

Effect of *Nepeta bracteata* Benth. on allergic rhinitis symptoms: A randomized double-blind clinical trial

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Background: Allergic rhinitis (AR) is one of the health problems in the world. It is necessary to develop new treatment procedure for control of this disease. The aim of this study was to assess the effect of *Zofa* (*Nepeta bracteata* Benth) on AR patients. **Materials and Methods:** In this double-blind randomized clinical trial study, 71 patients (37 patients in treatment and 34 in placebo group) participated. In treatment group, *N. bracteata* syrup (NBS) was used for 4 weeks as three times a day. The efficacy of the drug regarding AR symptoms (rhinorrhea, sneezing, nasal obstruction, itchy nose, and ocular symptoms) were evaluated through a visual analog scale (VAS) by 0–10 before administration and at the end of the whole treatment period. The collected information was entered in the SPSS software (version 18) and was analyzed using the Fisher's exact test, Chi-square test, independent sample *t*-test, and paired sample test. **Results:** The improvement of AR symptoms in the group receiving NBS was significantly higher compared to control group (4.73 ± 1.84 vs. 0.38 ± 2.06 ; $P < 0.0001$). Furthermore, the mean of total VAS before and after the treatment (in case group) was 7.10 ± 1.92 and 2.37 ± 1.76 , respectively ($P < 0.001$). **Conclusion:** The results of this study indicate that *N. bracteata* has significant effects on improving the symptoms of AR. Hence, it can be a good alternative to AR symptoms relief.

Key words: Allergic rhinitis, Persian medicine, *Nepeta bracteata* Benth

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INTRODUCTION

Allergic rhinitis (AR) is an inflammatory disease mediated by immune cells in the mucous membranes lining the nose and one of the most prevalent diseases so that the prevalence of the disease in the world and Iran have been reported between 9% and 42% and 7.2% and 23.6%, respectively.^[1-3] This is the inflammatory of the nasal mucosa with hypersensitivity symptoms after exposure to allergens such as pollen and dust. The prevalent symptoms are nasal congestion and ocular complications.^[4]

Immunoglobulin E has an essential role in allergic responses so that the initial response was initiated by an IgE-related allergic process.^[1] This process leads to release of mediators of inflammation such as histamine, neutral proteases, chemotactic factor, and acid hydrolases from basophils and mast cells.^[1] AR has two forms including seasonal and perennial forms. Symptoms of seasonal AR which usually caused by allergic sensitivity to airborne mold spores or pollens from grass, trees, and weeds can occur in spring, summer, and early fall. People with perennial AR experience symptoms year-round. It is generally caused by dust mites, pet hair or dander, cockroaches, or mold. Underlying or hidden food allergies rarely

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cause perennial nasal symptoms. About 20% of AR cases are seasonal, and 40% are perennial types. Other 40% of patients have a combination of these two types.^[5] Due to the high prevalence of AR, it affects community as impaired quality of life and related diseases such as atopy and asthma.^[1] In various studies, it is reported that this disease is developing whole around the world;^[6] although AR is not a fatal disease, it often leads to change and loss of quality of patients' life. The patients suffer from different problems such as impairment of behavior, learning, and memory. They are susceptible to more serious side effects such as asthma and sinusitis.^[1] Annually, the loss of 2 million workdays and 2–5 billion dollars in health costs are the most important complications of the disease in America.^[3] There are several available procedures for the treatment of AR. The common treatments include intranasal corticosteroids, oral and topical antihistamines, decongestants, intranasal cromolyn, intranasal anticholinergic, and leukotriene receptor antagonists. These procedures reduce the symptoms of disease temporarily and have low therapeutic effect. On the other hand, long-term use of these agents is associated with side effects.^[7] According to this problem and high prevalence of AR as well as tendency to medicinal plants, the development and finding of new herbal drugs for the treatment of this disease are beneficial.^[8] There are many successful experiments in the literature about medicinal plants such as the effects of *Nigella sativa*^[2] and *Petasites hybridus*^[9] on AR symptoms in the randomized clinical trial studies. Furthermore, it was investigated that some polyherbal formulations such as Biminne, a Chinese herbal formulation^[10] and Aller-7 a capsule from a standardized extract of seven Indian medicinal plants^[8] improved AR symptoms.

