The Efficacy of *Mentha longifolia* in the Treatment of Patients With Postprandial Distress Syndrome: A Double-Blind, Randomized Clinical Trial

Mahmoud Babaeian,[1] Mohsen Naseri,[2,*] Mohammad Kamalinejad,[3] Farzaneh Ghaffari,[4] Fatemeh Emadi,[1,2] Awat Feizi,[5] Rahmatollah Rafiei,[6] Mohammad Mazaheri,[7] Seyed Abbas Hasheminejad,[1] Jae-Woo Park,[8] and Peyman Adibi[9]

[1]Department of Traditional Medicine, Faculty of Medicine, Shahed University, Tehran, IR Iran
[2]Traditional Medicine Clinical Trial Research Center, Shahed University, Tehran, IR Iran
[3]Department of Pharmacognosy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran
[4]Department of History of Medicine, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran
[5]Assistant Professor of Biostatistics Department of Biostatistics and Epidemiology, School of Health, Isfahan University of Medical Sciences, Isfahan, IR Iran
[6]Internal Medicine Department, Islamic Azad University, Najafabad Branch, Isfahan, IR Iran
[7]Assistant Professor, Traditional Medicine, Medical School, Isfahan University of Medical Sciences, Isfahan, IR Iran
[8]College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea
[9]Integrative Functional Gastroenterology Research Center, Isfahan University of Medical Sciences, Isfahan, IR Iran

Corresponding author: Mohsen Naseri, Traditional Medicine Clinical Trial Research Center, Shahed University, Tehran, IR Iran. Tel/Fax: +98-2166464320, E-mail: naseri@shahed.ac.ir

Abstract

Background: Functional dyspepsia (FD) is a common gastrointestinal disease that has various treatments, including medicinal plants.

Objectives: The current study aimed to investigate the effect of *Mentha longifolia* on relieving the symptoms and improving the quality of life (QOL) in patients with functional dyspepsia from the subgroup of postprandial distress syndrome (PDS).

Patients and Methods: This randomized, double-blind, placebo-controlled trial was conducted in a gastroenterology clinic affiliated with Isfahan University of Medical Sciences. One hundred patients diagnosed with PDS according to the ROME III criteria were assigned to two groups: the *M. longifolia* capsules (three times daily for four weeks) group and the placebo group. Tools for gathering data were the FD severity scale and QOL (Persian version of the SF-36 questionnaire). Assessments of FD symptoms were obtained at baseline and also at the end of weeks 2, 4, and 12. QOL was evaluated at baseline and at the end of week 12.

Results: At the end of treatment period, the *M. longifolia* group reported a more significant improvement in the mean severity scales of FD symptoms than the placebo group (P < 0.001). A significant difference was also observed between FD symptoms and severity scores in the two groups eight weeks after the medication was stopped. At the end of the fourth week, the greatest degrees of relief regarding epigastric bloating (70.5% vs. 21.4%, P < 0.001), epigastric fullness (68.2% vs. 31%, P < 0.001), loss of appetite (34.1% vs. 9.5%, P = 0.014) and early satiety (36.3% vs. 21.4%, P = 0.02) were observed in the control group. With *M. longifolia*, significant improvement in the scores of QOL was observed for the dimensions of general health, role-physical, social functioning, bodily pain, vitality, and mental health.

Conclusions: This study showed the efficacy of *M. longifolia* in relieving PDS symptoms and improving the QOL of patients with PDS.

Keywords: Dyspepsia, Appetite, Herbal Medicine, Traditional Medicine, Mentha

1. Background

The presence of dyspepsia in the absence of any pathologic lesion or metabolic abnormality is known as functional dyspepsia (FD) and is a highly prevalent gastrointestinal (GI) disorder observed in one-tenth to over one-third of the population (1, 2). In the absence of GI pathology, the diagnosis is based on a constellation of symptoms as follows: bothersome postprandial fullness, early satiety, and epigastric pain for over 12 weeks that first began within the last 24 weeks (2).

In addition to its high incidence, functional dyspepsia prompts frequent referrals to primary and specialty clinics due to recurrent and irritating symptoms, which lower patients' quality of life. FD has also increased national health care costs. Different therapeutic interventions have been applied to treat the disorder, but long-term satisfaction has not been achieved (3).

In recent years, several plants have been obtained from

the traditional medicine practices of different countries to treat the symptoms of FD. Dyspepsia is considered a major gastrointestinal disorder in traditional Iranian medicine (TIM) that has various causes, such as gastric maltemperamental disorders (4, 5).

One medicinal plant with a warm and dry temperament that has been used in TIM to treat digestive disorders, such as bloating, nausea, gastric pain, and hiccups, is wild mint (Pouneh or Fudanaj in Persian) (4-6); the plant *(Mentha longifolia* L. family Lamiaceae) is native to Europe, Australia, South Africa, and the Mediterranean regions, especially Iran (7). Toxicological studies have reported that *M. longifolia* is an herb with a low toxicity, and its LD50 is 3.75 g/kg (8, 9). An acute toxicity study on five different flavonoids found in the mint plant revealed that acute toxicity effects of the plant in rats are small; the lowest is for quercetin with an LD = 5 mg/g (7).

No direct animal studies on the relationship between this plant and dyspepsia have been conducted; however, quasi-similar gastrointestinal studies have shown that *M. longifolia* has anti-spasmodic and antidiarrheal effects, which act by blocking calcium channel activity in the intestinal wall (10). *M. longifolia* also has anti-nociceptive, anti-ulcer, antioxidant, anti-inflammatory, and hepatoprotective effects (9, 11-13).

In a human study pertaining to gastrointestinal diseases and *M. longifolia*, it was observed that this herb could positively affect acute nonbacterial diarrhea in regards to volume, stool consistency, and the frequency of defecation (14). Also, in another study on the effect of *M. longifolia* on secondary amenorrhea, two sets of pleasant and unpleasant side effects were noticed in patients. Among the most pleasant effects reported were reductions in various gastrointestinal symptoms, including bloating, nausea, and stomach pain (15).

