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Effect of *Apium graveolens* and *Trachyspermum copticom* on clinical symptoms of patients with functional dyspepsia

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Abstract

Objectives: This study aimed at investigating the effect of Iranian traditional remedy prepared from *Apium graveolens* and *Trachyspermum copticom* (AT) on the severity and frequency of symptoms in patients with functional dyspepsia (FD).

Material and Methods: In total, 150 FD patients were included in this randomized double-blind trial, based on the ROME III diagnostic criteria, and they were divided into three intervention groups namely, AT, Placebo and omeprazole. Then, severity and frequency of symptoms during this eight-week trial were measured. Obtained information was analyzed using Chi-square test and repeated measures test.

Result: In general, the severity and frequency of symptoms after the 4th week significantly decreased in the AT group as compared to the omeprazole and placebo groups, and continued to reduce by the end of the eighth week. General reduction of symptom severity and frequency in the omeprazole group was significantly different from the placebo group by the end of the 4th and 8th weeks. With respect to each individual symptom, AT markedly improved symptoms, such as burning, pain, early satiation, fullness, bloating, belching and nausea, as compared to placebo-treated group. Moreover, AT significantly improved symptoms, like vomiting, and nausea, except for pain, as compared to omeprazole-treated subjects.

Conclusion: According to the results, AT, as Iranian traditional remedy, was more effective than omeprazole and placebo in reducing the symptoms in FD patients.

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Introduction

Functional dyspepsia is the most common gastrointestinal disorder, accounting for almost 50% of all patients visiting gastrointestinal specialty centers (Hirkawa et al., 1999; Lewis et al.,2016). The high prevalence of FD, as a functional disorder of the digestive system, has turned it into a major health issue in different societies (Jones, 2002; Hoky et al., 1998). Almost 25% of people experience dyspepsia symptoms at least six times a year. In addition, FD is the cause of 60% of all dyspepsia cases. According to the ROME III diagnostic criteria, FD is diagnosed when two or more of following symptoms are present: early satiation, postprandial fullness, and epigastric pain or epigastric burning in the absence of organic or metabolic diseases with symptom starting at least six months before diagnosis (Khademolhosseini et al., 2010; Longo et al., 2013). However, there are some other dyspepsia symptom, such as over-belching, bloating, vomiting, and nausea. FD is divided into two often-overlapping syndromes, namely, postprandial syndrome and epigastric pain syndrome (Masoumi et al, 2015). Lack of a standard treatment for FD, along with periodical and chronic signs in these patients has resulted in increased number of studies that have focused on discovering the pathophysiology and finding new treatments for this disease (Amini and Keshteli, 2012; Tack, 2005; Tack and Talley, 2006; Madish and Labenz, 2005).

Relative limitations of typical medications in controlling FD symptoms and the uncertainty about their mechanisms have increased patients' tendency to use complementary and alternative medicine, specifically acupuncture, as well as medicinal herbs and natural products to relieve the symptoms (Talley, 1995). Therefore, according to specific complementary and traditional medicine of each region, different studies, mainly on native plants, have been conducted in different countries. Moreover, the effectiveness of many simple and compound preparation of medicinal herbs produced in Iran, China, India, Australia, etc., has been proved (Ottillinger, 2013; Zheng et al., 2009). Remedies made from *Apium graveolens* and *Trachyspermum copticom* (AT) are among medications that have been widely mentioned in traditional medicine references of Iran as a treatment for dyspepsia. This preparation is comprised of an equal combination of AT, and is among the simplest medicinal compounds used for the treatment of dyspepsia (UNESCO, 2009; Aliasl, 2015; Melzer et al., 2004). According to different studies, medicinal herbs act concertedly in combination with each other and are able to relieve several clinical symptoms. This property is very important in the treatment of multifactorial diseases, such as functional gastrointestinal disease (Wegner and Wagner, 2006). Although, several studies have been done on the therapeutic effects of AT, no clinical trial on the effectiveness of AT Iranian traditional remedies for the treatment of FD has been performed.

