# Comparison of the therapeutic effect of the Persian Medicine Protocol with the common treatment of chronic rhinosinusitis: a randomized clinical trial

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## Abstract

**Background:** Chronic rhinosinusitis is one of the most common diseases affecting the quality of life of patients. Patients suffer from high costs in the diagnosis and treatment of the disease. Frequent recurrence and failure of therapeutic protocols are among the most important issues in the management of this disease. In view of this, the use of traditional and complementary therapies to promote the treatment of this disease has been increasingly taken into account.

**Objective:** Comparison of the effectiveness of the Persian Medicine Protocol with the conventional therapy in the treatment of chronic rhinosinusitis.

**Methods:** A randomized clinical trial was conducted at Imam Reza Hospital in Mashhad, Iran from July 2016 to March 2017. For patients with chronic rhinosinusitis symptoms, endoscopy of the sinuses was performed by an ENT specialist and in the case of negative endoscopy, paranasal sinus CT scan was requested. A total of 42 patients with chronic rhinosinusitis were randomly assigned to two groups. The first group (classical) received systemic and intranasal cortisone, and the second group (traditional) received a therapeutic Persian medicine protocol including intranasal lavender oil, and Liquorice Marjoram Tea (L. M. tea) for six weeks. The symptoms of the patients were evaluated using the SNOT-22 questionnaire at the beginning of the study and at the sixth week. If no improvement occurs, treatment continued for 12 weeks. Data were analyzed by SPSS version 16, using ANOVA, independent-samples and paired-samples t-test, Wilcoxon signed-rank test, and simple linear regression.

**Results:** In 20 patients in the traditional group, the decrease in SNOT score was observed as 56% after 6 weeks treatment (p=0.001), which is similar to the effect of the first group (classical). Although there was no statically significant difference between the two groups, in clinical terms, the difference in mean systemic symptoms such as confusion with 1.05 (p=0.5) and fatigue with 1.63 (p=0.01) had more improvement in the traditional group, and the difference in mean local symptoms such as nasal congestion with 2.37 (p=0.78) and runny nose with 1.95 (p=0.14) had a more decrease in the classical group.

**Conclusion:** The results of this trial indicate the effectiveness of the Persian Medicine Protocol (including Lavender oil and L.M tea) in the treatment of chronic rhinosinusitis, especially on improving systemic symptoms.

## 1. Introduction

Chronic rhinosinusitis refers to inflammation of the nasal mucosa and sinuses (1) and has several complications (2). Symptoms and signs are divided into two major and minor categories. The disease has a relatively high prevalence (3) and according to some evidence, its incidence and prevalence is increasing (4). The prevalence of this disease worldwide is about 13.5%. (3). The prevalence of this disease is high in Iranian society, as in a meta-analysis study, the rate of sinusitis in Iran of about 53% (between 40% and 65% with a 95% confidence interval) has been reported (5). However, it seems that this prevalence is more among patients with background illnesses. For example, in an examination of asthmatic patients in Iran, the prevalence of sinusitis in adults was 48.3% (6), and in children aged 2 to 16 years old 73.2% (7) has been reported. Chronic rhinosinusitis affects the quality of life, and is comparable to chronic disabling diseases (8) and regarding the burden of the disease and its complications, it is considered as one of the 10 most debilitating diseases (9). Economically, sinusitis treatment is expensive (10), as some studies show that its treatment costs are approximately 1.5 times more than other similar diseases (11). Meanwhile, during the treatment of this disease, there are frequent outpatient visits, numerous diagnostic and therapeutic measures and a reduction in the productivity of the workplace (12). Treatment options for acute and chronic sinusitis are currently proposed, including the use of corticosteroids, antibiotics, antihistamines and, if necessary, surgical procedures for sinuses (13). However, due to the heterogeneous nature of chronic sinusitis, many of these treatments cannot root out its background cause (14). In addition, in a number of patients who have been treated repeatedly with antibiotics or sinus surgery, there is an increased risk of colonization of antibiotic-resistant pathogens and surgical complications (1). The incidence of chronic rhinosinusitis after endoscopic surgery has been reported to be 60%, with 47% of them requiring re-surgical operation (15). Due to the low level of treatment in this disease and frequent recurrence, the use of traditional and complementary medicine is common (16), with about one third of patients with chronic rhinosinusitis using plant compounds to fix their problem (17). According to previous studies in Iran, one of the most common causes for referring to traditional medicine clinics was sinusitis (18). However, in the reported evidence, the effectiveness of medicinal plants in the treatment of chronic sinusitis is limited (19), but several studies have been conducted in relationship with using various medicinal herbs, including: Rumex patientia (Garden patience), Ecballium elaterium (Squirting cucumber), Stachys schtschegleevii (Poulk), Pelargonium sidoides (African geranium) (20-22). On the other hand, in the Persian medicine literature, a disease called "NAZLA" is mentioned whose symptoms and signs are compatible with chronic rhinosinusitis (23), and for which, various therapies have been mentioned (24). The main objective of this study was to determine the effectiveness of the Persian-based therapeutic protocol on chronic rhinosinusitis compared with classical drug therapy, and its specific objectives were the following: Determination of the effectiveness of the Persian Medicine Protocol in the treatment of chronic sinusitis based on the SNOT-22 test, determining the effectiveness of classical medicine in the treatment of chronic sinusitis according to the SNOT-22 test, and finally comparing the effectiveness of the Persian Medicine Protocol with conventional therapy for the treatment of chronic sinusitis, based on the SNOT-22 test. In this regard, the researchers have attempted to design and implement a clinical trial study of the effects of lavender, marjoram and licorice plants on chronic rhinosinusitis.