2. Objectives

Considering the traditional use and pharmacologic effects of *M. longifolia*, this study aimed to investigate the effect of *M. longifolia* on relieving symptoms in patients with functional dyspepsia from a subgroup of PDS.

3. Patients and Methods

The current study was a double-blind, randomized clinical trial study that used two parallel groups and was conducted in a referral governmental gastroenterology clinic affiliated with Isfahan University of Medical Sciences from August 2013 to March 2014. The study was approved by the local medical ethics committee of Shahed University of Medical Sciences (reference numbers: 41/1681152, 2013-04-10). The trial was registered in the Iran clinical trial center (IRCT Code: IRCT2013043013183N1).

One hundred and forty two patients were visited and assessed. Those who fulfilled the inclusion criteria and signed a written informed consent form were enrolled in the study. Inclusion criteria were an age of 18 - 65 years and a diagnosis of postprandial distress syndrome according to the ROME III criteria. The patients had experienced at least one of the following symptoms several times a week in the past six months: an uncomfortable feeling of postprandial fullness and/or early satiety. Patients had normal reports for upper gastrointestinal endoscopy and were negative for *Helicobacter pylori*.

Exclusion criteria included pregnancy, breastfeeding, peptic ulcer, gastroesophageal reflux disease, dysphagia, celiac sprue, gastrointestinal surgery, irritable bowel syndrome, abdominal pain, night diarrhea, greasy or black stool, blood in stool, mental retardation, immune system disorders, severe recent weight loss, cancer, renal disorders, and the current need for or use of the following medications: antibiotics, proton pump inhibitors, H2 blockers, bismuth, metoclopramide, domeperidone, lactulose, non-steroidal anti-inflammatory drugs, corticosteroids, and herbal medicines. Finally, 100 patients were allocated equally to the *M. longifolia* or placebo group. The evaluations were carried out at baseline and also at the end of weeks 2, 4, and 12.

3.1. Herbal Drug Preparation

The herbal medicine used in this trial was the dried extract of *M. longifolia* (MLE: Mentha *longifolia L.* extract). The extract was prepared from the aerial parts of the plant obtained in the highlands of Sirjan (Iran). The herbs were approved by the herbarium of the Shahid Beheshti School of Pharmacy (Voucher specimens No. 1078). Preparation of the MLE and placebo capsules was carried out in the herbal medicine laboratory of Shahed University (Tehran, Iran).

The dry extract of the herb was prepared using a method described in a previous study (16). The MLE was placed in 500-mg capsules containing 250 mg of the dry extract of the herb and 250 mg of cornstarch as a filler. The placebo contained only 500 mg of cornstarch and was placed in similar capsules. Their packages of capsules were identical in shape, color, size, and fragrance. The drug and placebo packages were carpeted with a thin layer of peppermint essence.

The total phenolic and flavonoid compound contents of the examined plant extract were determined using a spectrophotometric method (17, 18); the former was 39.1 ± 1.6 mg GA/g. Quercetin was used as the standard, and the

content of the flavonoids in the extract was 7.58 $\pm$ 1.47 mg QU/g.

3.2. Medication, Allocation, Blinding, and Compliance

Based on previous studies, the treatment course in this double-blind, randomized clinical trial was set at four weeks (19). The patients consumed a capsule three times per day (before breakfast, lunch, and dinner) for four weeks. Therefore, patients in the MLE group received 750 mg of the extract equal to 5 g of the herb/day for four weeks and were followed up for eight weeks.

Considering the inclusion and exclusion criteria, a convenient sampling method was used for recruiting the patients. Randomization and enrollment of the patients in the MLE and placebo groups were done by the gastroenterologist equally and alternatively using permuted random blocks with a block size of two.

The MLE and placebo were packaged and alphabetically labeled with the same appearance. An independent pharmacist set the codes on the drug or placebo packets using a confidential list that contained the secret codes and was kept in sealed, opaque envelopes until the end of the study and until they were needed for data analysis. The gastroenterologist, patients, and outcome assessor were not informed which participants had received the drug and which had been given the placebo. To ensure patient compliance, the outcome assessor asked them to verify how many pills had been taken, and the number of remaining capsules was also checked. Patients who took less than 80% of the dispensed medication or experienced any type of drug intolerance were withdrawn from the study.

3.3. Instruments and Outcomes

The dyspepsia severity of the patients was assessed at baseline and at the end of weeks 2, 4, and 12. The patients' QOL was also evaluated at baseline and during their week 12 visit.

FD was diagnosed using questionnaires that the participants filled out individually. A modified ROME III questionnaire was employed to assess the symptoms of FD according to previous studies (19-21).

Epigastric discomfort/bloating/pain/fullness/burning, pre-prandial and postprandial nausea and epigastric pain, night epigastric pain, morning nausea, vomiting, retching, belching, loss of appetite, and early satiety were assessed. A four-item Likert scale (never or rarely, not very unpleasant, very unpleasant but tolerable, and cannot tolerate) was employed to answer the questions. Each participant's total score ranged between 0 and 48.

The severity of the FD in follow-ups was evaluated with the FD severity scale, which uses a 5-item Likert scale [much worse (-2), somewhat worse (-1), not different (0), somewhat better (+1), and much better (+2)], and had a total score between -32 and 32.

QOL was evaluated using the Persian version of the Short Form-36 (SF36) questionnaire. Its reliability and validity has already been verified (22). The SF-36 contains 36 items that measure the following eight health domains: vitality, general health perceptions, physical functioning, physical role functioning, emotional role functioning, social role functioning, bodily pain, and mental health.

The patients were followed-up for 12 weeks. Any side effects from their medications were recorded at each follow-up. The primary and secondary end points were the mean score of the severity of FD and the frequency distribution of patients with various severities across the study period, respectively.

