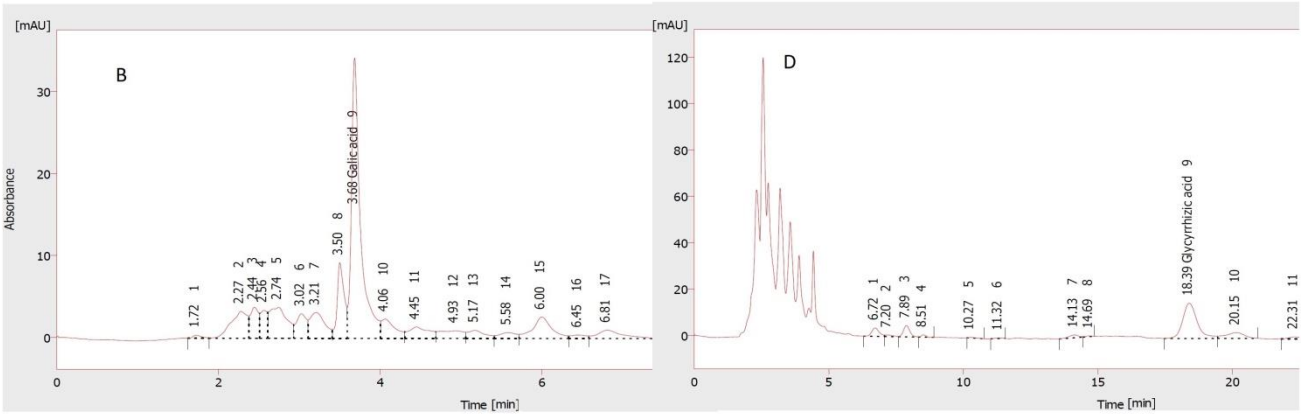


Figure 1. HPLC chromatograms of standards of gallic acid (A) and glycyrrhizic acid (C) and detection of them in Vard extract (B and D).

Baseline characteristics of population under the study

Of 307 patients, 70 subjects (35 in each group) were enrolled and randomly allocated in one of the two groups of the study and were included in the ITT analysis. Finally, 59 patients (30 in Vard and 29 in placebo group) finished the treatment period and were included in the per protocol analysis.

During this period the patients' drop out from placebo and Vard groups were 6 and 5 cases respectively. Complete information of randomization and treatment allocation and reasons for drop out of patients are shown in figure 2.

There were no significant differences in age, BMI and gender ($P > 0.05$ for all) between two groups. Baseline characteristics are shown in Table 1.

Assessments of outcomes

The adverse events in Vard group were abdominal pain and discomfort and bloating (1 case) in the 4th day of the drug consumption, and according to the study protocol we had to stop treatment.

Analysis based on 90% compliance indicated that in Vard and placebo groups, respectively 94.28% and 91.42% of subjects showed full medicine compliance (compliance over 90%,). The total score of GSRS (mean ± SD) at baseline in Vard and placebo groups were 30.54 ± 13.70 and 27.68 ± 15.18, respectively (P value = 0.411). After 2, 4 and 8 weeks of intervention, the differences between the total GSRS score in both groups were significant ($P < 0.001$). According to ITT analysis, the decrease in GSRS score was significantly higher in Vard group than that of placebo group ($P < 0.05$). In PP analysis the same result was obtained ($P < 0.05$), as well. The total GSRS scores for both groups at baseline and 3 follow ups are shown in table 2 and figure 3.

The scores of questions related to 6 symptoms (post prandial fullness & early satiety, reflux, abdominal pain, indigestion, constipation and diarrhea) are shown in table 2. Except reflux, all of the other symptoms were significantly decreased ($P < 0.05$) with a significantly greater change in Vard group.

