

New phytocomplex for chronic obstructive pulmonary disease: Development and clinical evidence of anti-inflammatory effect

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ABSTRACT

Chronic diseases of the bronchopulmonary system are common all over the world and the number of working-age population suffering from them is constantly growing. In some cases medications are insufficient, and combination therapy, involving dietary supplements, can be an effective solution. The present paper provides information about a new phytocomplex with active compounds demonstrating synergistic effects. Thirty-five patients diagnosed with chronic obstructive pulmonary disease took part in the clinical trial. Twenty patients (the experimental group) underwent combination therapy, which involved dietary supplement intake alongside medications. Two tablets of the dietary supplement taken daily ensured the supply of rutin – 16 mg, quercetin – 11.2 mg, ascorbic acid – 45 mg, as well as tannins – 24mg. The other fifteen patients (the control group) received the standard treatment. Clinical, instrumental, and laboratory tests were performed to study changes in elastase levels in sputum and blood, blood count, and sputum induction for the participants of both groups before and after the treatment. On Days 3 and 4 promoted sputum expectoration was recorded in the experimental group, and on Day 4 the number of patients with severe cough decreased. The supplement intake did not influence the composition of cellular elements.

Keywords: Dietary supplement, Obstructive pulmonary disease, Effectiveness, Functional properties

Introduction

About 12 million people in Russia are diagnosed with chronic obstructive pulmonary disease (COPD). Experts predict that the number of people suffering from it will increase. A similar tendency is documented in other countries [1-4]. COPD development may result in other pathologies and eventually

disability which is a worrying trend as most of the patients are working-age people under 50 [5-13].

COPD is a progressive disease, that is aggravated by long-term exposure to environmental pollution, as well as increased alcohol consumption and tobacco use. It is predicted to become the third leading cause of death in the world [14-24].

The bronchial tree infections are known to be the main cause of COPD exacerbation. Medical experts express different views on COPD, some considering the infection to be the pathogenesis of chronic inflammation in COPD; while others argue that COPD is an epiphenomenon. In COPD exacerbations, noninfectious factors account for 40-50 % of cases [25-27]. The main cause of the disease is the bronchial tree damage. Even when there is a disappearance of signs and symptoms of COPD, the chronic process in the bronchi can persist, the microflora of the lower respiratory tract influencing the degree of inflammation and the

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clinical remission of the disease [28-32]. Therefore, research aimed at developing new ways to improve bronchi ventilation, enhance local immunity, and increase the effectiveness of existing treatment is becoming increasingly relevant.

Treatment of respiratory tract diseases usually requires long-term and frequent administration of medications. It may cause several inconveniences for patients, especially for elderly people. The accumulated experience in treating COPD indicates the advantages of using different forms of dietary supplements and multi-component mixtures of plant or animal origin. Diet therapy increases the treatment effectiveness, minimizing side effects and reducing the number and frequency of prescribed medications [5, 17, 33-38].

Materials and Methods

The study objective was to develop a new dietary supplement, that can be used in combination therapy for people with COPD in the acute phase of the disease, and to evaluate its effectiveness. The study was conducted in accordance with the Declaration of Helsinki; the design of the clinical study was approved by the Institutional Review Board of Medical University Kemerovo (protocol #1030, approved February 2021). Clinical, instrumental, and laboratory tests performed during the clinical trial comply with the normative documents [7, 13, 15].

Thirty-five patients diagnosed with chronic obstructive pulmonary disease were selected by the doctors to participate in the clinical trial. The selection was carried out by medical professionals supervising the study. When considering the potential participants for the study, doctors took into consideration the etiology and pathogenesis of the disease. Medical records of the patients are kept at the hospital. The experimental group included twenty patients with COPD – 12 men and 8 women aged from 37 to 54 experiencing the acute phase of the disease. Thirteen patients (37 %) had stage 1 COPD, and seven patients (29 %) had stage 2.

