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Published online 2018 February 12. **Brief Report**

Effects of "*Satureja Hortensis* L." on Improving Adult Gastroesophageal Reflux Disease: A Double-Blind, Randomized, Controlled, Clinical Trial

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Abstract

Background: Gastro-esophageal reflux disease (GERD) is one of the most widespread gastrointestinal disorders. In addition, there is increasing evidence that not all patients respond to its current remedies.
Objectives: The aim of this pilot study was to investigate the effect of "*Satureja hortensis* L." on improving the symptoms of mild to moderate GERD in adults.
Methods: In this double-blind, randomized, controlled, clinical trial, we evaluated the efficacy of "*Satureja hortensis* L." compared to placebo in the symptoms of GERD in fifty-eight adults with GERD who referred to Hazrat Rasool-e-Akram hospital in Tehran, Iran, in 2015. In order to assess GERD symptoms, a standardized questionnaire of frequency scale (FSSG) was used before and after the intervention.
Results: Regarding within-group changes, a significant decrease was observed in FSSG, dysmotility-like symptoms and acid reflux related scores in both groups of the study after the intervention compared to baseline ($P < 0.001$). Regarding between-group analysis, no significant differences were observed between the two groups in terms of FSSG total scores ($0.05 < P$).
Conclusions: According to the results of the current study, *Satureja hortensis* L. with the dose of 500 mg three times per day failed to improve the symptoms of GERD in adults compared to placebo. The significant reductions in the GERD scores in both groups seem to be related to the lifestyle modification that was prescribed to both groups.

Keywords: Heartburn, GERD, Savory Plant, Saturejas, Herbal Medicine

1. Background

Gastro-esophageal reflux disease (GERD) is a condition that occurs when contents of the stomach reflux into the esophagus, leading to troublesome symptoms and/or mucosal lesions in the distal esophagus (1). GERD is a common problem affecting nearly 20% of people in Iran and so does in western countries, making it one of the most widespread gastrointestinal disorders (2, 3). Most of the people with reflux disease show mild symptoms and need little, if any, medication. Few patients will require surgery; and in the rest, control of symptoms needs continuing acid-suppression therapy; the latter requires maintenance of medical management (4, 5). Long-term usage of suppressing gastric acid has lately been associated with a multitude of side effects such as enteric infections, sustained hyper-gastrinemia , impaired vitamin B, and iron absorption, acute interstitial nephritis, colon or gastric malignancies, osteoporosis, myopathy, acute coronary syndromes, and rebound acid hypersecretion (4, 6). In addition, there is increasing evidence that not all patients respond satisfactorily to this kind of remedy and about one-third of the patients need additional intervention to manage symptoms (7). Besides conventional intervention, complementary and alternative medicine (CAM) has introduced many approaches for this disorder (8). As well, new investigations have introduced various methods such as natural approaches, lifestyle modification, and herbal medicine for the management of GERD symptoms (9-11).

The traditional Persian medicine (TPM), which dates back to thousands of years ago, consists of the assemblage of whole knowledge applied in diagnosis, prevention, and treatment of diseases in Iran from ancient times until now (12-18). TPM has given more regard and importance to the prevention of a disease rather than its treatment, so "lifestyle modification" is the first approach to the management of the diseases. After modifying the lifestyle, the use of simple remedies is the second approach to controlling diseases. Finally, if a disease does not improve through simple treatment, the third line will be the administration of compound medicines comprising two or more simple medicines (19, 20).

Satureja hortensis L (Savory) is an edible vegetable that Iranian people use as a flavor component in their diet. In addition, in Iranian folk medicine, *S. hortensis* has been used as a carminative and antispasmodic remedy for disorders like mild to moderate GERD (21). Studies have shown the effectiveness of *S. hortensis* as an anti-inflammatory factor in acute inflammation of the stomach and intestines, as well as carminative, anti-diarrhea, pain relieving, antibacterial, antiviral, antifungal, and anti-oxidant medication (22-24).

