

Pimpinella anisum in modifying the quality of life in patients with functional dyspepsia: A double-blind randomized clinical trial

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Background: We aimed to assess the effects of anise on quality of life (QOL) of patients with functional dyspepsia (FD) in a double-blind randomized clinical trial. **Materials and Methods:** Of 180 patients attending the gastroenterology clinic, 107 ones with the diagnosis of postprandial distress syndrome according to Rome III criteria were enrolled. They were randomized into two groups, anise and placebo. Anise group involved 47 patients and received anise powders, 3 g after each meal (3 times/day) for 4 weeks. Control group had 60 patients who received placebo powders (cornstarch), 3 g after each meal (3 times/day) for 4 weeks. The QOL was assessed by short-form (SF)-36 questionnaire. Mean scores of eight health domains of the two groups were compared at baseline and at the end of study. **Results:** The age, sex, body mass index, smoking history, tea and coffee drinking patterns of the two groups were not significantly different. All domains of SF-36 were similar between the two groups at baseline but were significantly different at week 12. At baseline, mean score of physical component summary was 159 in placebo group and 167 in anise group ($P = 0.1$). At week 12, the score was 141 in placebo group and 251 in anise group ($P = 0.0001$). Mean baseline score of mental component summary was 172 and 165 in placebo and anise groups, respectively ($P = 0.1$). At week 12, the score was 135 in placebo group and 233 in anise group ($P = 0.0001$). **Conclusion:** The current study revealed the effectiveness of anise in improvement of QOL in patients with FD.

Key words: Anise, functional dyspepsia, *Pimpinella anisum*, postprandial distress syndrome, quality of life, short-form-36

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INTRODUCTION

Functional dyspepsia (FD) is the most frequent gastrointestinal (GI) disorder. It is diagnosed by upper GI symptoms of bothersome early satiety, postprandial fullness, and epigastric pain/burning for ≥ 12 weeks began within the last 6 months with no evidence of structural pathologies.^[1] The prevalence of FD in most populations has roughly been around 10-40%.^[2-4] Its prevalence in Iran has been about 3-30%.^[5] The etiology of FD is multifactorial.^[6-11] Rome III criteria considered two main subtypes for FD: Epigastric pain syndrome and postprandial distress syndrome (PDS). PDS includes patients with meal-related symptoms of bothersome early satiety and postprandial fullness.^[12-14] The quality of life (QOL) in most patients is impaired^[15-19] which induces low work productivity,^[20,21] high economic costs on society,^[22] higher anxiety^[23-26]

and irregular health care seeking behavior.^[27-29] There were some observations that dysmotility-like symptoms more than other symptoms negatively affected the daily activities and QOL of patients with FD.^[30-32] The usual treatment of FD gained limited satisfaction among the patients.^[33] This led to seeking alternative approaches such as herbal medicines. One of the latter gained popularity in ancient Persian medicine was *Pimpinella anisum* (anise). It showed various therapeutic characteristics in GI system such as inhibition of mucosal damage in stomach, relieving constipation and alleviating nausea.^[34-36] There is no published study on the effects of anise on QOL in patients with FD. We used the most commonly used generic questionnaire in GI disorders, 36-item short-form (SF-36) general health (GH) survey,^[31] to compare the effects of anise fruit on physical and mental health (MH) status in these patients.

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MATERIALS AND METHODS

Study design

This was a double-blind randomized clinical trial carried out at GI Clinic of University Hospital (Alzahra) affiliated with the Isfahan University of Medical Sciences (IUMS). The study was registered in Iranian Registry of Clinical Trials (IRCT registration number, 2013101214980). Ethical Committee at IUMS approved the study protocol. A written consent was obtained from all patients. A total of 180 patients were evaluated from August 2013 to March 2014. Those aged 18-65 years and were diagnosed with PDS according to Rome III criteria were enrolled.

