Indian Journal of Traditional Knowledge
Vol 19(2), April 2020, pp 341-349

Effect of oregano oil (*Origanum Vulgare* L.) on chronic rhinosinusitis: A randomized, double-blind, clinical trial

MD Seyed Abdol-Reza Kamaneh[1,2,@], MD Marzieh Qaraaty*[1,2,+], MD Malihe Tabarrai[3,$], MD Mona Mazidi[4,%], MD Morteza Mojahedi[5,!], Masoumeh Mazandarani[6,#]& Nasser Behnampour[7,^]

[1]Infectious Diseases Research Center, Golestan University of Medical Sciences, Gorgan, Iran
[2]Department of Persian Medicine, School of Medicine, Golestan University of Medical Science, Gorgan, Iran
[3]Department of Persian Medicine, School of Persian Medicine, Tehran University of Medical Sciences, Tehran, Iran
[4]Department of Otorhinolaryngology, 5-Azar Hospital, Golestan University of Medical Science, Gorgan, Iran
[5]Traditional Medicine and History of Medical Sciences Research Center, Health Research Center, Babol University of Medical Sciences, Babol, Iran
[6]Department of Botany, Gorgan Branch, Islamic Azad University, Gorgan, Iran
[7]Health Management and Social Development Research Center, Golestan University of Medical Sciences, Gorgan, Iran

E-mail: [@]dr.kamaneh@goums.ac.ir;[+]dr.qaraati@goums.ac.ir;[$]dr.mtabarrai@yahoo.com;[%]Mona.mazidi58@gmail.com; [!]mortazamojahedy@gmail.com;[#]dr.mazandarani@gmail.com;[^]Behnampour@goums.ac.ir

Received 18 March 2019; revised 18 December 2019

According to new investigations, oregano oil nasal spray can be used to treat patients with chronic rhinosinusitis (CRS) effectively. The current study examines the incremental effect of oregano oil and the use of Persian medicine lifestyle modification (PML). 75 adult patients with CRS participated in this study; the clinical trial was done in Otolaryngology Clinic of the Fifth Azar Hospital from January 30 to June 25, 2018. A kit including saline bottle, identical PML instruction, and identical nasal sprays containing either oregano oil (intervention group), fluticasone (control group) or sesame oil (placebo group) was given to all participants for 4 weeks. The reduction of mean change in SNOT-22 scores were 51.52 (95% CI, -55.79 to -47.24), 21.60 (95% CI, -25.48 to -17.71) and 11.84 (95% CI, -13.18 to -10.51) points for those in the oregano, fluticasone and placebo group, respectively. The mean difference of oregano to fluticasone and oregano to placebo group were 29.92 (-35.78 to -24.05) to 39.68 (-45.54 to -33.81) point, respectively, in favor of the oregano group. This study shows that oregano oil results in clinically meaningful benefits beyond those of fluticasone and sesame oil for patients with CRS without nasal polyps. Nonetheless, its generalization should be explored further.

Keywords: *Origanum vulgare*, Persian medicine, Sinusitis, SNOT-22
IPC Code: Int. Cl.[20]:A61K 8/97, A61K 38/00

CRS is defined as persistent symptomatic inflammation of the nasal and sinus mucosa that lasts more than 3 months. Epidemiologic studies estimate that 10% to 15% of the US population has CRS[1] with a prevalence of up to 12% in Western populations[2]. CRS is defined as the symptomatic inflammation of the nose and paranasalsin uses with the distinction based on the duration of the complaints[3,4]. CRS is typically described more broadly as an inflammatory disorder and the importance of specific microbial agents in driving the process remains controversial. It is not clear what medical therapy should be followed as the proper treatment for CRS. The most common treatment of CRS include medical therapy and in cases resistant to medication, endoscopic sinus surgery might be an option[4].

CRS is mostly treated by antibiotics and intranasal steroids but due to limited evidence, results of treatment are unsatisfactory. Previous studies have not confirmed the efficiency of herbal medicine to treat rhinosinusitis, particularly in chronic cases. New investigations recommend that some herbal medicines, either alone or combined with other kinds of treatment might alleviate the symptoms of severe sinus infection[5]. Several trials reported that certain herbal medicines, either alone or combined with other kinds of treatment, might treat CRS effectively[6].

Oregano can be used for respiratory tract disorders such as bronchitis, cough and asthma, painful menstruation, rheumatoid arthritis, dyspepsia and urinary tract disorders. Studies have demonstrated the pharmacological effects of *O. vulgare*, including its antibacterial and antifungal activity, which is thought to be mainly due to the presence of carvacrol (3.5%),

*Corresponding author

thymol (11.6%), terpinen-4-ol (24.90%) and gamma terpinen (10.57%) in oreganoessential oil[7-9]. Seemingly, oregano could be a significant source of bioactive natural products (essential oil, extracts, or pure compounds). Some preclinical (*in vitro* and *in vivo*) studies argued that oregano could be potentially used as a protective agent in chronic-degenerative and infectious disease since its bioactive phytochemicals shows anticancer, anti-inflammatory, antioxidant and antimicrobial activities[10-12].CRS pathogenesis is best defined as a dysfunctional interaction that happen at the site of the connection between the host and the environment. In other words, a dysfunctional immune response to exogenous factors at the Sino-nasal mucosal border leads to mucosal inflammation, radiographic changes and symptoms that characterize CRS[13,14]. Immune system modulation is a change in the immune response that includes expression, induction, or inhibiting each step of the immune response[15,16]. Despite the well-proven effects of oregano, a clinical study of sinusitis has not been conducted. In the present study, we evaluated the influence of oregano oil spray for the treatment of CRS without nasal polyps as compared with fluticasone and sesame oil spray.

