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Effect of *Origanum vulgare* on perennial allergic rhinitis: A pilot randomized placebo-controlled clinical trial

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Abstract
Oregano is a medicinal plant; this study was conducted to evaluate the efficacy of nasal oregano spray in patients with allergic rhinitis. This study was a randomized double-blind placebo controlled trial on forty patients with perennial allergic rhinitis who were randomly allocated to receive either nasal oregano or placebo spray twice a day for6 weeks continuously. Evaluation of the participant's allergy score was performed before and after the intervention using the Rhinitis Quality of Life Questionnaire (RQLQ). Twenty-eight patients with allergicrhinit is completed the experiment (active 12, placebo 16) till the end of the 6thweek. With the adjustment of the allergy score at baseline, the symptoms of allergic rhinitis was significantly improved in the intervention group compared to the controls (regression coefficient= -2.5±1.11; P-value=0.03). This study suggests that nasal oregano spray could be an effective complementary treatment in patients suffering allergic rhinitis.

Keywords: Allergic rhinitis, herbal medicine, *Origanum vulgare*, Persian medicine

1. Introduction
Allergic rhinitis (AR) is an increasingly common disorder of upper respiratory system which has a major impact on human health. The presence of AR has been shown to impair school performance, reduce worker productivity, and may aggravate or lead to the development of other disorders, including asthma, rhinosinusitis, and middle ear diseases. Typical signs and symptoms of AR include congestion, rhinorrhea, sneezing, nasal itching, and pruritus of the eyes and oral mucosa [1-3].
Aeroallergen sensitization is associated with the risk of developing AR in sensitized individuals [4]. AR may be classified into seasonal allergic rhinitis (SAR) which occurs in particular pollen seasons and perennial allergic rhinitis (PAR) which occurs throughout the year [5].
Non-pharmacologic management of AR is avoidance of aeroallergens although it can be hard to achieve in practice. AR is best addressed with pharmacotherapy and/or immunotherapy. Pharmacological treatment mainly includes oral or topical antihistamines and inhalational corticosteroids; however, these drugs can fail in some patients [6, 7].
Herbal medicine or phytotherapy is one of the main branches of complementary and alternative medicines in which extracts of medicinal plants have been the basis for treatment of disorders [8]. The name of "oregano" includes a vast number of species in different families, the most species of which is *Origanum vulgare*. This flowering plant in the mint family (Lamiaceae) is native in western and southwestern Eurasia and the Mediterranean region. This perennial herb grows 20–80 cm in length with opposite leaves 1–4 cm in length. Oregano has purple flowers and spade-shaped, olive-green leaves. People around the Mediterranean region have used oregano for centuries in traditional and folklore medicine to treat some respiratory disorders such as sore throat, dyspnea and asthma as well as boost the overall health. Scientists have found evidence that extracts of oregano could have antibacterial, antiviral, and antifungal properties [9-15].
Oregano has been introduced firstly as a treatment for common cold and respiratory ailments according to a definition given in one of Iranian medical textbooks called Canon of Avicenna [16]. There are a few clinical trials with oregano in patients with PAR; therefore, the present study aimed to determine whether administration of oregano controls the symptoms of allergy in patients with PAR.

2. Materials and Methods
The present randomized, double-blinded placebo-controlled trial was conducted on 40 patients

with PAR who referred to an allergy unit at Imam Reza clinic affiliated to Shiraz University of Medical Sciences, Shiraz, Iran from December 2018 to March 2019.All patients were diagnosed with PAR according to ARIA (Allergic Rhinitis and its Impact on Asthma) 2016 by the same allergist [17].

2.1 Ethical consideration
The study protocol was approved by the ethics committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1395.92) in compliance with Iran Clinical Trials Registry under number IRCT2016061416925N2 to recruit volunteers.

2.2 Exclusion criteria
Patients who were being treated with antihistamines or systemic corticosteroids for the previous 7 days and pregnant women were excluded from the study. Patients were excluded if they had a history of allergy to oregano. After obtaining informed consent from the patients, demographic characteristics were collected.

2.3 Preparation of nasal sprays
The herb of oregano was purchased from an herbal shop in Yazd, Iran which is one of the main cultivating centers of this herb. The oregano sample was sent to the Herbarium Center at School of Pharmacy, Shiraz University of Medical Sciences and it was identified as *Origanum vulgare* L.from the Lamiaceae family (Voucher No. PM1086).Maceration extraction method (herb to water ratio of 1:10) was applied to prepare the aqueous extract of oregano from ground leaves of oregano. The remained extract was filtered and dried. Total phenol content was measured based on the amount of gallic acid and total flavonoid content was based on the amount of quercetin with acceptable results. All of the results were in accordance with the standards of the United States Pharmacopeia 41 (USP 41). For experimentation, the oregano preparation was used in the form of nasal spray. Nasal spray of sterile water with ethanol 70% (0.1% of the solution) was also used as placebo in the control group. The appearance of the two types of nasal sprays was the same.