Furthermore traditional, complementary and alternative medicine (TM/CAM) are good sources to find new suggestions, in particular, herbal remedies for evaluating in current medicine.^[11]

The use of TM/CAM in Western medicine has highly increased in recent decades. Many treating methods of TM/CAM, such as herbal remedies, are mainstream or traditional in many parts of the world. The World Health Organization (WHO) estimates that most of the world's people regularly using TM,^[12] such as traditional Chinese medicine. Regarding these issues, despite advances in conventional therapy, a great number of patients with AR are tending to complementary medicine for relief. The lifetime prevalence of TM/CAM use in patients with AR ranges from 27% to 46%, and many of the patients who have not yet used TM/CAM, intend to do so in the future.^[13]

Persian Medicine (PM) or Traditional Iranian Medicine (TIM) is one of such traditional systems of medicine. PM has the

sum total of all the knowledge and practices administered in prevention, diagnosis, and elimination in Persia in ancient and medieval times.^[14]

There are more than thousands of manuscripts in PM; it can be as treasure for researchers in this field as well as good advantage to develop the scientific and universal medicine.^[15]

Nepeta bracteata Benth. (Lamiaceae) called as *Zofa* in PM^[16] is one of the frequently cited medicinal herbs in the case of respiratory problems such as chronic cough (*Soale-mozmen*), catarrh (*Nazleh*), asthma (*Rabu*), and dyspnea (*Osral-Nafas*) in PM documents.^[17] Observed medicinal activities of *Nepeta* species are probably because of the presence of terpenoids, especially iridoids and diterpenes which are rich in this genus, flavanones, flavonoids, and phenolic acid derivatives.^[18] Two clinical studies that were conducted with *N. bracteata* compound syrup (Sharbat Zoofa Murakkab) on chronic bronchitis and productive cough showed improvement in all of signs and symptoms of above diseases significantly.^[19,20] This plant is one of the endemic species in Iran.^[16] Although current investigations support its effects on chronic cough, bronchitis, common cold, and asthma,^[18] there is no direct studies about the effect of this plant on AR. Hence, the aim of this study was to assess the effect of *N. bracteata* on the patients with AR.

MATERIALS AND METHODS

Study design

This double-blind clinical trial study conducted on all the referred patients with AR symptoms to otolaryngology clinic of Mustafa Khomeini Hospital in Tehran, Iran, from April 2015 to Mars 2016. Among them, 96 individuals were selected as sample size was calculated using sample size formula taking into account the 95% confidence level, 80% statistical power, and the proportion of AR in the mentioned clinic which approximately estimated as 12% and the error level of 0.1.

Ethical issues

The Ethics Committee of Shahed University approved the protocol (approval number: 41/215591). Furthermore, this study was registered in the Iranian Registry of Clinical Trials; IRCT ID: IRCT2013122615943N1. All patients were aware of the protocol of the study and fulfilled the informed consent form.

Inclusion and exclusion criteria

As inclusion criteria, all enrolled patients had symptoms of AR, based on the AR and its impact on asthma (ARIA) criteria.^[1] The patients were assessed and confirmed by ENT specialist, and also, all the patients were in the age range of

18–65 year old, suffered intermittent or perennial AR, and had not taken any medical treatment of AR at least 2 weeks before the admission. The patients who had a previous history of chronic diseases such as asthma, diabetes and cancer, taking any medication known to affect AR, recent trauma to the nose, recent surgery of the nose, as well as people exposed to irritants such as acid, pregnancy, and breastfeeding, ones with epilepsy, vasomotor rhinitis, alpha-blocker drug users, and acute sinusitis symptoms were excluded from the study.

Plant material

Dry plant of *N. bracteata* was purchased from a local spice market (*Attari*) in Tehran Bazaar, Iran, and identified in the Herbarium center of school of Pharmacy, Tehran University of Medical Sciences, by Professor Dr. Gholamreza Amin, under the voucher number PMP-324.