Materials and methods

The present study is a randomized, double blind, clinical trial with participants suffering from sinusitis for at least 3 months before the enrollment in the study and a clinical diagnosis of CRS without nasal polyps.Patientswith a diagnosis of CRS (presenting with two major criteria or one major and two minor criteria lasting for at least 12 weeks) were recruited from the Otolaryngology clinic of the Fifth Azar Hospital in Golestan University of Medical Science in Gorgan, Iran. The major criteria were purulent anterior/posterior nasal discharge, nasal obstruction, facial pain/pressure, hyposmia/anosmia and fever (acute rhinosinusitis only). The minor symptoms were headache, fever (non-acute), halitosis, dental pain, ear pain/pressure, cough and fatigue.

A diagnosis of CRS was confirmed by Coronal sinus CT scans. The scans were taken during a screening visit and was assessed from serial images on coronal and axial views. A Lund-Mackay CT score of 5 or more were considered as a diagnostic Imaging for CRS.

Patients within the age range of 18 to 60 years meeting the inclusion criteria took part in the study after signing the written informed consent. These criteria followed the European article on rhinosinusitis and nasal polyps 2012 (EPOS 2012).Patients were willing to use the medication and comply with all study guidelines. Inclusion and exclusion criteria are listed in Table1.

Ethical approval

This study was approved by the Ethics Committee of Golestan University of Medical Sciences (ir.goums.rec.1396. 241).The participants were briefed on the study objectives and they signed informed consent forms. The study also has been registered with the Iranian Clinical Trials Registry (no. IRCT20161022030439N2).

Table 1 — Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1- Between 18 and 60 years old.	1- Treated with other CRS medications 4 weeks before inclusion, such as steroids or macrolides, or another treatment, such as nasal lavage.
2- Patients signed informed consent.	2- Any one of the following diseases: Gross immunodeficiency (congenital or acquired); congenital mucociliary problems (eg, primary ciliary dyskinesia); cystic fibrosis, based on positive sweat test; systemic vasculitis and granulomatous diseases; cocaine abuse; or neoplasia.
3- Positive CT findings (Lund-Mackay CT score of 5 or more)	3- Patients who underwent sinonasal surgery less than5 years ago.
4- A diagnosis of CRS without nasal polyps (CRSsNP) according to EPOS 2012. Subjective symptoms: presence of ≥2 symptoms, 1 of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip): with/without facial pain/pressure and with/without reduction or loss of smell, for >12 weeks. Image: Positive CT findings (Lund-Mackay CT score of 5 or more).	4- Patients who had moderate to severe asthma, and acute attack less than 30 days ago. 5- Aspirin-exacerbated respiratory disease. 6- Presence of nasal polyps. 7- Severe systemic diseases affecting cerebrovascular, cardiovascular, hematologic, neurologic, immunologic, metabolic, or respiratory systems, with history of psychiatric disease or mental problems. 8- Participation in other clinical research within latest 30 days. 9- Pregnant or breastfeeding females. 10- Patients with acute bacterial sinusitis, (fever≥38.5). 11- Drug hypersensitivity reaction.

Herbal medicinal product

The herbal medicine applied in this study was oregano (*O. Vulgare* L.). The aerial parts of oregano were collected from the Ziarat mountainous region in Golestan province at approximately 900 m amsl (during the flowering period in July 2017). They were identified by Dr Masomeh Mazandrani and a voucher specimen was deposited in herbarium of the Research Center of Medicinal Plants at Islamic Azad University of Gorgan (voucher specimen no. 1613).

Characteristics of herbal product

The pharmacological treatment of sinusitis and decoction preparation in the medieval period was gathered from the major Persian pharmaceutical manuscripts of *Qarabadin-e-Kabir* by Aghili Shirazi in 1772AD[17] and *Qarabadin-e-Salehi* by Heravi 1765 AD[18]. In the present study, a Clevenger-type apparatus was used for extraction. This is a modified version of the traditional direct heat method.

The medicinal part of the plant is an aqueous extract from the dried leaves produced by steam distillation. For preparation, 150 g of oregano leaves and 900 mL of water were put in a Clevenger-type apparatus (2.5 L balloon) for 1 h, the essential oil was dried over anhydrous sodium sulfate and stored in dark-colored glass bottles at ±4°C until use. After removing the leaves from the water in the balloon, the remaining water (oregano aqueous extract) was boiled in 150 mL of sesame oil (used as vehicle transport for oregano oil) for 2 h to let the water to vaporize and the oil remain. The essential oil obtained in the first stage of the Clevenger-type apparatus was added to the oil obtained in the second step to prepare the final product (as oregano oil).