The control group was made up of 15 men and women of similar age and symptoms. The patients of the control group received antibiotics and bronchodilators prescribed by the supervising doctor (the data are kept in patients' medical records); while the combination therapy for the experimental group was comprised of antibiotics, bronchodilators and 2 tablets of the dietary supplement daily with meals for 21 days.

We studied elastase levels in sputum and blood, spirometry indicators, which characterized changes in external respiration, a complete blood count, and induced sputum characteristics. Tests were carried out in both groups before and after treatment.

The effectiveness of the therapy was evaluated on Days 7, 14, and 21 by applying the following parameters (scores on a scale from 1 to 4):

- Sputum (0 – none, 1 – coughing up sputum once or twice a day, 2 – coughing up sputum several times a day, 3 – a significant amount of sputum)

- Cough (0 – none, 1 – occasional, 2 – repeated during the day, 3 – paroxysmal, 4 – constant night and day)
- Shortness of breath (0 – none, 1 – slight shortness of breath on exertion, 2 – shortness of breath in normal conditions, 3 – on slight exertion, 4 – at night and rest).

The clinical trial was carried out in Hospital # 3 of the city of Tomsk and supervised by the head of the Department of Internal Diseases of Siberian State Medical University, Professor E. B. Bukreeva, Doctor of Medical Science.

A newly developed dietary supplement contains some plant-based components, which are widely used in traditional medicine and phytotherapy. The ingredients were selected for their biochemical properties and pharmacological activity [37, 39-46]. Beta-carotene acts as an antioxidant and protects the body from adverse exposure to free radicals, reactive oxygen species, and other xenobiotics. It also controls immune responses, processes of growth and development, as well as eyesight.

The grape seed extract is rich in bioflavonoids (proanthocyanidins) with their anti-oxidant properties being more active than those of ascorbic acid and tocopherol. Thanks to these properties, grape seed extract strengthens the blood vessel wall, protects the body from infectious diseases, activates peripheral blood circulation, and prevents aging changes in cells. Licorice root, which contains glycyrrhizin, has an anti-inflammatory effect and improves the function of the respiratory tract, and lung surfactant. Flavonoids also have antisecretory and antispasmodic effects on the gastrointestinal tract. The calming effect of licorice should also be noted.

Quercetin is a bioflavonoid with antioxidant, anti-allergic, and anti-inflammatory activity. It also demonstrates antimicrobial, antitumor, and antiviral properties, positively influences the cardiovascular system, and boosts the metabolic function of ascorbic acid.

Lemon balm contains oleanolic, ursolic, and caffeic acids, essential oils, tannins, vitamin C, resin, mucus, and beta-carotene. It is used as an analgesic, cardiac, and anticonvulsant medical product. It is also effective in treating anemia.

Pau d'Arco (ant tree bark) contains an active compound, lapachol, which fights fungi and bacteria and strengthens immunity. It is also used in small doses in the combination treatment for parasitic infections. It fights viruses and bacteria, relieves pain, and increases red blood cell count.

Anise (seed) is rich in essential oil and enhances the secretory and motor functions of the digestive tract. The anise seed oil also possesses expectorant and disinfecting properties.

Plantain leaf is known for its anti-inflammatory, expectorant, antimicrobial, and hemostatic properties thanks to the content of mineral salts, polysaccharides, phytoncides, mucus, steroid saponins, aucubin, choline, flavonoids, carotene, vitamins C and K, and tannins. Plantain leaf improves the function of the respiratory tract epithelium and bronchial glands. Moreover, it moderately reduces blood pressure.

Linden tree flowers contain several biologically active substances, such as phenol carboxylic acids, essential oil,

polysaccharides, tannins, vitamin C, and flavonoids, which have antirheumatic, sudorific, and bactericidal properties. Linden flowers are also used as an anti-inflammatory and antipyretic agent.

Bromelain is a proteolytic enzyme with high detoxification activity. It encourages the key processes of protein and carbohydrate metabolism, improves digestion, and demonstrates an anti-inflammatory effect.