The patients experienced discomfort feeling of postprandial fullness and/or early satiety several times per week in the last 6 months. The following conditions were considered as exclusion criteria: 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 antiinflammatory 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

Seventy-three patients were excluded from the study and 107 patients were enrolled in the study [Figure 1]. They were randomized by simple randomization method into intervention and placebo groups. Intervention group involved 47 patients who received anise powder, 3 g after each meal (3 times/day). According to the Barnes *et al.*,^[37] administration of up to 20 g/day anise powder is safe. The anise seeds were prepared by Barij Essence Pharmaceutical Company (Mashhad Ardehal, Iran) as a gift. This plant specimen was kept in their herbarium with number 1697.^[38] Control group involved 60 patients who received placebo powder, 3 g after each meal (3 times/day). Placebo powders consisted of corn starch. They were packed similar to anise powder in shape, color and size. Both powders were prepared in similar packages by Pharmacognosy Department of Isfahan School of Pharmacy at IUMS. The patients were supplied with the medications for 1-week at the beginning of the each week for 4 weeks. Doctors and patients were blind to the assigned treatments.

Instruments and outcomes

The presence of FD was assessed by modified Rome III questionnaire.^[12-14] FD was diagnosed according to the

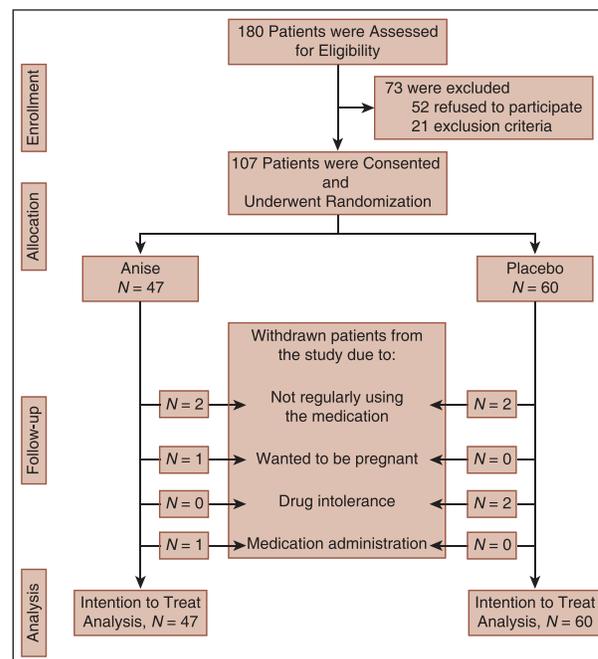


Figure 1: Consort flowchart of the study

questionnaire filled-out individually. The QOL was evaluated by Persian version of SF-36 questionnaire. Its reliability and validity has been verified before.^[39] SF-36 which has been employed successfully in both longitudinal and cross-sectional studies, has 36 items measuring the following eight health domains: Vitality (VT), GH, MH, physical functioning (PF), social functioning (SF), physical role (PR), emotional role (ER), and bodily pain (BP). The scores on each domain may range from 0 to 100, with the higher score indicating better QOL. They reliably assess two major clusters of health: Physical component summary (PCS) and mental component summary (MCS). BP, PF and PR assess the former, whereas MH, ER, and SF assess the latter. GH, SF and VT highly correlate with both PCS and MCS. PCS has showed the highest changes toward interventions targeted physical therapies. MCS has showed the highest changes toward interventions targeted mental therapies. The lowest score of PCS belongs to subjects with frequent feeling of fatigue, severe body pain and limitations in social, physical, role activities and self-care. The highest PCS score belongs to subjects with wellbeing, high levels of energy, no disability and no physical limitations. The lowest MCS score fits in subjects with frequent psychological distress and emotional problems causing social and role disabilities. The highest PCS score fits in subjects with frequent positive affects and no psychological distress and emotional problems causing social and role limitations.^[40] Follow-up period was 12 weeks. Patients were evaluated at baseline and at the end of week 12. The primary end points were the eight health domains of QOL.

