Original Article

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TANAFFOS

Efficiency of "Green Nature Deep Lung Support" in COPD Exacerbation Cases as a Novel Herbal Product: A Randomized, Double-Blind, Controlled Trial

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Background: There are no definitive treatment options yet for Chronic Obstructive Pulmonary Disease (COPD). This study investigated the efficacy of Green Nature Deep Lung Support, a novel herbal formulation derived from plant-based ingredients, in improving clinical outcomes during COPD exacerbations.

Materials and Methods: The present double-blind, randomized clinical trial was conducted on patients with COPD exacerbation grade D who needed rehabilitation. The first group received a placebo, whereas the second and third groups received one and three capsules daily, respectively. Clinical symptoms and inflammatory biomarkers, including IL-6, IL-8, CBC, and CRP, were compared among the three groups.

Results: The use of Green Nature Deep Lung Support led to a significant decrease in the values of indicators such as Systolic Blood Pressure (SBP), Respiratory Rate (RR), Cr, IL-8, and ESR, and an increase in SpO_2 after the intervention ($P<0.05$). Specifically, compared to pre-intervention values, SBP decreased from 131.25±13.76 to 126.25±8.41 ($P<0.01$). RR decreased from 17.10±1.21 to 16.00±0.65 ($P<0.01$), and SpO2 increased from 69.21±17.35 to 80.21±11.08 ($P<0.001$). No significant changes were observed in other indicators such as Diastolic Blood Pressure (DBP), pH, and pCO_2 ($P>0.05$). Furthermore, IL-8 and CRP decreased from 28.65±34.55 to 15.81±20.16 ($P<0.05$) and from 19.18±13.44 to 9.38±10.98 ($P<0.001$), respectively.

Conclusion: Green Nature Deep Lung Support supplement may be associated with modest improvements in inflammatory indices in COPD patients. Larger multicenter trials are required to confirm these preliminary findings and optimize dosing.

Keywords: Chronic obstructive pulmonary disease; Exacerbation; Inflammation; Herbal supplement

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the most common health-threatening diseases worldwide and currently the third leading cause of mortality (1, 2). According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition,

COPD is characterized by airflow limitation and chronic inflammation caused by harmful gases or airborne particulates. Unfortunately, a definitive treatment for this disease has not yet been introduced, but the most important goal that is considered in COPD patients is to improve clinical symptoms and prevent exacerbation with available drugs (3, 4). The two principal pathological features of this disease are chronic bronchitis and emphysema, which contribute to airway inflammation and hyperresponsiveness (5). Therefore, inflammation plays a central role in the pathogenesis and progression of COPD.

Currently, the COPD treatment approach is based on the use of long-acting antagonists along with corticosteroids and bronchodilators to reduce symptoms and prevent exacerbation (6). However, these methods have limited effectiveness in improving the general condition of the patient and reducing inflammation, and the use of COPD drugs is also associated with various side effects (7-9). Therefore, researchers are actively seeking alternative therapeutic strategies.

In recent years, interest in treatments based on traditional medicine has increased significantly. Several plant-derived compounds have shown potential therapeutic activity in respiratory diseases. For example, andrographolide, the main bioactive compound derived from Andrographis paniculata, has shown anti-inflammatory and immunomodulatory activity through intracellular signaling pathways including the STAT3-related response (10-13). An isosteroid alkaloid from *Fritillaria cirrhosa* reduces functional and structural pulmonary abnormalities and suppresses the inflammatory response in COPD (14). Taraxacum Officinale has been reported to reduce TNF-α, IL-6, and LPS-induced inflammatory injury (15). Echinacea species have shown immunomodulatory effects through macrophage activation and inhibition of TLR1/2-stimulated TNF-α production via the PI3K/Akt signaling pathway (16). Similarly, Eriobotrya japonica leaf extract improved airway inflammation and reduced inflammatory cytokines such as BALF's NO, EPO, MMPs, IL-4, IL-13, and serum IgE in experimental asthma models (17).