## 2. Material and Methods

### 2.1. Research design

This study was a randomized, single-blind clinical trial on patients with chronic rhinosinusitis from July 2016 to March 2017.

### 2.2. Population studied

The population under study was people with chronic rhinosinusitis and the statistical sample included individuals with chronic rhinosinusitis symptoms referring to the specialized centers of ENT and the Persian medicine of Imam Reza Hospital, a recessive center affiliated to Mashhad University of Medical Sciences (MUMS) in northeastern Iran. Patients with typical symptoms of chronic rhinosinusitis (based on the latest diagnostic criteria for chronic rhinosinusitis [AAO-HNS] in the United States of America in 2015) with the diagnosis of ENT, were examined by

endoscopic sinuses or spinal paranasal sinus CT scans and entered the research plan if they had entry criteria (Figure 1).



**Figure 1.** Flowchart of the clinical trial based on CONSORT

### 2.3. Entry and exit criteria
The following cases were considered as inclusion criteria: aged 18 to 50 years, having at least two signs of symptoms: Mucosal septic secretion (anterior, posterior, or both), nasal obstruction (congestion), pain, pressure, decreased sense of sme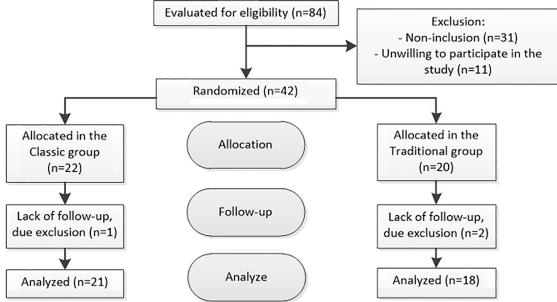ll, the presence of the above symptoms for at least 12 weeks, proven inflammation with at least one of the following ways: Observing mucosal septic secretions (non-transparent) or edema in the middle meatus or anterior region of ethmoid, the presence of polyps in the nasal cavity or middle meatus, or radiological imaging indicating inflammation in the paranasal sinuses. Exit criteria included chronic sinusitis with acute infection of respiratory microbial infections, chronic sinusitis associated with anatomical obstruction requiring surgery, sensitivity or contraindication to the components of the drug combination of traditional and Persian medicine in patients, pregnancy, immunodeficiency or history of hypertension.