3.4. Sample Size Calculation

The sample size in the current study was determined based on the following formula:

$$n = \frac{2\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2}{\Delta^2} \tag{1}$$

Where α and β are type one and two error rates that were set to 5% and 20% (or the statistical power was considered to be 80%), respectively, and Δ is the standardized effect size that was set to at least 0.6 based on the results of a previous study and resulted in 45 patients for each study group (23, 24).

3.5. Statistical Analysis

Data are reported as mean $\pm$ standard deviation (SD) or as a number and (%) for continuous and categorical data, respectively. The normality of the data was evaluated using Kolmogrov-Smirnov and Q-Q plot. Log transformation was conducted for positive skew data. Non-normal data were compared between the two groups both before and after the intervention using Mann-Whitney U-test, while the student t-test was employed for the normally distributed variables. The total FD severity scales within each group and between the two groups were compared by repeated measure analysis of variance (ANOVA). Mauchly's sphericity test was conducted to assess sphericity as a perquisite assumption. A Huynh-Feldt correction was applied when this assumption was not satisfied. Within-group comparisons at each follow-up time point were tested using repeated contrasts. All statistical analyses were conducted based on an intention-to-treat approach. P-values less than 0.05 were considered statistically significant. The Statistical Package for the Social Sciences (SPSS), version 18 (Chicago, IL), was applied for the statistical analysis.

4. Results

4.1. Participant Characteristics

In total, 142 patients who attended the clinic from August 2013 to March 2014 were assessed for eligibility, and 100 of them were randomized to receive either the *M. longifolia* or placebo (50 patients in each group). Fourteen patients dropped out during the four-week study duration; Six and eight patients were withdrawn from the study in the intervention and control groups, respectively (Figure 1). The most common complications in the intervention groups were drug intolerance (n = 2) and dermatitis (n = 1).

The mean ($\pm$ SD) age of patients was 42.8 ($\pm$ 14) years in the control group and 43 ($\pm$ 12.3) years in the intervention group (P = 0.314). Other demographic characteristics between the two groups are compared in Table 1. No significant difference was seen in any demographic characteristic or in the baseline sum means ($\pm$ SD) of different symptoms of PDS in the two groups (13.9 $\pm$ 7.60 vs. 14.2 $\pm$ 7.23, P = 0.84). All symptoms were distributed similarly between the two groups.

4.2. Effects of an Intervention on the Symptoms of PDS

Table 2 shows the results of the t-test for comparing the PDS severity between the two studied groups at different follow-up points. The observed PDS severity in the MLE group for all study points was significantly better than that in the control group (Figure 2). In addition, this tabulation presents the results of a repeated-measure ANOVA for both within and between group comparisons across the study period. The within-group differences (time effect) were only statistically significant in the MLE group (P < 0.001). Furthermore, the MLE group experienced more improvement than the control group (P < 0.001) when the between groups statistical difference (treatment interaction) was evaluated throughout the study period. The non-significance of the treatment interaction variable showed that the MLE group uniformly experienced much more improvement than the control group during the study.

In this study, the severity of baseline symptoms was not significantly associated with the proportion of drug responses. Table 3 shows that in the fourth week of the treatment, the two ROME III criteria of early satiety and epigastric fullness were significantly better in the MLE group than in the placebo group. In addition, less important symptoms, like epigastric bloating, belching, loss of appetite, epigastric pain, and post-prandial epigastric pain, were much improved in the MLE group. The greatest improvements (better and much better) were observed for epigastric bloating (70.5% vs. 21.4%, P < 0.001), epigastric fullness (68.2% vs. 31%, P < 0.001), early satiety (36.3% vs.

21.4%, P = 0.02), belching (36.3% vs. 11.9%, P = 0.001), loss of appetite (34.1% vs. 9.5%, P = 0.014), epigastric pain (31.8% vs. 21.4%, P = 0.046), and post-prandial epigastric pain (22.7% vs. 11.9%, P = 0.016), respectively.

In the second, fourth, and twelfth week of treatment, certain symptoms, such as belching, epigastric pain, and post-prandial epigastric pain, were more significantly improved in the MLE group than they were in the placebo group. However, some other symptoms, like vomiting, retching, pre-prandial epigastric pain, night epigastric pain, and epigastric burning, were not affected during the treatment course.

4.3. Effects of the Intervention on the Different Components of SF-36

Table 4 shows the different health domains of SF-36 within each group and also between the two groups. There were significant differences between the MLE and placebo scores for QOL in general health (P = 0.023), role-physical (P = 0.039), social functioning (P = 0.001), bodily pain (P = 0.002), vitality (P = 0.027), and mental health (P = 0.016) after the intervention.

5. Discussion

This study showed that four-week treatment with *M. longifolia* could relieve symptoms in patients with PDS. The etiology of PDS is multi-factorial and mainly includes delayed gastric emptying, hypersensitivity to gastric distension, local micro-inflammations, and psychological factors (25-28).

The mechanism of the effect of *M. longifolia* on the digestive system has been investigated in multiple studies (7). *M. longifolia* has a broad spectrum of pharmacological effects on the gastrointestinal, nervous, muscular, and immune systems, such as anti-inflammatory (12), antimicrobial (29), and anti-nociceptive effects (9), and also antiulcer activity (11).

In a study on five flavonoids extracted from *M. longifolia*, it was observed that the quercetin of the plant had strong antibacterial activity. It is widely accepted that flavonoids have anti-inflammatory, anti-oxidant, and hepatoprotective properties (30). In addition, since this herb contains phenolic compounds, it can heal damage inflicted by radical factors on the gastric mucosa using its free radical scavengers and antioxidant qualities (30, 31).