The Green Nature Deep Lung Support formulation investigated in our study is a newly developed combination of seven herbal extracts, including *Andrographis paniculata* leaf extract, *Echinacea purpurea* root and rhizome, *Eriobotrya japonica* leaf, *Fritillaria cirrhosa* whole plant, *Scutellaria baicalensis* root, *Taraxacum officinale* whole plant, and *Olea europaea*. To our knowledge, this is the first clinical evaluation of this product in COPD patients. Given the proven anti-inflammatory potential of these compounds and the lack of clinical studies evaluating this particular compound, the present trial was designed to investigate whether Green Nature Deep Lung Support could contribute to improving clinical and inflammatory parameters in COPD patients.

MATERIALS AND METHODS

Ethical considerations

The present study is a double-blind clinical trial that was conducted with the approval of the ethics committee in biomedical research (ethical code: IR.SBMU.MSP.REC.1401.455) on patients with COPD referred to Masih Daneshvari Hospital, Tehran, Iran. After receiving the ethical code, this project was registered in the clinical trial system with code IRCT20200611047727N5.

Patients

The participants in the study were selected from patients with COPD exacerbation based on the GOLD criteria in grade D who needed rehabilitation, 18<BMI<21, and smoking. During the study, patients who declined to continue participation for any reason, had incomplete or defective medical records, or were drug-sensitive were excluded. All eligible patients were enrolled after receiving a comprehensive explanation of the study and providing written informed consent, and were then randomly assigned to one of three study groups. Researchers who collected the data and all of the patients were blinded to the group allocation.

Sample size

The sample size for this study was determined using a power analysis for a one-way ANOVA with three groups.

To detect a large effect size (f = 0.4) with a power of 0.80 and an alpha level of 0.05, the total sample size required was 60 participants, with 20 participants in each of the three groups. A large effect size was selected based on previous studies and clinical experience with COPD treatments, where large effect sizes have been observed for interventions aimed at reducing inflammation. A large effect size reflects the substantial clinical impact of the treatment of inflammatory markers such as IL-6, IL-8, and CRP, which are critical in the management of COPD exacerbations (18-20). Given the significance of these markers in determining disease outcomes, the chosen effect size ensures that even modest but meaningful differences between treatment groups can be reliably detected with adequate statistical power. This calculation was performed using G*Power software. In this study, 16 patients were assigned to each group. By accounting for sample dropouts and increasing the effect size, the sample size increased to 60 patients. Finally, 20 patients were allocated to each group. The selection of patients to be placed in the groups was done by simple random selection using methods A, B, and C when they entered the relevant treatment departments of the hospital.

Study protocol

After randomly assigning the patients to three groups using random number generation software (R4.4.1), the first group received one placebo capsule daily, the second group was given one capsule of Deep Lung Support daily, and the third group received three capsules of this supplement daily. The randomization process was conducted using R software, ensuring that group allocation was unbiased and concealed until the intervention was assigned. To prevent any possible complications, the physician and clinical caregiver were aware of the study group allocation. Participating patients and researchers responsible for data collection and analysis were blinded.

McBoben sourced the finished product from Green Nature. Each batch undergoes extensive quality control, including testing for microbial contaminants (e.g., Salmonella, *E. coli*, *Staphylococcus aureus*, yeasts/molds), mycotoxins (including aflatoxin), allergens, banned substances, and elemental impurities (lead, mercury, cadmium, arsenic), in accordance with Therapeutic Goods Administration (TGA) guidelines for listed medicines. Certificates of Analysis (CoAs) are maintained for each batch and confirm compliance with batch-specific specifications.

Except for the difference in the amount of supplements used, the line therapy and the drugs used by the patients in all three groups were the same, including the administration of Tiotropium and inhaled corticosteroids. Blood samples (2 cc) were obtained from all patients on the first day and the day of discharge (ten days later). Clinical symptoms and factors, including IL-6, IL-8, CRP, and hemodynamic markers, were compared across all patients. Primary outcomes included changes in inflammatory markers, including IL-6, IL8, CRP, and ESR. Secondary outcomes included changes in respiratory parameters. The flowchart of the study is presented in Figure 1.