### 2.4. Interventions
Patients who had inclusion criteria were randomly assigned to traditional and classical groups, and questionnaires of demographic and clinical information were completed. Each group was treated in parallel with one of two treatments in the following way: 1) Patients in the classical group (control group), inhaler corticosteroid (flixonase), received 2 puffs per day, plus daily nasal washings with normal saline serum at two times in the morning and at night. In cases of no recovery, systemic corticosteroid (as prednisone tablets at a dose of 1 mg / kg) that was tapered within 5 days was prescribed; 2) Patients in the traditional group (intervention group) received L.M tea as a combination of 5-gram packs containing 2 grams of Licorice root (Glycyrrhiza glabra) and 3 grams of Marjoram leaves (Origanum vulgare). The patient adds the contents of each package to 200 cc of boiling water which is steeped for 20 minutes and then filtered. Consumption, was three times an hour after food, in a lukewarm and sipping manner. In addition, an intranasal oily product was prepared for these patients. Patients in the intervention group dropped this oil locally up to 2-3 drops per nostril every night before bedtime. The method of preparation of this oil was 3 weeks maceration of lavender (Lavandula angustifolia) flower in pure olive oil. The method of oil extraction was based on the sources of Persian medicine. According to this instruction, to get the oil of the flowers, they should be put in oil and placed in an appropriate place (such as the sunlight), and once a week (for up to three weeks) they should be cleaned and refilled (25). For this purpose, 20 grams of lavender flowers were placed inside a beaker containing 300 cc of olive oil (Extra virgin type, Minodasht brand), so that about one third of the beaker contained only olive oil without lavender. After 10 days of initial immersion, all the lavender flowers of the above composition were separated from the oil first by metallic filter and then by sterilized gauze, and again, the same amount of lavender flower was added to the remaining oil, and then immersed. After 10 days from the second immersion, the plant mass was isolated by

using sterile gauze and under pressure, and the obtained oil was poured into 15 centrifuge tubes and centrifuged for 20 minutes at 3000 rpm. Two grams of licorice and three grams of marjoram were packed in nylon bags and were ready to be delivered to the patients after labeling. The originality of the plants used in this study was confirmed by a botanical expert of the Plant Sciences Research Center of Ferdowsi University of Mashhad (Herbarium Numbers 14328 and 14261 belonging to marjoram and licorice, respectively).

### 2.5. Outcomes
Based on the Persian version of the SNOT-22 questionnaire whose validity and reliability was confirmed by Jalessi et al. (2013), (Cronbach's Alpha coefficient = 0.898) (26), the change in the score of the questionnaire and each single symptom was considered as the primary outcome, and the symptom recovery time was also considered as the secondary outcome. The SNOT-22 questionnaire contains 22 questions. These questions relate to the prominent features of the nose and throat (such as nasal congestion, runny nose), localized non-nasal symptoms (such as pain and fullness of ear), symptoms associated with sleep quality (such as difficulty falling asleep) and general symptoms (such as fatigue and dizziness). Question scores vary based on six degrees (from 0 to 5). The SNOT-22 questionnaire was filled at the beginning of the study (week zero) and the end of the week 6 and evaluated for changing the severity of the symptoms. The treatment was stopped for patients who had clinical symptom relief and patients with all or part of the symptoms were treated for 12 weeks. Finally, the SNOT-22 questionnaire was completed for them. In case of possible complications, the patient was registered in the relevant form and in case of severe complication the patient was excluded from the study.

### 2.6. Sample size
With the help of the PASS software and based on the 90% confidence estimate for the difference between the mean scores of the SNOT-22 questionnaire, with an error estimation of 8 scores and a standard deviation of 15 for both groups, the sample size was considered to be 20 in each group with a 10% drop in each group, 22 samples were selected.

### 2.7. Allocation, blinding and randomization
Patients who had the criteria for entering the study were randomly assigned to traditional and classical groups and demographic information questionnaires were filled out with clinical information. Each group was treated with one of two treatments in parallel. Due to the difference in the type of drug interventions and how it was used in two groups that were differentiated by patients, blindness was not possible in this regard. But each patient was unaware of the treatment received by other participants in the study, and the analyst was not aware of the results of the patients. Therefore, this study was done randomly and single blind.

### 2.8. Statistical analysis
Data were entered into the computer after evaluation and analyzed by SPSS software version 16. At first, the characteristics of each group based on descriptive statistical methods including central indices, distribution and frequency distribution were studied and described. Then, for quantitative variables, the normality of their distribution was first measured using the Kolmogorov-Smirnov test. Data were analyzed using independent and paired-samples t-test, repeated measures (ANOVA), Wilcoxon signed-rank test, and simple linear regression. In all calculations, α 0.05 was considered as the significant level.