Considering the pathophysiological factors involved in PDS, the effect of *M. longifolia* on relieving symptoms is achieved by facilitating gastric emptying (28, 32). Multiple studies have shown that prokinetic drugs are effective at relieving the complaints of dyspeptic patients with delayed gastric emptying (33). Based on a meta-analysis of
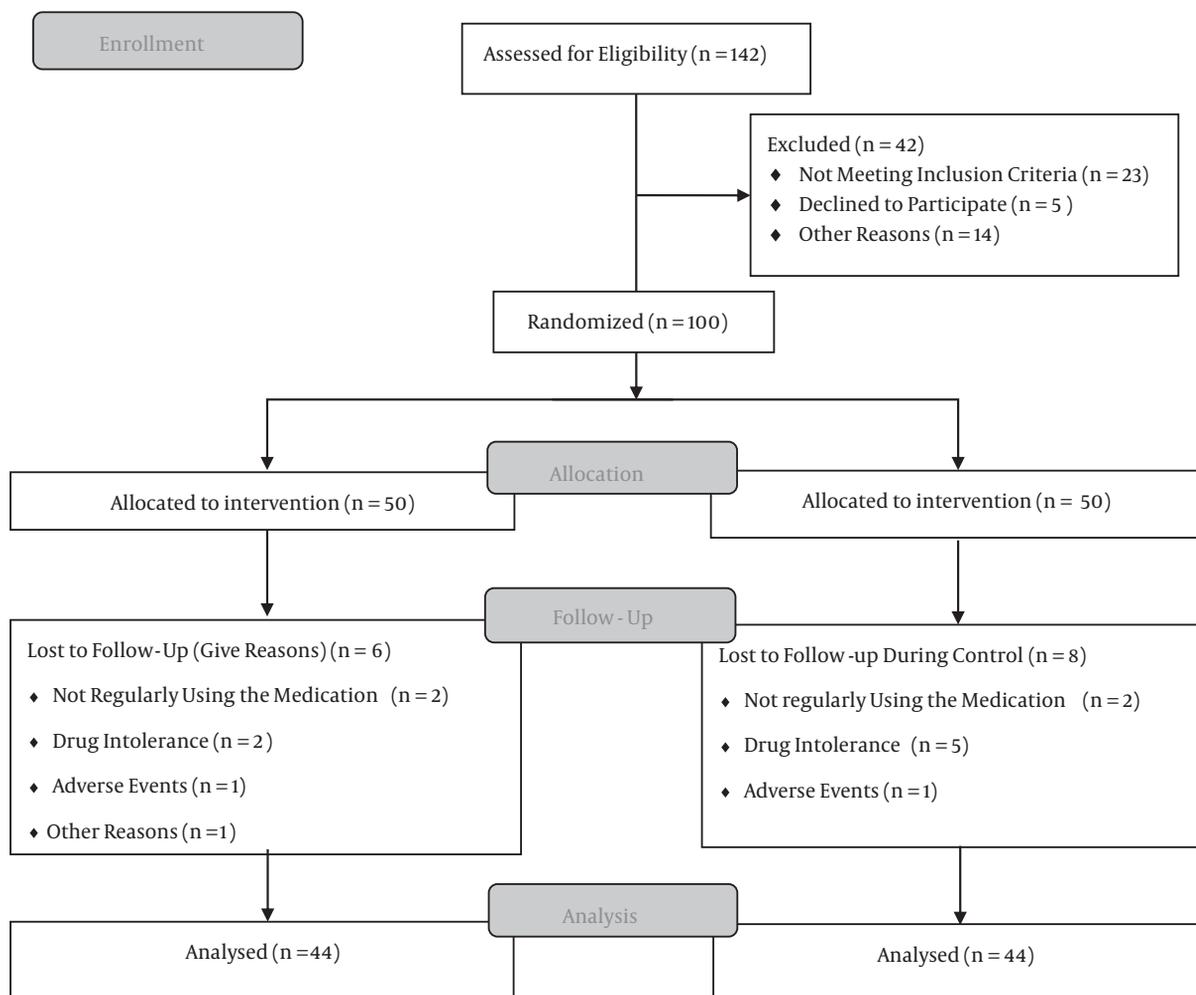
Figure 1. Flowchart of Participants Through Each Stage of the Randomized Trial

clinical trials, these drugs were significantly more effective than placebo (57% vs. 47%) (34). However, the consumption of some prokinetic drugs, such as cisapride and tegaserod, has been limited due to the presence of significant adverse events (34, 35).

Certain medicinal plants, such as modified xiaoyao san in Chinese herbal medicine, have shown better curative effects than prokinetic drugs. However, the studies for these plants have had methodological flaws, like concealment of allocation, lack of blinding, and a lack of statistical power (36).

In recent years, one of the most influential herbal compounds on gastric motility has been Iberogast (STW) (37). Iberogast is a fixed combination of several plants, such as Iberis, peppermint, chamomile, and Limon balm, that is highly effective in relieving FD symptoms in 52% - 68% of patients due to its antispasmodic and radical scavenging properties (38).

Another apparent result of this study was the significant effect of *M. Longifolia* on bloating (70.5% vs. 21.4%, P < 0.001). The prominent effect of *M. longifolia* on bloating could be due to its antispasmodic activity produced mainly through varying calcium mobilization and partly by the activation of potassium channels (7, 39). This feature of *M. longifolia* is similar to the effect of peppermint oil on abdominal distention (40).

This study also showed a significant difference between FD symptom severity scores in the two groups eight weeks after the medication was cut, which is of great importance in TIM, where medicinal or non-medicinal treatment of digestive disorders prevents the infliction of many other health problems. Owing to different effects of drugs,

Table 1. Demographic Characteristics of Patients in the *M. longifolia* and Placebo Groups (n = 50)[a]

Demographic Characteristics	Control (n = 50)	M. longifolia	P Value[b]
Sex			> 0.999
Male	10 (20)	10 (20)	
Female	40 (80)	40 (80)	
Body mass index, kg/m²[b]			0.071
< 18.5	6 (12)	1 (2)	
18.5 - 24.99	27 (54)	21 (42)	
25 - 29.99	13 (26)	24 (48)	
≥ 30	4 (8)	4 (8)	
Marital status			0.612
Single	9 (18)	7 (14)	
Married	41 (82)	43 (96)	
Literacy			0.222
< High School Diploma	46 (92)	38 (76)	
≥ High School Diploma	4 (8)	12 (24)	
Smoking			0.501
Current Smoker	3 (6)	5 (10)	
Nonsmoker	47 (94)	45 (90)	
Coffee consumption			0.634
≥ 2 cups	1 (2)	1 (2)	
1 cup	0	1 (2)	
0 cups	49 (98)	48 (96)	
Tea consumption			0.465
≥ 4 cups	20 (40)	17 (34)	
1 - 3 cups	26 (52)	31 (62)	
0 cups	4 (8)	2 (4)	

[a] Values are expressed as No. (%).
[b] Chi-square Test.