Interventions

The participants were randomized to either the oregano oil (intervention group), fluticasone (control group) or sesame oil (placebo group). All study participants were provided with a 4-week supply of commercial pharmaceutical preparation, a saline bottle (Sina-Darou; Iran) and PML. The oregano group participants were provided with a supply of oregano oil inhaler (16 mg/dose) and the fluticasone and sesame groups were provided with supplies of a fluticasone inhaler (50 µg/dose) (Sina-Darou; Iran) or sesame oil (0.1 mL/dose) (Barij Essence; Iran), respectively. The spray bottles for the treatment and controlled groups were of similar size, shape and color (Sina Darou). All patients performed nasal irrigation (240 mL) with normal saline in both nostrils. The oregano and sesame groups then applied either oregano oil or sesame oil (0.1 mL) nasal spray to each nostril, respectively. the oregano group received 1 spray of oregano oil (64 mg/day) and the fluticasone group received 1 spray of fluticasone propionate 0.05% (200 µg/day), while participants in sesame group received 1 spray of sesame oil (0.4 mL/day). All groups continued their designated treatments twice daily for 4 weeks. PML for rhinosinusit is comprised: avoiding sleeping in a supine position; avoiding exposure to cool weather; avoiding nasal irritation and sneezing at the beginning of therapy; avoiding intense physical activity; reducing consumption of garlic, radishes, celery, mustard and onions; use of laxatives such as carrots, currants; reduced daytime sleep; reinforcing the brain by inhaling rose, apple and saffron aromas; reducing food intake; reducing beverages; keeping the head warm and covered; and foot massage[19-21].

Compliance to take medication and evaluations for undesirable effects was logged at each weekly visit. Noncompliance was defined by not taking medicationless than 5 days in a week as self-reported by the patient. Primary and secondary outcomes were measured at baseline and 4 weeks post treatment.

Outcomes

The primary outcome measure was intra-participant change, pre-treatment to post-treatment, on VAS and SNOT-22 scores between the oregano group compared with the fluticasone and sesame groups. Subjective symptoms were accessed by VAS with scores from 0 (no symptom) to 10 (most troublesome) and the following 5 nasal symptoms were measured for nasal blockage, rhinorrhea, headache, facial pain and anosmia.

The rhinosinusitis-specific scale, the 22-item Sino-Nasal Outcome Test (SNOT-22)[22]was used for measuring quality of life. Each item is categorized into6 levels (0 for no problem to 5 for the problem is as bad as it can be). The totalscore is gained by adding the score of each item (range 0-110) with lower scores implying a better health-related quality of life. The reliability and validity of SNOT-22have been established in Iranian patients[23]. It covers a widerange of health-related quality of life that may affect patient outcomes[24]. SNOT subscales include 5 questions on rhinological symptoms, 4 questions on ear/facial symptoms, 3 questions on sleep function and 6 questions on psychological function. As with

the total SNOT scale, higher scores indicate worse symptoms and lowerquality of life[22].

The patient reported response to treatment measured by major and minor criteria scores was considered as secondary outcome measure.

Oregano analysis

The qualitative analysis of the oregano essential oil and oregano oil were processed by GC/MS analysis performed with an Agilent 7890A GC system and their relative percentages of various components in the samples were obtained. The major components (area %) of oregano essential oil and oregano oil were: p- cymene (11.7%-26.48%), γ-terpinene (12.78%-23.02%), terpinen-4-ol (6.01%-4.72%), β-ocymene (18.52%-13.47%) and thymol (4.78%-2.81%), respectively.

Safety and tolerability

Oregano was well tolerated by study participants. No major adverse events were reported during the trial, except one patient in the fluticasone group reporting mild nasal dryness.

Data collection

Descriptive characteristics, including demographics, SNOT-22 questionnaire, VAS score, major and minor criteria score were recordedat baseline and postintervention. Following 4 weeks of treatment, participants returned to the clinic again for assessment and SNOT-22 questionnaire, VAS score, major and minor criteria score in analogous fashion.

Sample size

The preliminary data reported by Vazifehkah *et al*. was used for estimating the sample size[26]. Using a 2-sided α of 0.05 with 80% power, confidence level of 0.95 and the effect size of 10.44, it was estimated that a sample size of 27 participants per group (total n=81) would be required. Considering the limited number of eligible patients (N=100) and by applying a sample size formula in a finite population, it was estimated that a sample size of 25 participants per group (total n=75) would be needed.

Randomization

The patients were assigned to the codes by the research coordinator (DA) who saved the allocated codes. To conceal the allocation, a unique code was assigned to each patient by research coordinator after eligibility screening. This code was linked with a computer-generated randomization schedule done in blocks of 6. Study researchers, attending care teams, and patients were blinded to treatment allocation. The study evaluations were done with no knowledge of the allocation and the research coordinator was excluded from evaluation or investigation. The study statistician (DB) generated a randomized block design and then participants were put into the treatment, control, or placebo groups by the study coordinator after enrollment. Based on randomization, the patients were put into 3 groups of 25 and all participants were provided with verbal and written directives to take the medications and follow PML appropriately.

