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Effect of *Nepeta bracteata* Benth. on Chronic Obstructive Pulmonary Disease: A Triple-Blinded, Randomized Clinical Trial

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) imposes a substantial, direct, and indirect economic burden and health complications on healthcare systems. It seems that Persian medicine could facilitate the process of new drug discoveries through reverse pharmacology for the treatment of chronic respiratory diseases.
Objectives: This study aimed to determine the preliminary efficacy of *Nepeta bracteata* Benth. (*N. bracteata*) in patients with mild to moderate COPD.
Methods: In a four-week, triple-blind, randomized, placebo-controlled trial, 78 patients with mild to moderate COPD were randomly allocated to receive either 10 ml syrup of *N. bracteata* or placebo three times a day, as an add-on to their routine treatment (long-acting beta2-agonist and inhaled corticosteroid). The Spirometry was performed on patients at baseline and end of the intervention to evaluate the effect of the treatment. Forced Expiratory Volume in the first second (FEV_1) and FEV_1/Forced Vital Capacity (FVC) ratio were considered the primary outcomes. COPD Assessment Test (CAT) was also used for the subjective evaluation of patients' responses.
Results: 64 patients completed the study. The results showed a significant improvement in the CAT score in the *N. bracteata* group (-9.05) compared to the placebo (-2.78) and control (-2.05) groups (P value = 0.001). The comparison of FEV_1 and FEV_1/FVC changes showed a significant difference in the *N. bracteata* group. However, when comparing the three groups, the difference was not statistically significant at the beginning and four weeks after the intervention.
Conclusions: It seems that the appropriate response of COPD patients to this drug, especially regarding the quality of life, could make it a choice for complementary therapy in chronic respiratory diseases.

Keywords: Alternative Medicine, Chronic Obstructive, Clinical trial, *Nepeta bracteata* Benth, Pulmonary Disease, Spirometry

1. Background

Chronic obstructive pulmonary disease (COPD) is a health-threatening disease that imposes a substantial, direct, and indirect economic burden on healthcare systems. It is estimated that COPD will be the world's third leading cause of death by the year 2020 (1, 2). Smoking is the main risk factor for COPD; however, only a small number of smokers develop this disease (3).

COPD is associated with airway obstruction and inflammation of the lung and respiratory tract. It is diagnosed with symptoms such as chronic productive cough and dyspnea. The progression of the disease has significant adverse impacts on the patients' quality of life. Common treatments to relieve the symptoms and reduce acute exacerbation of COPD are limited, and there is no exact treatment to control the disease (4).

The high cost of medications administered for COPD and the side effects of some bronchodilators along with the side effects of corticosteroids, higher absorption of inhalation medicines through the gastrointestinal system, as well as the complications arising from the use of systemic corticosteroids, highlight the need for medicines with lower costs and side effects.

Today, many people in developed and even developing communities have turned to traditional and complementary medicine. Several recent studies have focused on the effect of these traditional medicaments on respiratory diseases including COPD (5).

Persian medicine, with about ten thousand years of

history, is one of the world's leading medicine systems and has (for several years) increased in knowledge and potency, which has been attested to by proficient physicians (6). Persian medicine attempts to treat diseases by making recommendations for better lifestyle along with the consumption of exeptional food and herbal medicines (7). That herbal medicines have been accepted by patients for centuries leads to this hypothesis that they are available, safe, and affordable, and they are effective, as well. This could be a route to finding new effective drugs. This procedure is commonly utilized in alternative medicine (8, 9).

It seems that Persian medicine could facilitate the process of new drug discoveries through reverse pharmacology for the treatment of chronic respiratory diseases. The use of herbal medicines to treat pulmonary diseases is common in Persian medicine (10, 11). One of the greatest Persian medicine and complementary physicians, Avicenna and other scientists in this field have recommended different herbal medicines to relieve symptoms of pulmonary diseases, particularly dyspnea, sputum, and cough. *Nepeta bracteata* Benth. (*N. bracteata*) (Zoofa) is one of the most important plants recommended for the treatment of the dyspnea and chronic cough (12).