Statistical analysis

The results for quantitative variables were expressed as mean and standard deviation (mean ± SD), and categorical qualitative variables were presented as percentages. Paired t-tests were used to compare within-group changes (pre- vs. post-intervention) for each of the three groups (placebo, Deep Lung Support 1 capsule, and Deep Lung Support 3 capsules). One-way ANOVA was applied for between-group comparisons to assess the differences among the three groups. Post-hoc analysis was performed when necessary to identify specific group differences. A significance level of less than 0.05 was considered for all statistical tests. All statistical analyses were conducted using SPSS software version 23.

RESULTS

Based on the results presented in Table 1, which evaluated the effect of placebo on the study outcomes, the normality assumption was assessed, and the parametric independent-samples t-test was subsequently used for analysis. At a significance level of 0.05, the observed P-values indicated significant differences in the mean values of SBP, SpO_2, HCO_3^-, creatinine, CRP, and ESR before and after placebo administration.

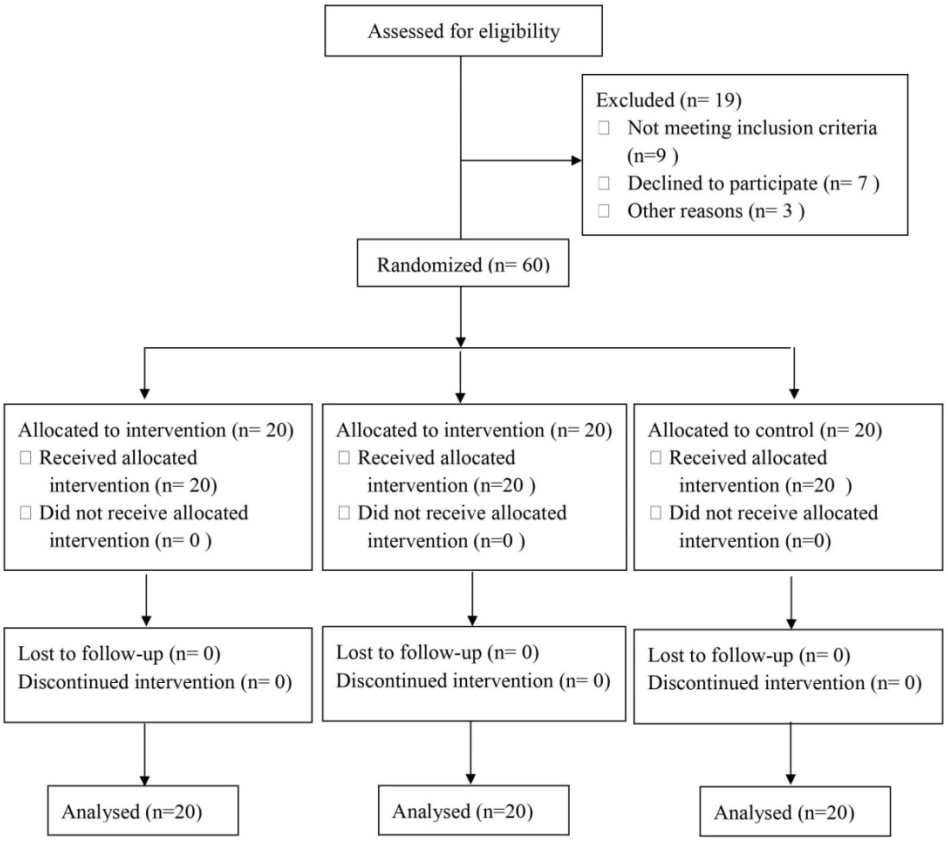


Figure 1. CONSORT chart of the study

Table 1. Descriptive statistics and t-test results for the placebo group

Outcome	Before intervention (Mean±SD)	After intervention (Mean±SD)	Mean ±SD	*p*-value	t
SBP	130.28 ±13.11	126.67±9.07	3.61±6.37	<0.05*	2.40
DBP	80.28 ±7.76	79.17±6.00	1.11±3.234	0.163	1.45
RR	16.44±1.20	15.75±1.00	0.688±1.815	0.151	1.51
HR	83.44±9.55	80.28±7.68	3.16±8.075	0.114	1.66
SpO_2	69.50±22.74	85.67±7.28	-16.16±20.194	<0.01*	-3.39
PH	7.34 ±0.06	7.37±0.032	-0.025±0.073	0.161	-1.46
pCO_2	68.94±16.24	60.11±11.565	8.83±18.082	0.054	2.07
HCO_3	37.33±6.74	33.39±3.89	3.94±7.182	<0.05*	2.33
Lymphocytes	8483.53±4260.88	9201.1±4524.03	-717.64±3961.64	0.466	-0.74
Neutrophils	8483.53±4260.88	9142.3±4469.44	-658.824±4071.93	0.514	-0.66
Urea	42.53±15.92	52.59±23.15	-10.05±22.018	0.078	-1.88
Cr	0.959±0.203	1.11±0.316	-0.15±0.229	<0.05*	-2.47
CRP	11.72±11.137	5.59±4.625	6.12±7.935	<0.01*	3.18