Statistical analysis

The demographic and clinical features and evaluations of the study population were summarized using descriptive statistics. The effect size was measured as the pre-treatment to post-treatment change in SNOT-22, VAS and the major and minor criteria scores. Normality of data was confirmed by Shapiro-Wilk test and homogeneity of variances was confirmed with Levene's Test (for Equality of Variances). ANOVA and Scheffé analysis was used to compare means between groups. All statistical analyses was performed with G*Power 3.1.9.2 and R software, 3.3.2 (27). Effect size and 95% CIs around the effect size have been reported.

Results

Patient characteristics

A total of 140 patients were enrolled between January 30 and June 25, 2018. Of those, 65 patients were not eligible for the study. The remaining 75 patients were randomized to either the oregano (n=25), fluticasone (n=25) or placebo (n=25) groups. None of the participants withdrew after intervention and 75 completed the post- intervention assessments. The mean (SD) age was 40.80 (10.79) years and most participants were women (n=41; 54.7%). There were no significant difference between treatment groups in the distribution of baseline demographic characteristics, SNOT-22 and VAS scores. Demographics and baseline information about all participants are shown in Table 2.

Treatment outcomes

All symptom scores decreased significantly after the end of treatment among the three groups. After 4-weeks of medication, all SNOT-22 scores had

Table 2 — Comparison of baseline characteristics between the 3 treatment groups

Baseline Characteristic	Oregano group(n= 25)	Fluticasone group(n= 25)	Placebo group(n= 25)	Effect size
Age (years), mean ± SD	40.36 (11.17)	42.72 (10.88)	39.32 (10.48)	0.13
Sex (M/F), n (%)	9/16 (36.0/64.0)	12/13 (48.0/52.0)	13/12 (52.0/48.0)	0.36
Educational level, n (%)				0.40
High school	20 (80.0)	20 (80.0)	21 (84.0)	
Bachelor's degree	4 (16.0)	4 (16.0)	4 (16.0)	
Postgraduate	1 (4.0)	1 (4.0)	0 (0.0)	
SNOT-22 score, mean ± SDa	57.32 ± 12.35	59.20 ± 13.82	60.28 ± 10.33	0.01
VAS score, mean ± SDa	30.76 ± 9.13	30.92 ± 8.41	35.28 ± 9.09	0.23
Likert score	57.24 (4.78)	56.64 (5.08)	57.40 (2.96)	0.07

SD = standard deviation; **SNOT-22** = 22-item Sino-Nasal Outcome Test; **VAS** = visual analog scale.
SNOT-22 score, (0 = no problem, 1 = very mild problem, 2 = mild or slight problem, 3 = moderate problem, 4 = severe problem, 5 = problem as bad as it can be), **Likert score=** Persian Medicine lifestyle modification

decreased markedly and this reduction was significantly greater in the oregano group. The mean (SD) pre-intervention SNOT-22 score in the oregano group was 57.32 (12.35), while reduction in the mean (SD) post-intervention score was 5.80 (3.10). Quality of life improved in all treatment arms according to SNOT-22 after treatment.The mean change and effect size in SNOT-22 scores pre-treatment to post-treatment in the oregano group was (95% CI, -55.79 to -47.24) and 4.62, respectively; thus, quality of life measures of CRS was significantly improved from a clinical standpoint.In addition, the VAS scores for all symptoms decreased markedly, so the reduction of mean change in VAS scores were 27.96 (95% CI, -31.41 to -24.51), 12.64 (95% CI, -15.38 to -9.89) and -5.16 (95% CI, -6.20 to -4.12) points for those in the oregano, fluticasone and placebo group, respectively, in favor of the oregano group. There was a significant decrease in VAS scores in oregano group, so the mean (SD) pre-intervention VAS score was 30.76 (9.13) and the mean (SD) post-intervention score was 2.80 (2.93), resulted insignificant improvement in overall symptomatology (Effect size= 3.46, 95% CI, -31.41 to -24.51).The mean difference in SNOT-22 scores for participants in the oregano compared with fluticasone group was 29.92 in favor of the oregano group (95% CI, -35.78 to -24.05). Moreover, the mean difference in SNOT-22 scores for participants in the oregano compared with placebo group was 39.68 in favor of the oregano group (95% CI, -45.54 to -33.81), which represents a statistically significant difference.