### 2.9. Ethics of research
The present study has been approved by the Ethics Committee for Research at Mashhad University of Medical Sciences (Ref: 931673, dated November 07, 2015). Patients were informed about this study and signed the consent form individually. Participation was completely voluntary and participants were allowed to leave at any time. In order to ensure that no financial, mental or physical harm occurred to the participants, an accessible telephone number was provided to contact at any time if information on the research or medical assistance was required. All participants' data were received and kept confidential.

## 3. Results
### 3.1. Entry, screening and completing intervention
During the period from July 2016 to March 2017, 86 patients with symptoms of chronic rhinosinusitis referred to the specialized otorhinolaryngology and Persian medicine clinics of Imam Reza Hospital in Mashhad. Of these patients, after examination by an ENT, and performing endoscopic sinuses or CT scan of paranasal sinuses, 42 patients who were diagnosed with chronic rhinosinusitis were eligible to enter the trial. During the clinical trial, 2 patients in the

group were treated with traditional medicine due to complications (one due to hypertension and another for the exacerbation of symptoms) failed to complete the treatment process, and 1 patient from the classical medicine department (due to the lack of recovery of symptoms leading to surgery) failed to complete the treatment.

### 3.2. Demographic findings

The mean age of participants in the study was 38.86 years with a standard deviation of 10.35. Of the patients studied, 64.3% were male and 35.7% were female. A total of 59.5% of the participants in the study had university education and the rest had lower qualifications. Furthermore, 76.2% of the patients in the project were employed (Table 1).

**Table 1.** Demographic information of the participants

| Variable | | n | % |
|---|---|---|---|
| Sex | Male | 27 | 64.3 |
| | Female | 15 | 35.7 |
| Education | Illiterate | 2 | 4.8 |
| | Primary School | 4 | 9.5 |
| | Secondary School | 6 | 14.3 |
| | High School | 5 | 11.9 |
| | University | 25 | 59.5 |
| Employment | Working | 32 | 76.2 |
| | Workless | 10 | 23.8 |
| Marital status | Yes | 37 | 88.1 |
| | No | 5 | 11.9 |
| Smoking | Yes | 3 | 7.3 |
| | No | 38 | 92.7 |

### 3.3. Intervention findings

In paraclinical examination, 82% of patients had endoscopic evidence of chronic rhinosinusitis. Also, in 81% of patients, chronic rhinosinusitis was found in paranasal sinus CT scans. Among the criteria for diagnosis of chronic rhinosinusitis, based on the American Academy of Otorhinolaryngology and the American Academy of Neck Surgery (AAO-HNS), all patients had nasal congestion or nasal-anterior or posterior secretion (100% of cases), however, pain or pressure in the face, and reduced or absent olfaction were reported from 78.6% and 85.7% of patients, respectively. Kolmogorov Smirnov test was used to check the normality of the quantitative variables used in the study. The results finally showed that all the variables used in the study had normal distribution. In examining the SNOT scores in the two traditional and classical groups whose results are presented in Table 2, SNOT scores were not significantly different in the two groups in the three stages of follow-up, but in analyzing the effect of intervention by group analysis, variance analysis showed that the scores were significantly different during the three stages. On the other hand, as shown in Table 3, comparison of SNOT scores in the third monitoring (the 12th week treatment) with the second monitoring (6th weeks treatment) indicates a decrease in the SNOT score in the traditional group and increase in the classical group. The evaluation of classified SNOT scores in both groups before and after intervention, as shown in Table 3, indicates that SNOT scores vary in both groups before and after intervention and the severity of symptoms in both groups decreased after intervention, especially as the percentage of "very severe" stage was much less than "very mild" stage, and this decrease in intensity from stage 3 is very tangible. Table 4 compares the single marker of patients' symptoms before and after intervention in comparing the two treatment groups.