The aim of this study was to assess the efficacy of "lifestyle modification" and "*S. hortensis*" in improving the symptoms of GERD in a pilot open-label clinical trial.

2. Methods

2.1. Study Design

This study is a randomized, double-blind, placebo-controlled clinical trial performed at Iran University of Medical Sciences. In this trial, we evaluated the effect of lifestyle modification" and "*S. hortensis*" on improving the symptoms of GERD in a pilot open-label clinical trial. No changes occurred to methods after trial commencement.

2.2. Sample Size Calculation

The sample size was calculated by considering a one-sided significance level of 0.05 and 0.80 power based on the comparison of means of FSSG to detect the mean difference of 6 ± 9 before and after the intervention, and a probable 10% dropout rate totaling 29 patients in each group. The sample size was calculated using the PASS 11 software.

2.3. Selection of Patients and Assessment Criteria

In this randomized pilot study, fifty-eight patients with symptoms of GERD visited by gastroenterology specialist were gathered from Hazrat Rasool-e-Akram hospital in Tehran, Iran (It is a governmental and referral hospital). Written informed consent was obtained from patients before participating in this study. Patients aged 18 - 65 with mild to moderate symptomatic GERD (discomfort enough to interfere with ordinary activities such as sleep or work) diagnosed by a gastroenterologist were included in the study. The exclusion criteria consisted of occult blood (OB) positive, risk of cancer, risk of peptic ulcer, pregnancy and breastfeeding, any digestive disorder requiring new protocols, abnormalities of laboratory tests (such as low hemoglobin, high ESR, CRP positive, and so on), significant surgical or medical disorders, hospitalization, and non-users of *S. hortensis* capsules for 2 weeks. A standardized questionnaire of frequency scale for the symptoms of GERD (FSSG) was filled out by patients. FSSG is a useful questionnaire for objective assessment of the therapeutic response of GERD (25). This questionnaire included twelve questions with five dysmotility-like (DS) symptoms (DS questions about flatulence, feeling heavy or sick after meals, feeling full while eating meals, as well as much burping) and seven acid reflux-related symptoms (RS questions about heartburn, regurgitation into the throat, chest rubbing, heartburn after meals or while bending, burning sensation in throat, and difficulty swallowing). The utmost scores of total FSSG, DS, and RS were 48, 20, and 28, respectively. Also, with this questionnaire, patients had no difficulty in rating their symptoms as occurring occasionally (about 30% of the time), sometimes (50%), often (70%), or always (100%) (25, 26). At the end of the intervention, the same questionnaire was completed by patients. In addition, the efficacy of each treatment was assessed by subjects using the visual analogue scale (27). VAS scores were compared within each group and between the two groups before and 4 weeks after the intervention.

2.4. Randomization

Fifty-eight eligible patients were randomized into two parallel groups. Then, the patients were randomly assigned to one of the groups with simple block randomization method that was carried out by applying NCSS (statistical software). Only statisticians were blind to the allocation of the patients.

2.5. Preparation of Plant Material

S. hortensis was collected from Varamin, Iran, in 2015 and identified by a botanist (whose name is Mohammad Kamalinejad) at Shahid Beheshti University of Medical Sciences. *S. hortensis* plants were dried in indirect light at 25°C in the room, and the whole dried plants were powdered by micronized steel mill and passed through a 32 mesh-sized sieve. The powders were packaged in 500 mg capsules, and placebo capsules were filled with cornstarch in accurately

same-looking capsules as used for the *S. hortensis* group. Savory is an edible vegetable for which the usage dose has been mentioned 1 to 4 g daily (28); in this study, savory capsules were administered at a dosage of 500 mg three times a day (equivalent to 1.5 g). *S. hortensis* medications were prepared in gelatin capsule form.