N. bracteata grows in the Northeast regions of Iran, Khorasan (13, 14) (Figure 1). Previous studies have demonstrated its antibacterial effects (15) and antioxidant activities (16). Another study showed the positive effect of *N. bracteata* on cytokines and inflammatory factors in animal models with asthma (17). A recent study revealed that *N. bracteata* could relieve the symptoms of allergic rhinitis (18). To the best of our knowledge, there is no study of the treatment effects of *N. bracteata* on COPD.

Figure 1. *Nepeta bracteata* Benth

2. Objectives

This pilot study, as a randomized, triple-blind, clinical trial, aimed to evaluate the effect of *N. bracteata* on the improvement of symptoms in patients with mild to moderate COPD, compared to placebo and control groups.

3. Methods

3.1. Patients

Patients with mild to moderate COPD referring to the Respiratory Diseases Clinic of Masih Daneshvari Hospital, National Research Institute of Tuberculosis and Lung Disease (NRITLD), Tehran, Iran, from April to December 2016 were enrolled in the current study. The subjects were diagnosed by an expert pulmonologist using the results of pulmonary function test and compliance of the signs and symptoms of the patients with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria of the American Thoracic Society (ATS), as well as the criteria of the European Respiratory Society (ERS).

Patients with a history of allergy to the genera of Lamiaceae, diabetes mellitus, history of seizure, pregnant and lactating females, and patients with COPD exacerbation were excluded from the study.

3.2. Sampling and Setting

According to Inui et al. study (19) the standard deviation (SD) for the COPD Assessment Test (CAT) score change was considered 4.7. The mean difference between score changes of groups was expected to be four units. With α = 0.05 and power = 0.8, at least 22 cases in each group were needed to detect the desired difference.

3.3. Study Design

The study was a triple-blinded, randomized clinical trial, pilot study. The ethics committee of Shahed University approved the study with number IR.Shahed.REC.1394.84 and it was registered in the Iranian Clinical Trial Registry (IRCT2015121925598N1).

The subjects signed a written informed consent, and were randomly assigned to three groups of intervention, placebo, and control. Demographic data and CAT (COPD Assessment Test) completed questionnaires were obtained from all patients. Arterial oxygen saturation (S_aO_2) was measured using the Pulse Oximeter (Md300c20 by Omron, India) and the Spirometry was conducted with a calibrated SuperSpiro (Micro Medical, United Kingdom) according to the ATS and ERS guidelines. All subjects in the three groups received conventional treatment according to the therapeutic protocol of patients with mild to moderate COPD.

The subjects were free to withdraw from the study at any time. The study was conducted following the CONSORT statement (Figure 2).

3.4. Drug Preparation

Dry plants of *N. bracteata* were purchased from a local market in Tehran, Iran, and were identified at the Faculty of Pharmacy, Tehran University of Medicinal Sciences, under voucher number PMP-324. 20 g of the dried plant was macerated in 1 L of water for 24 h, filtered, and mixed with 200 g of each of sugar and honey to a consistency of 60%. The mixture was then prepared as a syrup in a 250 mL glass. The placebo was prepared in a similar method without *N. bracteata* extract. The dosage was 10 mL three times a day administered for four weeks.

3.5. Standardization of the Drug

Standardization of the drug was done by measuring the phenolic and flavonoid content of the syrup determined using Folin-Ciocalteu and Gallic acid by a spectrophotometer. At different concentrations of Gallic acid, we obtained a standard curve and then the absorption of the samples, as well as Gallic acid solutions, was measured at 750 nm wavelength.

For measuring the total phenol flavonoid of the samples, we used aluminum chloride and routine flavonoid as a standard. At different concentrations of routine flavonoid, the standard curve was obtained, and then the absorption of samples, as well as routine flavonoid solutions, was measured at 414 nm.

Finally, the total amount of phenol and flavonoid in the syrup was obtained by the standard curve line equation of Gallic acid.

