Pimpinella anisum in the treatment of functional dyspepsia: A double-blind, randomized clinical trial

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ORIGINAL ARTICLE

Pimpinella anisum in the treatment of functional dyspepsia: A double-blind, randomized clinical trial

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Background: We aimed to evaluate the effects of *Pimpinella anisum* (anise) from Apiaceae family on relieving the symptoms of postprandial distress syndrome (PDS) in this double-blind randomized clinical trial. **Materials and Methods:** Totally, 107 patients attending the gastroenterology clinic, aged 18-65 years, diagnosed with PDS according to ROME III criteria and signed a written consent form were enrolled. They were randomized to receive either anise or placebo, blindly, for 4 weeks. Anise group included 47 patients and received anise powders, 3 g after each meal (3 times/day). Control group involved 60 patients and received placebo powders (corn starch), 3 gafter each meal (3 times/day). The severity of Functional dyspepsia (FD) symptoms was assessed by FD severity scale. Assessments were done at baseline and by the end of weeks 2, 4 and 12. Mean scores of severity of FD symptoms and the frequency distribution of patients across the study period were compared. **Results:** The age, sex, body mass index, smoking history, and coffee drinking pattern of the intervention and control groups were not significantly different. Mean (standard deviation) total scores of FD severity scale before intervention in the anise and control groups were 10.6 (4.1) and 10.96 (4.1), respectively ($P = 0.6$). They were 7.04 (4.1) and 12.30 (4.3) by week 2, respectively ($P = 0.0001$), 2.44 (4.2) and 13.05 (5.2) by week 4, respectively ($P = 0.0001$), and 1.08 (3.8) and 13.30 (6.2) by week 12, respectively ($P = 0.0001$). **Conclusion:** This study showed the effectiveness of anise in relieving the symptoms of postpartum depression. The findings were consistent across the study period at weeks 2, 4 and 12.

Key words: Anise, functional dyspepsia, *Pimpinella anisum*, postprandial distress syndrome

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INTRODUCTION

Functional dyspepsia (FD) is a prevalent gastrointestinal (GI) disorder. Its prevalence is different in various populations and outpatient clinics.[1] The patients suffer from dyspepsia, but no pathologic lesion, or metabolic abnormality is identified.[2] They complain about epigastric pain/burning or upper abdomen postprandial discomforts. According to Rome III criteria, FD includes two main subtypes of epigastric pain syndrome and postprandial distress syndrome (PDS).[3,4] The latter involves patients with meal-related symptoms of bothersome postprandial fullness and early satiety. Its etiology is very complex and may include gastric dysmotility (delayed gastric emptying),[5-7] *Helicobacter pylori* infection,[8-12] local inflammations,[2,13-17] abnormal brain-gut interactions,[18-26] abnormal acid secretion,[27,28] genetic susceptibility,[29-31] imbalanced autonomic nervous system and visceral hypersensitivity.[32-37] Although the regular pharmacologic treatments for FD include antacids, kinetic-modifying agents, anti-*H. pylori* antibiotics, anxiolytics, and antidepressants, their benefits are limited in many cases and remained unsatisfactory.[38,39] That's why the search for optimum treatment is continued, and alternative medicine has gained more and more popularity among the patients and even physicians. It has been estimated by World Health Organization that probably 80% of the population around the world may trust traditional medicine to meet their primary health care needs.[40] Unfortunately, there isn't enough satisfactory evidence based on randomized clinical trials to demonstrate the efficacy and safety of the majority of herbal medicines. One of the herbs in the latter group used to treat patients in over 4000-year history of Iranian medicine was *Pimpinella anisum* (Apiaceae).[41] Different therapeutic effects have been

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reported for anise including antioxidant, antifungal,[42] antimicrobial,[43] analgesic,[44] anticonvulsant[45,46] and antispastic[47] properties. It also has many GI effects. For instance, anise implemented its antiulcer effects by inhibiting gastric mucosal damage.[48] The aromatic effects of anise have been effective in the palliation of nausea.[49] Its laxative property has been effective in the treatment of constipation.[50] The aim of current clinical trial was to assess the effects of anise fruit on patients with PDS.

