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# Effects of Pleuran (B–Glucan from *Pleurotus Ostreatus*) Supplementation on Incidence and Duration of COPD Exacerbations

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**Abstract**

**BACKGROUND:** 1,3/1,6-β–glucans are recognised as immunomodulators in human and veterinary medicine for over 50 years.

**AIM:** To assess the effects of pleuran (1,3/1,6-β–glucan from *Pleurotus ostreatus*) on incidence and duration of bacterial exacerbations in patients with COPD.

**METHODS:** We performed an observational, non-randomized, open-label study including 32 COPD patients (Group D) in whom besides the recommended chronic treatment for the stable disease were administered supplement combination containing pleuran 100 mg, vitamin C 60 mg and zinc 5 mg once daily over a three month-period (Group 1). Also, an equal number of Group D COPD patients who besides the recommended treatment for stable disease received the supplement combination containing vitamin C 60 mg and zinc 5 mg once daily, matched to the study subjects of the Group 1 by sex and age served as control (Group 2).

**RESULTS:** Over the study period 57 exacerbations (24 in the Group 1 and 33 in the Group 2) were documented. A mean number of exacerbations over the study period was significantly lower in the Group1 (0.7 ± 0.4) as compared to their mean number in the Group 2 (1.0 ± 0.6) (P = 0.0218). Furthermore, a mean duration of exacerbations expressed in days needed for cure or clinical improvement (i.e. complete resolution of symptoms or return of the symptoms to their baseline severity) in the Group 1 (6.7 ± 0.8 days) was significantly shorter than the mean duration of exacerbations in the Group 2 (7.4 ± 1.3 days) (P = 0.0118). There was not reported any adverse effect during the study period by study subjects from both examined groups.

**CONCLUSION:** Our findings indicated that pleuran might impact the incidence and duration of bacterial exacerbations in patients with COPD. There is a need for further studies for more precise determination of the influence of pleuran on the course of COPD.

## Introduction

Chronic obstructive pulmonary disease (COPD) represents one of the principal demands of the public health at global level due to high morbidity, early mortality, high date rates and significant costs to health systems. The projection of the Global Burden of Disease Study indicates that COPD in 2020 will be the third leading cause of death worldwide (from sixth in 1990) and fifth leading cause of years lost (disability-adjusted life years - DALYs) through early mortality or handicap (12th in 1990) [1]. In addition, exacerbations of COPD, defined as acute events characterized by worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations leading to a change in medications, have substantial impact in the course of the disease because they negatively affect a patient's quality of life, accelerate the rate of decline of lung function and are associated with significant mortality, particularly in those requiring hospitalization. The most common cause of COPD exacerbations is believed to be bacterial respiratory infections [2, 3].

β–glucans comprise a diverse group of polysaccharides in which glucose molecules are linked by β-linkages. β-1,3/1,6-glucans are branched

chains of glucose molecules connected by β-1,3-glycosidic bonds in which the branching points are β-1,6 linkages. Some β-1,3/1,6-glucans are bioactive interacting with receptors on immune cells eliciting specific biological responses. The ability of β-1,3/1,6-glucans to activate innate immune cells depends on its branched structure, i.e. the chain length and the frequency of side chains are essential for immunomodulating properties of these β–glucans. Also, results of several studies indicated that insoluble β–glucans (i.e. non-absorbable and non-digestible) possessed higher immunomodulating activity than soluble ones [4-6].

β–glucans can be extracted from the cell walls of yeast, oat, barley, seaweeds, algae and bacteria, but the foremost source of medical glycans turns out to be fungal cell walls [7]. Pleuran is an insoluble 1,3/1,6-β–glucan from mushroom Pleurotus ostreatus. Some experimental studies on an animal model, as well as some experimental and clinical studies in humans, indicated immunomodulatory properties of pleuran that are based on its effects on immune cells of the Peyer's patches in the gut. After oral administration, pleuran comes in contact with immune cells of the Peyer's patches which expressed several receptors (e.g. Dectin-1, complement receptor-3, scavenger receptors, etc.) capable of recognising β–glucans in their various forms. Upon pleuran's binding to these receptors, a cascade of intracellular signaling that stimulates innate and subsequently adaptive immune responses is initiated, mainly through release of pro-inflammatory cytokines (complement components, interleukin-1α/β, interleukin-6, interleukin-8, interleukin-12, tumor necrosis factor-, eicosanoids, etc.) which improves the resistance to invading pathogens [8-11].