2.6. Intervention

When the diagnosis of GERD was confirmed by a gastroenterologist, the patients were divided into two groups. Patients were randomly assigned to receive either a four-week capsule of "*S. hortensis*" three times per day before meals for a period of four weeks as the intervention group, or placebo capsule with the same method as the control group. Participants in both groups received lifestyle modification commands by a written form during the study period. Items of lifestyle modification form were: avoid eating at least 3 hours prior bedtime and elevate the head of the bed, eat a light meal for dinner and avoid fries, chili or salty foods, avoid tobacco, chocolate, caffeine or coffee, citrus, mint or spicy food, avoid drinking water and beverage between meals and at least two hours thereafter, chew your food morsel well until it is almost a liquid.

Then, a standardized questionnaire of frequency scale for the symptoms of GERD (FSSG) was filled out by patients before and after the intervention (25, 26). In addition, the efficacy of each treatment was assessed by subjects using the visual analogue scale (27).

2.7. Ethical Issues

The study protocol was according to the declaration of Helsinki (Hong Kong revisions, 1983), approved by the ethics committee of Iran University of Medical Sciences, and registered in the Iranian registry of clinical trials (IRCT2015072215860N2).

2.8. Statistical Analysis

Data are shown as mean + standard deviation and were analyzed using SPSS Version 16. A significance level equal to or greater than 0.05 was considered. The changes in FSSG parameters score before and after the intervention in each group and between the two groups were statistically analyzed by paired samples test, Chi-square, and independent T-test. In addition, Mann-Whitney U test and sign test were used for independent and dependent samples, respectively.

3. Results

A total of 58 patients were enrolled as subjects in this study. The mean age was 38.29 ± 13.29 in the *S. hortensis* group and 36.06 ± 9.24 in the placebo group. There was no significant difference between the two groups in terms of demographic characteristics (Table 1). In addition, no significant difference was seen in the FSSG total score, DS, RS, VAS, flatulence, and burp baseline scores between the two groups. Figure 1 is a flow diagram of the enrollment, groups' allocation, interventions, follow-up, and the analysis of the results. In both groups, FSSG total score, DS, RS, VAS, flatulence, and burp scores decreased significantly in comparison with the respective baselines (Table 2), but at the end of the study, the comparison of the two groups revealed no significant difference in any of the investigated options.

4. Discussion

The results of this study indicate that the scores of FSSG total, DS, and RS, VAS, flatulence, and burp significantly decreased in comparison with the respective baselines; that is, dysmotility-like symptoms, as well as acid reflux-related symptoms, were better than before the study. Esophageal motility disturbances and esophageal clearance reduction, respectively, are shown as pathological mechanisms of GERD (29). Esophageal dysmotility can be an additive factor which leads to an increase in the esophageal acid contact time and increases the severity of reflux disease from non-erosive to erosive reflux disease, also, causing chronic mucosal inflammation and impaired esophageal acid clearance (30-32).

S. hortensis has a historical background in folklore medicine as a food spice, gastro tonic, and antiseptic (21, 33). Several known effects have been discovered for *S. hortensis* in vitro and in vivo studies, such as antinociceptive, antimicrobial, antifungal, and anti-inflammatory activities as well as a cholesterol-lowering effect (22, 29, 34).

This study is the first clinical trial that investigated the effectiveness of *S. hortensis* in patients with GERD, to the best of our knowledge. In spite of the fact that there were several studies on the efficacy of *S. hortensis* and its derivatives, especially carvacrol, in many diverse conditions as an antimicrobial, antifungal, antitumor, analgesic, antispasmodic, and anti-inflammatory agent, there was no information about its role in GERD.

In this study, the improvement of dysmotility-like symptoms may be due to carvacrol as a major component of *S. hortensis*. Many useful effects of carvacrol on gastrointestinal ailments found in this study are consistent with other studies (21-24). Furthermore, the beneficial effects (anti-inflammatory antibacterial, antiviral, antifungal, anti-oxidant, and pain relieving) of *S. hortensis* might affect heartburn and pain as symptoms of GERD, a fact that