**Table 2.** Mean and standard deviations of SNOT scores by groups

| Follow up level based on SNOT | Traditional group (Mean ± SD) | Classic group (Mean ± SD) | Results of Independent-samples t-test |
|---|---|---|---|
| SNOT 1 | 48.31±18.78 | 48.29±14.7 | t= -0.002; p-value=0.998 |
| SNOT 2 | 21.31±12.57 | 22.57±9.29 | t= 0.147; p-value=0.884 |
| SNOT 3 | 15.25±12.46 | 28.71±20.68 | t= 1.94; p-value= 0.065 |
| Result of the ANOVA | F= 33.07; p-value<0.001 | F= 17.42; p-value<0.001 | - |

SNOT 1: SNOT scores at the patient's admission, SNOT 2: SNOT scores in the second checking (sixth week of treatment), SNOT 3: SNOT scores in the final checking (12th week of treatment)

**Table 3.** Frequency and percentage of groups before and after intervention

| Group | Severity of rhinosinusitis according to SNOT score | Percent before intervention | Percent in the first follow up | Result of Wilcoxon signed-rank test |
|---|---|---|---|---|
| Traditional | 1 (Very mild problem) | 15 | 60 | Z= -3.12; p-value= 0.002 |
| | 2 (Mild or slight problem) | 35 | 30 | |
| | 3 (Moderate problem) | 40 | 5 | |
| | 4 (Severe problem) | 10 | 0 | |
| | 5 (Problem as bad as it can be) | 0 | 0 | |
| Classic | 1 (Very mild problem) | 9.1 | 68.2 | Z= -3.78; p-value<0.001 |
| | 2 (Mild or slight problem) | 50 | 27.3 | |
| | 3 (Moderate problem) | 36.4 | 4.5 | |
| | 4 (Severe problem) | 4.5 | 0 | |
| | 5 (Problem as bad as it can be) | 0 | 0 | |

**Table 4.** Comparison of treatment response on the symptoms of patients before and after intervention in each group

| Symptom | Mean before intervention (Mean ± SD) | | | Mean after intervention (Mean ± SD) | | | Mean difference | |
|---|---|---|---|---|---|---|---|---|
| | Traditional | Classic | p-value | Traditional | Classic | Value | Traditional | Classic |
| Need to blow nose | 2.68±1.6 | 2.59±1.5 | 0.85 | 1.68±1.1 | 0.82±1.2 | 0.02 | 1 | 1.77 |
| Blockage / congestion of nose | 3.32±1.2 | 4.14±1 | 0.24 | 1.63±1.2 | 1.77±1.9 | 0.78 | 1.69 | 2.37 |
| Sneezing | 1.58±1.3 | 1.32±1.6 | 0.58 | 0.47±0.6 | 0.45±1 | 0.94 | 1.11 | 0.87 |
| Runny nose | 2.47±1.4 | 2.77±1.6 | 0.54 | 1.47±1.5 | 0.82±1.2 | 0.14 | 1 | 1.95 |
| Cough | 1.89±1.3 | 1.73±1.7 | 0.73 | 0.74±1 | 0.5±0.8 | 0.43 | 1.15 | 1.23 |
| Post nasal discharge | 3.73±1.2 | 3.36±1.4 | 0.70 | 1.48±1.1 | 1.18±1.2 | 0.86 | 2.25 | 2.18 |
| Thick nasal discharge | 3.16±1.5 | 2.77±1.6 | 0.44 | 1.21±0.91 | 0.91±1 | 0.34 | 2.95 | 1.86 |
| Ear fullness | 1±1.5 | 1.32±1.6 | 0.48 | 0.58±1 | 0.14±0.3 | 0.07 | 0.42 | 1.18 |
| Dizziness | 1.58±1.38 | 0.86±0.88 | 0.06 | 0.53±0.9 | 0.36±0.8 | 0.5 | 1.05 | 0.5 |
| Ear pain | 0.63±0.8 | 0.46±0.8 | 0.5 | 0 | 0.14±0.3 | 0.99 | 0.63 | 0.32 |
| Facial pain / pressure | 2.68±1.7 | 1.77±1.5 | 0.08 | 1.16±1.3 | 0.68±1.2 | 0.24 | 1.52 | 1.09 |
| Sense of smell / taste | 2.84±1.7 | 3.86±1.5 | 0.05 | 2.32±2.1 | 2.18±1.9 | 0.83 | 0.52 | 1.68 |
| Difficulty falling asleep | 1.21±1.7 | 2.23±1.9 | 0.91 | 0.26±0.7 | 0.86±1.2 | 0.07 | 0.95 | 1.37 |
| Waking up at night | 1±1.5 | 2.36±2 | 0.02 | 0.37±0.8 | 0.68±1.1 | 0.33 | 0.63 | 1.68 |
| Lack of a good night's sleep | 1.89±1.7 | 2.23±1.9 | 0.57 | 0.26±0.9 | 0.41±0.9 | 0.62 | 1.63 | 1.82 |
| Waking up tired | 2.11±1.8 | 2.09±1.9 | 0.98 | 0.89±1 | 0.82±1 | 0.81 | 1.22 | 1.27 |
| Fatigue | 2.79±1.1 | 1.95±1.4 | 0.83 | 1.16±0.8 | 0.5±0.7 | 0.01 | 1.63 | 1.45 |
| Reduced productivity | 2.47±1.5 | 1±1.2 | 0.002 | 0.68±1 | 0.41±0.7 | 0.33 | 1.79 | 0.59 |
| Reduced productivity | 2.63±1.5 | 1.14±1.3 | 0.002 | 0.95±1 | 0.45±0.8 | 0.1 | 1.68 | 0.69 |
| Frustrated / restless / irritable | 2.42±1.6 | 1.55±1.4 | 0.08 | 0.74±0.9 | 0.45±0.7 | 0.3 | 1.68 | 1.1 |
| Sad | 2±1.5 | 0.68±1.1 | 0.003 | 0.32±0.7 | 0.36±0.7 | 0.04 | 1.68 | 0.32 |
| Embarrassed | 1.05±1.5 | 0.32±1 | 0.08 | 0.26±0.7 | 0 | 0.1 | 0.79 | 0.32 |