The mean (SD) change in VAS scores from pre-treatment to post-treatment was 27.96 (8.36) for participants in the oregano group and 12.64 (6.65) for those in the fluticasone group, for a mean difference in score of 15.32 in favor of the oregano group (95% CI, -19.80 to -10.83). The mean difference in changes in the major and minor criteria scores from pre-treatment to post-treatment scores was 5.6 (95% CI, -7.60 to -3.60) and 6.28 (95% CI, -7.88 to -4.68) for the oregano and fluticasone groups, respectively, in favor of oregano. The mean difference in changes in major and minor criteria scores from pre-treatment to post-treatment was 8.3 (95% CI, -10.30 to -6.31) and 8.48 (95% CI, -10.08 to -6.88) for the oregano and sesame groups, respectively, in favor of the oregano group. A decrease of 9 or more in the SNOT-22 score was considered clinically meaningful (22). A total of 25 participants (100%) in the oregano group experienced a decrease of 47.24 or more in their SNOT-22 scores (95% CI; -55.79 to -47.24), while a total of 25 participants (100%) in the fluticasone and placebo group experienced a decrease of 17.71 and 10.51 or more in their SNOT-22 scores (95% CI; -25.48 to -17.71 and 95% CI; -13.18 to -10.51), respectively.The average change of effect size in the major criteria scores from pre-treatment to post-treatment scores was 3.60 (95% CI, 2.33 to 3.16) and 2.09 (95% CI, 1.11 to 1.58) for the oregano and fluticasone groups, respectively, in favor of oregano. The average change of effect size in the minor criteria scores from pre-treatment to post-treatment scores was 4.30 (95% CI, 1.87 to 2.36) and 1.69 (95% CI, 0.69 to 1.03) for the oregano and fluticasone groups, respectively, in favor of oregano.

The correlation between posttreatment SNOT-22 score and PML score is -0.453in the oregano group. It means that there is an inverse correlation between the SNOT-22 score and PML score, as a result, significantly better therapeutic outcome in this group. The inverse correlation between the SNOT-22 score and PML score were observed among the three

Table 3 The within group treatment effect

Treatment	Score	Before treatment (mean ± SD)	After treatment (mean ± SD)	(A-B) (mean ± SD)	95% CI of the difference	Effect size
Oregano	SNOT 22	57.32 ± 12.35	5.80 ± 3.10	-51.52 ± 10.36	-55.79 to -47.24	4.62
Fluticasone	SNOT 22	59.20 ± 13.82	37.60 ± 11.04	-21.60 ± 9.41	-25.48 to -17.71	1.70
Placebo	SNOT 22	60.28 ± 10.33	48.44 ± 9.51	-11.84 ± 3.24	-13.18 to -10.51	1.19
Oregano	VAS	30.76 ± 9.13	2.80 ± 2.93	-27.96 ± 8.36	-31.41 to -24.51	3.46
Fluticasone	VAS	30.92 ± 8.41	18.28 ± 6.61	-12.64 ± 6.65	-15.38 to -9.89	1.65
Placebo	VAS	35.28 ± 9.09	30.12 ± 8.28	-5.16 ± 2.53	-6.20 to -4.12	0.59

Table 4 — The between-group treatment effect

	Oregano and Fluticasone (Mean Difference)	95% CI of the difference	Effect size	Oregano and Sesame (Mean Difference)	95% CI of the difference	Effect size
SNOT-22 score	-29.92	-35.78 to -24.05	3.02	-39.68	-45.54 to -33.81	5.16
VAS score	-15.32	-19.80 to -10.83	2.02	-22.8	-27.28 to -18.31	3.69
Major criteria score	-5.6	-7.60 to -3.60	1.72	-8.3	-10.30 to -6.31	2.70
Minor criteria score	-6.28	-7.88 to -4.68	2.48	-8.48	-10.08 to -6.88	3.57
Rhinological symptoms	-10.08	-13.55 to -6.61	1.74	-16.2	-19.67 to -12.37	3.67
Ear and facial symptoms	-4.28	-6.47 to -2.09	1.16	-5.84	-8.03 to -3.65	1.82
Sleep function	-3.64	-6.02 to -1.26	0.91	-4.12	-6.50 to -1.74	1.15
Psychological issue	-11.92	-15.49 to -8.36	1.96	-13.52	-17.08 to -9.96	2.58

Rhinological symptoms, Need to blow nose, Sneezing, Runny nose, Nasal obstruction, Loss of smell or taste, Post-nasal discharge, Thick nasal discharge; **Ear and facial symptoms,** Ear fullness, Dizziness, Ear pain, Facial pain/pressure; **Sleep function,** Difficulty falling asleep, waking up at night, Lack of a good night's sleep; **Psychological issues,** Waking up tired, Fatigue, Reduced productivity, Reduced concentration, Frustrated/restless/irritable, sad, Embarrassed.

groups of this study, as a result, significantly better therapeutic outcome in all groups.Table 3 lists the effects of treatment within groups and Table 4 lists the effects of treatment between groups.

In this study the patient compliance with nasal spray usage were as high as 100% and with PML instruction were relatively high (98.53%). We found a relatively low compliance with diet recommendations of PML in this population (84.8%).

Discussion

According to the findings of this randomized, double-blind, clinical trial, applying oregano oil as a daily nasal spray for 4 weeks resulted in a clinically meaningful improvement inself-reported functional status and quality of life measurements of CRS from a clinical standpoint.The upper bound of the confidence interval and effect size and lower bound of standard deviation suggests that this effect can also be very favorable. Oregano was tolerated readily, and undesirable adverse effectslinked with its use were not reported.