MATERIALS AND METHODS

Study design

The current study was a double-blind, randomized clinical trial conducted in Isfahan University of Medical Sciences (IUMS). Patients attending Gastroenterology Clinic of the university hospital from August 2013 to March 2014 were evaluated. Totally, 180 patients were visited and assessed. Those who fulfilled the inclusion criteria and signed a written consent form were enrolled in the study. The research protocol was approved by Ethical Committee. The study was registered in Iranian Registry of Clinical Trials (registration number, 2013101214980). Inclusion criteria were age of 18-65 years and diagnosed with PDS according to ROME III criteria. The patients had at least one of the following symptoms occurring several times a week in the past 6 months: The discomfort feeling of postprandial fullness and/or early satiety. Exclusion criteria included pregnancy, breastfeeding, peptic ulcer, gastroesophageal reflux disease, dysphagia, celiac, GI surgery, irritable bowel syndrome, abdominal pain, night diarrhea, greasy or black stool, blood in stool, mental retardation, immune system disorders, major depression, bipolar disorder and psychosomatic disorders, severe recent weight loss, cancer, renal disorders, current use of antibiotics, proton pump inhibitors, H2 blockers, bismuth, metoclopramide, domperidone, lactulose, nonsteroid anti-inflammatory drugs, corticosteroids, herbal medicines and drug abuse. Patients who took <80% of administered medication or had drug intolerance were withdrawn from the study.

Subjects and intervention

Totally, 107 patients were enrolled in the study [Figure 1]. They were randomized by simple randomization method to blindly receive either anise or placebo for 4 weeks. Intervention group consisted of 47 patients and received anise powder, 3 gafter each meal (3 times/day). According to the Barnes *et al*.,[51] administration of up to 20 g/day anise powder is safe. The anise seeds were prepared by Barij Essence Pharmaceutical Company (MashhadArdehal, Iran) as a gift. This plant specimen was kept in their herbarium with number 1697.[52] Control group included 60 patients and received placebo powder, 3 g after each meal (3 times/day). The latter included corn starch and were similar

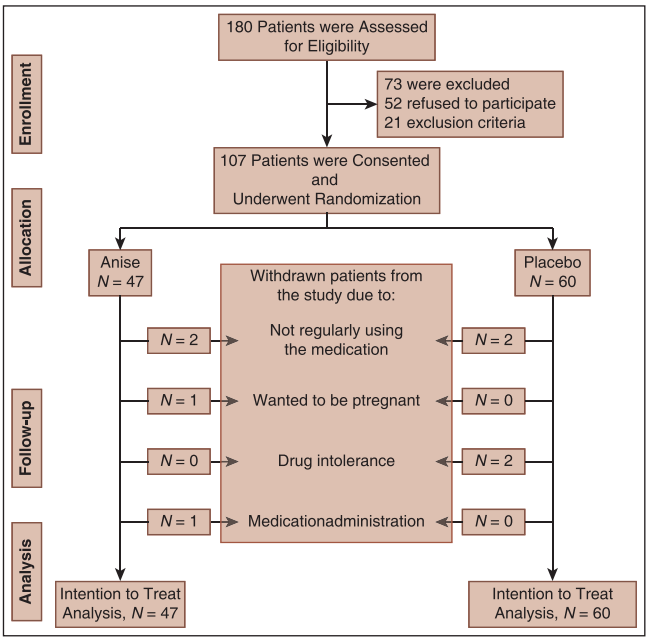

Figure 1: Consort flowchart of the study

to anise package in shape, color, and size. Both powders were prepared in similar packages by Pharmacognosy Department of Isfahan School of Pharmacy at IUMS. One week medications were supplied to the patients at the beginning of the each week for 4 weeks. Both patients and doctors were blind to the treatments.

Instruments and outcomes

To evaluate the presence or absence of symptoms of FD, modified ROME III questionnaire,[3,53] was used. Its validity and reliability have been tested before.[54] The diagnosis of FD was based on the questionnaire filled out individually. To assess the severity of the disorder, FD severity scale was employed.[55] 4-item Likert scale (never or rarely, not very unpleasant, very unpleasant but tolerable, and can't tolerate) was employed to answer the questions. Each participant's total score was between 0 and 48. A detailed questionnaire was prepared to record the medication side effects too.

All patients were followed-up for 12 weeks. The primary and secondary endpoints were the mean score of severity of FD and the frequency distribution of patients with various severities across the study period, respectively. Assessments were carried out at baseline and at the end of weeks 2, 4 and 12.