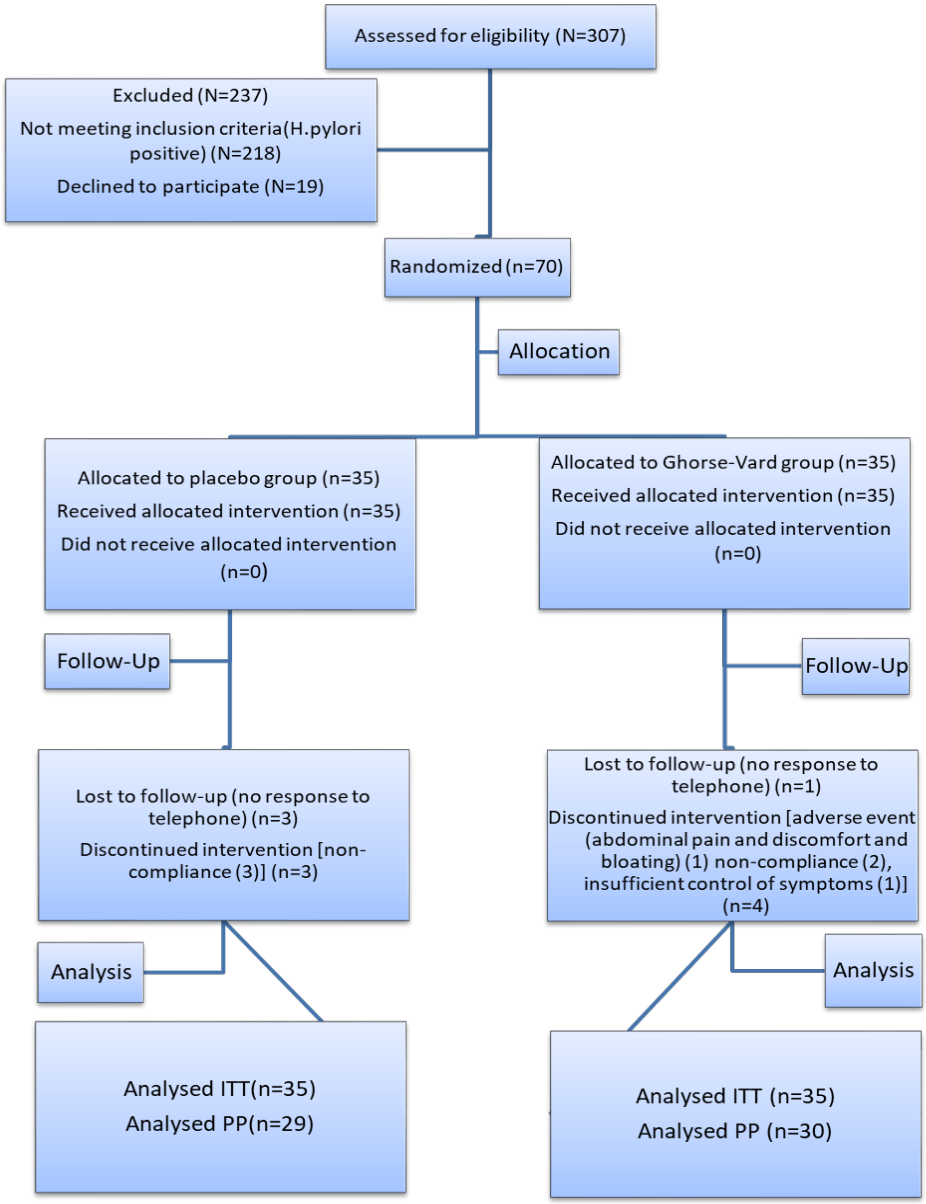


Figure 2. Information of randomization and allocation and reasons for drop out of patients

Table 1. Demographic information

Variable		P value	Placebo	Vard
Sex	Male	11(15.7%)	15(21.4%)	0.322
	Female	24(34.2%)	20(28.5%)	
Age		43.05±11.18	47.05±9.73	0.115
BMI		25.63±3.08	27.15±4.63	0.111
Marital Status	Single	2	1	0.5
	Married	33	34	
	Divorced/separated	0	0	
Education level	Illiterate	6	6	0.89
	High school	13	14	
	Diploma certificate	8	10	
	Bachelor Degree	7	4	
	Master Degree	1	1	

Profession	Cultural	3	1	0.055
	Student	3	1	
	Employee	0	4	
	Housewife	21	18	
	Manual worker	2	8	
	Self-employed	6	3	

Table 2. Total score of GSRS and the scores of its sub-domains and PD questions at baseline and 3 follow ups