The results of the spectrophotometric method for measuring the total amount of phenol and flavonoid in each 100 mg of the syrup were 293 ± 7 Gallic acid equivalent and 285 ± 5 routine flavonoid equivalent (Figure 3).

3.6. Randomization and Masking

A simple randomization method was used in this study. The drug and placebo were coded by a non-dependent colleague and the drugs were prescribed by another pharmacist who was blinded to the coding of the drug and placebo. This pharmacist kept the sealed code of the package until the end of the trial. The patients and clinical investigators were unaware of group assignment throughout the study and outcome variables were evaluated by physicians who were unaware of the study groups.

3.7. Outcome Measures

Changes in the CAT score and the Spirometry indices were assessed as the primary outcomes. Oxygen saturation and pulse rate were also evaluated as the secondary outcomes in all groups. The CAT questionnaires were completed by patients at the beginning of the study, as well as two and four weeks after the intervention, for all the study subjects. Spirometry was conducted at the beginning of the study, as well as four weeks after the intervention, and Forced Expiratory Volume in the first second (FEV_1) and FEV_1/Forced Vital Capacity (FVC) were recorded and expressed as percentages.

3.8. Clinical Complications and Side Effects

A number of common side effects including a headache, insomnia, nausea, skin rashes, itching, and gastrointestinal symptoms were investigated in *N. bracteata* and placebo groups before and after the study.

3.9. Statistical Analyses

Normal distribution was assessed using the Kolmogorov-Smirnov test. The comparison of outcome measurements between drug, placebo, and control groups was made using repeated measures ANOVA followed by Bonferroni test. The IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, N.Y., USA) was used for statistical analysis. All hypothesis tests were two-sided, and the significance was accepted at $P < 0.05$.

4. Results

Of the 78 subjects in the current study, 72 were males, and six were females who developed mild to moderate COPD with a mean age of 62.4 ± 10.43 years. About 82% of the subjects had a history of smoking with a mean pack-year of 33.96 ± 33.76. The patients were randomly assigned to each of the intervention, placebo, and control groups. Of the 78 enrolled subjects, 64 (21 in the intervention, 23 in the placebo, and 20 in the control groups) completed the study (Figure 2). The groups were evaluated for age, smoking level, S_aO_2, weight, pulse rate, FEV_1, FEV_1/FVC, and CAT score at the beginning of the study. The Kolmogorov-Simonov test showed that the distributions of all the variables were normal except for the smoking level for which, the non-parametric test of Kruskal-Wallis was utilized for making comparisons.

The comparison of quantitative variables using one-way ANOVA and Kruskal-Wallis qualitative variables using the Pearson chi-square test showed the homogeneity of the groups at the beginning of the study (Table 1).