Preparation of syrup and placebo

NBS was prepared according to “*Qarabadin*” texts as PM pharmaceutical manuscripts.^[21,22]

To prepare 160 bottles of syrup for 40 patients, 1.6 kg *N. bracteata* was weighed and crushed with grinder (Tooshekan T8500, Iran) and engulfed with 48 L boiling water. After half an hour boiling, the extract was filtered and sweetened by adding 3.2 kg of sugar and honey (1:1). The syrup was heated until sugar and honey was completely dissolved. Methylparaben (0.1%) and propylparaben (0.015%) were added as microbial preservatives. Then, it was packed in 250 mL bottles containing either medication or placebo.

Placebo was prepared in the same method. However, *N. bracteata* extract was replaced by distilled water and approved color additives (B1, Magnolia flavor and fragrance Co., Iran) were added to make the same color of drug.

Standardization of drug based on total phenolic and flavonoid contents

Total phenolic and flavonoid contents of NBS were detected using spectrophotometric method. To determine phenolic concentration in the syrup, ethanol solution of syrup (1 mg/ml) was prepared and the reaction mixture was used by mixing ethanol solution (0.5 ml), 10% Folin-Ciocalteu’s reagent (2.5 ml), and 7.5% NaHCO₃ (2.5 ml). Blank was prepared the same as reaction solution just using ethanol without syrup. After that, the samples were incubated at 45°C for 45 min. The absorbance was detected using spectrophotometer at $\lambda_{max} = 765$ nm. The mentioned samples were prepared in triplicate for analysis. The same procedure was repeated for the gallic acid standard solution. To achieve phenolic concentration, the gallic acid calibration curve based on the detected absorbance was construed.^[23]

To determine the flavonoids contents, the samples consisting 1 ml of ethanol solution of syrup (1 mg/ml) and 1 ml of 2% AlCl₃ solution dissolved in methanol were prepared. After that, samples were incubated for 1 h at room temperature. The absorbance was determined at $\lambda_{max} = 415$ nm. The same procedure was performed for the rutin standard solution, and the calibration line was construed.^[24]

In both mentioned methods, based on the measured absorbance, the phenolic and flavonoid contents were read according to the calibration line and then were expressed in terms of gallic acid and rutin equivalent, respectively.

Randomization and blinding

We performed a permuted block randomization with fixed block size of four and one-to-one allocation using a computer-generated random allocation to sequentially numbering. All patients were informed that there was a fifty percent chance of receiving placebo treatment. The physicians and patients were blinded to the medications.

Intervention and main outcome measures

The primary measure was the efficacy in severity and frequency of AR symptoms. The patients in the groups used 10 ml of NBS or placebo, three times a day (30 ml/day) for 4 weeks.

The long of intervention based on similar studies in this field (Herbal medicines on AR) was 4 weeks.^[8]

All the patients were evaluated for the efficacy of the drug and placebo on each AR symptoms, by using the AR symptom questionnaire which consists of 5 items according to ARIA criteria^[1] (rhinorrhea, sneezing, nasal obstruction, itchy nose, and ocular symptoms), and the changes of severity of symptoms were measured by VAS (visual analog scale from 0 to 10 cm), scoring by patients, before treatment and at the end of the intervention period.^[25]

Furthermore, total VAS scores were registered in the beginning and the end of treatment according to ARIA criteria. The frequency was measured according to the ARIA questionnaire (a WHO confirmed questionnaire)^[1] by patients and practitioner.

Statistical analysis

Finally, the collected data were entered into Statistical Package for the Social Sciences (version 18.0; SPSS Inc., Chicago, Ill., USA) and were represented by frequency (percent) or Mean \pm standard deviation (SD). According to the results of the Kolmogorov-Smirnov test indicating the normality of data distribution, independent sample *t*-test was used for comparing the mean of ARIA score between two groups, and paired sample test was

used for comparing the mean of ARIA score in each of the two groups; also, Fisher's exact test was used to compare the frequency distribution of qualitative data among the two groups. In all analyses, the significance level was considered <0.05 .

RESULTS

Standardization of drug

Total phenols and flavonoid contents were determined, as follows: 293 ± 7 mg gallic acid equivalent/100 ml and 258 ± 5 mg rutin equivalent/100 ml of syrup, respectively.