Table 2. Within- and Between-Group Comparisons of the Mean Severity Score of Postprandial Distress Syndrome[a]

	Mean (SD) Severity Score of all Symptoms			Time[b]	Treatment[b]	Time by Treatment[b]
	Week 2	Week 4	Week 12			
Group					F = 18.30, P < 0.001	F = 2.35, P = 0.1
M. longifolia	3.523 ± 4.79	4.244 ± 6.05)	0.182 ± 3.39	F = 10.02, P < 0.001		
Placebo	0.024 ± 3.412	0.027 ± 5.29)	-1.238 ± 2.67	F = 1.02, P = 0.21		
T Value	4.18	3.45	2.15			
P Value[c]	< 0.001	0.001	0.034			

[a] Values are expressed as mean ± SD.
[b] Analysis of variance (ANOVA) repeated measures test for assessing the time effect, treatment effect, and the interaction between time and treatment.
[c] Manne Whitney U Test.

Table 3. Distributions of Symptoms Compared Between the Two Groups Across the Study Period[a]

Symptom	Mentha longifolia					Placebo					P Value[b]
	-2[c]	-1[c]	0[c]	+1[c]	+2[c]	-2[c]	-1[c]	0[c]	+1[c]	+2[c]	
Epigastric discomfort											
Week 2	0	4.4	66.7	24.4	4.4	0	4.7	88.4	7	0	0.017
Week 4	0	9.1	56.8	31.8	2.3	0	7.1	78.6	11.9	2.4	0.17
Week 12	0	2.3	93.2	4.5	0	0	7.1	88.1	4.8	0	0.5
Early satiety											
Week 2	0	8.9	57.8	26.7	6.7	0	9.3	76.7	14	0	0.05
Week 4	0	4.5	59.1	29.5	6.8	0	16.7	61.9	21.4	0	0.02
Week 12	0	6.8	77.3	15.9	0	0	7.1	92.9	0	0	0.057
Epigastric bloating											
Week 2	0	6.7	31.1	60	2.2	0	18.6	67.4	14	0	< 0.001
Week 4	0	6.8	22.7	59.1	11.4	0	21.4	57.1	21.4	0	< 0.001
Week 12	0	22.7	52.3	25	0	0	26.2	66.7	7.1	0	0.12
Pre-prandial nausea											
Week 2	0	0	80	20	0	0	4.7	90.7	4.7	0	0.012
Week 4	2.3	0	77.3	18.2	2.3	0	14.3	71.4	14.3	0	0.13
Week 12	2.3	6.8	81.8	9.1	0	0	11.9	85.7	2.4	0	0.45
Post-prandial nausea											
Week 2	0	0	80	17.8	2.2	0	2.3	93	4.7	0	0.018
Week 4	0	0	79.5	18.2	2.3	0	2.4	88.1	9.5	0	0.09
Week 12	2.3	2.3	90.9	4.5	0	0	0	100	0	0	0.7
Belching											
Week 2	0	6.7	60	33.3	0	0	32.6	58.1	7	2.3	0.001
Week 4	0	11.4	52.3	29.5	6.8	0	38.1	50	11.9	0	0.001
Week 12	2.3	9.1	70.5	18.2	0	2.4	31	54.8	11.9	0	0.047
Loss of appetite											
Week 2	0	6.7	73.3	17.8	2.2	0	7	81.4	11.6	0	0.3
Week 4	0	9.1	56.8	31.8	2.3	0	14.3	76.2	9.5	0	0.014
Week 12	0	13.6	70.5	15.9	0	0	7.1	81	11.9	0	0.8
Epigastric fullness											
Week 2	0	13.3	22.2	62.2	2	0	25.6	53.5	20.9	0	< 0.001
Week 4	2.3	11.4	18.2	47.7	20.5	7.1	31	31	28.6	2.4	< 0.001
Week 12	0	40.9	31.8	27.3	0	0	45.2	31	23.8	0	0.65
Epigastric pain											
Week 2	0	17.8	57.8	24.4	0	0	32.6	55.8	11.6	0	0.049
Week 4	0	13.6	54.5	27.3	4.5	0	31	47.6	21.4	0	0.046
Week 12	0	0	88.6	11.4	0	2.4	33.3	52.4	11.9	0	0.002
Post-prandial epigastric pain											
Week 2	0	0	84.4	15.6	0	0	11.6	81.4	7	0	0.021
Week 4	0	2.3	75	18.2	4.5	0	16.7	71.4	11.9	0	0.016
Week 12	0	0	90.9	9.1	0	0	11.9	83.3	4.8	0	0.036

[a] Values are expressed as percentages.
[b] Between Groups P value assessed by Chi-square test
[c] Much Worse, -2; Somewhat Worse, -1; No Different, 0; Somewhat Better, +1; Much Better, +2.

TIM also recommends limited medicinal treatment periods for digestive disorders. Therefore, it seems preferable to consider the patient's characteristics when prescribing medicinal herbs. Combinations of medicinal herbs should also be used so that their interactions have a cumulative effect. This TIM viewpoint is similar to the theory of synergistic effect in modern herbal studies (5, 41).