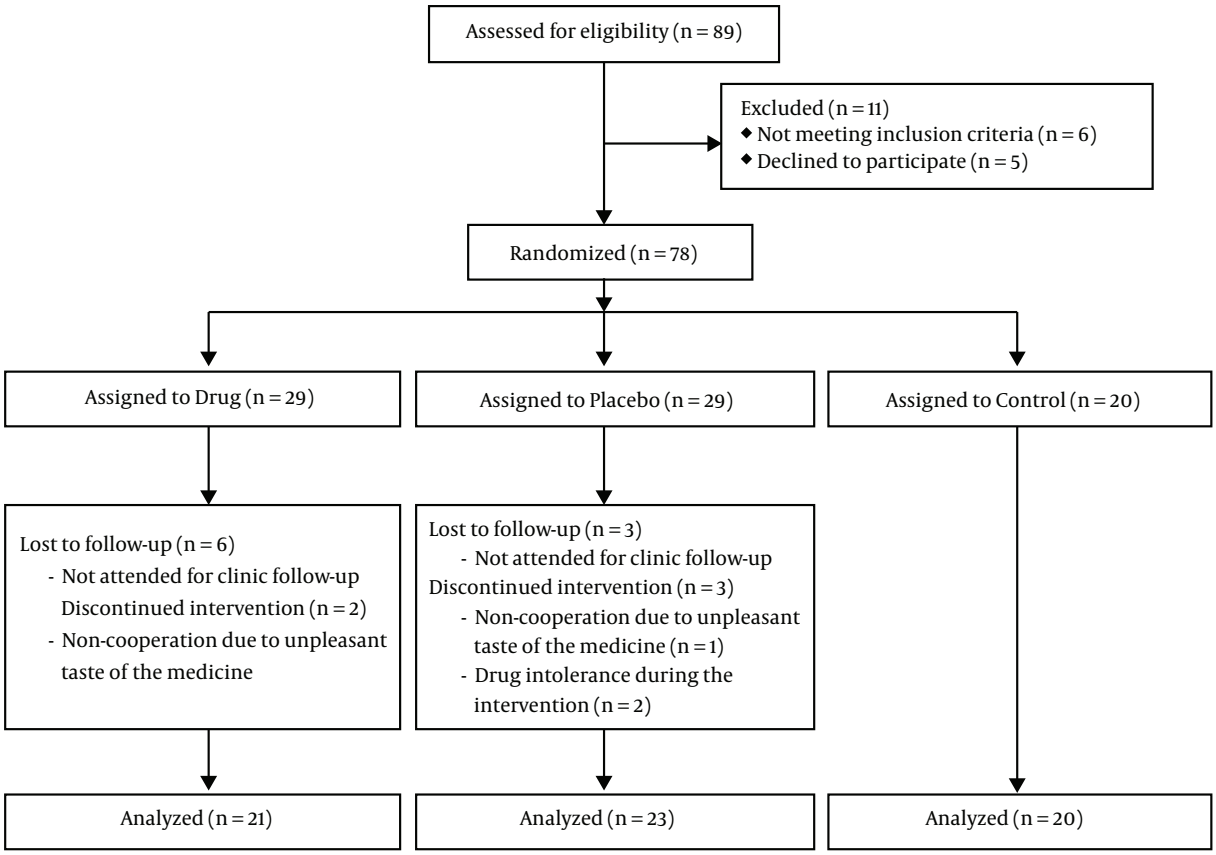

Figure 2. CONSORT flowchart of the study

Table 1. Demographic Characteristics of the Patients

Variable	Groups			P Value
	Nepeta	Placebo	Control	
Sex, No. (%)				0.79[a]
Male	26 (89.7)	27 (93.1)	19 (95)	
Female	3 (10.3)	2 (6.9)	1 (5)	
Age, y	63.41 ± 11.93	62 ± 10.63	61.55 ± 7.87	0.804[b]
Cigarette, pack year[c]	20 (0, 30)[c]	30 (4.25, 45)[c]	40 (20, 50)[c]	0.053[d]
Weight, kg	68.72 ± 10.61	68.44 ± 11.15	69.05 ± 9.31	0.928[b]
BMI, kg/m^2	24.97 ± 3.77	24.77 ± 4.65	25.33 ± 3.86	0.901[b]

[a] Chi-square.
[b] One-way ANOVA.
[c] Median (IQR).
[d] Kruskal-Wallis.

The CAT questionnaires were obtained in all three groups at the beginning of the study, as well as two and four weeks after the intervention. The repeated measures ANOVA and Bonferroni test used to compare CAT changes between the groups showed a significant difference in the mean CAT score four weeks after the intervention between the intervention, placebo, and control groups ($P < 0.05$). There was no significant correlation among the study groups when comparing the changes at the beginning of the study and two weeks after the intervention.