2.4 Intervention
After initial interview, 40 patients were allocated to either drug or placebo group (n=20 patients in each group using block randomization, block size: 4) twice a day for continuous 4 weeks. The participants applied a nasal spray containing the *Origanumvulgare* L. extract (equal to 0.04 gr active ingredients per day) or the one with water and ethanol (placebo). None of the patients and the physicians knew the administrated type of nasal spray. Any abnormal reaction after starting the intervention was asked to report from the patients in the six visits.

2.5 Questionnaire
A modified questionnaire was designed based on recommendation by the European Medical Agency as the primary measures of clinical efficacy of various trials for AR [18]. The questionnaire was categorized into four parts; the first part included four nasal symptoms (runny nose, blocked nose, sneezing, and itchy nose), the second part three ocular symptoms (red eyes, itchy eyes, and watery eyes), the third part one itching of the mouth, and the last part one sleep disturbance symptoms with allergic symptoms. Symptom scores were measured from 0 to 6byseverity rating scale: 0 = no symptoms; 1 = low mild symptoms; 2 = mild symptoms;3 = low moderate symptoms; 4 = moderate symptoms, 5= low severe and6 = severe. The maximum of the sum of the severity of symptoms was 54. The patients were scored weekly based on the severity of their nine symptoms using this scale. All the patients were visited by a physician (other than researchers with no information about the intervention status of the patients) in weeks 1, 2, 3, 4, 5 and 6after starting the intervention to fill the questionnaire. Nasal smear eosinophil count was measured for all patients with PAR at the time of study.

2.6 Data analysis
The study data were analyzed using SPSS software (version 16.0). Chi-square test was applied to compare the distribution of the nominal variables between the intervention and control groups. In addition, t-test was used to compare the distribution of numeric variables between the groups. Linear regression with the groups and severity score at the baseline as independent variable and the score at the end of the last measurement as dependent variable was used to measure the effect of the intervention. Moreover, a P-value less than 0.05 were considered as statistically significant.

3. Results and Discussion
Forty patients with PAR agreed to participate in this study,20 in the intervention group (8 male and 12 female) and 20 in the control group (7 male and 13 female).Of these, twenty-eight patients completed the study, 12 in the intervention group (4 male and 8 female) and 16 in the control group (4 male and 12 female).The demographic data of the intervention and control groups are displayed in Table 1; there was no significant difference for age, sex, BMI, and duration of AR between the two groups.

Table 1: Demographic data of the drug and placebo groups

Characteristic	Group	Mean	SD	P-value
Age (Years)	Intervention	28.93	9.137	0.94
	Placebo	29.16	7.594	
Body Mass Index (Kg/m^2)	Intervention	24.16	2.321	0.97
	Placebo	24.10	4.861	
Duration of allergic rhinitis (year)	Intervention	5.67	3.546	0.38
	Placebo	7.54	6.975	
Nasal eosinophil count/ high power field	Intervention	0.46	0.22	0.1
	Placebo	0.42	0.28	

The mean of PAR score after serial weeks 1 till weeks 6 after administration of oregano starting from the first to the 6^{th}weekin both intervention and control groups is shown in Table 2.There was a significant association between the baseline score and the effect of treatment (regression coefficient= -.849±0.26; P-value=0.004) in the intervention group.

Table 2: Variations trend of allergic rhinitis score in the two study groups

Study groups		Allergic rhinitis score						
		Baseline	week 1	weeks 2	weeks 3	weeks 4	Weeks 5	Weeks 6
Intervention	Mean	50.12	35.25	26.07	24.00	20.35	22.23	29.66
	Number	20	16	14	12	14	13	12

	SD	16.80	22.64	23.24	22.15	18.16	22.12	26.92
Control	Mean	44.42	28.30	29.10	28.44	27.29	24.41	21.93
	Number	20	20	19	18	17	17	16
	SD	20.58	21.81	22.09	20.91	20.90	19.29	13.26

After adjusting for the allergy score at baseline, the results of multivariable regression analysis (R square = 0.557) showed that the symptoms in the intervention group was improved significantly (regression coefficient= -2.5±1.11; P-value=0.033) compared to the control group (Fig. 1). None of the other factors including gender, age, BMI and nasal eosinophil count as well as duration of AR showed any statistically significant association with the treatment effect.