Trachyspermum copticom belong to the family Umbelliferrae, and gamma-terpinen, thymol and p-cymene are the most abundant substances found in its essence (Malekinejad et al., 2012). Furthermore, therapeutic effects of *Trachyspermum copticum* on digestive system include antifungal (Khosravi et al., 2015; Sharifzadeh and Shokri, 2016); antibacterial and antiparasitic (Zomorodian et al., 2015; Zomorodian and Ghdiri, 2015); anti-diarrhea (Balaji et al., 2012); anti-spasmodic, anti-inflammatory, strong antioxidant (Kazemi, 2014; Alavinezhad and Boskabadi, 2014); analgesic (Dashti-Rahmatabadi et al, 2007); anti-*Helicobacter pylori* (Nariman et al,2016); gastric-ulcer healing (Tajic et al, 2016), and Ileum relaxant (Hejazian et al, 2007) activities.

Apium graveolence is a member of the family Umbelliferrae, and d-Limonene and

selinene are the most important compounds found in its essence (Sowbhagya, 2014). *A. graveolence* effects on digestive system include significant inhibitory effects on gastric ulcers and inflammation (Powanda et al., 2015) and analgesic, anti-oxidant and anti-bacterial properties (Kooti et al., 2014; Nguyen et al.,2014) as well as *H. pylori* and inhibitory effects on gastric cancer cells (Kooti et al, 2014).

A. graveolens and *T. copticom* are among Iran's native plants with several therapeutic applications in Iranian traditional medicine. This study aimed at investigating the effects of AT as Iranian traditional remedy on clinical symptoms of patients with FD.

Materials and Methods

Setting and participants

This randomized double-blind trial was conducted in Kerman University of Medical Sciences. In total, 180 FD patients visiting Afzalipour Hospital between August 2015 and April 2016, were first gastroenterologist, first examined in the study by a gastroenterologist, and selected based on the ROME III diagnostic criteria. Among them, 150 subjects who satisfied inclusion criteria were enrolled in the study after signing the informed consent forms. The inclusion criteria were FD patients, aged 18-60 years old, who based on the ROME III diagnostic criteria, did not meet exclusion criteria.

The exclusion criteria were pregnancy, breastfeeding, having active urinary tract infection, history of seizure, concurrent use of other FD-related chemicals and herbal drugs, occurrence of severe side effects associated with the drugs, history of peptic ulcer and reflux disease, consumption of anticoagulants, having irritable bowel syndrome, history of esophageal, stomach, and intestinal surgeries, serious organic diseases (e.g. diabetes and cardiovascular diseases), consumption of narcotic substances, severe mental retardation, unwillingness of subject for participation, not completing the informed consent form, and emergence of warning symptoms (e.g. weight loss, anemia, blood in the stool, and dysphagia)

Intervention

In this study *T. copticum* (L.) with a herbarium number of KF1447, and *A. graveolence* (L.) with a herbarium number of KF1138 were kept in School of Pharmacy, Kerman University of Medical Sciences. After two-weeks screening period, patients were divided into three groups through randomization by minimization. The investigated traditional remedy comprised of an equal mixture of *A. graveolens* and *T. copticom*, prepared as 500 mg capsules by Pharmacognosy Department of Kerman University of Medical Sciences. Standardization and quality control procedures for this preparation were carried out by Barij Essence Pharmaceutical Company. Two capsules of AT (500mg) were administered per day, one after breakfast and one after dinner for four weeks. In the placebo group, two 500 mg capsules of cornstarch were administered per day, one after breakfast and one after dinner. The omeprazole group took one 20 mg omeprazole capsule per day (Ivanova NG, 2002) on an empty stomach. All three groups took the medications for four weeks and were assessed during a 4-week follow-up period.

Outcome and measurement

In this trial, the severity and frequency of symptoms during the treatment period, after the completion of treatment period, and after the 4-week follow-up, were evaluated. The Stangellini's symptom severity questionnaire and ROME III symptom frequency questionnaire, were used to assess the outcomes. These questionnaires were completed on enrollment, and after two, four and eight weeks (Baohai et al., 2013). The symptom severity questionnaire includes eight items

with the final score ranging between 8 and 32. The symptom frequency questionnaire is comprised of eight items with the final score ranging between 8 and 48.