The aim of the present study was to assess the effects of pleuran on incidence and duration of bacterial exacerbations in patients with COPD.

## Methods

### *Study design and setting*

An observational, non-randomized, open study (a real life-study) was realized as a comparison of frequency and duration of bacterial exacerbations between a group D COPD patients who received the supplement combination containing pleuran 100 mg, vitamin C 60 mg and zinc 5 mg over a three month-period besides the chronic pharmacological treatment for stable disease recommended by actual GOLD and a group D COPD patients treated over a three month-period with the recommended chronic treatment for stable disease and the supplement combination containing vitamin C 60 mg and zinc 5 mg. It was performed in a period December 2016-April 2017 at the Institute for Occupational Health of Republic of Macedonia, Skopje.

### *Study subjects*

The study population included 64 COPD patients, classified into group D according to the combined assessment of the disease, divided into two groups. The first group included 32 patients (18 males and 14 females, aged 48 to 71 years) who took the supplement combination containing pleuran 100 mg, vitamin C 60 mg and zinc 5 mg once daily in three months besides the recommended pharmacological treatment for the stable disease. The second group included an equal number of COPD patients (18 males and 14 females, aged 47 to 73 years) who received the supplement combination containing vitamin C 60 mg and zinc 5 mg once daily besides the recommended treatment for the stable disease, matched to the first group by sex, age and smoking status.

Patients with a history of asthma, lung cancer, or another significant respiratory disease, as well as those unable to complete diary cards, were excluded from the study. All study subjects were recruited in the stable phase of the disease, i.e. without any evidence of exacerbation for at least three weeks.

All study subjects were informed about the study, and their written consent was obtained.

Daily stable respiratory symptoms (baseline symptoms), medication use and history of exacerbations were noted in all subjects before entering the study. All study subjects underwent baseline and post-bronchodilator spirometry according to the actual recommendations of European Respiratory Society (ERS) and American Thoracic Society (ATS) [3, 12].

The Body Mass Index (BMI) as a measure of body fat based on height and weight that applies to adult population was determined in all study subjects by computed calculation using BMI calculator [13].

Classification of smoking status was done by the World Health Organization (WHO) recommendations [14]. Passive smoking or exposure to environmental tobacco smoke was defined as exposure to tobacco combustion products from smoking by others (at home, workplace, etc.), i.e. as a presence of at least one smoker in the household and the workplace [15, 16].

### *Diagnosis and assessment of COPD*

According to the actual Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations, COPD was considered by finding of a post-bronchodilator ratio between forced

expiratory volume in one second and forced vital capacity (FEV1/FVC ratio) less than 0.70 in symptomatic subjects (dyspnea, chronic cough or sputum production) with a history of exposure to risk factors for the diseases (noxious particles and gases).

Subjects with diagnosed COPD were classified according to the combined COPD assessment which included assessment of symptoms, the degree of airflow limitation and risk of exacerbations. COPD patients classified as a Group D were characterized by frequent symptoms (overall score of the COPD Assessment Test [CAT] equal or higher than 10), severe or very severe airflow limitation (FEV1 value ranging from 30 to 50% of its predicted value or less than 30% of its predicted value) and high risk of exacerbation (two or more exacerbations per year or one or more exacerbations requiring hospitalization per year) [2, 3].

### *Diagnosis and treatment of COPD exacerbation*

According to the actual GOLD recommendations, COPD exacerbations were considered as acute events characterised by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and led to a change in medication. The diagnosis of exacerbation was defined by the patient's symptoms, using the criteria described by Anthonisen et al. [17]. Probable bacterial aetiology was established when the exacerbation was Anthonisen type I (presence of three cardinal symptoms: increased dyspnea, sputum volume and purulence) or type II (presence of two cardinal symptoms) if increased purulence of sputum was one of the two symptoms.