Efficacy

In total, 96 volunteer patients of AR, after obtaining informed consent participated in this study, and some of 86 eligible patients who met inclusion criteria were divided into two groups, randomly. Finally, 71 patients completed the trial, 37 patients in treatment, and 34 ones in placebo groups [Figure 1].

The demographic data of two groups were summarized in Table 1. As shown in this table, no significant differences were identified between patients in the groups with regard to basic demographic data including sex, age, and smoking.

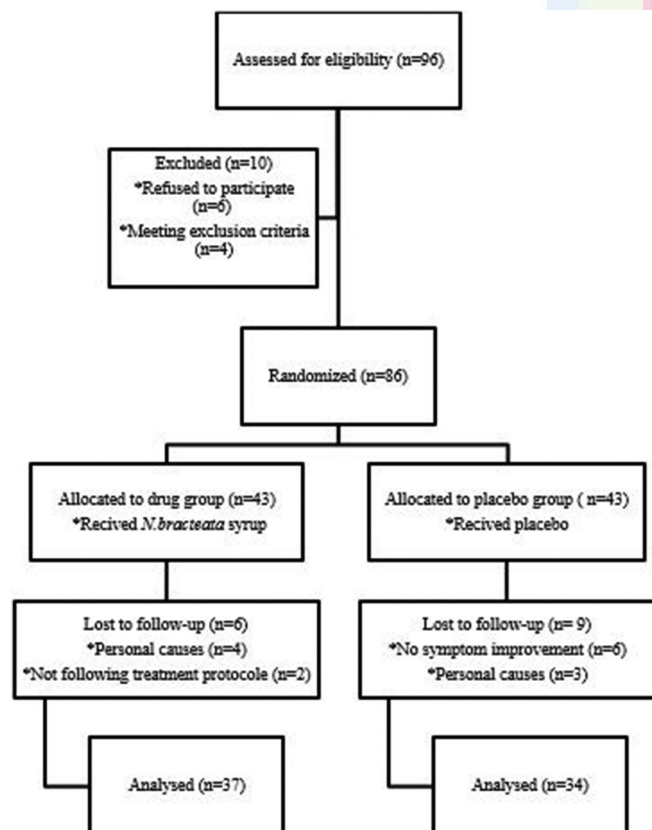


Figure 1: Consort chart study of clinical trial *Nepeta bracteata* and placebo on allergic rhinitis patients

A comparative examination of these two groups in mean AR symptoms proved that the severity of symptoms in both groups was the same at baseline ($P > 0.05$). Afterward (treatment), this mean in the group of treatment with NBS was significantly less compared to control group ($P < 0.001$). Thus, overall improvement in symptoms in treatment group (mean \pm SD = 1.84 ± 4.73) was significantly more than control group (mean \pm SD = 2.06 ± 0.38) ($P < 0.0001$) [Table 2]. On the other hand, NBS improved all symptoms of AR, significantly in the treatment group ($P < 0.001$). In the control group, observed difference before and after treatment with placebo was not significant ($P = 0.065$). Furthermore, the mean of severity of symptoms was 7.10 ± 1.92 and 2.37 ± 1.76 before and after treatment by NBS, respectively ($P < 0.001$), but the mean of severity of symptoms was 6.38 ± 2.18 and 6.00 ± 1.95 before and after treatment by placebo, respectively ($P = 0.096$), showed in Table 2.

DISCUSSION

Four-week treatment of AR with *N. bracteata* showed that these syrups could significantly reduce the symptoms of AR without side effects while the placebo group had no significant effect. Our study is the first experiment on the effect of *N. bracteata* on AR on humans, and interesting results were acquired. We indicated that NBS improved all symptoms of AR ($P < 0.001$). The symptom relief was from 78% to 87% in drug group, while in comparison with similar previous studies such as the effect of *N. sativa* (from 66.4% to 70%)^[2] and a Chinese nine herbal compound, 60.7% improvement rate of drug^[26] had better affect.