Sample size

According to parameters obtained from the pilot study, the sample size was 42. However, the final sample size was calculated to be 50 in each group.

Randomization and blinding

Randomization was done by minimization. Then, patients were purposively assigned to these groups based on possible confounding factors, namely, age and gender, to match these three groups with respect to these factors. The initial symptoms of the patients were well matched as possible.

This trial was a double-blind study. Drugs were identically packaged and coded in the Pharmacognosy Department of Kerman University of Medical Sciences. The person who did the coding was not involved in the study. The examinations and follow-up assessments were done by someone who was unaware of the coding procedure. A third person, who was unaware of research objectives, divided the patients in one of these three groups and gave them the medications based on their initial descriptions. The statistical analysis was done by a fourth person, who was unaware of the grouping.

Statistical methods

Demographic information including age, sex, marital status, and educational level of patients in three groups was compared using Chi-square test. To compare the severity and frequency of changes in these three groups at four different time points (on enrollment, and after two, four, and eight weeks), the repeated-measures test was used. The statistical analysis was done using SPSS 23 and a $p<0.05$ was considered significant.

Ethics

The Medical Research Ethics Committee of Kerman University of Medical Sciences approved the present study (code: IR.KMU.REC.1394.233). They were assured of the confidentiality and anonymity of the study (Registration code: IRCT2015092724228N1

Results

In total, 150 subjects were equally divided in three research groups. In the AT group, one subject was excluded after two weeks due to irregular consumption of the medication, and finally the treatment and follow-up periods were completed with 49 subjects. In the placebo group, two subjects were excluded due to irregular consumption of the medication, two due to drug intolerance (sensitivity to gelatin capsule shells and diarrhea after taking the placebo), two due to consumption of self-prescribed dyspepsia drugs, and one due to pregnancy. In total, 43 subjects in the placebo group completed the treatment and follow-up periods. In the omeprazole group, two subjects were excluded due to irregular consumption of medication, two due to consumption of dyspepsia drugs, and one due to drug intolerance (severe headache following consumption of omeprazole). In total, 45 subjects in the omeprazole group completed the treatment and follow-up periods (Figure 1).