Statistical analysis

The mean scores of eight domains of SF-36 questionnaire were assessed within each group and between the two groups. Mann-Whitney U-test and Kruskal-Wallis tests were used to compare nonparametric characteristics, and Student's *t*-test was employed to compare parametric characteristics. Intention to treat analysis was applied to analyze the data. $P < 0.05$ was considered as significant. Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 17 for Windows was used to conduct statistical analysis.

RESULTS

Seventy-three and 107 patients were excluded from and included in the study, respectively. Demographic characteristics of patients in the two groups are compared in Table 1. No significant difference was seen in demographic characteristics between the two groups. The mean (standard deviation [SD]) age of patients in the control and intervention group was 41 (11.7) and 45.5 (15.5) years, respectively ($P = 0.1$). The mean (SD) number of drinking tea in control group was 4.76 (2) cups in control group and 4.8 (2.1) cups in anise group. The difference was not significant ($P = 0.9$).

Table 2 shows the range and mean (SD) scores of different domains of SF-36 compared within each group and between

the two groups. None of the evaluated eight domains of health showed a significant difference between the two groups at baseline whereas all demonstrated a significant difference at week 12. Furthermore, all eight health domains improved significantly within anise group, whereas all worsened significantly within the placebo group but BP [Table 2].

Mean baseline PCS score was around 159 and 167 in placebo and anise groups, respectively ($P = 0.1$). At week 12, the score was 141 in placebo group and 251 in anise group which was significantly different ($P = 0.0001$). Mean baseline MCS was about 172 and 165 in placebo and anise groups, respectively ($P = 0.1$). At week 12, the score was 135 in placebo group and 233 in anise group, which was significantly different ($P = 0.0001$). Overall, in anise group PCS score improved more than MCS score whereas in placebo group MCS score worsened more than PCS score by week 12.

DISCUSSION

The current study demonstrated that anise may improve the QOL in patients with FD. The most important components of aniseeds essential oils responsible for the observed effects might be trans-anethole, estragole, γ -hymachalen, p-anisaldehyde, and methyl chavicol.^[41] The improvement was observed in all health domains of intervention group and in none of the health domains of placebo group. More than five points increase in score of any domain of SF-36 has been translated as clinically relevant.^[42,43] The score of all eight health domains improved >5 points in anise group as follows in decreasing order: BP, 53 points, health transition (HT), 42 points, GH, 34 points, SF, 28 points, MH, 24 points, VT, 23 points, PR, 20 points, ER, 15 points and PF, 10 points. The scores of all domains, but BP, in placebo group decreased >5 points by week 12. One item of 36 items of SF-36 is not used in scoring the eight health domains. That is self-evaluated HT item which estimates the changes in overall health status compared to the status of a year ago. "Somewhat better" means an average improvement in HT score of 5.8 points whereas "much better" equals an average score improvement of 13.2.^[40] More than 42 points increase in HT score in anise group was probably equal to very much better health status compared with that a year ago. On the other hand, "much worse" means an average decline in HT score of 34.4 and "somewhat worse" equals an average score decline of 10.8 points.^[40] The HT score in placebo group declined >15 points which suggested somewhat worse condition of health status of these patients. Although the improvements of QOL in patients with FD by some therapeutic approaches of modern medicine have been shown in some clinical trials,^[44-48] there are few studies showing the effects of herbal medicine on QOL in these patients.^[49]

Table 1: Demographic characteristics of the two groups

Demographic characteristics	Placebo, n = 60 number (%)	Anise, n = 47 number (%)	P
Sex			
Male	28 (46.7)	26 (55.3)	0.3
Female	32 (53.3)	21 (44.7)	
BMI, kg/m ² *			
<19	1 (1.7)	1 (2.1)	0.4
19-24.99	33 (55)	31 (66)	
25-29.99	25 (41.7)	12 (25.5)	
≥30	1 (1.7)	3 (6.4)	
Marital status			
Single	13 (21.7)	8 (17)	0.6
Marriage	47 (78.3)	39 (83)	
Literacy			
<High school diploma	37 (61.7)	31 (66)	0.6
High school diploma	19 (31.7)	14 (29.8)	
>High school diploma	4 (6.7)	2 (4.25)	
Smoking			
Current smoker	13 (21.7)	11 (23.4)	0.9
Past smoker	2 (3.3)	1 (2.1)	
Never smoked	45 (75)	35 (74.5)	
Coffee			
4 cups	0	1 (2.1)	0.1
2 cups	2 (3.3)	1 (2.1)	
1 cups	0	2 (4.25)	
0 cups	58 (96.7)	43 (91.5)	