Variable	Time	Groups (Mean ± SD)		P-value		Partial Eta Squared
		Vard	Placebo	Baseline	Week 8, Between groups	
Post Prandial Fullness & Early Satiety (PD	Baseline	4.08±2.81	4.48±3.50	0.600	<0.001	0.155
	2w	1.34±1.42	3.85±3.12			
	4w	0.70±1.03	3.68±3.33			
	8w	0.76±0.85	3.69±3.19			
Reflux	Baseline	4.02±2.87	5.05±3.33	0.171	0.199	0.022
	2w	0.69±11.64	4.74±4.28			
	4w	0.60±8.84	4.40±3.94			
	8w	0.28±3.41	2.81±3.61			
Abdominal Pain	Baseline	6.65±4.03	6.25±3.97	0.677	<0.001	0.117
	2w	2.00±1.56	5.62±4.05			
	4w	0.40±6.40	5.57±6.45			
	8w	1.30±2.13	4.6±3.56			
Indigestion	Baseline	10.17±5.89	7.94±5.56	0.109	<0.001	0.271
	2w	3.42±3.10	6.68±5.33			
	4w	0.67±2.86	6.63±5.38			
	8w	2.23±3.80	6.23±4.68			
Constipation	Baseline	6.25±4.39	5.71±4.59	0.615	<0.001	0.217
	2w	1.55±1.96	5.08±4.39			
	4w	0.13±1.62	4.85±4.73			
	8w	1.16±2.41	4.82±4.42			
Diarrhea	Baseline	3.42±3.98	2.71±2.93	0.396	<0.001	0.142
	2w	0.53±0.99	2.52±2.73			
	4w	0.11±1.34	2.12±2.35			
	8w	0.55±1.77	2.44±2.30			
Total GSRS	Baseline	30.54±13.70	27.68±15.18	0.411	<0.001	0.487
	2w	8.17±6.93	24.12±15.19			
	4w	4.00±4.37	21.47±13.94			
	8w	2.76 ±11.63	22.69±13.64			

Furthermore, total score of DASS-21 (mean ± SD) at baseline were 29.51±13.23 in Vard and 23.17±16.20 in placebo groups (P-value = 0.077). According to DASS-21 the reduction in mean total score after intervention was significantly lower in Vard group compared to placebo group (P<0.001). The comparisons of scores of DASS-21 and its 3 subtypes (depression, anxi-

ety and stress) at baseline and 2 follow ups separately have been shown in table 3 and figure 4 respectively. The mean (± SD) total scores SF-36 at baseline in Vard and placebo were 95.06 ± 13.87 and 97.34 ± 17.3, respectively (P-value = 0.473). The differences of total SF-36, mental component summary, vitality and mental health scores before and after the intervention between two groups were statistically significant with a superior change in Vard group (P < 0.001).

The total SF-36 score and 10 subtypes (physical component summary, mental component summary, general health, vitality, social functioning, physical functioning, mental health, bodily pain, physical role, and emotional role) at baseline and 2 follow ups separately are shown in table 4 and figure 5.

Minimally important differences for the Patient-Reported Outcomes Measurement Information System (PROMIS) GI scales using GSRS anchor and the count of Risk Ratio, Absolute Risk Difference and Number Needed to Treat (NNT) of 5 subtypes of GSRS score are separately shown in tables 5 and 6.

In placebo group, 92.25% of patients were in "about the same" category. In comparison with placebo group, 34.66 and 8.66% of patients in Vard group located in "somewhat better" and "much better" category respectively (Table 5)