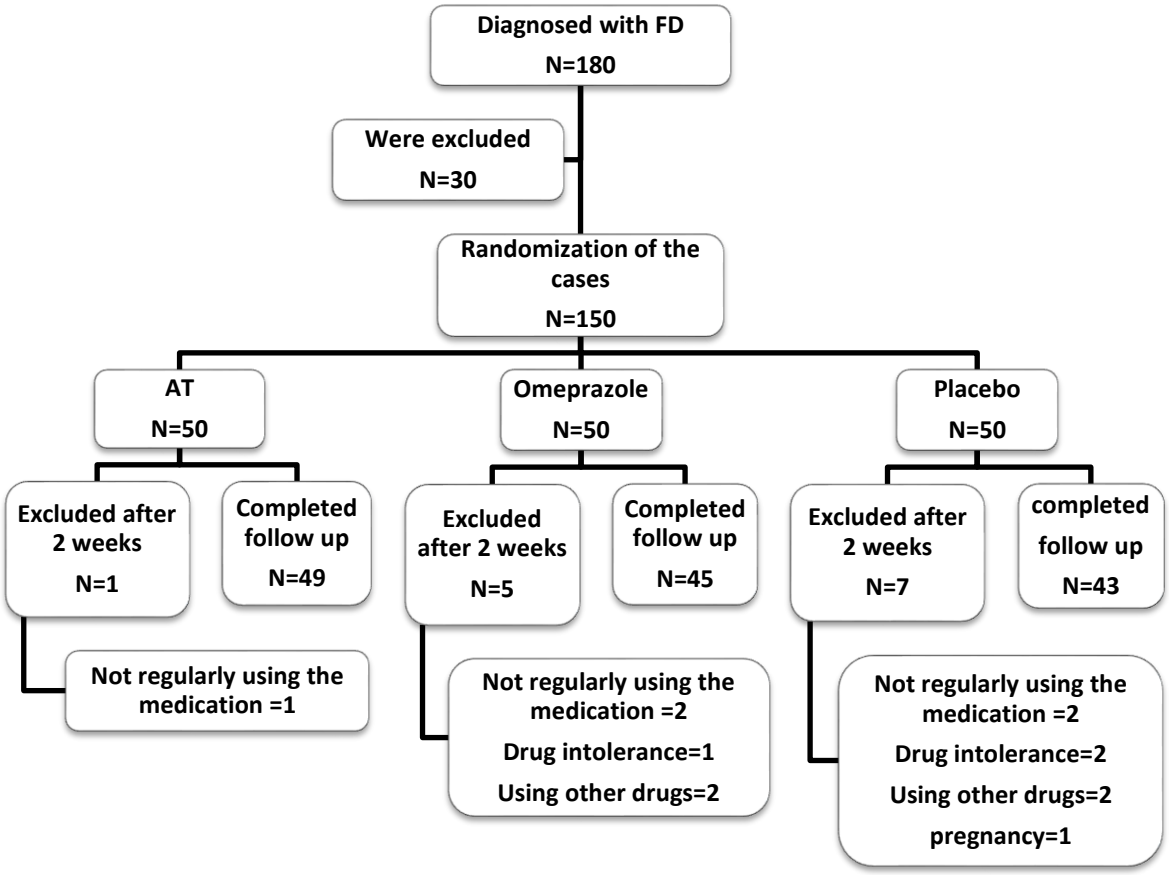

Figure 1. Flowchart of study design and protocol

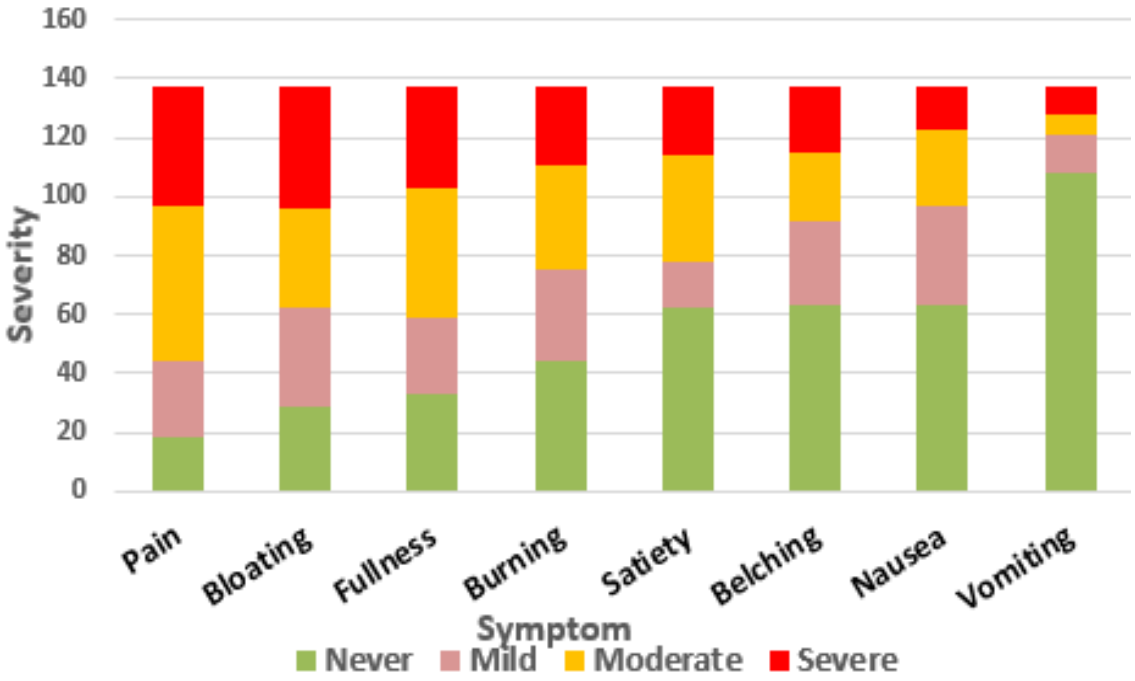

Figure 2. Prevalence of symptoms in enrolled patients (150 patients)