Some clinical studies on *N. bracteata* confirmed its anti-inflammatory mechanisms of action such as reducing basophil and neutrophil infiltration in the experimental study on asthma.^[27] Another clinical study on productive cough showed that *N. bracteata* compound syrup (*Sharbat Zoofa Murakkab*) had high significant reduction in

Table 1: Demographic data of participants in the study

Characteristics	Case group (n=37), n (%)	Control group (n=34), n (%)	P
Sex			
Male	13 (35.1)	11 (32.4)	0.741*
Female	24 (62.2)	23 (67.6)	
Age (year)	33.53 ± 12.04	31.85 ± 13.21	0.577**
Allergy type			
Perennial	25 (67.6)	23 (64.7)	0.132*
Intermittent	12 (32.4)	11 (32.3)	
Smoking	1 (2.7)	1 (2.9)	0.952*

*Significant level of using Fisher's exact test; **Significant level of using independent sample t-test. Data shown mean \pm SD or n (%). SD = Standard deviation

Table 2: Comparison mean of severity of allergic rhinitis symptoms before and after treatment in two groups

Symptoms	Case group (n=37)			Control group (n=34)			P ₁	P ₂	P ₃
	Percentage	Before	After	Percentage	Before	After			
Rhinorrhea	97.3	6.05±2.11	1.28±1.80	88.2	5.33±2.12	5.16±2.09	<0.001	0.111	<0.0001
Sneezing	81.1	4.96±2.59	0.66±1.09	85.3	5.20±2.15	4.80±2.31	<0.001	0.072	<0.0001
Nasal obstruction	67.6	5.68±2.44	1.04±1.51	76.5	6.32±2.53	5.46±2.83	<0.001	0.060	<0.0001
Itchy nose	62.2	4.20±2.64	0.84±1.31	58.8	5.70±2.69	4.65±2.79	<0.001	0.054	0.0001
Ocular symptoms	43.2	4.09±2.99	0.90±1.26	47.1	4.41±2.83	3.58±2.98	<0.001	0.106	0.0002
Total	-	7.10±1.92	2.37±1.76	-	6.38±2.18	6.00±1.95	<0.001	0.831	<0.0001

Data shown mean±SD. P₁ = Significant level of using paired sample t-test for comparing mean of symptoms between before and after treatment in case group; P₂ = Significant level of using paired sample t-test for mean of symptoms between before and after placebo in control group; P₃ = Significant level of using independent sample t-test for comparing mean of improvement symptoms between two groups; SD = Standard deviation

erythrocyte sedimentation rate, eosinophil, and anti-allergic properties.^[19]

Investigations considered flavonoids and related compounds as possible natural inhibitors of IgE; these agents have anti-allergic activities such as prevention of the expression of CD40 receptor ligand by basophiles and inhibition of the release of histamine by interleukin (IL-4) and IL-3.^[28]

Furthermore, flavonoids have anti-inflammatory effects by inhibiting of both cyclooxygenase and 5-lipoxygenase pathways, degranulation of neutrophils, other known and unknown mechanisms.^[29] Furthermore, luteolin and its derivatives were clinically effective to relieve AR nasal symptoms in rat.^[30]

Recent findings showed that flavonoids, phenolic compounds, and terpenes act with the mechanisms of reduction of eosinophils and basophils, neutrophil infiltration, and inhibition of inflammation pathways and IgE as well as anti-allergic activity.^[27-29] Therefore, improvement of the symptoms such as congestion, runny nose, and irritation in this study can cause due to these compounds.

On the other hand, based on PM beliefs, the effect of *N. bracteata* on AR can be due to its molifying (*Molattef*) and laxative (*Moshel*) effects on phlegm (*Balgham*).^[17]

It seems that traditional beliefs and current concepts meet together in this case and our investigation approved the efficacy of this plant on AR.

CONCLUSION

According to obtained results, *N. bracteata* has significant effects on the AR symptoms. Therefore, it can be a good alternative remedy for relieving the symptoms of AR.

Limitations of the study

The sample size and short duration of intervention may be not enough to mention definitely about "Adverse Reactions" and safety of this treatment option.

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Conflicts of interest

There are no conflicts of interest.

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