## 4. Discussion

The results of this trial showed that the treatment protocol based on Persian medicine, including the lavender oil, along with L.M tea, could be effective in treating patients with chronic rhinosinusitis and its effects on reducing or eliminating the 22-digit symptoms in the SNOT22 questionnaire are similar to the therapeutic effect of the current protocol of classic medicine. Comparing the scores of SNOT items between the traditional and classical groups also showed three categories of results: Accordingly, the symptoms of the first category (which didn't show statistical or clinical difference between two groups) were sneezing, coughing, ear pain, fatigue after sleep, disappointment, restlessness, and irritability. In the second category of symptoms, there were fatigue and sadness, which both were clinically and statistically lower in the traditional group than the classical, and this difference was statistically significant. In the case of "sadness", there was a significant improvement in the severity of symptoms in the traditional group compared with classical, while the difference was statistically significant. Of course, in the case of the sign "blowing the nose", this difference was significant in favor of classical treatment. In addition to the above

symptoms, 13 other symptoms are classified in the third category, showing a notable difference in the severity of post-treatment symptom between the traditional and classical groups, but this difference is not statistically significant. Accordingly, all of the local symptoms of the nasal cavity (including nasal secretion, nasal congestion, decreased olfactory sensation and post nasal discharge), with the exception of reduced thickness of nasal secretions, which responded better to classical treatment, although it was not statistically significant. But systemic symptoms of patients, with the exception of the difficulty of falling asleep (including confusion, waking up and not having a good night's sleep, decreased efficacy, decreased focusing and embarrassment), better responded to traditional treatment and, despite not being statistically significant, compared to the classical treatment group, were more decreased.