Statistical analysis

Intention to treat analysis was used to avoid the bias associated with nonrandom loss of patients. Characteristics of the two groups were compared before and after intervention using Mann-Whitney U and Kruskal-Wallis tests for nonparametric variables and Student's *t*-test for parametric variables. The changes from the baseline to the end of study period within

Table 1: Comparison of mean (SD) scores of severity of FD within and between the two groups across the study period

Symptom/time	FD severity score, mean (SD)		Between groups
	Anise, *n* = 47	Placebo, *n* = 60	*P***
Epigastric discomfort			
Baseline	0.47 (0.58)	0.50 (0.59)	0.80
Week 2	0.30 (0.55)	0.42 (0.56)	0.20
Week 4	0.09 (0.35)	0.40 (0.62)	0.001
Week 12	0.09 (0.35)	0.38 (0.66)	0.003
Within group	0.0001	0.02	
*P**			
Early satiety			
Baseline	0.92 (1.20)	0.93 (1.1)	0.90
Week 2	0.66 (0.94)	0.88 (1.1)	0.45
Week 4	0.30 (0.62)	0.90 (1.2)	0.008
Week 12	0.04 (0.20)	0.80 (1.2)	0.0001
Within group	0.0001	0.8	
*P**			
Epigastric bloating			
Baseline	0.74 (0.77)	0.55 (0.62)	0.20
Week 2	0.51 (0.72)	0.53 (0.67)	0.70
Week 4	0.15 (0.36)	0.58 (0.79)	0.001
Week 12	0.02 (0.14)	0.72 (0.95)	0.0001
Within group	0.0001	0.1	
*P**			
Preprandial nausea			
Baseline	0.04 (0.20)	0.03 (0.18)	0.80
Week 2	0.02 (0.14)	0.08 (0.42)	0.45
Week 4	0.02 (0.14)	0.08 (0.42)	0.45
Week 12	0.06 (0.32)	0.08 (0.42)	0.85
Within group	0.6	0.4	
*P**			
Postprandial nausea			
Baseline	0.04 (0.20)	0.07 (0.31)	0.85
Week 2	0.02 (0.14)	0.07 (0.31)	0.45
Week 4	0.06 (0.32)	0.05 (0.22)	0.90
Week 12	0.06 (0.32)	0.08 (0.42)	0.85
Within group	0.7	0.4	
*P**			
Morning nausea			
Baseline	0.02 (0.14)	0.03 (0.18)	0.70
Week 2	0.02 (0.14)	0.03 (0.18)	0.70
Week 4	0.02 (0.14)	0.03 (0.18)	0.70
Week 12	0.02 (0.14)	0.03 (0.18)	0.70
Within group	1.0	1.0	
*P**			
Vomiting			
Baseline	0.06 (0.24)	0.03 (0.18)	0.45
Week 2	0.06 (0.24)	0.08 (0.42)	0.80
Week 4	0.02 (0.14)	0.08 (0.42)	0.45
Week 12	0.02 (0.14)	0.08 (0.42)	0.45
Within group	0.1	0.4	
*P**			
Retching			
Baseline	0.02 (0.14)	0.08 (0.33)	0.25
Week 2	0.02 (0.14)	0.07 (0.25)	0.30
Week 4	0.06 (0.32)	0.07 (0.25)	0.65
Week 12	0.06 (0.32)	0.10 (0.43)	0.60
Within group	0.4	0.5	
*P**			
Belching			
Baseline	1.44 (0.83)	1.46 (0.85)	0.95
Week 2	0.87 (0.79)	2.05 (1.15)	0.0001
Week 4	0.21 (0.65)	2.28 (1.22)	0.0001
Week 12	0.10 (0.47)	2.13 (1.26)	0.0001
Within group	0.0001	0.0001	
*P**			
Loss of appetite			
Baseline	0.19 (0.45)	0.13 (0.43)	0.30
Week 2	0.19 (0.45)	0.13 (0.43)	0.20
Week 4	0.10 (0.31)	0.16 (0.58)	0.04
Week 12	0.02 (0.14)	0.17 (0.59)	0.02
Within group	0.001	0.5	
*P**			
Epigastric fullness			
Baseline	2.00 (0.95)	2.07 (0.84)	0.85
Week 2	1.25 (0.79)	2.23 (0.99)	0.0001
Week 4	0.34 (0.56)	2.21 (1.13)	0.0001
Week 12	0.10 (0.31)	2.18 (1.17)	0.0001
Within group	0.0001	0.03	
*P**			
Epigastric pain			
Baseline	1.76 (0.84)	1.81 (0.81)	0.80
Week 2	1.10 (0.84)	2.01 (0.99)	0.0001
Week 4	0.38 (0.70)	2.05 (1.18)	0.0001
Week 12	0.13 (0.39)	2.11 (1.19)	0.0001
Within group	0.0001	0.01	
*P**			
Postprandial epigastric pain			
Baseline	0.63 (0.82)	0.81 (0.83)	0.20
Week 2	0.55 (0.83)	1.05 (1.14)	0.02
Week 4	0.23 (0.63)	1.30 (1.33)	0.0001
Week 12	0.12 (0.49)	1.31 (1.42)	0.0001
Within group	0.0001	0.0001	
*P**			
Preprandial epigastric pain			
Baseline	0.29 (0.62)	0.41 (0.69)	0.30
Week 2	0.21 (0.50)	0.43 (0.81)	0.15
Week 4	0.10 (0.37)	0.53 (0.98)	0.008
Week 12	0.06 (0.24)	0.75 (1.15)	0.001
Within group	0.0001	0.03	
*P**			
Night epigastric pain			
Baseline	0.32 (0.59)	0.31 (0.53)	0.85
Week 2	0.29 (0.65)	0.35 (0.63)	0.45
Week 4	0.15 (0.55)	0.50 (0.96)	0.02
Week 12	0.12 (0.53)	0.65 (1.14)	0.004