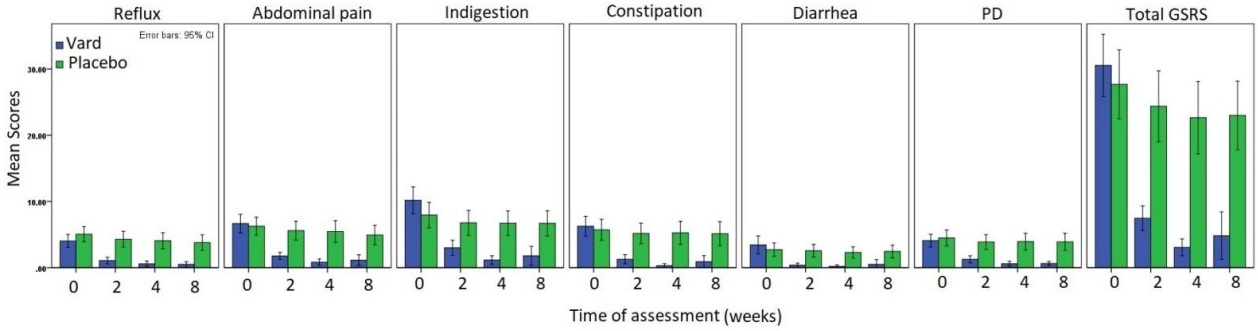


Figure 3. The scores of GSRS and its subset questions relevant to GI symptoms and the scores of questions related to postprandial distress (PD) at baseline and 3 follow ups

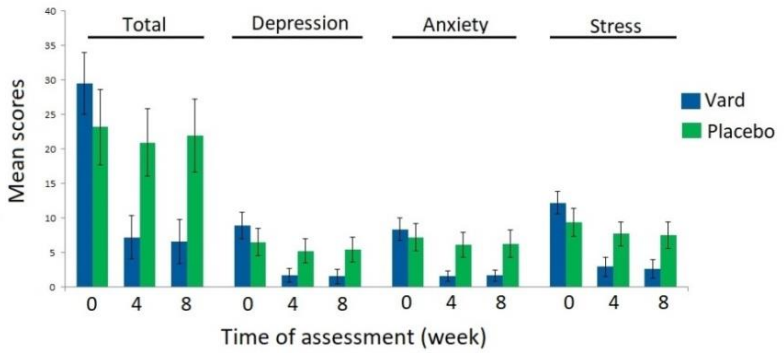


Figure 4. The mean scores of total DASS-21 and 3 subtypes, at baseline and 2 follow ups

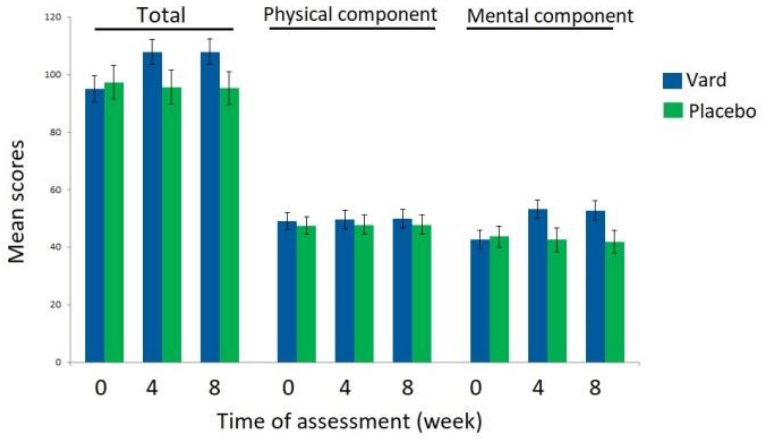


Figure 5. The scores of total SF-36 and 2 subtypes of physical and mental components summaries at baseline and 2 follow ups

Table 3. The scores of total DASS-21 and 3 subtypes at baseline and 2 follow ups

Variable	Time	Groups (Mean ± SD)		P-value	Partial Eta Squared
		Vard	Placebo	After 8 weeks, Between groups	
Depression	Baseline	8.91±5.65	6.51±5.83	<0.001	0.274
	4w	1.68±2.87	4.93±5.30		
	8w	1.40±3.02	5.31±5.56		
Anxiety	Baseline	8.40±4.87	7.22±5.77	<0.001	0.149
	4w	1.57±2.17	5.93±5.21		
	8w	1.29±3.18	1.29±3.18		
Stress	Baseline	12.20±4.79	9.42±5.95	<0.001	0.338
	4w	2.94±4.03	7.39±5.46		
	8w	2.34±4.20	7.76±7.05		
Total DASS21	Baseline	29.51±13.23	23.17±16.20	<0.001	0.360
	4w	8.28±11.62	20.04±13.70		
	8w	8.07±11.85	20.73±14.16		