Mullein flowers' active substances are mucus and some other biologically active compounds, such as essential oil, saponins, iridoids, and flavonoids. Their combination ensures antispasmodic, expectorant, and emollient properties, which help relieve the symptoms of bronchial system diseases.

Marshmallow root contains mucous substances (hexosans and pentosans), macronutrients (magnesium, calcium, potassium) and micronutrients (boron, manganese, iodine, iron, strontium,

copper, nickel, zinc, selenium, cobalt, aluminum, chromium) as well as pectin, starch, phytosterol, asparagine, sucrose and betaine. So, it serves as an anti-inflammatory, expectorant, and emollient remedy. It also protects the body from the adverse impact of xenobiotics.

Vitamin C, with its antioxidant and antibacterial properties, strengthens the immune system and improves the body's resistance to the exposure of internal and external environment. It boosts metabolism by regulating redox reactions and improves the metabolism of iron and folic acid.

Birch leaf oil includes glucose, sesquiterpene alcohol, phytocides, and vitamins E, PP, and C. Hence, it possesses anti-inflammatory, diuretic, detoxifying, and choleric properties and has a metabolic boosting effect.

The composition of the dietary supplement is presented in **Table 1**.

Table 1. Chemical composition of the dietary supplement

| Ingredients | Content, mg |
|---|--------------------------------------|
| | Content, mg (1 Tablet Weight—500 mg) |
| Marshmallow root | 37.5 |
| Mullein flowers | 25 |
| Vitamin C | 25 |
| Birch leaf | 12.5 |
| Pau d'Arco (bark extract) | 12.5 |
| Anise seed | 12.5 |
| Plantain leaf | 12.5 |
| Linden flowers | 12.5 |
| Bromelain | 12.5 |
| Licorice root | 6.25 |
| Quercitin | 6.25 |
| Lemon balm leaf | 6.25 |
| Grape seed | 0.25 |
| Vitamin A | 0.16 |
| Inactive ingredients | |
| Microcrystalline cellulose (carrier) | 220.29 |
| Potato starch | 58.05 |
| Hydroxypropyl methylcellulose (carrier) | 12.188 |
| Cafos (anti-caking agent) | 10 |
| Talc (anti-caking agent) | 10 |
| Titanium dioxide (coloring agent) | 4.9 |
| Polyethylene glycol (carrier) | 1.87 |
| Maltodextrin (carrier) | 1.0 |
| Chlorophyllin copper complex (coloring agent) | 0.042 |

Summarizing all the information, we can state that the biocomplex components have synergistic, tonic, mild antibacterial, anti-inflammatory, and expectorant properties, which contribute to thinning and clearing mucus. The dietary supplement can be suggested as a prophylactic and restorative

remedy for patients with respiratory viral infections, bronchitis, pneumonia, and bronchial asthma. The anti-inflammatory and antibacterial effects of the supplement are enhanced by a combination of herbs that help thin and clear mucus, protect and

heal mucous membranes of the upper airways, and relieve edema and allergies. The specialized product is enriched with antioxidants such as vitamin C, beta carotene, flavonoids, and anthocyanins.

Results and Discussion

Twenty patients (the experimental group) with COPD who took the developed dietary supplement demonstrated beneficial

changes. We observed positive dynamics on Days 3 and 4. All the participants of the experimental group reported the ease of sputum expectoration. On Day 14, a significant reduction of cough and sputum, milder shortness of breath, and easier breathing were registered. At the end of the trial, the clinical symptoms for the participants from the experimental and control groups did not differ much (**Table 2**), but their different dynamics were evident (**Figures 1-3**).