(Continued)

Table 1: Contiuned

Symptom/time	FD severity score, mean (SD)		Between groups
	Anise, *n* = 47	Placebo, *n* = 60	*P***
Within group *P**	0.0001	0.02	
Epigastric burning			
Baseline	1.59 (0.85)	1.70 (0.91)	0.55
Week 2	0.93 (0.64)	1.87 (1.19)	0.0001
Week 4	0.19 (0.39)	1.80 (1.33)	0.0001
Week 12	0.02 (0.14)	1.70 (1.42)	0.0001
Within group *P**	0.0001	0.2	
Mean total score			
Baseline	10.6 (4.1)	10.96 (4.1)	0.6
Week 2	7.04 (4.1)	12.30 (4.3)	0.0001
Week 4	2.44 (4.2)	13.05 (5.2)	0.0001
Week 12	1.08 (3.8)	13.30 (6.2)	0.0001
Within group *P**	0.0001	0.0001	

*Friedman test was applied; **Mann-Whitney U-test was applied; SD = Standard deviation; FD = Functional dyspepsia

each group were tested using Friedman test and related samples Friedman's two-way analysis of variance by ranks test. $P < 0.05$ were considered significant. Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA), version 17 for Windows was used to conduct statistical analysis.

RESULTS

Totally, 107 patients were enrolled in the study. Totally, 32 (53.3%) and 21 (44.7%) females were included in the control and intervention groups, respectively. The difference was not significant ($P = 0.3$). The mean (standard deviation [SD]) age of patients in the control group was 41 (11.7) and in the intervention group was 45.5 (15.5) years ($P = 0.1$). Totally, 34 (56.7%) and 32 (68%) patients had body mass index ≤25 in the control and intervention groups, respectively ($P = 0.4$).Totally, 47 (78.3%) patients in the control group and 36 (76.6%) patients in the intervention group never smoked cigarettes ($P = 0.9$). Totally, 58 (96.7%) and 43 (91%) patients didn't drink coffee in the control and intervention groups, respectively ($P = 0.1$). Four patients were withdrawn from the study in each group [Figure 1]. No serious medication side effect was reported in anise group.

Mean (SD) scores of 16 questions of FD severity scale in the two groups across the study period are shown in Table 1. Among all symptoms, epigastric fullness showed the highest severity and nausea demonstrated the lowest severity in both groups before the intervention [Table 1]. In other words, about 90% of patients had epigastric fullness whereas ≤5% suffered from nausea in both groups at baseline. The baseline mean scores of different FD symptoms were not significantly different between the two groups. After intervention, all symptoms were significantly different between the two groups at weeks 4 and 12, but retching, nausea and vomiting. Similarly, mean total scores of FD severity scale were not significantly different between the two groups before the intervention. But, they were significantly different between the two groups at weeks 2, 4 and 12 [Table 1].

Mean severity scores of epigastric fullness, epigastric discomfort, epigastric burning/pain, early satiety, bloating, belching, and loss of appetite decreased significantly within anise group after intervention whereas only epigastric discomfort showed similar pattern within placebo group. On the other hand, mean severity scores of epigastric pain, epigastric fullness and belching increased significantly within the placebo group after intervention whereas no symptom revealed such an increasing score pattern within anise group [Table 1].

Distributions of the patients in different scales of severity of FD symptoms across the study period are demonstrated in Table 2. Similar to the mean severity scores, the distributions of patients before intervention were not significantly different between the two groups [Table 2]. Furthermore, the patterns of significance and nonsignificance of distributions of patients within each group and between the two groups were similar to those of the severity scores.