Table 4. The scores of total SF-36 and 10 subtypes at baseline and 2 follow ups

Variable	Time	Groups (Mean ± SD)		P-value		Partial Eta Squared
		Vard	Placebo	Baseline	Week 8, Between groups	
Physical Component Summary	Baseline	49.11±8.37	47.51±8.72	0.696	0.317	0.017
	4w	49.69±8.82	47.77±9.17			
	8w	49.87±8.78	47.70±9.03			
Mental Component Summary	Baseline	42.71±9.41	43.65±10.69	0.494	<0.001	0.396
	4w	53.23±8.90	42.55±10.85			
	8w	52.72±9.23	41.82±10.69			

General health	Baseline	12.94±2.72	11.94±2.73	0.877	0.507	0.010
	4w	13.39±2.57	12.14±3.08			
	8w	13.30±2.51	11.96±3.02			
Vitality	Baseline	13.48±3.83	14.28±4.40	0.490	<0.001	0.372
	4w	18.19±3.86	13.55±4.55			
	8w	18.03±3.94	13.43±4.45			
Social functioning	Baseline	7.17±1.65	6.74±2.25	0.039	0.730	0.005
	4w	7.25±1.61	6.74±2.25			
	8w	7.17±1.54	6.61±2.42			
Physical functioning	Baseline	23.25±5.29	23.02±5.99	0.169	0.228	0.021
	4w	23.12±5.40	23.08±5.99			
	8w	23.37±5.27	23.02±6.03			
Mental health	Baseline	17.48±4.89	17.88±5.03	0.694	<0.001	0.351
	4w	23.24±4.73	17.52±4.97			
	8w	22.96±5.07	16.97±4.91			
Bodily pain	Baseline	6.71±1.97	6.08±2.10	0.789	0.358	0.015
	4w	6.93±2.19	6.07±2.12			
	8w	6.96±2.22	6.24±1.91			
Physical role	Baseline	6.20±1.36	6.45±1.59	0.079	0.988	<0.001
	4w	6.23±1.36	6.45±1.60			
	8w	4.62±1.30	4.81±1.27			
Emotional role	Baseline	4.57±1.28	4.74±1.24	0.675	0.143	0.028
	4w	4.53±1.26	4.72±1.26			
	8w	4.54±1.26	4.79±1.26			
Total Sf-36	Baseline	95.06±13.87	97.34±17.31	0.473	<0.001	0.583
	4w	107.86±12.24	95.72±17.34			
	8w	107.96±12.68	95.37±16.52			

Table 5. Minimally important differences for the PROMIS GI scales using GSRS anchor*

Group	PROMIS GI scales	Duration	Mean (N)				
			Much better	Somewhat better	About the same	Somewhat worse	Much worse
Vard	Reflux	2w	−7 (4)	−5 (4)	0 (22)	1 (0)	5 (0)
		4w	−7 (5)	−5 (7)	0 (17)	1 (1)	5 (0)
		8w	−7 (5)	−5 (7)	0 (18)	1 (0)	5 (0)
	Diarrhea	2w	−8 (3)	−5 (2)	1 (25)	6 (0)	10 (0)
		4w	−8 (3)	−5 (2)	1 (25)	6 (0)	10 (0)
		8w	−8 (2)	−5 (2)	1 (26)	6 (0)	10 (0)
	Constipation	2w	−11(1)	−5 (10)	0 (19)	6 (0)	7 (0)
		4w	−11(3)	−5 (9)	0 (18)	6 (0)	7 (0)
		8w	−11(2)	−5 (8)	0 (20)	6 (0)	7 (0)
	Belly pain	2w	−13 (1)	−6 (8)	0 (21)	6 (0)	9 (0)
		4w	−13 (1)	−6 (14)	0 (15)	6 (0)	9 (0)
			−13 (1)	−6 (11)	0 (18)	6 (0)	9 (0)
	Gas/bloat/ flatulence	2w	−17 (0)	−6 (15)	−1(15)	6 (0)	10 (0)
		4w	−17 (1)	−6 (20)	−1(9)	6 (0)	10 (0)
		8w	−17 (1)	−6 (19)	−1(10)	6 (0)	10 (0)