Regarding the higher clinical improvement of systemic symptoms in response to traditional treatment, it can be preferable in some instances. For example, in a patient with the prolonged period of rhinosinusitis and recurrence after treatment with classical treatments, the use of a full 12-week course of treatment with the traditional protocol may be more appropriate; while, in a patient who recently had chronic rhinosinusitis or no resistance and has no long-term desire for treatment, any of the protocols in classical medicine or traditional medicine, depending on the patient's preference, can be selected. Few studies have been done about the effects of the plants used in the present clinical trial (i.e. licorice, marjoram, lavender and olive oil). Madani et al. studied the effect of marjoram on 32 patients (compared with 32 controls) in a randomized, double-blind clinical trial (27). Based on this study, all symptoms of the patients, including headache, nasal congestion, sinus pain, throat secretions, etc. (except reduction of sense of smell and nasal secretion) were found to be remarkably decreased (27), which is similar to the effects observed in our research. In a study by Neher et al., several oily extracts were tested on the ciliary movement of nasal mucosa, and concluded that some herbal remedies, including lavender oil, could increase the ciliary beat frequency (CBF), which its impairment leads to chronic rhinosinusitis (28). The antimicrobial, anti-inflammatory, augmentative, and mucosal effects that can be effective in the treatment of chronic rhinosinusitis are reported in each of the above plants (whose major active ingredients are listed in Table 5). In a study by Giovannini et al. on the effect of Lavandula angustifolia essential oil on macrophage reaction from Staphylococcus aureus infection, this essential oil increased phagocytosis speed and increased the defense of intracellular antibacterial activity by macrophages (29). Another study by Ozogul on a number of herbal essential oils affecting food-borne pathogens showed that lavender essential oil can be effective as an antimicrobial against these pathogens (30). Prusinowska et al. also reported antimicrobial and antioxidant properties in lavender (31). These antimicrobial effects may confirm the findings of the present study on the local use of lavender oil in the pathophysiology of microbial contamination. In another study, conducted by Georgiev et al. on the lavender immune effects, lavender flowers contain polysaccharides that are immune-augmenter and can protect immune deficiencies (32). In a similar study, Gostner et al. concluded in a laboratory study that the effects of lavender on the immune system and neuroendocrine were due to its effect on tryptophan metabolism (33). Of course, in studies of short-term exposure to lavender through inhalation of oil, no significant changes were observed in immunological parameters (such as interleukins 6 and 10) (34, 35). In the case of olive oil, although some studies indicate its anti-inflammatory effects in topical use (36), most studies have shown antimicrobial effects (37), immunosuppressive (38, 39) and antioxidant (40-43) effects on systemic use.

**Table 5.** Major active ingredients in plants used in the study

| Medicinal plant | Active ingredients |
| --- | --- |
| Lavandula angustifolia | *Linalool, Linalyl acetate, Tannins, Hydroxcoumarins, Caffeic acid* |
| Glycyrrhiza glabra | *Triterpene saponins, Flavonoids, Isoflavonoids, Hydroxycoumarins, Steroids* |
| Origallum vulgare | *Volatile oil (carvacrol, gamma-terpinene, p-cymene), Flavonoids, Caffeic acid* |
| Olea europaea | *Chief fatty acids (oleic acid, palmitic acid, linoleic acid), Steroids, Tocopherols* |

The study of the use of marjoram in the treatment of sinusitis, with the exception of the study by Madani et al., did not show any results. However, antibacterial effects (44-46), antifungal (47, 48), and antioxidant (49) of this plant have been evaluated and shown to be positive. Licorice also has showed anti-viral (50), antibacterial (51), antifungal (52), anti-oxidant (53), anti-inflammatory (54, 55) and immune enhancer (56) effects in various research but based on the studied articles, it hasn't been used directly in the treatment of chronic sinusitis. In addition to the above mentioned findings about the effectiveness of the plants used in the current trial, teachings in Persian Medicine Literature also reveals significant effects in justifying its usage for rhinosinusitis. Among the writings of Bu-Ali Sina in the Book of Law, he attributes the effects of breakdown of waste materials and the opening of obstruction to marjoram (57), and Hakim Jorjani regards it as a treatment for nasal congestion (58). Among the effects of licorice in these books is the excretion of thick mucus (59). The therapeutic effects of lavender on NAZLA have been

mentioned in Persian medicine books (60) and its use has been shown to enhance brain functions and improve mental status (61). Considering the above points, it might be possible to justify the better result of Persian protocol in reducing systemic symptoms of patients, and in patients with prolonged recurrence, reduced mental and emotional functioning, and reduced social and occupational activity due to chronic rhinosinusitis, this therapy package is preferred.

## 5. Limitations
The main limitation of the present study was the lack of ease of use of an oral remedy in Persian medicine compared to common forms. From the phytochemical point of view, due to the use of four different herbs, it is not possible to attribute the effects of the research to a particular active ingredient or at least a certain plant.

## 6. Conclusions
In summary, the present study showed that a therapeutic package based on Persian medicine can be effective in the treatment of chronic rhinosinusitis, and in addition, it would promote systemic symptoms, especially the symptoms of subjective emotional and social efficacy, more than classical treatment.

## Trial registration:
This trial has been registered with IRCT ID: IRIC IRCT2015112425217N1 at the Iranian Center for Clinical Trials.

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## Conflict of Interest:
There is no conflict of interest to be declared.

## Authors' contributions:
All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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