DISCUSSION

The current study demonstrated that anise was effective in the treatment of postpartum depression (PPD). Since the pathophysiology of FD is multifactorial and since anise has broad spectrum of pharmacological effects on GI, nervous, muscular and immune systems, it is not a surprise to see significant improvements of symptoms in patients with FD. The spasmolytic feature[50] of anise and its pain relieving character may explain the improvement of postprandial pain and epigastric discomfort. Antimicrobial effects[43] of anise against most bacteria may decrease or inhibit the activities of *H. pylori* in these patients. Inhibitory effects of anise on gastric mucosal damage[48] may decrease the micro-inflammation of FD. The most important constituents of aniseeds essential oils responsible for the reported effects are trans-anethole, estragole, γ-hymachalen, p-anisaldehyde, and methyl chavicol.[56]

Some other herbs have also been investigated to find out their effectiveness on FD treatment with various results. The most famous ones were Iberogas (a herbal combination preparation, STW 5) which improved the symptoms of FD in 52-68% of cases and peppermint which was effective in 67-97% of patients.[57] Some of them have also been recognized to relieve bloating and intestinal gas. They are

Table 2: Distributions of the patients according to various degrees of severity of FD and comparison of distributions within and between the two groups across the study period

Symptom/ time	Anise (*n* = 47), number (%)				Placebo (*n* = 60), number (%)				Between groups
	Never or rarely	Not very unpleasant	Very unpleasant but tolerable	Can't tolerate	Never or rarely	Not very unpleasant	Very unpleasant but tolerable	Can't tolerate	*P***
Epigastric discomfort									
Baseline	27	18	2	0	33	24	3	0	0.96
Week 2	35	10	2	0	37	21	2	0	0.30
Week 4	44	2	1	0	40	16	4	0	0.003
Week 12	44	2	1	0	42	14	3	1	0.02
Within group									
*P**	0.0001				0.02				
Early satiety									
Baseline	28	1	12	6	35	2	15	8	0.98
Week 2	28	10	6	3	35	4	14	7	0.08
Week 4	37	6	4	0	35	6	9	10	0.02
Week 12	45	2	0	0	39	4	7	10	0.001
Within group									
*P**	0.0001				0.85				
Epigastric bloating									
Baseline	21	17	9	0	31	25	4	0	0.15
Week 2	29	12	6	0	33	23	3	1	0.24
Week 4	40	7	0	0	34	19	5	2	0.009
Week 12	46	1	0	0	34	13	9	4	0.0001
Within group									
*P**	0.0001				0.1				
Preprandial nausea									
Baseline	45	2	0	0	58	2	0	0	0.8
Week 2	46	1	0	0	57	2	1	0	0.6
Week 4	45	1	1	0	57	2	0	1	0.5
Week 12	45	2	0	0	57	2	1	0	0.6
Within group									
*P**	0.6				0.4				
Postprandial nausea									
Baseline	45	2	0	0	57	2	1	0	0.6
Week 2	46	1	0	0	57	2	1	0	0.6
Week 4	45	1	1	0	57	3	0	0	0.4
Week 12	45	1	1	0	57	2	0	1	0.5
Within group									
*P**	0.7				0.4				
Morning nausea									
Baseline	46	1	0	0	58	2	0	0	0.7
Week 2	46	1	0	0	58	2	0	0	0.7
Week 4	46	1	0	0	58	2	0	0	0.7
Week 12	46	1	0	0	58	2	0	0	0.7
Within group									
*P**	1.0				1.0				
Vomiting									
Baseline	44	3	0	0	58	2	0	0	0.5
Week 2	44	3	0	0	57	2	1	0	0.5
Week 4	46	1	0	0	57	2	1	0	0.6
Week 12	46	1	0	0	57	2	1	0	0.6

(Continued)