Placebo	Reflux	2w	−7 (1)	−5 (1)	0 (30)	1 (2)	5 (0)
		4w	−7 (1)	−5 (1)	0 (26)	1 (3)	5 (0)
		8w	−7 (1)	−5 (3)	0 (22)	1 (3)	5 (0)
	Diarrhea	2w	−8 (0)	−5 (0)	1 (34)	6 (0)	10(0)
		4w	−8 (0)	−5 (0)	1 (31)	6 (0)	10(0)
		8w	−8 (0)	−5 (0)	1 (29)	6 (0)	10(0)
	Constipation	2w	−11(0)	−5 (2)	0 (31)	6 (0)	7 (1)
		4w	−11(0)	−5 (1)	0 (28)	6 (0)	7 (2)
		8w	−11(0)	−5 (2)	0 (26)	6 (0)	7 (1)
	Belly pain	2w	−13 (0)	−6 (0)	0 (34)	6 (0)	9 (0)
		4w	−13 (0)	−6 (0)	0 (30)	6 (1)	9 (0)
		8w	−13 (0)	−6 (2)	0 (27)	6 (0)	9 (0)
	Gas/bloat/ flatulence	2w	−17 (0)	−6 (1)	−1(33)	6 (0)	10(0)
		4w	−17 (0)	−6 (3)	−1(28)	6 (0)	10(0)
			−17 (0)	−6 (3)	−1(25)	6 (1)	10(0)

*PROMIS GI Reflux scale versus GSRS Reflux scale; PROMIS GI Diarrhea scale versus GSRS Diarrhea scale; PROMIS GI Constipation scale versus GSRS Constipation scale; PROMIS GI Belly pain scale versus GSRS Abdominal pain scale; and PROMIS GI Gas/bloat/flatulence scale versus GSRS Indigestion scale GSRS Gastrointestinal Symptom Rating Scale; Negative score denotes improvement.

For reflux and constipation, the absolute risk reduction is 28.57%. The 95% confidence interval for this difference ranges from 11.07% to 46.08% and the NNT is 4. This means that about one in every 4 patients will benefit from the treatment. The 95% confidence interval for the NNT ranges from 2.2 to 9.0 (Table 6).

For diarrhea, the absolute risk reduction is 14.29%. The 95% confidence interval for this difference ranges from 2.69% to 25.88%. The NNT is 7. This means that about one in every 7 patients will benefit from the treatment. The 95% confidence interval for the NNT ranges from 3.9 to 37.1

For belly pain, the absolute risk reduction is 37.14%. The 95% confidence interval for this difference ranges from 19.03% to 55.25%. The NNT is 3. This means that about one in every 3 patients will benefit from the treatment. The 95% confidence interval for the NNT ranges from 1.8 to 5.3

For indigestion, the absolute risk reduction is 51.43%. The 95% confidence interval for this difference ranges from 32.74% to 70.12%. The NNT is 2. This means that about one in every 2 patients will benefit from the treatment. The 95% confidence interval for the NNT ranges from 1.4 to 3.1.

Table 6. The count of Risk Ratio, Absolute Risk Difference and NNT of 5 subtypes of GSRS score.

Variation	Vard	placebo	RR†	ARD‡	NNT§
Reflux	12	2	6.00	28.57	4
Diarrhea	5	0	--	14.29	7
Constipation	12	2	6.00	28.57	4
Belly pain	15	2	7.50	37.14	3
Gas/bloat/flatulence	21	3	7.00	51.43	2

†: Risk Ratio. ‡: Absolute Risk Difference. §: Number Needed to Treat

Discussion

The present study aimed to compare the effect of Vard traditional herbal medicine consisting of *R. damascena, G. glabra* and *N. jatamansi* with placebo for improving the symptoms of subjects with FD who were prescribed PPI (omeprazole).

According to the results, improvement of GI symptoms based on decrease in the GSRS score was greater in the group receiving Vard as add-on to omeprazole compared to the group taking the placebo. Of each sub-set symptoms, except in reflux, significant alterations were observed in Vard group over the placebo group especially in abdominal pain, indigestion, constipation and postprandial distress, suggesting the notable functionality range of Vard to improve GI symptoms in FD. Compared to baseline, within-group analyses for both placebo and Vard groups showed also statistically significant difference ($P < 0.001$) in the improvement of postprandial fullness and early satiety, and GSRS scores after intervention.