Table 4. Short Form (SF-36) Health Survey Scores in the *M. longifolia* and Placebo Groups Before and After the Intervention

| SF-36 Domains	Groups Median (IQR)		P Value[a]
	M. longifolia	Placebo	
General health			
Before	50 (35.94 - 64.06)	50 (31.25 - 68.75)	0.803
After	55.25 (37.5 - 70.19)	47.75 (31.25 - 51.56)	0.023
Physical functioning			
Before	80 (63.75 - 90)	82.5 (55 - 90)	0.627
After	80 (60 - 90)	83 (58.75 - 90)	0.314
Role-physical			
Before	40.2 (30 - 75)	45 (25 - 75)	0.405
After	43 (35 - 75)	35 (18.75 - 50)	0.039
Role-emotional			
Before	33.33 (33.33 - 66.66)	32.34 (32.3 - 65.26)	0.908
After	34.33 (30.75 - 67)	32 (29.25 - 66)	0.803
Social functioning			
Before	61.5 (37 - 75)	63.5 (37.5 - 78.13)	0.612
After	65.50 (50 - 75)	50 (46.88 - 75)	0.001
Bodily pain			
Before	50 (36 - 62.5)	50 (25 - 65.63)	0.915
After	55.8 (40.63 - 62.5)	46 (34.38 - 62.5)	0.002
Vitality			
Before	42.5 (30 - 55)	47.5 (30 - 70)	0.192
After	48.25 (36.25 - 60)	41.5 (30 - 56.25)	0.027
Mental health			
Before	50 (36 - 64)	48 (32 - 60)	0.363
After	57 (40 - 67)	48 (35 - 60)	0.016

[a]Independent sample t-test

This study was the first clinical trial to show the effects of *M. longifolia* on the QOL in patients with PDS. In the current study, general health, role-physical, social functioning, bodily pain, vitality, and mental health improved clinically within the intervention group.

Some studies on QOL in patients with FD that used the SF-36 questionnaire have indicated that the disorder affects all aspects of quality of life, particularly the physical ones (42). Other studies on QOL in patients with FD have concluded that somatization and chronic fatigue are the chief risk factors of dyspeptic patients (43).

M. longifolia can affect the multifactorial nature of FD and target different pathophysiological features of FD, including epigastric discomfort, micro-inflammation, and postprandial pain. The quercetin present in *M. Longifo-*

lia is a bioflavonoid with various pharmacological effects, such as antioxidant, anti-inflammatory, and neuroprotective properties. Quercetin can stop the production of excessive corticotrophin-releasing factor (44, 45) and therefore influence some aspects of life, particularly anxiety, depression, and inflammatory pain.

The current study had some limitations. FD is a qualitative disorder and therefore subjective; its evaluation was an overall variable. The severity of FD is spectral, and its generalization to all patients is low. The single-center design of research also led to the inclusion of a more homogeneous study population and raised the possibility of limited external validity of the results. The sample size could have been larger, and the follow-up period could have been longer. Hence, future investigations might include larger
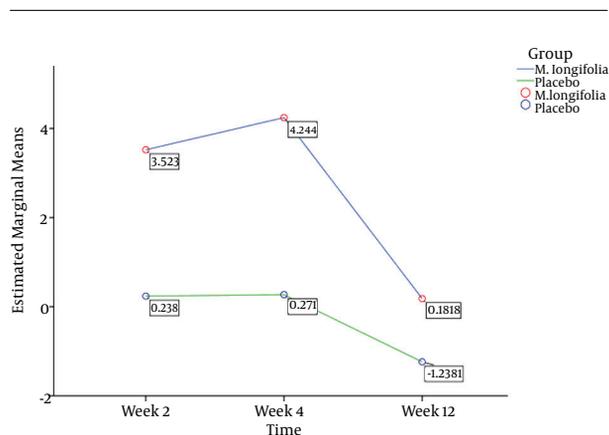
Figure 2. Mean Severity Score for all Symptoms in the Intervention and Placebo Groups Over the Study Period

numbers of patients with longer periods of follow-up with multi-center designs.

5.1. Conclusions

M. longifolia was effective and tolerable in relieving the symptoms of PDS and improving the QOL of patients with PDS. Many of these effects were observed even eight weeks after discontinuation of *M. longifolia*.

Acknowledgments

Footnotes

Authors' Contribution: Mahmoud Babaeian carried out the design and coordinated the study, participated in the clinical investigation, and drafted the manuscript; Mohsen Naseri contributed to the conception and design of the work, revised the draft, and agreed with all aspects of the work; Peyman Adibi aided in the study design, data analyses, and interpretation; Rahmatollah Rafiei contributed to participant recruitment and data gathering; Awat Feizi was the statistical consultant and conducted an analysis of the data; Mohammad Mazaheri participated in the data collection and preparing of the final draft of the manuscript; Mohammad Kamalinejad, Farzaneh Ghaffari, Fatemeh Emadi, Seyed Abbas Hasheminejad, and Jae-Woo Park coordinated the study idea and design and oversaw the grant writing. All authors contributed to the design and writing of the manuscript.