The treatment of exacerbations with antibiotic was started empirically following the actual GOLD recommendations. In the cases with positive result of microbiological evaluation of sputum, the treatment was continued following the finding of the sensitivity of bacterias to a certain antibiotic. Oral corticosteroids were given as needed (a dose of 40 mg oral prednisone per day for five days). The course of exacerbation was evaluated as a function of the resolution of symptoms, and the treatment was considered to be successful if a cure or clinical improvement was achieved. The cure was defined as complete resolution of the cardinal symptoms, whereas the clinical improvement was defined as the return of the symptoms to their baseline severity [2, 3, 17].

### *Data collection (Daily diary card)*

All study subjects maintained daily diary cards on which they noted any appearance of an increase in the intensity of major symptoms (dyspnea, sputum amount and sputum purulence) or minor symptoms (nasal discharge/congestion, sore throat, wheezing, cough, etc.) over their chronic (stable) symptoms. A member of the study team saw study subjects within 48 hours of the detection of deterioration in symptoms and diagnosis was confirmed of each case. Exacerbation and its resolution were defined as it is mentioned above. Exacerbation number and their duration were calculated for each study subjects based on data from diary cards for a three month-period of follow-up.

### *Statistical analysis*

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 11.0 for Windows. Continuous variables were expressed as mean values with standard deviation (SD), and the nominal variables as numbers and percentages. Analyses of the data included testing the differences in prevalence and comparison of the means by chi-square test (or Fisher's exact test where appropriate) and independent-samples T-test. A P-value less than 0.05 were considered as statistically significant.

## Results

Demographic characteristics of the study subjects are shown in Table 1.

**Table 1: Demographics of the study subjects**

| Variable | Group1 (n = 32) | Group 2 (n = 32) |
|---|---|---|
| M/F ratio | 1.4 | 1.4 |
| Mean age (years) | 58.7 ± 6.4 | 59.4 ± 7.2 |
| Mean BMI (kg/m$^2$) | 25.9 ± 3.3 | 26.6 ± 2.8 |
| Mean duration of COPD (years) | 11.7 ± 4.2 | 10.9 ± 5.1 |
| Mean values | | |
| of spirometric parameters (% pred.) | 67.6 ± 7.1 | 68.7 ± 6.8 |
| FVC | 42.3 ± 4.4 | 43.4 ± 4.1 |
| $FEV_1$ | 0.63 ± 0.03 | 0.64 ± 0.02 |
| $FEV_1$/FVC ratio | | |
| Treatment of stable COPD | 25 (78.1%) | 26 (81.2%) |
| LA $\beta_2$-agonist + ICS | 22 (68.8%) | 23 (71.8%) |
| LA anticholinergic | 6 (18.7%) | 5 (15.6%) |
| Oral theophylline | | |
| Number of exacerbations in the previous year | 2.6 ± 0.3 | 2.7 ± 0.4 |
| Smoking status | | |
| Active smokers | 11 (34.3%) | 9 (28.1%) |
| Ex-smokers | 17 (53.1%) | 19 (59.4%) |
| Never smokers | 4 (12.5%) | 4 (12.5%) |
| Exposed to ETS | 15 (46.8%) | 18 (56.2%) |
| Comorbidities | | |
| Arterial hypertension | 9 (28.1%) | 8 (25.0%) |
| Osteo-muscular disorders | 5 (15.6%) | 7 (21.8%) |
| Ischaemic heart disease | 4 (12.5%) | 5 (15.6%) |
| Diabetes mellitus type 2 | 3 (9.4%) | 4 (12.5%) |

Numerical data are expressed as a mean value with standard deviation; frequencies as number and percentage of study subjects with a certain variable.

COPD: chronic obstructive pulmonary disease; M: male; F: female; BMI: body mass index; kg: kilogram; m: meter; % pred.: % of the predicted value; FVC: forced vital capacity; FEV1: forced expiratory volume in one second; LA: long-acting; ICS: inhaled corticosteroid; ETS: environmental tobacco smoke.