In terms of gender, 67.7%, 62.8%, and 62.2% subjects in the AT, placebo, and omeprazole groups were female, respectively. In addition, 65.5%, 86.1%, and 73.3% subjects in the AT, placebo, and omeprazole groups were married, respectively. In terms of age, 46.9%, 44.2%, and 42.4% in the AT, placebo, and omeprazole groups were in the most common age group (31-45 years). In terms of education, 55.1%, 39.5%, and 42.2% of subjects in the AT, placebo, and omeprazole groups were in the most common education group (subjects with academic education).

To analyze demographic information of patients, Chi-square test was used. According to Table 1, there was no significant between-group difference in terms of demographic information ($p<0.05$).

According to Figure 2, the most frequent symptoms among the subjects on enrollment were epigastric pain (82%), bloating (71%), postprandial fullness (67%), and epigastric burning. On the other hand the least common symptoms on enrollment were vomiting (22.2%), nausea (27%) and belching (27%).

According to Figure 3, there was no significant between-groups difference in terms of overall severity and frequency of symptoms on enrollment ($p>0.05$). Two weeks after initiation of the treatment, the overall score of symptom severity was significantly decreased in AT group compared to the placebo group ($p<0.001$) and omeprazole group ($p<0.001$), and trend continued until the end of the fourth ($p<0.001$) and eighth weeks ($p<0.001$). Two weeks after initiation of the treatment, the overall score of symptom severity was significantly decreased in omeprazole group as compared to the placebo group ($p<0.001$), and this trend continued until the end of the fourth ($p=0.009$) and eighth weeks ($p<0.001$).

In terms of frequency (Figure 3), the overall score significantly decreased in the AT group as compared to the placebo after two weeks ($p=0.003$), and remained significantly remained low until the end of the follow-up period. In addition, this score significantly decreased in the AT group as compared to the omeprazole group after four weeks ($p<0.001$), and remained significantly remained low until the end of the follow-up period ($p<0.001$). After four weeks of treatment, the overall score of symptom frequency was significantly decreased in the omeprazole group as compared to the placebo group ($p=0017$), however, this difference was not significant after eight weeks ($p=0.103$).

Table1. Demographic characteristics of participants

D.C	Sub group	AT group	Placebo group	Omeprazole group	p-value (At baseline)
Age (years)	18-30	15 (30.6%)	12 (27.9%)	16 (35.6%)	0.94
	31-45	23 (46.9%)	19 (44.2%)	18 (40%)	
	46-60	11 (22.4%)	11 (22.4%)	11 (24.3%)	
Sex	Male	16 (32.7%)	16 (37.2%)	17 (37.8%)	0.85
	Female	33 (67.3%)	27 (62.8%)	28 (62.2%)	
Marital status	Single	12 (24.5%)	6 (13.9%)	12 (26.7%)	0.30
	Married	37 (65.5%)	37 (86.1%)	33 (73.3%)	
Education level	Pre-high school diploma	5 (10.2%)	6 (14%)	8 (17.8%)	0.52
	Old school diploma	17 (34.7%)	20 (46.5%)	18 (40%)	
	Academic degree	27 (55.1%)	17 (39.5%)	19 (42.2%)	

Abbreviations: AT: *A. graveolence* and *T. copticom*, DC: Demographic characteristics, $p<0.05$ shows significant differences based on chi-square test.