BMI = Body mass index

Table 2: Different domains of SF36 compared within each group and between the two groups

SF36 Domains	Placebo, n = 60			Anise, n = 47			Between groups P
	Range	Mean	SD	Range	Mean	SD	
GH							
Baseline	15-85	51.2	19.1	15-85	51.3	18.9	0.98
Week 12	0-65	23.8	15.4	40-100	85.8	12.7	0.0001
Within group P = 0.0001				Within group P=0.0001			
HT							
Baseline	25-75	46.9	12.7	0-75	44.8	12.9	0.5
Week 12	0-100	31.7	21.1	0-100	87.2	19.2	0.0001
Within group P = 0.0001				Within group P=0.0001			
PF							
Baseline	5-100	60.2	27.4	10-100	69.5	23.8	0.08
Week 12	0-100	53.9	28.2	15-100	79.9	18.4	0.0001
Within group P=0.0001				Within group P=0.0001			
PR							
Baseline	50-100	73.9	19.4	50-100	72.9	16.3	0.8
Week 12	50-100	58.3	12.9	50-100	93.6	11.0	0.0001
Within group P=0.0001				Within group P=0.0001			
BP							
Baseline	2-51	24.6	14.1	2-51	24.6	11.2	0.98
Week 12	0-87	29.0	24.4	50-100	77.9	14.9	0.0001
Within group P=0.046				Within group P=0.0001			
ER							
Baseline	50-100	73.2	13.7	50-100	67.8	9.9	0.1
Week 12	50-100	67.3	10.0	65-100	82.9	6.8	0.0001
Within group P=0.006				Within group P=0.0001			
SF							
Baseline	0-87	47.1	23.1	12-100	50.3	19.8	0.5
Week 12	0-87	31.0	21.5	25-100	78.8	16.9	0.0001
Within group P=0.0001				Within group P=0.0001			
MH							
Baseline	20-84	52.0	16.8	4-80	47.3	15.2	0.2
Week 12	8-68	36.8	15.9	12-88	71.6	15.6	0.0001
Within group P=0.0001				Within group P=0.0001			
VT							
Baseline	15-95	52.8	22	25-85	51.3	17.7	0.7
Week 12	5-80	35.7	16.6	40-95	74.5	11.8	0.0001
Within group P=0.0001				Within group P=0.0001			

SD = Standard deviation; HT = Health transition; SF = Social functioning; PR = Physical role; PF = Physical functioning; BP = Bodily pain; MH = Mental health; VT = vitality; ER = Emotional role; GH = General health

The current investigation was the first randomized clinical trial evaluating the effects of anise on QOL of patients with FD. We employed SF-36 SF GH survey to assess the QOL. SF-36 is used universally to evaluate the impact of FD on all aspects of QOL. This is a generic questionnaire to assess patient oriented outcomes of QOL in relation to treatment. It is especially important when comparisons between the two groups are carried out.^[50] One of the limitations of the study was its single center-based design. This ended to assessment of a homogenous study population and consequently, limited external validity of the findings. Furthermore, the sample size could be larger and the follow-up period could be longer. We suggest including larger sample size with

longer periods of follow-up in multiple centers in the future studies. In conclusion, anise was effective in improvement of QOL in patients with FD.

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AUTHOR'S CONTRIBUTION

SAG contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. MM contributed in the conception and design of the work, conducting the study, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. AG contributed in the design of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. AF contributed in data analysis, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. MB contributed in revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. MT contributed in conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. MK contributed in conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. AS contributed in drafting and revising the draft, data analysis, approval of the final version of the manuscript, and agreed for all aspects of the work. PA contributed in the design of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

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