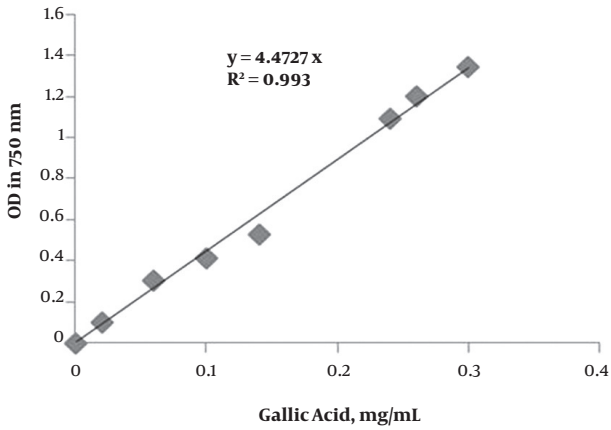

Figure 3. Gallic acid concentration

In addition, statistical analysis showed a significant difference in the intervention group regarding the CAT changes at the considered intervals (Table 2 and Figure 4).

The levels of FEV_1 and FEV_1/FVC at the beginning of the study and four weeks after the intervention were measured in all groups. The comparison of FEV_1 and FEV_1/FVC changes showed a significant difference in the *N. bracteata* group. However, when conducting between-group comparisons, the difference was not statistically significant at the beginning and four weeks after the intervention. Self-limited vomiting was reported in two patients of the *Nepeta bracteata* Benth. group and one patient of the placebo group. No other important complications were reported by the patients.

5. Discussion

The results of this study showed that *N. bracteata* could improve symptoms in patients with mild to moderate COPD. The CAT score improved by about 56% in the intervention group but this improvement was 20% in the placebo and 15% in the control group after four weeks.

Treatment is difficult in patients with COPD, due to the prevalence of irreversible airflow obstruction and formation of pulmonary fibrosis. Thus, its management is limited to supportive care. Hence, any non-invasive intervention, which can improve the quality of life in such patients, is suggested. The use of herbal medicines to treat dyspnea and cough is of great importance as an alternative approach in complementary medicine (20, 21).

To assess the level of patients' response to this treatment, different scales were used in studies, including COPD Assessment Test (CAT) (22), the St. George respiratory questionnaire (SGRQ) (23), clinical COPD questionnaire (CCQ) (24), the six-minute walk distance (6MWD), lung function tests, and measuring inflammatory factors such as cytokines and interleukins.

CAT is a standard patient-completed questionnaire that assesses all aspects of the COPD's impact on patient's life (a cough, sputum, breathlessness, chest tightness, confidence, activity, sleep, and energy levels) and includes eight questions on a 0 to 5-point scale and the total score range of 0 - 40. Higher scores denote a more severe adverse impact of COPD on the patient's life (25). The validity of this questionnaire and its Persian translation were approved in previous studies (26).

In the current study, the CAT questionnaire and the Spirometric changes including FEV_1 and FEV_1/FVC were studied to evaluate the response to treatment with *Nepeta bracteata* Benth. Today, different medications such as bronchodilators and steroids are used to improve symptoms in patients with COPD (27, 28).

The study by Cheng et al. revealed that the daily usage of high dose Fluticasone 1,000 μg and Salmeterol 100 μg in COPD patients for one year can reduce the CAT score significantly by about 20% compared to its moderate dosage (29) while Asai et al. showed no significant changes in CAT scores following the use of combination therapy with Salmeterol 50 mcg and Fluticasone propionate 250 mcg (SFC 250) (30).

After four weeks, the changes in CAT scores were statistically significant in the intervention group compared to the other groups. This reduction effect of *N. bracteata* on CAT scores was stronger than that reported in other comparative studies on COPD patients (nine points in four weeks versus three points in one year) (31-33).

Mukaida et al. studied the effect of Bakumondoto on the quality of life according to SGRQ and showed that it could be effective in suppressing cough in elderly patients with COPD (34). In another study conducted by Liu et al. on Sugarcane bagasse dietary fiber, they found that this regimen could improve symptoms of COPD patients by more than 50% in scores compared to controls (35).

Although the study on Buzhong Yiqi granule as a Chinese herbal remedy showed improved quality of life CAT (MD -2.56 points, 95% CI -3.40 to -1.72) when compared with conventional treatment alone or plus placebo in stable COPD, this effect was less than the effect of *N. bracteata* in our study (36). The study of Hong et al. on the effect of Chinese formula Yufeining on COPD resulted in a significant decrease in CAT score after two and four months compared to the baseline, but it could not make a significant difference compared to the placebo group (5).