Table 2: Continued

Symptom/ time	Anise (*n* = 47), number (%)				Placebo (*n* = 60), number (%)				Between groups
	Never or rarely	Not very unpleasant	Very unpleasant but tolerable	Can't tolerate	Never or rarely	Not very unpleasant	Very unpleasant but tolerable	Can't tolerate	*P***
Within group									
*P**	0.1				0.4				
Retching									
Baseline	46	1	0	0	56	3	1	0	0.5
Week 2	46	1	0	0	56	4	0	0	0.3
Week 4	45	1	1	0	56	4	0	0	0.3
Week 12	45	1	1	0	56	3	0	1	0.5
Within group									
*P**	0.4				0.6				
Belching									
Baseline	9	9	28	1	11	13	33	3	0.9
Week 2	16	23	6	2	10	8	11	31	0.0001
Week 4	41	4	0	2	11	5	0	44	0.0001
Week 12	44	2	0	1	12	8	0	40	0.0001
Within group									
*P**	0.0001				0.0001				
Loss of appetite									
Baseline	39	7	1	0	54	4	2	0	0.4
Week 2	39	7	1	0	54	4	2	0	0.4
Week 4	42	5	0	0	54	4	0	2	0.4
Week 12	46	1	0	0	54	4	0	2	0.2
Within group									
*P**	0.001				0.5				
Epigastric fullness									
Baseline	5	6	20	16	5	4	33	18	0.5
Week 2	9	18	19	1	6	6	16	32	0.0001
Week 4	33	12	2	0	9	6	8	37	0.0001
Week 12	42	5	0	0	10	6	7	37	0.0001
Within group									
*P**	0.0001				0.03				
Epigastric pain									
Baseline	5	8	27	7	5	11	34	10	0.9
Week 2	10	26	7	4	6	11	19	24	0.0001
Week 4	34	9	3	1	10	10	7	33	0.0001
Week 12	42	4	1	0	10	9	5	36	0.0001
Within group									
*P**	0.0001				0.01				
Postprandial epigastric pain									
Baseline	26	13	7	1	25	23	10	2	0.5
Week 2	30	9	7	1	25	19	4	12	0.005
Week 4	40	4	2	1	25	13	1	21	0.0001
Week 12	43	3	0	1	29	7	2	22	0.0001
Within group									
*P**	0.0001				0.0001				
Preprandial epigastric pain									
Baseline	37	6	4	0	42	11	7	0	0.6

(Continued)

Table 2: Continued

Symptom/ time	Anise (n = 47), number (%)				Placebo (n = 60), number (%)				Between groups
	Never or rarely	Not very unpleasant	Very unpleasant but tolerable	Can't tolerate	Never or rarely	Not very unpleasant	Very unpleasant but tolerable	Can't tolerate	*P***
Week 2	39	6	2	0	43	11	3	3	0.3
Week 4	43	3	1	0	43	8	3	6	0.05
Week 12	44	3	0	0	39	7	4	10	0.002
Within group									
*P**	0.0001				0.03				
Night epigastric pain									
Baseline	35	9	3	0	43	15	2	0	0.6
Week 2	37	7	2	1	43	14	2	1	0.7
Week 4	43	2	1	1	44	8	2	6	0.1
Week 12	44	1	1	1	43	5	2	10	0.03
Within group									
*P**	0.0001				0.02				
Epigastric burning									
Baseline	9	3	33	2	9	9	33	9	0.1
Week 2	11	28	8	0	12	11	10	27	0.0001
Week 4	38	9	0	0	17	9	3	31	0.0001
Week 12	46	1	0	0	22	5	2	31	0.0001
Within group									
*P**	0.0001				0.2				

*Test of related samples Friedman's two-way analysis of variance by ranks was applied; **Chi-square test was applied; FD = Functional dyspepsia

called carminatives. Anise, peppermint, and cinnamon are the prototypes of these herbs but few clinical trials have been carried out to show the evidence.[58] This was the first randomized clinical trial assessing the therapeutic effects of anise on patients with FD. But, this study had the following limitations. First, it was conducted in a single center. Thus, the study population was homogenous which limited the external validity of the results. Second, the sample size was small, and the follow-up period was relatively short. It is suggested to include larger numbers of patients with longer periods of follow-up in multiple centers in the future investigations.

CONCLUSIONS

Anise was effective and tolerable in the relieving the symptoms of PPD. These effects were observed even 8 weeks after discontinuation of anise administration.

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AUTHOR'S CONTRIBUTION

MM was the principal investigator of the study. MT participated in preparing the design of the study and collecting the data. PA participated in preparing the design of the study, revisited the manuscript and critically evaluated the intellectual contents. AF conducted the analysis of data. AG participated in preparing the final draft of the manuscript, revisited the manuscript and critically evaluated the intellectual contents. MK coordinated in study design and data collection. SAG participated in the preparation of the final draft of the manuscript, revisited the manuscript and critically evaluated the intellectual contents. MB participated in data collection and preparation of the final draft of the manuscript, revisited the manuscript and critically evaluated the intellectual contents.

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