IL6	1.19±0.825	1.66±1.711	-0.46±1.759	0.276	-1.12
IL8	2.24±3.609	7.724±16.788	-5.48±16.940	0.201	-1.33
LDH	444.92±101.528	398.25±72.846	46.66±102.591	0.143	1.57
ESR	16.67±14.35	8.33±8.98	8.33±11.777	<0.01*	3.00

SBP, Systolic Blood Pressure; **DBP,** Diastolic Blood Pressure; **RR**, Respiratory rate; **HR**, Heart rate; **Cr**, creatinine; **CRP**, C-reactive protein; **IL6**, Interleukin-6; **LDH**, Lactate dehydrogenase; **ESR**, Erythrocyte sedimentation rate.

* Significant *p* value<0.05.

Comparison of the results obtained from patients receiving one capsule of Deep Lung Support daily revealed significant differences in the mean values of SBP, respiratory rate, SpO_2, CRP, and IL-8 before and after treatment. Specifically, for SBP, the mean decreased from 131.25±13.76 before the intervention to 126.25±8.41 after ($P < 0.01$), indicating a significant reduction. For RR, the mean decreased from 17.10±1.21 to 16.00±0.65 (P<0.01), showing a significant decrease in respiratory rate. SpO_2 increased significantly from 69.21±17.35 to 80.21±11.08 (P<0.001), reflecting a notable improvement in oxygen saturation. CRP levels also showed a significant decrease from 19.18±13.45 to 9.38±10.98 (P<0.001), indicating a reduction in inflammation. Lastly, IL-8 levels decreased from 28.65±34.55 to 15.81±20.16 (P<0.05), showing a reduction in this inflammatory marker (Table 2).

Comparison of the results obtained from the patients in the group taking three capsules of Deep Lung Support daily showed significant differences in some markers before and after taking the drug. Specifically, for SBP, the mean decreased from 134.25 ± 8.47 before the intervention to 131.50±7.45 after (P=0.164), showing no significant change. For RR, the mean decreased from 17.20±1.51 to 16.40±1.05 (P=0.057), indicating a marginal decrease in respiratory rate. However, IL-8 levels showed a significant reduction from 33.32±27.52 to 13.41±7.90 (P<0.01), reflecting a notable decrease in this inflammatory marker. ESR also decreased significantly from 24.44±24.66 to 13.06±20.07 (P<0.01), indicating a reduction in inflammation (Table 3).