Table 2. Changes in clinical indicators (Standard deviation)

| Indicator | Characteristics (scores) | | Reliability (Mann-Whitney U test) |
|---------------------|--------------------------|---------------|-----------------------------------|
| | Experimental group | Control group | |
| Cough | 1.33±0.11 | 1.54±0.21 | 0.16 |
| Sputum | 1.26±0.14 | 1.33±0.17 | 0.25 |
| Shortness of breath | 1.88±0.12 | 1.94±0.09 | 0.32 |

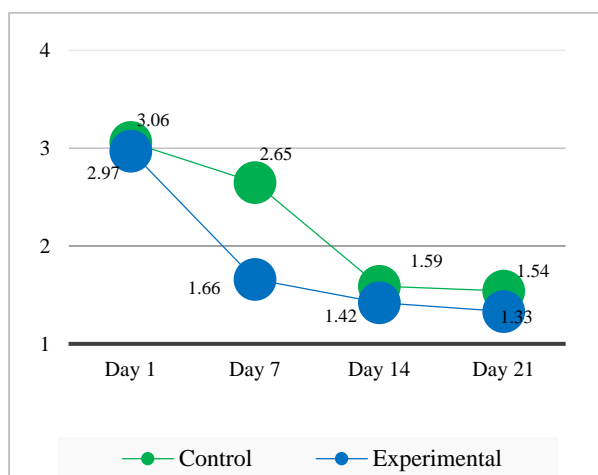


Figure 1. Changes in clinical indicator (Cough) in COPD patients

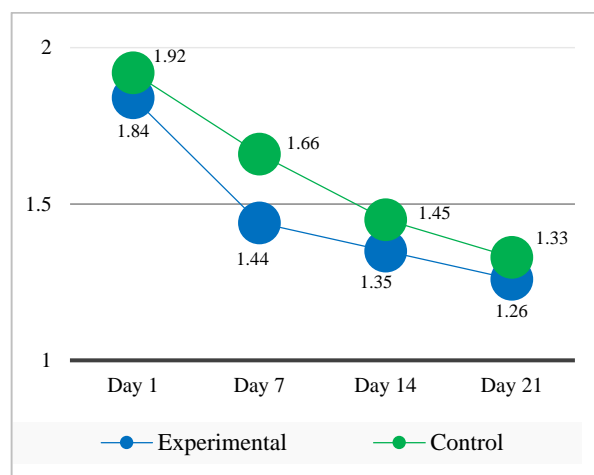


Figure 3. Changes in clinical indicators (Shortness of breath) in COPD patients.

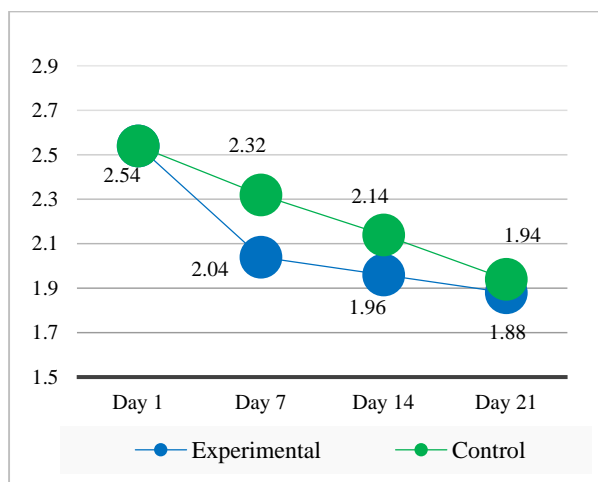


Figure 2. Changes in clinical indicator (Sputum) in COPD patients

The obtained data reveal that the combination therapy significantly reduces the duration of symptoms. The combined treatment with both medications and the dietary supplement reduces the number of patients with severe coughs during the first 4 days.

The participants without pronounced mucus hypersecretion and dyscrinia (predominant thick viscous mucus) reported a reduction of sputum and easier coughing up. Patients with excessive production of sputum showed positive changes in 50% of cases. These data indicate that patients should be taken the dietary supplement for a longer period and the product might be considered for use as a prophylactic.