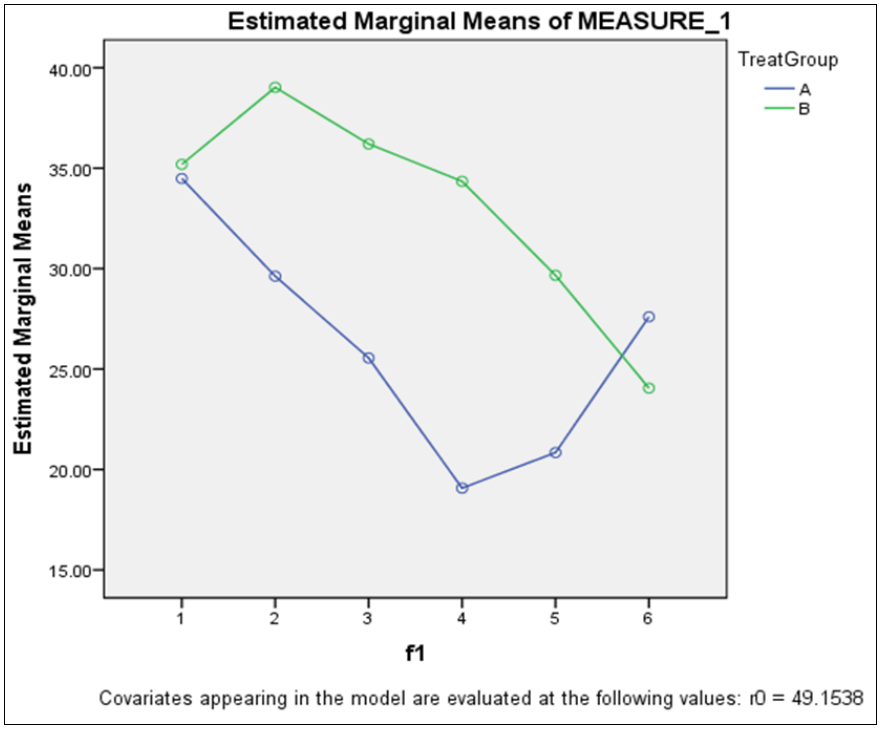

Fig 1: Allergy score of the intervention group compared to placebo after adjusting by multivariable regression analysis; A: Intervention group, B: Control group

Only one patient reported itching after using nasal oregano spray and had no desire to continue the treatment.

To the best our knowledge, this is the first human study using nasal spray of *Origanum vulgare* for patients who suffer from PAR. Our result revealed the beneficial effect of oregano in patients with PAR compared to the control group. Sagit *et al.* investigated therapeutic effect of quercetin (main content of oregano) in 35 rats with AR; they concluded that quercetin was effective in AR of rats both histopathologically and serologically [19].

The pathophysiology of AR is complex; the early phase reaction is characterized by histamine release together with pro-inflammatory cytokines such as leukotriene and prostaglandins, and the late phase reaction is characterized by cellular recruitment of basophils, neutrophils, T-lymphocytes, monocytes, and eosinophil [20].

Oregano has anti-inflammatory effects by decreasing the synthesis of pro-inflammatory IL-1β, IL-6, and TNF-α cytokines and increasing the anti-inflammatory cytokine IL-10 production [21]. It is explained that anti-inflammatory activity of oregano can be a reason for decreasing allergic rhinitis symptoms in the early phase.

Quercetin, as the main flavonoid content of oregano, is known for its anti-inflammatory effect. The role of quercetin in AR is suppression of the ability of the cells to produce eosinophil chemo attractant and suppression of nitric oxide (NO) production from the nasal epithelial cells after IL-4 stimulation [22]. It is also effective in the balance of TH1 to TH2 and the suppression of inflammatory mediators [23]. Kashiwa Bara *et al.*'s study confirmed the effect of quercetin in decreasing the symptoms of AR through suppression of neuropeptide production in animal models [24].Therefore, oregano with large amounts of quercetincan be effective in the control of late phase of AR.

The main limitation of this study was small sample size and short duration of follow-up; larger studies with longer follow up could help to better detect the efficiency of oregano.

4. Conclusion

Given that medicinal herbs have natural origin, are not expensive and have fewer adverse effects, oregano could be used as an effective complementary remedy for the management of patients with PAR.

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6. Conflict of interest

The authors have no conflict of interest in this study.

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