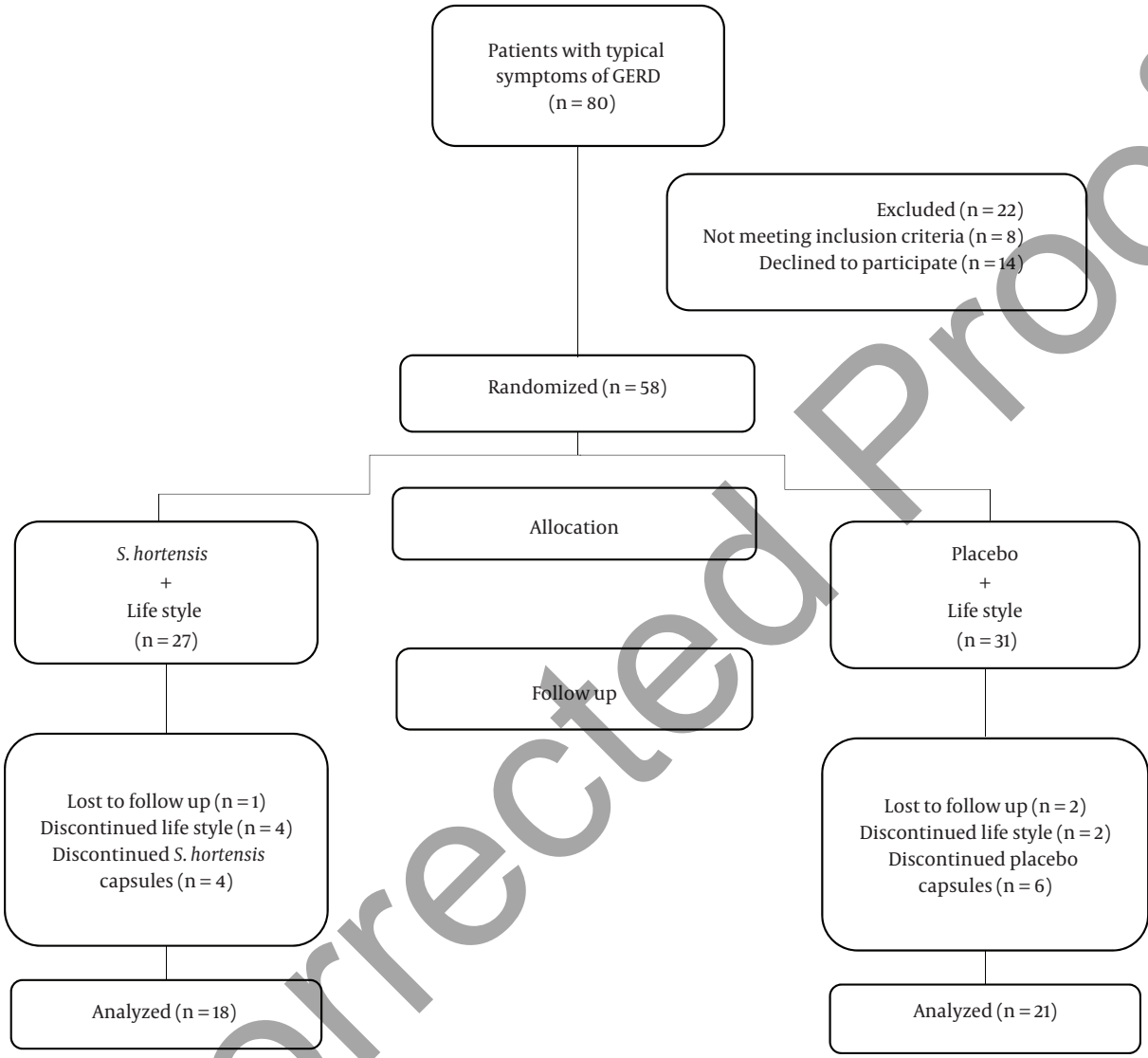

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) Flow Diagram

Table 1. Demographic Data of the Patients[a]

Variable	*Satureja* (N = 21)	Placebo (N = 18)	P Value
Age, y	38.29 ± 13.29	36.06 ± 9.24	0.117
Male/female	12/9	11/7	0.346
Duration of illness, mo	30.04 ± 40.28	37.36 ± 45.36	0.778
Marital Status: Single/Married	5/10	5/11	0.197