Over the study period, 57 exacerbations were documented (24 in the Group 1 and 33 in the Group 2) of which 12 required hospital treatment (five in the Group 1 [20.8%] and seven in the Group 2 [21.2%]). 43 of the 57 (75.4%) were treated only with oral antibiotics (19/24 [79.2%] in the Group1 and 24/33 [72.7%] in the Group 2) and 14 (24.6%) were treated with antibiotics and oral prednisolone (5/24 [20.8%] in the Group 1 and 9/33 [27.3%] in the Group 2).

A mean number of exacerbations over the study period was significantly lower in the Group1 (0.7 ± 0.4) as compared to their mean number in the Group 2 (1.0 ± 0.6) (P = 0.0218) (Figure 1).

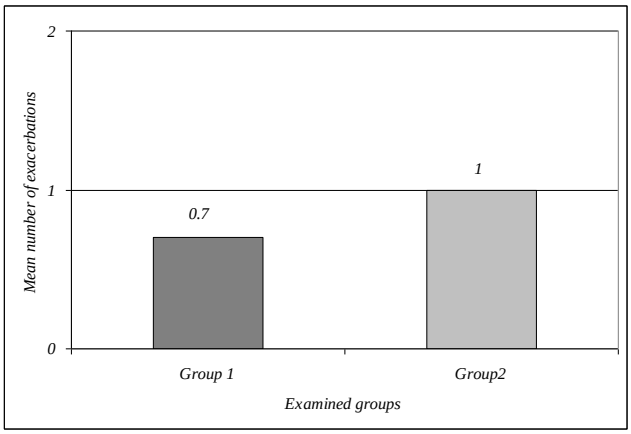


*Figure 1: Mean number of exacerbations in the examined groups*

A mean duration of exacerbations expressed in days needed for cure or clinical improvement (i.e. complete resolution of symptoms or return of the symptoms to their baseline severity) in the Group 1 (6.7 ± 0.8 days) was significantly shorter than the mean duration of exacerbations in the Group 2 (7.4 ± 1.3 days) (P = 0.0118) (Figure 2).

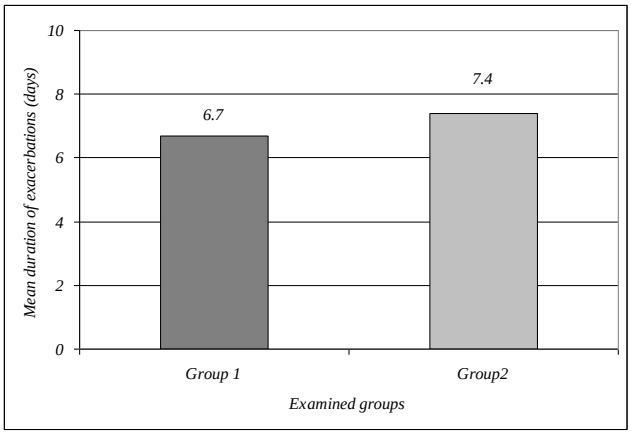


*Figure 2: Mean duration of the exacerbations in the examined groups*

Side effects of the used medicaments over the study period were not reported by any study subject from both examined groups.

## Discussion

Pharmacological treatment of stable COPD is used to reduce symptoms, reduce frequency and severity of exacerbations, and improve health status and exercise tolerance. Existing medications for stable COPD have not been conclusively shown to modify the long-term decline in lung function that is the hallmark of the disease [2, 3]. As it is mentioned above, COPD is one of the most important public health problems in the last decades worldwide, so there are many investigations into new and more effective therapeutic options.

In the present study, we assessed the effects of pleuran (1,3/1,6-β–glucan from *Pleurotus ostreatus*) on the incidence and duration of exacerbations in patients with COPD. To our knowledge, the present study was the first one that investigated effects of pleuran on prevention of exacerbations in COPD patients. Examined groups included COPD patients classified into Group D, i.e. the COPD patients characterised by frequent symptoms, severe or very severe airflow limitation and high risk of exacerbation. Study subjects from both examined groups had similar demographic characteristics. Although tobacco smoke is recognised as the most important risk factor of COPD, in both groups, we found a large proportion of active and passive smokers which did not differ significantly from their prevalence in the general population in R. Macedonia documented in our previous studies [18, 19]. These findings suggested insufficient anti-smoking activities of healthcare workers among COPD patients besides smoking cessation is recommended as the first therapeutic option in the non-pharmacological treatment of the disease [2, 3].