FD is a chronic and recurrent disease [46]. Due to its multifactorial pathogenesis, treatment of FD is problematic and a combination of medications is needed to modify its essential pathology [47]. Current treatments like *H. pylori* eradication, antacids, prokinetics, and antidepressants have been indicated to have the overall rate of symptom relief at only 50% [48]. Nearly 15 -20 % of patients have stable symptoms, and 30-35% of them suffer from symptoms variations [5, 49]. In this way, phytotherapy can be helpful because it can generally be effective through several mechanisms of action [50].

Recent studies have reported the effectiveness of some herbal products in FD [51]. For instance, Rikkunshito [52] and STW-5 [53] have been shown to be clinically effective in FD by improvement of GI motility and visceral pain. In the present study, decrease in the total GSRS score and 5 sub-dimensions of GI symptoms were shown after 2 and 4 weeks of intervention as well as one month follow up. While, there was no significant difference between the two groups in the improvement of reflux. Among symptom subtypes, it seems that the most likely affected symptoms by Vard were indigestion (Gas/bloat/flatulence), abdominal pain and constipation (Table 6). These results can be explained mechanistically by pointing out the effects of *R. damascena* on gastrointestinal smooth muscle motility [54] which might be associated with its gallotannins content [55]. *R. damscena* has previously been shown to affect intestines through histaminergic and cholinergic receptors, *in vivo* [56,57]. In addition, it has been indicated that *G. glabra* extract could improve gastric emptying in rats which was comparable to the effect of a gastroprokinetic drug, mosapride [30]. However, another study showed that *G. glabra* extract decreased the contractions of rat isolated duodenum suggesting probable effect of its phytochemical, isoliquiritigenin, on calcium channels [16]. This effect might be considerable in FD cases with duodenal resistance due to uncoordinated spasms [58]. In this regard, the dual dose-related effect of isoliquiritigenin on gastric and intestinal muscles has been shown, *in vivo*. It was reported that intestinal relaxation occurs by isoliquiritigenin at lower concentra-

tions and dominates over its prokinetic effect on stomach fundus stimulation. While, at high concentrations the stimulation of stomach fundus predominates over the intestinal relaxation [59]. In addition, it is worth to point out the anti-inflammatory effects of licorice [60] and rose [61] via their several bioactive compounds such as polyphenols [60,61]; because probable impaired proximal duodenal mucosal integrity and low-grade inflammation can affect the development of FD [62].

There is no previous clinical study that evaluated Vard efficacy in FD, but there are some relevant studies on licorice and rose water. A traditional formula from rose water, Jollab, has been reported to alleviate the severity and frequency of FD symptoms as well as decrease in depression score in FD patients [63]. Also, in another study, the effectiveness of GutGard, a flavonoid rich, root extract of G.glabra (75 mg, twice daily for 30 days) was shown in patients with FD via alterations in the before and after intervention scores of the Nepean dyspepsia index compared to placebo [64].

Similar to our study, Bordbar *et al.*, evaluated the efficacy of a polyherbal preparation containing *Trachyspermum ammi* (L.) Sprague, *Anethum graveolens* L., and *Zataria multiflora* Boiss. in 64 FD patients by using GSRS and SF-36 as measurement tools [13]. Unlike our study, in which we added the intervention to omeprazole, they used omeprazole (20 mg, once a day) as control drug [13]. However, in their trial, no investigation was performed for *H. pylori* infection. Similar to our results, a significant decrease was observed in scores of pain and indigestion sub-scales of GSRS, total GSRS, and postprandial distress in both groups of the aforementioned study. However, they did not measured the reflux symptoms [13]. Like our findings, the total SF-36 score at the end of the intervention increased in both groups with a significantly higher improvement in intervention group [13].