More than half of the patients from the experimental group demonstrated milder shortness of breath, or significantly reduced shortness of breath, which means that the severity of broncho-obstructive syndrome decreased. The patients with advanced respiratory failure experienced symptom relief at a lower degree. There was a 75 % increase in forced expiratory flow. In addition, airway patency was improved.

The indicators of the external respiration function are presented in **Table 3**.

Table 3. Indicators of external respiration function (Standard deviation)

| Indicators | Experimental group | Control group |
|------------|--------------------|---------------|
| ECG (HR) | 72.5±2.5 | 74.1±1.9 |
| VC (%) | 64.9 ±2.37 | 63.5±3.01 |
| FEV1 (%) | 52.44±2.45 | 53.07±1.89 |
| FEF 25 (%) | 48.23±5.55 | 47.68±2.54 |
| FEF 50 (%) | 35.98±2.34 | 34.01 ±2.11 |
| FEF 75 (%) | 29.57±1.44 | * 22.39±3.36 |

* - reliability of differences $p < 0.05$.

Analyzing the cytological parameters of induced sputum, we established that the dietary supplement intake by patients with COPD produced a better anti-inflammatory effect. This is confirmed by the cytogram of the bronchial tree mucous membrane and by the lower cytosol level of induced sputum when compared with the control group patients.

On Day 21 of the treatment, sputum cytosol for the patients from the control group was registered at $2.1 \pm 0.4 \times 10^9/l$. The intake of the dietary supplement assisted in lowering the level to $1.6 \pm 0.3 \times 10^9/l$ ($p < 0.05$).

The supplement intake did not influence the composition of cellular elements. The spectrophotometric and microscopic research methods were applied to study elastase, with a Student's t-test used to obtain the statistical significance. The combination therapy resulted in a lower level of elastase both in the blood and sputum of patients with COPD (**Table 4**).

Elastase is a proteolytic enzyme, its higher level indicates the inflammatory process exacerbation. The normal level of the enzyme is 90 nmol/min/ml in blood, and 0.2nmol/min/ml in sputum. The combined therapy with the dietary supplement contributed to a verifiable decrease.

Table 4. Blood coagulation properties in patients with peripheral atherosclerosis during treatment (Standard deviation)

| Indicators | Experimental group | | Control group | | Changes | |
|----------------------------------|--------------------|-----------------|------------------|-----------------|------------------|-----------------|
| | Before treatment | After treatment | Before treatment | After treatment | Before treatment | After treatment |
| Elastase in blood (nmol/min/ml) | 122±52 | 101±11 | 124±23 | 115±13 | 0.25 | 0.037 |
| Elastase in sputum (nmol/min/ml) | 0.9±0.2 | 0.4±0.2 | 1.0±0.3 | 0.7±0.2 | 0.41 | 0.048 |

COPD progression is known to lead to impaired lung function, which is accompanied by a significant change in the respiratory mucosa. This condition worsens the quality of life.

The recommended dietary supplement intake ensures the supply of rutin – 16 mg (53 % of Recommended Dietary Allowance), quercetin – 11.2 mg (37 % of RDA), ascorbic acid – 45 mg (50 % of RDA), tannins – 24mg (12 % of RDA), which allows us to consider adding the dietary supplement to combined therapy for stages 1 and 2 COPD.

The developed product is manufactured at the facilities of the Research and Manufacturing Company “Art Life” located in the city of Tomsk. The manufacturing process and the ingredients were tested to guarantee the product quality and competitiveness in accordance with ISO 9001:2015, ISO 22000:2018, and GMP regulations.

Conclusion

The main line of COPD treatment combined with the dietary supplement significantly alleviated the severity of COPD symptoms, as the supplement improves the bronchial mucosa

condition and has a distinct anti-inflammatory and expectorant effect. The decrease in the elastase level indicates the expediency of using the supplement to prevent exacerbations of respiratory system diseases.

The developed product is recommended in the prophylactic treatment and combination therapy of COPD when taken 2 tablets daily for 21 days.

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