To check the difference in the average serum level of each of the three groups, we first calculated the difference before and after within each group and then determined the equality of the average serum level in all three test groups. Since we have more than two groups to compare, ONE-WAY ANOVA was used for analysis. Assuming a significance level of 0.05, according to the *p*-value, the mean serum levels of SpO_2 and IL8 were different from the other two groups in at least one group. According to the Tukey-HSD test, the average SpO_2 of groups one and three was different, but there was no difference between the average SpO_2 of groups two and three. The mean IL-8 serum level of group one was significantly different from groups two and three. However, there was no statistically significant difference in the mean IL-8 in groups two and three.

Table 2. Descriptive statistics and t-test results for the intervention group with one capsule daily

Outcome	Before intervention Mean±SD	After intervention Mean±SD	Mean± SD	*p*-value	t
SBP	131.25±13.756	126.25±8.410	5.00±7.071	<0.01*	3.16
DBP	80.75±5.200	76.50±18.715	4.25±17.865	0.301	1.06
RR	17.10±1.210	16.00±0.649	1.10±1.373	<0.01*	3.58
HR	83.60±10.85	82.20±9.55	1.40±10.323	0.551	0.61
SpO_2	69.21±17.35	80.21±11.08	-11.00±16.090	<0.001*	-2.98
PH	7.38±0.070	7.36±0.091	0.02±0.102	0.428	0.81
pco2	62.58±16.37	65.68±10.99	-3.10±17.792	0.457	-0.76
HCO3	36.05±5.730	37.11±5.626	-1.05±6.096	0.461	-0.75
Lymphocytes	9696.92±4300.16	10305.38±2679.647	-608.46±4049.91	0.598	-0.54
Neutrophils	9696.92±4300.16	18613.08±30664.54	-8916.15±30579.082	0.314	-1.05
Urea	43.71±14.657	44.86±10.967	-1.143±21.332	0.844	-0.20
Cr	0.96±0.193	0.98±0.265	-0.02±0.172	0.560	-0.59
CRP	19.18±13.445	9.38±10.977	-9.81±9.399	<0.001*	-4.549
IL6	2.44±3.705	1.80±2.484	0.65±1.527	0.074	1.89
IL8	28.65±34.547	15.81±20.157	12.84±22.294	<0.05*	2.58
LDH	452.33±197.91	345.83±128.846	106.50±242.113	0.156	1.52
ESR	26.00±25.670	21.35±26.474	4.65±12.592	0.115	1.65

SBP, Systolic Blood Pressure; **DBP,** Diastolic Blood Pressure; **RR**, Respiratory rate; **HR**, Heart rate; **Cr**, creatinine; **CRP**, C-reactive protein; **IL6**, Interleukin-6; **LDH**, Lactate dehydrogenase; **ESR**, Erythrocyte sedimentation rate.

* Significant *p* value<0.05.

Table 3. Descriptive statistics and t-test results for using three capsules daily

Outcome	Before intervention Mean±SD	After intervention Mean±SD	Mean±SD	*p*-value	t
SBP	134.25±8.472	131.50±7.452	2.75±8.50	0.164	1.44
DBP	81.25±3.193	80.50±2.236	0.75±4.06	0.419	0.82
RR	17.20±1.508	16.40±1.046	0.80±1.76	0.057	2.03
HR	80.50±7.480	78.48±8.256	2.30±9.54	0.295	1.08
SpO2	76.25±15.32	73.55±18.40	2.70±24.20	0.624	0.49
PH	43.74±162.701	7.37±0.041	36.36±162.70	0.330	1.0
pco2	60.25±19.103	60.75±15.082	-0.50±16.110	0.891	-0.14
HCO3	33.43±10.318	34.60±9.202	-1.17±11.284	0.648	-0.46
Lymphocytes	10311.76±3268.769	10194.71±3967.758	117.06±4595.65	0.918	0.11
Neutrophils	1031176±3268.769	10194.71±3967.758	117.06±4595.65	0.918	0.11
Urea	42.65±13.043	49.47±12.425	-6.82±14.78	0.075	-1.91
Cr	1.10±0.346	1.12±0.335	-0.01±0.176	0.787	-0.27
CRP	11.02±11.388	15.22±18.913	-4.20±20.965	0.407	-0.85
IL6	15.11±28.918	23.71±78.227	-8.60±82.508	0.646	-0.466
IL8	33.32±27.524	13.41±7.904	19.90±25.723	<0.01*	3.46
LDH	444.69±125.975	373.50±149.610	71.19±142.393	0.064	2.00
ESR	24.44±24.658	13.06±20.066	11.389±14.983	<0.01*	3.22