References

1. Brun R, Kuo B. Functional dyspepsia. *Therap Adv Gastroenterol.* 2010;**3**(3):145–64. doi: 10.1177/1756283X10362639. [PubMed: 21180597].
2. Chang L, Toner BB, Fukudo S, Guthrie E, Locke GR, Norton NJ, et al. Gender, age, society, culture, and the patient's perspective in the functional gastrointestinal disorders. *Gastroenterology.* 2006;**130**(5):1435–46. doi: 10.1053/j.gastro.2005.09.071. [PubMed: 16678557].
3. Collingwood S, Witherington J. Therapeutic approaches towards the treatment of gastrointestinal disorders. *Drug News Perspect.* 2007;**20**(2):139–44. [PubMed: 17440638].
4. Ibn-e-sina . The Canon of Medicine. Matbooat; 2005.
5. Babaeian M, Naseri M, Kamalinejad M, Ghaffari F, Emadi F, Feizi A, et al. Herbal Remedies for Functional Dyspepsia and Traditional Iranian Medicine Perspective. *Iran Red Crescent Med J.* 2015;**17**(11):ee20741. doi: 10.5812/ircmj.20741. [PubMed: 26734483].
6. Sahib AS. Treatment of irritable bowel syndrome using a selected herbal combination of Iraqi folk medicines. *J Ethnopharmacol.* 2013;**148**(3):1008–12. doi: 10.1016/j.jep.2013.05.034. [PubMed: 23707209].
7. Mikaili P, Mojaverrostami S, Moloudizargari M, Aghajanshakeri S. Pharmacological and therapeutic effects of Mentha Longifolia L. and its main constituent, menthol. *Anc Sci Life.* 2013;**33**(2):131–8. doi: 10.4103/0257-7941.139059. [PubMed: 25284948].
8. Alamgeer MS, Jabeen Q, Bashir S, Malik MNH, Khan HU, Rahman MSU, et al. Antihypertensive and toxicity studies of aqueous methanolic extract of Mentha longifolia L. *JAPS.* 2013;**23**(6).
9. Amabeoku GJ, Erasmus SJ, Ojewole JA, Mukinda JT. Antipyretic and antinociceptive properties of Mentha longifolia Huds. (Lamiaceae) leaf aqueous extract in rats and mice. *Methods Find Exp Clin Pharmacol.* 2009;**31**(10):645–9. doi: 10.1358/mf.2009.31.10.1441861. [PubMed: 20140273].
10. Shah AJ, Bhulani NN, Khan SH, Ur Rehman N, Gilani AH. Calcium channel blocking activity of Mentha longifolia L. explains its medicinal use in diarrhoea and gut spasm. *Phytother Res.* 2010;**24**(9):1392–7. doi: 10.1002/ptr.3263. [PubMed: 20669262].
11. Gul H, Abbas K, Qadir M. Gastro-protective effect of ethanolic extract of Mentha longifolia in alcohol-and aspirin-induced gastric ulcer models. *Bangladesh J Pharmacology.* 2015;**10**(1):241–5.
12. Karimian P, Kavoosi G, Amirghofran Z. Anti-inflammatory effect of Mentha longifolia in lipopolysaccharide-stimulated macrophages: reduction of nitric oxide production through inhibition of inducible nitric oxide synthase. *J Immunotoxicol.* 2013;**10**(4):393–400. doi: 10.3109/1547691X.2012.758679. [PubMed: 23350953].
13. Mimica-Dukic N, Popovic M, Jakovljevic V, Szabo A, Gašic O. Pharmacological studies of Mentha longifolia phenolic extracts. II. Hepatoprotective activity. *Pharmaceutical biol.* 1999;**37**(3):221–4.
14. Ghazanfarpour M, Sadeghi R, Kiani M, Khorsand I, Saeidi M. Most Common Herbal Medicines in the Treatment of Iranian Children: A Systematic Review. *Int J Ped.* 2014;**2**(4.3):437–44.
15. Mokaberinejad R, Zafarghandi N, Bioos S, Dabaghian FH, Naseri M, Kamalinejad M, et al. Mentha longifolia syrup in secondary amenorrhea: a double-blind, placebo-controlled, randomized trials. *Daru.* 2012;**20**(1):97. doi: 10.1186/2008-2231-20-97. [PubMed: 23351184].
16. Freire RB, Borba HR, Coelho CD. Ruta graveolens L. toxicity in Vampirolepis nana infected mice. *Indian J Pharmacol.* 2010;**42**(6):345–50. doi: 10.4103/0253-7613.71898. [PubMed: 21189902].

17. Marinova D, Ribarova F, Atanassova M. Total phenolics and total flavonoids in Bulgarian fruits and vegetables. *UCTM.* 2005;**40**(3):255–60.

18. Beketov EV, Pakhomov VP, Nesterova OV. Improved method of flavonoid extraction from bird cherry fruits. *Pharmaceutical Chem J.* 2005;**39**(6):316–8.

19. Holtmann G, Adam B, Haag S, Collet W, Grunewald E, Windeck T. Efficacy of artichoke leaf extract in the treatment of patients with functional dyspepsia: a six-week placebo-controlled, double-blind, multicentre trial. *Aliment Pharmacol Ther.* 2003;**18**(11-12):1099–105. [PubMed: 14653829].

20. Drossman DA, Corazziari E, Delvaux M, Spiller R, Talley NJ, Thompson WG. Appendix B: Rome III diagnostic criteria for functional gastrointestinal disorders. *Revista de gastroenterologia de Mexico.* 2010;**75**(4):511.

21. Adibi P, Keshteli AH, Esmaillzadeh A, Afshar H, Roohafza H, Bagherian-Sararoudi R, et al. The study on the epidemiology of psychological, alimentary health and nutrition (SEPAHAN): overview of methodology. *J Res Med Sci.* 2012;**17**.

22. Motamed N, Ayatollahi AR, Zare N, Sadeghi-Hassanabadi A. Validity and reliability of the Persian translation of the SF-36 version 2 questionnaire. *East Mediterr Health J.* 2005;**11**(3):349–57. [PubMed: 16602453].

23. Fleiss JL. Reliability of measurement. ; 1986.

24. Bortolotti M, Coccia G, Grossi G, Miglioli M. The treatment of functional dyspepsia with red pepper. *Aliment Pharmacol Ther.* 2002;**16**(6):1075–82. [PubMed: 12030948].

25. Mayer EA, Collins SM. Evolving pathophysiologic models of functional gastrointestinal disorders. *Gastroenterology.* 2002;**122**(7):2032–48. [PubMed: 12055608].

26. Mizuta Y, Shikuwa S, Isomoto H, Mishima R, Akazawa Y, Masuda J, et al. Recent insights into digestive motility in functional dyspepsia. *J Gastroenterol.* 2006;**41**(11):1025–40. doi: 10.1007/s00535-006-1966-z. [PubMed: 17160514].