Oregano is one of the most widely used medicinal plants in PM for the treatment of rhinosinusitis[28]. *O. vulgare*L. has been identified as best candidate for modulation of the immune system and inflammation[29]. Oregano extracts canbe used as novel options for treatment of chronic diseases involving inflammatory processes by increasing the anti-inflammatory secretions in activated macrophages and reducing the release of proinflammatory cytokines[30]. According to experimental studies, oregano can be used potentially as a protective agent in chronic-degenerative and infectious disease since its bioactive phytochemicals show anti-inflammatory antimicrobial, antioxidant and anticancer features[10]. Natural products containing secondary metabolites such as aromatic compounds and terpenoids (essential oils) are a good choice for the treatment and preventionof chronic infection[31]. It is known that γ-terpinene andcarvacrol are natural monoterpenes metabolites and their presence in essential oil of oregano has been reported to possess strong anti-inflammatory activity[32].Thymoland carvacrol, the two main constituents of oregano, contribute to the immunomodulatory effect of disorders with immune dysregulation. The major components of oregano essential oil are carvacrol, thymol and γ –terpinene[33]. Carvacrol decreased the IL-4 content and increased the IFN-c and IFN-c/IL4 ratios (Th1/Th2 balance) demonstrating the stimulatory effect of carvacrol on Th1 and the inhibitory effect on Th2 activity[34]. Thymol is the main component of oregano and effectively induces lymphocyte proliferation[35] and decreases inflammation and wound size[36,37].Moreover, thymol as a potent antioxidant, protects against cell

damage and has useful health effects, such as its anti-inflammatory, antimicrobial, antioxidant, antiviral, anticancer, antispasmodicand growth enhancement properties[38].Similar results have been found with the use of herbal medicine in CRS. Vazifehkah *et al*. compared the effects of *Pimpinella anisum*-based herbal medicine and fluticasone nasal spray for treating CRS over a 1-month treatment period in a study population. It was concluded that *P. anisum*-based herbal medicine may be an effective treatment for sinusitis based on the SNOT-22 scores[26]. The mean (SD) change in SNOT-22 scores for participants in the sinupim study was 20.80 (16.24; 95% CI, -14.24 to 27.36). For those in the oregano study, it was 51.52 (10.36; 95% CI, -47.24 to 55.79) for a mean difference of 30.72 in favor of the oregano study. Also, Vazifehkah *et al* found a clinically improvement in the mean change in SNOT-22 scores, in patients with CRS without nasal polyps treated with fluticasone spray group (10.36; 95% CI, 5.79 to 14.90). In the current trial, a clinically significant improvement was observed in the mean change in SNOT-22 scores in patients with CRS without nasal polyps treated with the fluticasone inhaler group (21.60; 95% CI, 17.71 to 25.48), with mean difference of 11.24 in favor of our present trial. These results are surprising and suggest that our improved treatment and better results in our trial may be due to use of PML.

Tait *et al*. reported a clinically significant improvement in SNOT-22 scores in patients with CRS treated with budesonide added to large-volume, low-pressure saline sinus irrigation[39]. The mean (SD) change in SNOT-22 scores for participants in the Budesonide study was 20.7 (17.9) and for those in the oregano study, it was 51.2 (10.36) for a mean difference of 30.82 in favor of the oregano study. Many factors, including the ability of the oregano extract and essential oil to stick to the nasal mucosa leading to decreased inflammation and modulated immune response resulting in the penetration of the sinus cavities could explain the advantage of using oregano among participants in the current paper.

Limitations

There were several limitations to this study. First, the trial lasted only 4 weeks that may not be adequate for producing a thorough effect for oregano therapy.Additionally, our patients were all topically managed for CRS, which included topical intranasal corticosteroids or herbal-based product. However, a controlled group of topical intranasal herbal products in combination with the oral herbal product should be considered, with and without PML. Future research on medical outcomes will be needed to determine whether or not the treatments have efficacy in these endotypes and whether specific markers can be identified that predict the response. The current objective measures are often nonspecific; thus, future objective measures should includepost-treatmentCT scanning, local inflammatory cytokine levels or other molecular markers characteristics of specific endotypes.

Conclusion

This study showed that the use of *O. vulgare*-based herbal product resulted in clinically meaningful benefits for patients with CRS without nasal polyps. Its beneficial effects, availability, safety and low cost were remarkable and recommend its use for chronic rhinosinusitis. Additional randomized clinical trials on the effect of oregano product and PML for those with CRS versus the fluticasone-alone controls and, oregano-alone versus fluticasone-alone nasal spray are needed to help define the true effect of oregano in unique patient subgroups.