SBP, Systolic Blood Pressure; **DBP,** Diastolic Blood Pressure; **RR**, Respiratory rate; **HR**, Heart rate; **Cr**, creatinine; **CRP**, C-reactive protein; **IL6**, Interleukin-6; **LDH**, Lactate dehydrogenase; **ESR**, Erythrocyte sedimentation rate.

* Significant *p* value<0.05.

Table 4. Examining the difference between the mean serum levels of each of the three groups

Outcome	Placebo M±SD	One capsule daily M±SD	Three capsule daily M±SD	*p*-value	F
Age	66.56±8.024	65.32±11.284	64.15±7.700	0.722	0.328
Day hospitalization	13.24±4.176	11.70±3.975	15.30±8.749	0.187	1.732
ASTpre	29.56±13.69	39.05±52.13	32.05±23.53	0.676	0.394
ALTpre	32.00±23.838	71.55±185.172	40.10±80.942	0.556	0.593
ALPpre	228.60±81.532	229.53±62.282	247.65±120.150	0.778	0.253
Ferritinpost	234.82±152.908	249.13±154.501	239.40±185.759	0.975	0.026
SBP	-3.61±6.372	-5.00±7.071	-2.75±8.503	0.628	0.470
DBP	-1.11±3.233	-4.25±17.864	-0.75±4.063	0.545	0.614
RR	-0.69±1.815	-1.10±1.372	-0.80±1.765	0.735	0.310
HR	-3.17±8.075	-1.40±10.323	-2.30±9.547	0.846	0.167
SpO_2	16.17±20.193	11.00±16.090	-2.70±24.198	<0.05*	4.349
PH	0.026±0.073	-0.019±0.102	0.02±0.055	0.187	1.733
PCO_2	-8.83±18.082	3.10±17.791	0.50±16.109	0.099	2.420
HCO_3	-3.94±7.182	1.05±6.096	1.17±11.284	0.127	2.146
Lymphocytes	717.65±3961.6419	608.46±4049.913	117.06±4595.657	0.827	0.191
Neutrophils	658.82±4071.932	8916.15±30579.082	117.06±4595.657	0.278	1.317
Urea	10.05±22.018	1.14±21.332	6.82±14.782	0.452	0.809
Cr	0.15±0.229	0.025±0.171	0.011±0.176	<0.10	2.693
CRP	-6.13±7.935	-9.81±9.399	4.20±20.965	<0.05	4.889
IL6	0.47±1.759	-0.64±1.527	8.60±82.508	0.808	0.214
IL8	5.48±16.940	-12.84±22.293	-19.90±25.723	<0.01*	6.289
LDH	-46.67±102.591	-106.50±242.113	-71.18±142.392	0.688	0.378
ESR	-8.33±11.777	-4.65±12.591	-11.38±14.982	0.295	1.250

SBP, Systolic Blood Pressure; **DBP,** Diastolic Blood Pressure; **RR**, Respiratory rate; **HR**, Heart rate; **Cr**, Creatinine; **CRP**, C-reactive protein; **IL6**, Interleukin 6, **LDH**, Lactate dehydrogenase; **ESR**, Erythrocyte sedimentation rate.

* Significant *p* value<0.05.