As an add-on treatment to PPIs, our study can be compared with the study of Puasripun *et al.*, [65] on 78 *H. pylori*-negative FD patients, taken clidinium/chlordiazepoxide or placebo as an add-on therapy to omeprazole. They used different measurement tools including global overall symptom scale (GOSS) and the short form Nepean dyspepsia index (SF-NDI) to assess FD symptoms and quality of life. Nevertheless, like our study, significant improvement in quality of life as well as FD symptoms, were observed in the intervention group compared to the placebo group. As a different result to our study, reflux symptoms (heartburn or regurgitation) were also improved in the intervention group significantly over the placebo group. The researchers hypothesized that this finding may be related to the antispasmodic and modulatory effect of clidinium on small bowel dysmotility. However, symptoms of acid reflux may be exacerbated by anticholinergics and benzodiazepines [65].

As a polyherbal preparation containing *G. glabra*, STW5 (Iberogast®), has also been clinically shown to decrease symptoms in FD patients. The efficacy of a 4-week treatment by STW5 in FD patients was shown by alteration of the gastrointestinal symptom (GIS) score, and GSRS on FD symptoms. In contrast to our study,

STW5 showed considerable effect in decreasing the concomitant reflux symptoms (heartburn/acid regurgitation, distinct from GERD) compared to placebo [66]. This effect was explained by several mechanisms related to the herbs in STW5 which could enhance the tonicity of the lower esophageal sphincter, reduce intragastric pressure, and help to the gastric emptying [66]. In our study, one participant reported abdominal pain and discomfort, and bloating as adverse event in Vard group which can be associated with the prokinetic [67] and laxative effects of *R. damascena* [27] which might occur in some patients because of potential osmotic penetration of fluids into the intestine [27].

So far, several studies have shown the antidepressant and anxiolytic effects of *R. damscena* [68], *N. jatamansi* [69] and *G. glabra* and their bioactive compounds [70,71]. It has been demonstrated that glycyrrhizic acid from *G. glabra* might restrain high mobility group box 1 protein (HMG-1) which results in improvement of chronic stress-induced depression through regulating kynurenine pathway [70]. Also, valerenic acid, the main active component of *N. jatamansi*, is known as agonist of gamma-aminobutyric acid (GABA) which can help sleep and mood stabilization, decrease mental and physical stress, and reduce anxiety [72]. More, its extract previously was shown to improve the symptoms of 16 FD voluntary patients [3].

As secondary outcomes, significant difference in total score of DASS-21 and its 3 subtypes (depression, anxiety and stress) in Vard group compared to placebo group suggests its effectiveness in psychiatric aspects of FD. This alteration has also been reflected in the improvement of the mental component and the total score of SF-36.

Regarding the positive effects of Vard on anxiety and depression scores as well as quality of life, these effects can be mostly attributed to *R. damascena* and *N. jatamansi* [68,69]. It seems this polyherbal medicine may play a remarkable role as a complementary agent in FD treatment that may retrieve from several mechanisms of action of these herbs in FD. However, further investigations are necessary to reveal different aspects of the effect of this medication on FD.

Limitations of the study

The limitations of our study were the short duration of intervention and follow-up. Also for long-term use, the adverse effects and compliance of this herbal drug need further investigations. More, as FD is a chronic disease, the recurrence of the symptoms is possible after discontinuing the intervention. Thus, a longer follow-up duration is also needed. More, since our studied intervention was add-on to PPIs, further studies are needed to evaluate the effect of Vard separately from PPIs. As another point, according to some evidence indicating that meals trigger at least some of the symptoms of FD, dietary and lifestyle modifications are often recommended in the management of patients with FD [73]. In our study, apart from general recommendations, we did not assess the effect of dietary habits and life style changes; so, future studies are needed to evaluate dietary habits along with medication intervention.

Conclusion

In conclusion, the results of the present study revealed that improvement of gastrointestinal symptoms including abdominal pain, indigestion, constipation, and diarrhea, along with depression, stress, and anxiety, as well as the quality of life in Vard group was significantly superior to the placebo group. These findings suggest that the Ghors-e-Vard, as a complementary therapy, may have a promising effect on resolving the FD symptoms. Additional studies need to perform in order to evaluate the effect of Vard in FD and other gastrointestinal diseases.

Conflict of Interests

There is no conflict of interest.

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