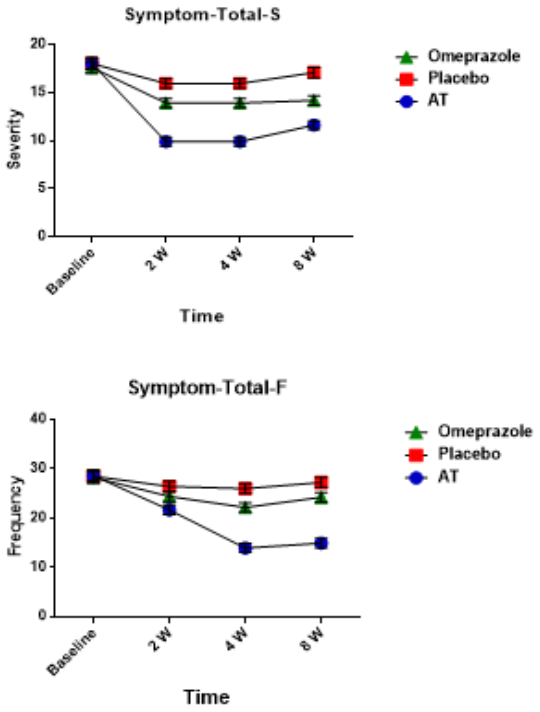

Figure 3. Total score of symptoms. w: week

The between-group difference in severity and frequency score of each symptom was not significant on enrollment. However, the reduction rate of each symptom's score was relatively different after the intervention period. These reductions are presented below in order of symptom prevalence:

The most common symptom amongst the subjects was epigastric pain. Between-groups comparison, showed that reduction of the severity of pain was significantly greater in the AT group than in the placebo group, and remained significantly low until the end of the follow-up period; whereas, the difference between the AT and omeprazole groups was not significant. The difference between the omeprazole and placebo groups was significant until the end of the follow-up period. Variations of pain frequency and severity were similar among the groups (Figures 4 and 5).

The decrease in the frequency and severity of the second most common symptom (i.e. bloating) was significantly greater in the AT group than in the two other groups until the end of the follow-up period. The difference between the omeprazole and placebo groups in this regard was not significant throughout the study (Figures 4 and 5).