Acknowledgement

All data in the study have been thoroughly accessed by Dr Qaraaty who is responsible for the data integrity and the data analysisprecision.*Study concept and design:* Kamaneh, Qaraaty, Tabarrai, Mazidi, Mazandarani. *Acquisition of data:* Kamaneh. *Analysis, or interpretation of data*: Kamaneh, Behnampour. *Drafting of the manuscript:* Kamaneh, Qaraaty, Tabarrai, Mazidi, Mazandarani, and Behnampour. *Critical revision of the manuscript for important intellectual content and read and approved the final manuscript:* Qaraaty, Tabarrai, Mazidi, Mojahedi, Mazandarani, and Behnampour. *Obtained funding:* Qaraaty. *Administrative, technical, or material support:* Qaraaty, Tabarrai, Mazidi, Mojahedi, Mazandarani, Behnampour. *Study supervision:* Qaraaty

Conflict of Interest Statement

Authors have not any conflict of interest.

Funding Infectious Diseases Research Center, Golestan University of Medical Sciences, Gorgan, Iran.

Role of the Funder/Sponsor The funder did not play any role in designing and conducting the study, managing, collecting, analyzing, and interpreting the

data, reviewing, preparing, or approving the manuscript and decision for submitting the manuscript to be published.

Additional Contributions The authors are grateful to thank VC research affairs at the Golestan University of Medical Sciences and 'Clinical Research Development Unit (CRDU), 5Azar Hospital' for their scientific support. The authors gratefully acknowledge the help of the following individuals: Dr Vahid Khori, Dr Ramin Azarhoosh, for assisting with design in the study. The authors gratefully acknowledge the help of Dr Bahram Abrary for assisting with the study coordination. We acknowledge the Sina-Darou Company for providing the spray bottles and saline. Contributors received no compensation for their contributions.

References

1 Soler ZM, Mace JC, Litvack JR, Smith TL. Chronic rhinosinusitis, race, and ethnicity. American journal of rhinology & allergy.26 (2) (2012) 110.
2 Hastan D, Fokkens W, Bachert C, Newson R, Bislimovska J, Bockelbrink A, et al. Chronic rhinosinusitis in Europe–an underestimated disease. A GA2LEN study. Allergy. 66 (9) (2011) 1216-23.
3 Lanza DC, Kennedy DW. Adult rhinosinusitis defined. Otolaryngology–Head and Neck Surgery. 117 (3_suppl) (1997) S1-S7.
4 Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, *et al*. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology. 50 (1) (2012) 1-12.
5 Pleis JR, Ward BW, Lucas JW. Summary health statistics for US adults: National Health Interview Survey, 2009. Vital and health statistics Series 10, Data from the National Health Survey. (249) (2010) 1-207.
6 Anushiravani M, Bakhshaee M, Taghipour A, Naghedi-Baghdar H, Farshchi MK, Hoseini SS, *et al*. A systematic review of randomized controlled trials with herbal medicine on chronic rhinosinusitis. Phytotherapy Research. 32 (3) (2018) 395-401.
7 Escop, Phytotherapy ESCo. ESCOP Monographs: the scientific foundation for herbal medicinal products: Thieme,2003.
8 Gruenwald. J, Brendler. T, Jaenicke. C. Physician's Desk Reference for Herbal Medicines, third edition: Thomson PDR at Montvale, NJ 07645.1742.729-30. (2004) 729-30.
9 Jnaid Y, Yacoub R, Al-Biski F. Antioxidant and antimicrobial activities of Origanum vulgare essential oil. International Food Research Journal. 23 (4) (2016) 1706.
10 Pezzani R, Vitalini S, Iriti M. Bioactivities of Origanum vulgare L.: an update. Phytochemistry Reviews. 16 (6) (2017) 1253-68.
11 Miraj S. Antioxidant, anticancer, antimicrobial potential of Origanum vulgare. Der Pharmacia Lettre. 8 (13) (2016) 89-97.
12 BAHMANI M, KHAKSARIAN M, RAFIEIAN-KOPAEI M, ABBASI N. Overview of the Therapeutic Effects of Origanum vulgare and Hypericum perforatum Based on Iran's Ethnopharmacological Documents. Journal of Clinical & Diagnostic Research. 12 (7) (2018).
13 Littman DR, Pamer EG. Role of the commensal microbiota in normal and pathogenic host immune responses. Cell host & microbe. 10 (4) (2011) 311-23.
14 Kern RC, Conley DB, Walsh W, Chandra R, Kato A, Tripathi-Peters A, *et al*. Perspectives on the etiology of chronic rhinosinusitis: an immune barrier hypothesis. Am J Rhinol. 22 (6) (2008) 549-59.
15 Abood W. Immunomodulatory and Natural Immunomodulators. J Allergy Inflamm. (2017) 1:e101.
16 Amirghofran Z, Ahmadi H, Karimi MH. Immunomodulatory activity of the water extract of Thymus vulgaris, Thymus daenensis, and Zataria multiflora on dendritic cells and T cells responses. Journal of immunoassay & immunochemistry. 33 (4) (2012) 388-402.
17 Agqili Khorasani Shirazi M. Qarabadin-e-Kabir. Tehran: Research Institute for Islamic and Complementary Medicine (RICM).(2007) 750-1267.
18 Heravi MG. Qarabadin-e-Salehi. Tehran, Iran: Dar-ol-khalafeh (Litograph in Persian).1765.
19 Arzani M. Tebbe Akbari [Akbari's Medicine]. First ed: Ehya Teb e Tabiee O, editor. Tehran: Jalaleddin Press.(2008) 152-9.
20 Aazam Khan Chashti M. The Grater Exir (persian). 2. 1 ed: Tehran: Research Institute for Islamic and Complementary Medicine (RICM).(2008) 524-5.
21 Kamaneh SA-R, Qaraaty M, Tabarrai M, Mazidi M, Mojahedi M, Azizkhani M. Sinusitis and the related remedies in Persian medicine. 17(4) (2018) 654-662.
22 Hopkins C, Gillett S, Slack R, Lund V, Browne J. Psychometric validity of the 22-item Sinonasal Outcome Test. Clinical otolaryngology. 34 (5) (2009) 447-54.
23 Jalessi M, Farhadi M, Kamrava SK, Amintehran E, Asghari A, Hemami MR, *et al*. The reliability and validity of the persian version of sinonasal outcome test 22 (snot 22) questionnaires. Iranian Red Crescent medical journal. 15 (5) (2013) 404.
24 Browne JP, Hopkins C, Slack R, Cano SJ. The Sino-Nasal Outcome Test (SNOT): can we make it more clinically meaningful? Otolaryngology-head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 136 (5) (2007) 736-41.
25 Lund VJ, Mackay IS. Staging in rhinosinusitis. Rhinology. 31 (1993) 183.
26 Vazifehkah S, Shams-Ardekani MR, Kamalinejad M, Saderhossein SM, Hosseini H, Shams SM, *et al*. Evaluation of a novel natural drop for treatment of chronic rhinosinusitis without nasal polyps: a single blind randomized trial. International forum of allergy & rhinology. 6 (9) (2016) 943-9.
27 Team RC. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing. Available: http. www R-project org [accessed 20 January 2015], 2015.
28 Agqili Khorasani Shirazi M. Makhzan ol Advieh [Storehouse of Medicaments]. Tehran: Shams Ardakani MR, Rahimi R, Farjadmand F, editors. Tehran University of Medical Sciences.(2009) 463-541.