27. Tack J, Lee KJ. Pathophysiology and treatment of functional dyspepsia. *J Clin Gastroenterol.* 2005;**39**(5 Suppl 3):S211–6. [PubMed: 15798487].

28. Karamanolis G, Caenepeel P, Arts J, Tack J. Association of the predominant symptom with clinical characteristics and pathophysiological mechanisms in functional dyspepsia. *Gastroenterology.* 2006;**130**(2):296–303. doi: 10.1053/j.gastro.2005.10.019. [PubMed: 16472585].

29. Mkaddem M, Bouajila J, Ennajar M, Lebrihi A, Mathieu F, Romdhane M. Chemical composition and antimicrobial and antioxidant activities of Mentha (longifolia L. and viridis) essential oils. *J Food Sci.* 2009;**74**(7):M358–63. doi: 10.1111/j.1750-3841.2009.01272.x. [PubMed: 19895481].

30. Kumar S, Pandey AK. Chemistry and biological activities of flavonoids: an overview. *ScientificWorldJournal.* 2013;**2013**:162750. doi: 10.1155/2013/162750. [PubMed: 24470791].

31. Min YS, Lee SE, Hong ST, Kim HS, Choi BC, Sim SS, et al. The Inhibitory Effect of Quercetin-3-O-beta-D-Glucuronopyranoside on Gastritis and Reflux Esophagitis in Rats. *Korean J Physiol Pharmacol.* 2009;**13**(4):295–300. doi: 10.4196/kjpp.2009.13.4.295. [PubMed: 19885013].

32. Said O, Saad B, Fulder S, Khalil K, Kassis E. Weight loss in animals and humans treated with "weighlevel", a combination of four medicinal plants used in traditional arabic and islamic medicine. *Evid Based Complement Alternat Med.* 2011;**2011**:874538. doi: 10.1093/ecam/nen067. [PubMed: 18952688].

33. Saad RJ, Chey WD. Review article: current and emerging therapies for functional dyspepsia. *Aliment Pharmacol Ther.* 2006;**24**(3):475–92. doi: 10.1111/j.1365-2036.2006.03005.x. [PubMed: 16886913].

34. Miwa H, Ghoshal UC, Fock KM, Gonlachanvit S, Gwee KA, Ang TL, et al. Asian consensus report on functional dyspepsia. *J Gastroenterol Hepatol.* 2012;**27**(4):626–41. doi: 10.1111/j.1440-1746.2011.07037.x. [PubMed: 22142407].

35. Pasricha PJ. Desperately seeking serotonin... A commentary on the withdrawal of tegaserod and the state of drug development for functional and motility disorders. *Gastroenterology.* 2007;**132**(7):2287–90. doi: 10.1053/j.gastro.2007.04.057. [PubMed: 17570201].

36. Qin F, Huang X, Ren P. Chinese herbal medicine modified xiaoyao san for functional dyspepsia: meta-analysis of randomized controlled trials. *J Gastroenterol Hepatol.* 2009;**24**(8):1320–5. doi: 10.1111/j.1440-1746.2009.05934.x. [PubMed: 19702899].

37. Hohenester B, Ruhl A, Kelber O, Schemann M. The herbal preparation STW5 (Iberogast) has potent and region-specific effects on gastric motility. *Neurogastroenterol Motil.* 2004;**16**(6):765–73. doi: 10.1111/j.1365-2982.2004.00548.x. [PubMed: 15601427].

38. Ottillinger B, Storr M, Malfertheiner P, Allescher HD. STW 5 (Iberogast(R))–a safe and effective standard in the treatment of functional gastrointestinal disorders. *Wien Med Wochenschr.* 2013;**163**(3-4):65–72. doi: 10.1007/s10354-012-0169-x. [PubMed: 23263639].

39. Bahmani M, Zargaran A, Rafieian-Kopaei M. Identification of medicinal plants of Urmia for treatment of gastrointestinal disorders. *Revista Brasileira de Farmacognosia.* 2014;**24**(4):468–80.

40. Liu JH, Chen GH, Yeh HZ, Huang CK, Poon SK. Enteric-coated peppermint-oil capsules in the treatment of irritable bowel syndrome: a prospective, randomized trial. *J Gastroenterol.* 1997;**32**(6):765–8. [PubMed: 9430014].

41. Wagner H. Multitarget therapy–the future of treatment for more than just functional dyspepsia. *Phytomedicine.* 2006;**13 Suppl 5**:122–9. doi: 10.1016/j.phymed.2006.03.021. [PubMed: 16772111].

42. Aro P, Talley NJ, Agreus L, Johansson SE, Bolling-Sternevald E, Storskrubb T, et al. Functional dyspepsia impairs quality of life in the adult population. *Aliment Pharmacol Ther.* 2011;**33**(11):1215–24. doi: 10.1111/j.1365-2036.2011.04640.x. [PubMed: 21443537].

43. Van Oudenhove L, Vandenberghe J, Vos R, Fischler B, Demyttenaere K, Tack J. Abuse history, depression, and somatization are associated with gastric sensitivity and gastric emptying in functional dyspepsia. *Psychosom Med.* 2011;**73**(8):648–55. doi: 10.1097/PSY.0b013e31822f32bf. [PubMed: 21949416].

44. Valerio DA, Georgetti SR, Magro DA, Casagrande R, Cunha TM, Vicentini FT, et al. Quercetin reduces inflammatory pain: inhibition of oxidative stress and cytokine production. *J Nat Prod.* 2009;**72**(11):1975–9. doi: 10.1021/np900259y. [PubMed: 19899776].

45. Bhutada P, Mundhada Y, Bansod K, Ubgade A, Quazi M, Umathe S, et al. Reversal by quercetin of corticotrophin releasing factor induced anxiety- and depression-like effect in mice. *Prog Neuropsychopharmacol Biol Psychiatry.* 2010;**34**(6):955–60. doi: 10.1016/j.pnpbp.2010.04.025. [PubMed: 20447436].