DISCUSSION

Patients with COPD usually have intolerance to physical activity and impaired functional status, which plays a significant role in reducing their quality of life. Another important factor affecting the health-related quality of life of these patients is the frequency of exacerbations. The severity of the disease is assessed by examining lung function criteria and laboratory indicators. In COPD patients, the concentration of inflammatory markers such as interleukin-6 (IL6), C-reactive protein (CRP), and tumor necrosis factor (TNF-α) is significantly higher than in other people (21,22). In addition, researchers have shown that higher CRP levels are significantly associated. It directly affects lung function, exercise capacity, and quality of life in COPD patients (23). Therefore, in the present study, we evaluated the effects of an herbal supplement on inflammatory markers in patients experiencing acute exacerbations of COPD. The use of herbal medicines has long been a major focus of pharmaceutical companies and healthcare professionals worldwide. In the meantime, combining and formulating different plants with consistent or coordinated clinical effects has led to new developments in the treatment of some chronic diseases. The results of our research, which examines the effect of the use of the Green Nature Deep Lung Support product on the clinical condition of patients with COPD exacerbation, are discussed in two main areas: the effect of consumption and the effect of the dose.

The overall effect of consumption

Based on the obtained results, the use of Green Nature Deep Lung Support caused a significant decrease in the values of indicators such as SBP, RR, Cr, IL-8, ESR, and an increase in SpO_2 after the intervention. In this way, we have shown that the use of the mentioned supplement can effectively improve the hemodynamic status and inflammatory indicators of the examined patients. Although several changes were observed that were statistically significant, the short duration of our intervention may not clearly indicate robust clinical improvement resulting from the supplement used. Therefore, the distinction between statistical significance and clinical improvement should be considered when evaluating our results.

Studies on changes in systemic inflammation during COPD are conflicting

Given the complexity of herbal formulations, the mechanistic pathways described below are a summary of previous documentation that may help interpret the clinical findings of this study. Based on what we showed in our study, two important inflammatory indicators, IL-8 and ESR, have significantly decreased in patients undergoing intervention. Previously, the effect of some sources used in Green Nature Deep Lung Support medicine on inflammation was shown. Kim et al. previously showed the effect of Eriobotrya japonica leaf extract on improving inflammation (17). Researchers showed that this plant can prevent the penetration of inflammatory cells by reducing BALF's NO, EPO, MMPs, IL-4, IL-13, and serum IgE. In addition, the anti-inflammatory properties of Taraxacum officinale, another source used in our supplement, have also been shown in the studies of Koh et al. (24).

Another important point is the results of reducing hemodynamic and respiratory indicators of patients, parallel to the reduction of inflammation. Several studies have shown that reducing inflammation can improve the respiratory condition of patients (25-27). Therefore, the improvement of the observed clinical condition following the use of the supplement can be attributed to its positive effects on the state of inflammatory indicators.

The effect of dosage

Although the one capsule group showed numerically greater improvement in several parameters, the differences between the one capsule and 3 capsule groups were not statistically significant. Considering that the present study is the first investigation of the effect of Green Nature Deep Lung Support on patients with COPD, it is not possible to

state a definite reason for what was observed. Therefore, conducting studies with a larger statistical population, more groups (use of different doses), and the involvement of several different centers should be on the agenda of future studies. It should be noted that part of the patients' improvement may be due to the placebo effect or regression to the mean, which is common in short-term studies.

Our study had limitations that should be considered. First, our intervention period was 10 days, which may not be sufficient to assess the anti-inflammatory or functional effects of the herbal formulation used. Second, the small sample size and single-center nature limit the generalizability of these results to a larger population of COPD patients. Finally, while the composition of the product used is standardized, its pharmacokinetic interactions require further investigation.

CONCLUSION

The findings of this clinical trial suggest that supplementation with Green Nature Deep Lung Support may be associated with modest short-term improvements in selected inflammatory and clinical parameters in patients with COPD. However, given the small sample size, short intervention duration, and single-center design, these findings should be interpreted with caution. Multicenter studies with larger sample sizes and longer follow-up are needed to determine the optimal dose of the drug and confirm our findings.

Conflicts of interest

The authors have no conflicts of interest.

Availability of data and material

All data used and analyzed in this study are available from the corresponding author upon reasonable request.

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