29 Ayrle H, Mevissen M, Kaske M, Nathues H, Gruetzner N, Melzig M, *et al*. Medicinal plants–prophylactic and therapeutic options for gastrointestinal and respiratory diseases in calves and piglets? A systematic review. BMC veterinary research. 12 (1) (2016) 89.

30 Ocana-Fuentes A, Arranz-Gutierrez E, Senorans F, Reglero G. Supercritical fluid extraction of oregano (Origanum vulgare) essentials oils: anti-inflammatory properties based on cytokine response on THP-1 macrophages. Food and Chemical Toxicology. 48 (6) (2010) 1568-75.

31 D Mogosanu G, M Grumezescu A, Huang K-S, E Bejenaru L, Bejenaru C. Prevention of microbial communities: novel approaches based natural products. Current pharmaceutical biotechnology.16 (2) (2015) 94-111.

32 de Cássia da Silveira e Sá R, Andrade LN, de Sousa DP. A review on anti-inflammatory activity of monoterpenes. Molecules. 18 (1) (2013) 1227-54.

33 Teixeira B, Marques A, Ramos C, Serrano C, Matos O, Neng NR, et al. Chemical composition and bioactivity of different oregano (Origanum vulgare) extracts and essential oil. Journal of the science of food and agriculture. 93 (11) (2013) 2707-14.

34 Jalali S, Boskabady MH, Haeri Rohani A, Eidi A. The effect of carvacrol on serum cytokines and endothelin levels of ovalbumin sensitized Guinea-pigs. Iran J Basic Med Sci. 16 (4) (2013) 615-9.

35 Amirghofran Z, Hashemzadeh R, Javidnia K, Golmoghaddam H, Esmaeilbeig A. In vitro immunomodulatory effects of extracts from three plants of the Labiatae family and isolation of the active compound(s). Journal of immunotoxicology. 8 (4) (2011) 265-73.

36 Riella KR, Marinho RR, Santos JS, Pereira-Filho RN, Cardoso JC, Albuquerque-Junior RL, *et al*. Anti-inflammatory and cicatrizing activities of thymol, a monoterpene of the essential oil from Lippia gracilis, in rodents. J Ethnopharmacol. 143 (2) (2012) 656-63.

37 Pascual ME, Slowing K, Carretero E, Sanchez Mata D, Villar A. Lippia: traditional uses, chemistry and pharmacology: a review. J Ethnopharmacol. 76 (3) (2001) 201-14.

38 Ezzat Abd El-Hack M, Alagawany M, Ragab Farag M, Tiwari R, Karthik K, Dhama K, et al. Beneficial impacts of thymol essential oil on health and production of animals, fish and poultry: a review. Journal of Essential Oil Research. 28 (5) (2016) 365-82.

39 Tait S, Kallogjeri D, Suko J, Kukuljan S, Schneider J, Piccirillo JF. Effect of budesonide added to large-volume, low-pressure saline sinus irrigation for chronic rhinosinusitis: a randomized clinical trial. JAMA Otolaryngology–Head & Neck Surgery, 2018.