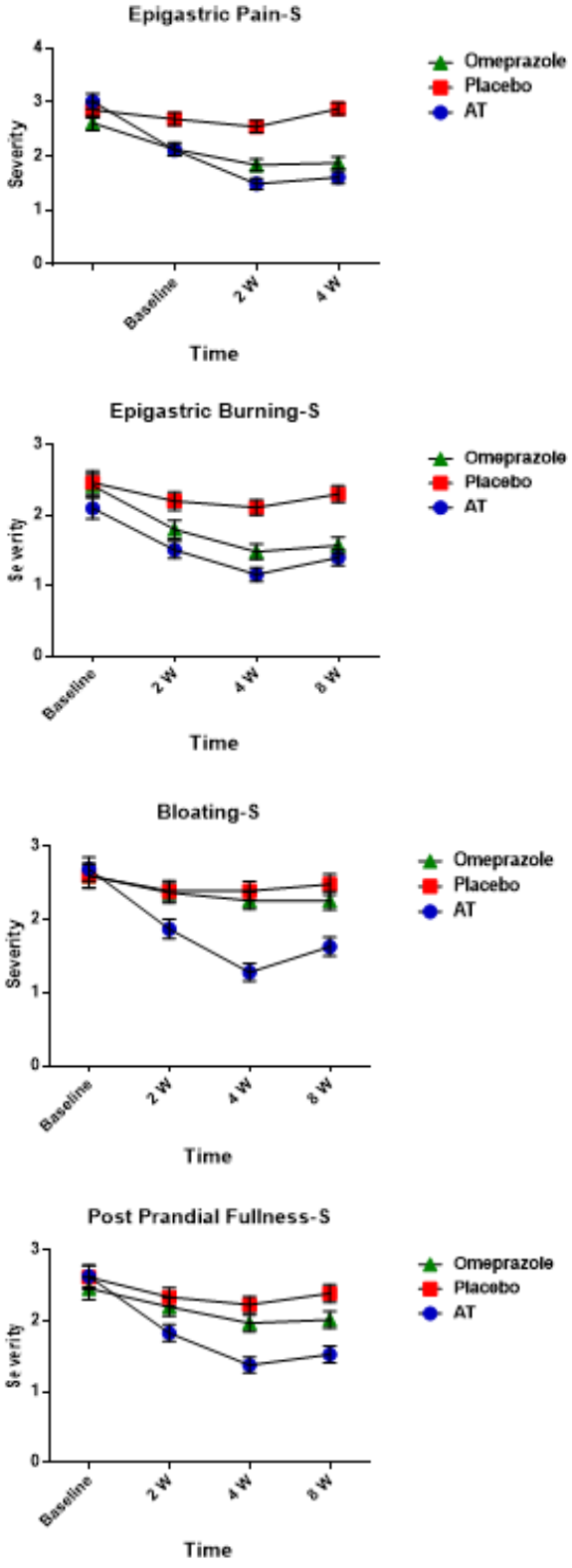

Figure 4. Severity of symptoms. w: week

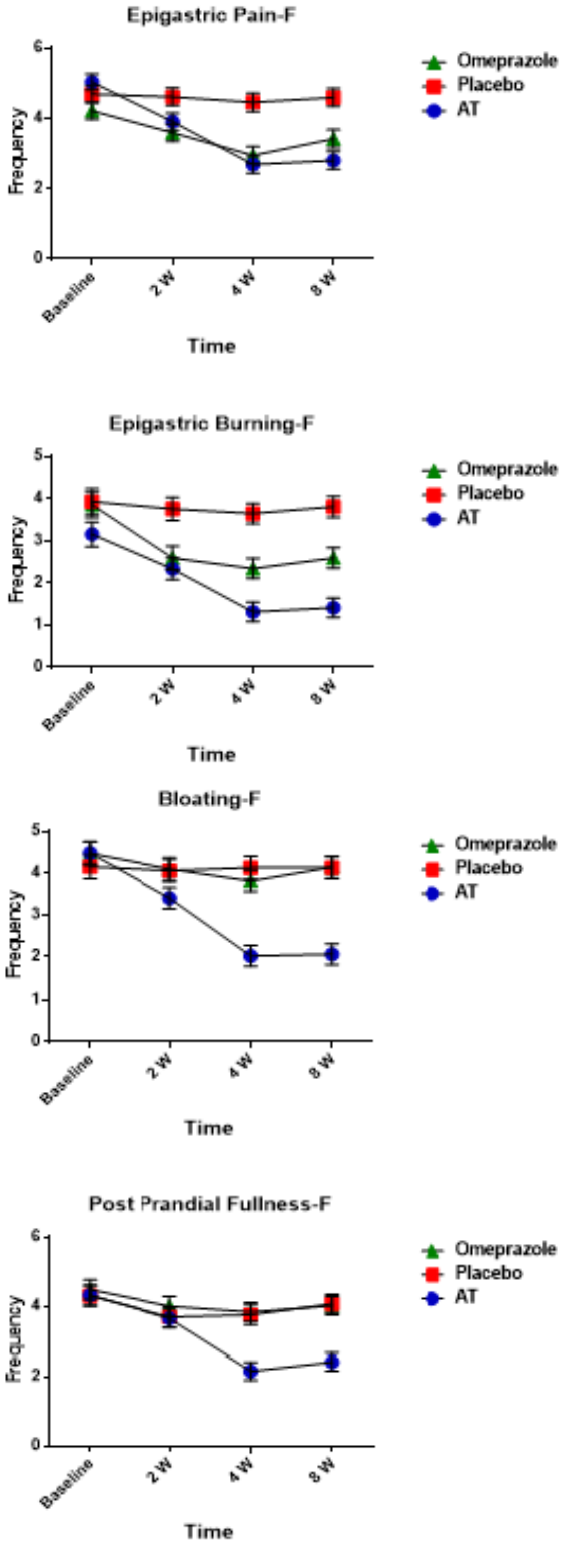

Figure 5. Frequency of symptoms. w: week

The decrease in the frequency and severity of the third most common symptom (i.e. postprandial fullness) was significantly greater in the AT group than in the two other groups until the end of the follow-up period. The difference between the omeprazole and placebo groups in this regard was not significant throughout the study (Figures 4 and 5).

The decrease in the frequency and severity of the fourth most common symptom (i.e. epigastric burning) was significantly greater in the AT and omeprazole groups than in the placebo group. The difference between the omeprazole and AT groups in terms of the symptom severity was not significant whereas, AT was significantly more effective than omeprazole in reducing the frequency of epigastric burning (Figures 4 and 5). The decrease in the frequency and severity of early satiation and belching was significantly greater in the AT than in the placebo and omeprazole groups whereas, the difference between the omeprazole and placebo was not significant.