The immunomodulatory properties of fungal β -glucans were studied and described almost 50 years ago. Shortly afterwards, in experimental animals were described their effects against a tumour. Finally, there is evidence that β-glucans may modulate other conditions (cholesterol level, glucose tolerance, etc.). [20-22]. As it is mentioned above, many studies have reported the ability of pleuran to activate innate immunity with effects also on adaptive immunity, inducing humoral and cell-mediated immune responses. Pleuran was found to increase the antimicrobial activity of mononuclear cells and neutrophils and enhance the functional activity of macrophages.

Findings of our studies showed significantly

lower incidence, as well as the significantly shorter duration of exacerbations in COPD patients treated with pleuran besides regular treatment of stable disease as opposite to their incidence and duration in COPD patients treated only with the regular treatment of stable disease. Similar findings were reported by several studies which investigated effects of pleuran on incidence, duration and severity of respiratory infections in both children and adults. Results from the double-blinded, placebo-controlled, randomized, multicentric study carried out by Jesenak et al. including 175 children (mean age 5.65 ± 2.39 years) treated with pleuran over the 12 month-period indicated significant reduction of the frequency of recurrent respiratory tract infections in children treated with pleuran as compared to children who did not use it [23]. Similar findings were obtained from the study carried out by Pico Sirvent et al. including 166 children aged 1 to 10 years from 20 pediatric departments in Northeast Spain [24].

Results from the double-blind, placebo-controlled, randomized study carried out by Bergendiova et al. including 50 athletes treated with pleuran over the 3 month-period indicated significant reduction of the frequency of upper respiratory tract infections as compared to their frequency in athletes treated with placebo. Furthermore, the authors found significantly higher number of circulating natural killers cells in pleuran group as compared to their number in the placebo group [25]. In addition, in the study which investigated effects of pleuran on changes in the peripheral blood cells after acute, exhausting physical load in 22 elite athletes Bobovcak et al. found no statistically significant reduction in natural killers cell activity in the group treated with pleuran as opposite to the finding of significant reduction in natural killer cell activity after intensive exercise in the placebo group [26].

As it is mentioned above, pleuran as an insoluble substance is non-absorbable and non-digestible, so systemic adverse effects could not be expected. As in the case of the present study, local (i.e. gastrointestinal) adverse effects were not registered in all cited studies.

The present study must be interpreted within the context of its limitations. The results should be viewed with caution, since the study was neither blinded nor randomized and, therefore, can be a subject to possible selection bias. On the other hand, the study design may be its strength, as it is documented by other real life-studies. Also, the small number of the subjects in the examined groups could have certain implications on the data obtained and its interpretation. The short follow-up period could also have certain implications on the data obtained and its interpretation. Furthermore, in the study groups were included only Group D COPD patients that that could impact results of the study.

In conclusion, in an observational, non-randomized, open-label study including a Group D COPD patients who received the supplement combination containing pleuran 100 mg, vitamin C 60 mg and zinc 5 mg besides recommended chronic pharmacological treatment for stable disease over three months we found significantly lower incidence and significantly shorter duration of bacterial exacerbations as compared to their incidence and duration in a Group D COPD patients who took the supplement combination containing vitamin C 60 mg and zinc 5 mg besides the recommended treatment for stable disease in the same period. Our findings suggested that the use of pleuran may be beneficial in the prevention of exacerbations in the patients with COPD. Further investigations, as well as comparisons to the other therapeutic modalities, are needed for assessment of the preventive effects of pleuran regarding the COPD exacerbations.

### *Ethical Approval*

The Ethical Committee of the Institute of Occupational Health of R. Macedonia, Skopje – WHO Collaborating Center and GA2LEN Collaborating Center approved for performing the study and publishing the results obtained (03-48/23.01.2017).

### *Authors Participations*

JM participated in the study design, data collection, managing the analyses of the study, and writing all versions of the manuscript. JKB and TP participated in the study design and managing the analyses of the study. KV performed the statistical analysis and participated in the managing the analyses of the study. SS and DM participated in the data collection and the managing the analyses of the study. All authors read and approved the final manuscript.

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