[a]Values are expressed as mean ± SD or number.

could be related to its anti-inflammatory effect on the mucosa of the esophagus and its pain relief (21-23). Overall, our results showed that some of the pathological mechanisms of GERD can be affected by *S. hortensis*, as well as flatulence

Table 2. Pre- and Post-Treatment DS, RS, FSSG, VAS, Flatulence, and Burp Total Scores

Variables	Groups		P Value
	S. hortensis	Plplacebo	
DS (Dysmotility-like symptoms)			
Before	10.33±4.98	9.83±5.13	0.760
After	6.09±4.72	5.66±4.02	0.764
P value	0.000	0.000	
RS (acid reflux- related symptoms)			
Before	7.90±5.93	8.27± 5.80	0.844
After	4.04± 3.52	4.22± 4.37	0.891
P value	0.000	0.000	
FSSG (questionnaire of frequency scale for the symptoms of GERD)			
Before	18.83± 8.41	18.23± 8.63	0.829
After	10.11± 6.69	10.14± 7.05	0.989
P value	0.000	0.000	
VAS (visual analogue scale)			
Before	6.43±1.85	6.11±1.56	0.214
After	3.57±1.53	3.89±1.87	0.239
P value	0.001	0.001	
Flatulence			
Before	2.62 ± 1.24	2.50 ± 1.46	0.785
After	1.48 ± 1.16	1.56 ± 1.09	0.829
P value	0.001	0.001	
Belching			
Before	2.43 ± 1.16	1.67 ± 1.15	0.349
After	2.00 ± 1.64	1.17 ± 1.38	0.226
P value	0.006	0.005	

and burp that significantly decreased compared to the respective baselines. Seemingly, *S. hortensis* can be useful in dyspepsia; however, further studies should be done to confirm this suggestion.

The results of the current study showed that in groups, *S. hortensis* and placebo, GERD symptoms improved, though we expected improvements in the *S. hortensis* group to be more than those in the placebo group. However, the comparison of these two groups showed no significant differences in the improvement of GERD symptoms. Thus, it would be better to conduct a study with another group to evaluate only the effect of lifestyle without taking placebo; this was one of the limitations of our study. It seems that one of the main reasons for this outcome is lifestyle modification in both groups based on previous studies (35, 36). Moreover, the small sample of the study could be another reason; also, it might be because of pharmaceutical dosage forms of *S. hortensis* capsules. Since the pharmaceutical form used in this study was powdered *S. hortensis*, it is possible the rates of carvacrol and other main components of the aerial parts were probably less than in syrup or other pharmaceutical forms. In addition, the applied dose of *S. hortensis* is mentioned to be 1 to 4 g daily (28); in this study, *S. hortensis* capsules were administered at a dosage of 500 mg three times daily (equivalent to 1.5 g), so it is likely that if the intervention was done with a higher dose of *S. hortensis*, or in the syrup form, the results between the two groups (S. hortensis and placebo) would be significantly different.

4.1. Study Limitations

Our study had some limitations. The small sample size of the study should be considered as a major limitation. It is probable that if the study sample size was higher, we

would obtain better results from the study. The functional status of the participant was measured by the FSSG questionnaire, as a reliable and valid tool. Therefore, another important limitation was the absence of objective measures for assessment of participants' functionality. In addition, this study was faced with another constraint: open-label studies may have some bias. Possibly, we could opine better about the effectiveness *S. hortensis* in GERD if we had a third group that received only placebo capsule without lifestyle modification. Finally, the lack of dose adjustment or multiple dose evaluation of *S. hortensis* in the present trial is yet one more problem, which should be considered in oncoming trials.

4.2. Conclusion

According to the results of the current study, *Satureja hortensis* L. with a dose of 500 mg three times per day failed to improve the symptoms of GERD in adults compared to placebo. The significant reductions in GERD scores in both groups seem to be related to lifestyle modification that was prescribed to both groups.

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