Wang et al. in a study on mice showed that the extract of *N. bracteata* reduced the level of eosinophils and neutrophils in the pathological examination of lungs and

Table 2. Distributions of Symptoms Compared Between the Three Groups of Patients with COPD[a,b]

	Baseline	Two Weeks	Four Weeks	P Value*
S_aO_2				0.254
Nepeta	91 ± 5.12		92.62 ± 3.70	
Placebo	89.59 ± 4.45		90.85 ± 3.329	
Control	91.05 ± 4.78		91.63 ± 3.48	
PR				0.501
Nepeta	83.45 ± 15.03		84.67 ± 15.48	
Placebo	83.37 ± 14.88		81.80 ± 14.746	
Control	79.75 ± 14.24		79.47 ± 11.43	
FEV_1				0.288
Nepeta	54.14 ± 9.23		59.38 ± 10.65	
Placebo	55.15 ± 10.25		55.25 ± 9.17	
Control	53.53 ± 10.61		54.79 ± 9.34	
FEV_1/FVC				0.496
Nepeta	62.86 ± 8.81		65.52 ± 8.86	
Placebo	62.20 ± 7.20		64.15 ± 8.19	
Control	61.42 ± 7.58		62.53 ± 7.84	
CAT score				0.001
Nepeta	16.19 ± 6.84	11.14 ± 5.99	7.14 ± 4.75	
Placebo	14.13 ± 3.32	12.26 ± 4.24	11.35 ± 4.30	
Control	14.70 ± 6.34	12.80 ± 5.88	12.65 ± 5.29	

Abbreviations: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; PR, pulse rate; S_aO_2, O_2 saturation.
[a]Values are expressed as mean ± SD.
[b]The trial group was treated with conventional medication plus *Nepeta bracteata* Benth. Syrup (three times a day for four weeks); the placebo group was treated with conventional medication plus placebo syrup (three times a day for four weeks); the control group was treated with conventional medication.

could also decrease the Th17 and increase IL-10 levels. In addition, the extract of *Nepeta bracteata* Benth. could inhibit TGF-β mediated airway remodeling. The effectiveness of this herb in the asthmatic animal model was high enough to introduce it as a novel candidate for the future treatment of asthmatic patients (17). It seems that the anti-inflammatory effects of *N. bracteata* Benth. could improve the symptoms of COPD.

Although *N. bracteata* significantly improved FEV_1 and FEV_1/FVC after four weeks in the intervention group, the changes were not enough to make a significant difference with those of the other groups.

5.1. Limitations and Strengths

This study is one of the first interventional trials that investigated the treatment of COPD by Persian medicine. This study evaluated the drug effect through one-month follow-up, and further studies with more extended follow-up evaluations are needed. We assessed the response of patients to *N. bracteata* administration by CAT scoring and improvement of Spirometric indices. Other laboratory tests such as assessment of inflammatory mediators like IL 6, IL10, Th17, and TGF-β before and after the intervention are useful. Further investigations with larger sample sizes are recommended.

5.2. Conclusion

Nowadays, Iranian scientists are working on clinical trials to evaluate the effects of herbal medicines recommended in traditional texts (37, 38). The results of the current study indicated that the CAT score significantly reduced four weeks after the consumption of *N. bracteata* in patients with mild to moderate COPD compared to the placebo and control groups. The improvement of disease symptoms in patients with COPD following the consumption of *N. bracteata* would encourage clinicians to use this herb to treat patients with chronic respiratory diseases. Lower cost and higher efficiency of herbal medicines along with lower side effects are the valuable advantages for patients with COPD and their therapists. It seems that