The decrease in the frequency and severity of nausea was significantly greater in the AT group than in the placebo group. The difference between the AT and omeprazole groups in this regard was not significant. This symptom showed no significant difference when comparing the omeprazole and placebo groups

In terms of vomiting, between-groups difference was not significant.

In the AT group, a slight increase in the frequency of intestinal movement and belching was observed in the first few days after taking the medication in some patients. Also, a slight increase was observed in menstrual bleeding of two patients.

Discussion

According to the findings of this study, AT as Iranian traditional remedy proved to be more effective than placebo and omeprazole in improvement of symptoms until the end of the follow-up period. In a study conducted in 2005 by Rafieian-kopaei and Hosseini, the overall decrease of functional dyspepsia symptoms was significantly greater in the *Ocimum*

bacillicum-treated group than in the placebo group (Rafieian-Kopaei and Hosseini, 2005). Another study showed that the overall decrease of functional dyspepsia symptoms was significantly greater in the *Glycyrrhiza glabra*-administered group than in the placebo group (Raveendra et al., 2012). Moreover Mohtashami et al.demonstrated that the overall decrease of functional dyspepsia symptoms was significantly greater in the group received honey-based preparation of *Nigella sativa* as compared to the placebo group (Mohtashami et al., 2015). Pasalar et al. (2015) performed a study on the effect of Jollab, an Iranian traditional remedy on FD patients and observed that the decrease in overall severity and frequency scores were higher in Jollab-treated group than in the placebo group (Pasalar et al, 2015).

Considering each individual symptom the improvement in symptoms, such as epigastric pain, bloating, early satiation, postprandial fullness, burning, nausea and belching was significantly greater in the AT group than in the two others groups throughout the trial. It is worth noting that symptom severity improvement initiated from two weeks after the intervention and continued until the end of the follow-up period. Regarding the symptoms frequency, the improvement initiated with a short delay from the fourth week and continued until the end of the follow-up period. In a study conducted by Ghoshegir et al. (2015), it was found that the improvement of FD was greater in the *Pimpinella anisum*-treated group than in the placebo group. Considering each individual symptom *P. anisum* was more effective than placebo in the improvement of symptoms such as postprandial fullness, early satiation, belching, burning, and loss appetite (Ghoshegir et al. 2015).

AT, as an Iranian traditional remedy was significantly more effective than omeprazole in the improvement of symptoms such as belching, bloating, postprandial fullness, early satiation, and epigastric burning. Considering epigastric pain improvement, both medications were effective and there was no significant difference between them. Regarding the improvement of nausea and vomiting, there was no significant difference between AT and omeprazole in addition, the difference between omeprazole and placebo groups was not significant. Zohaninezhad et al. (2015) evaluated the clinical symptoms of children with gastroesophageal reflux, and did not observe any significant difference between the effects of Quin syrup and omeprazole (Zohalinezad et al., 2015). Zohalinezhad et al. in a study (2016) found no significant difference between the therapeutic effect of *Myrtus communis* and omeprazole on clinical symptoms of patients with gastroesophageal reflux (Zohalinezad et al, 2016).

In comparison between omeprazole and placebo, although the former was more effective in reducing the total score of symptoms, the difference was not significant, except for pain and epigastric burning. In a study conducted by Talley et al. (1998) on the effect of omeprazole on FD, no significant difference was observed between omeprazole and placebo in reducing dysmotility syndrome-related symptoms. However, omeprazole was more significantly effective than the placebo against ulcer-like symptoms (Talley et al., 1998).

According to the present study, AT, Iranian traditional remedy was more effective than omeprazole and placebo in improving FD symptoms (postprandial distress syndrome and epigastric pain syndrome). This study was associated with some limitations, such as being a single-center study, limited sample size, and short follow-up period. Therefore, results of this study are not generalizable to all FD patients. However, AT can be prescribed as an adjuvant medication, with few side effects, for FD patients after theconduction of further studies.

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Conflict of interest

The authors declare that there is no conflict of interests.

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