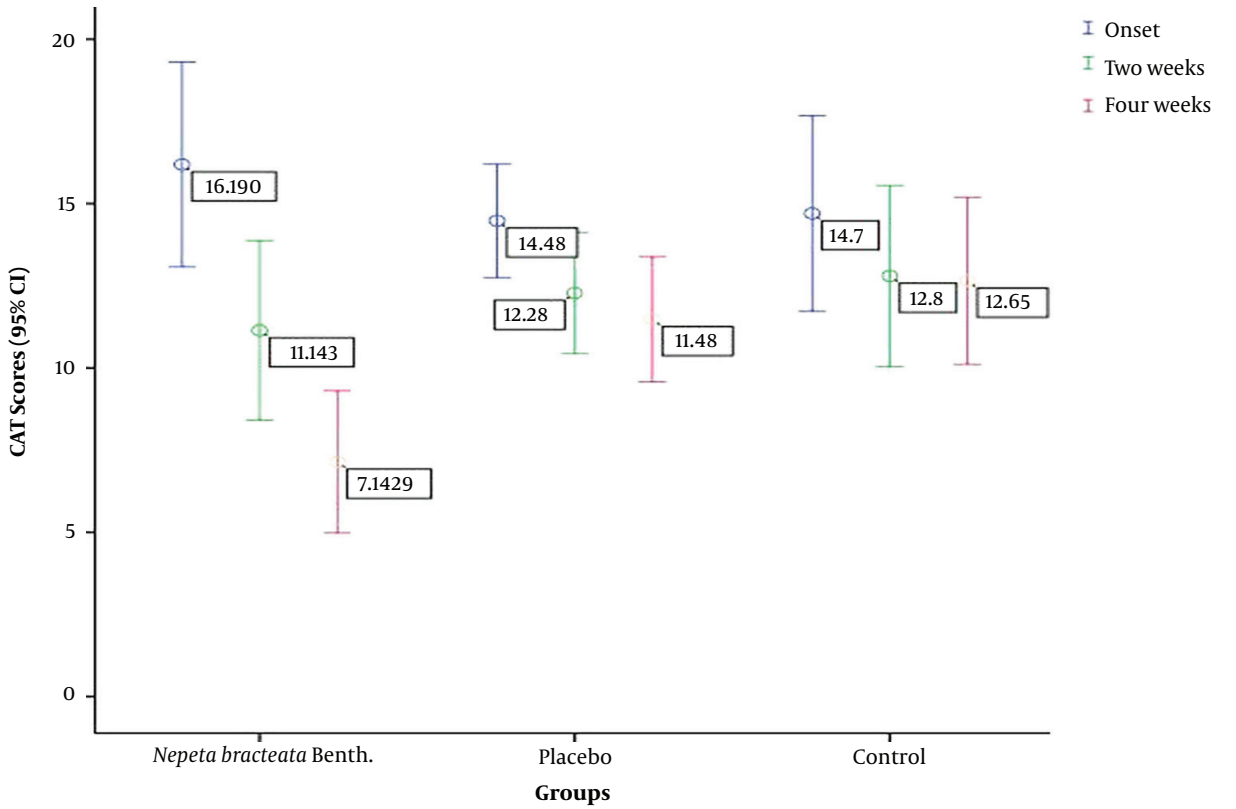

Figure 4. CAT score changes at the beginning of the study, as well as two and four weeks after the intervention

the appropriate response of COPD patients to this drug, especially regarding the quality of life, could make it a choice for complementary therapy in chronic respiratory diseases.

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Footnotes

Authors' Contribution: Study concept and design: Mohsen Naseri and Aliakbar Velayati; acquisition of data: Ali Abdolahinia and Alireza Eslaminejad; analysis and interpretation of data: Mohsen Naseri, Ali Abdolahinia and Alireza Eslaminejad; drafting of the manuscript: Ali Abdolahinia and Farzaneh Ghaffari; statistical analysis: Ali Abdolahinia; administrative, technical, and material support: Mohsen Naseri and Ali Abdolahinia; final approval of the article draft: Mohsen Naseri and Ali Abdolahinia.

Ethical Considerations: The Ethics Committee of Shahed University approved the study with number IR.Shahed.REC.1394.84 and it was registered in the Iranian clinical trial registry (IRCT2015121925598N1).

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