
# Title: The Impact Of Diabetes Mellitus On The Course Of Interstitial Pneumonia In An Experimental Model And The Possibility Of Correcting The Detected Disorders


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ABSTRACT

**Background.** Given the growing recognition of the interplay between metabolic disorders and chronic lung diseases, this study aimed to assess, based on biochemical parameters of lung tissue, the effectiveness of vegetable oils in preventing interstitial lung lesions in rats with alloxan-induced diabetes and experimental interstitial pulmonary fibrosis.

**Methods.** Fifty male albino rats (150–200 g) were used. Interstitial pneumonia was induced by 2.5-month exposure to tobacco smoke in a Kurlandsky chamber, followed by alloxan administration (170 mg/kg, twice) to induce type 1 diabetes in 30 animals. The rats were divided into five groups: intact controls, COPD only, COPD with diabetes (control), COPD with diabetes + Herbion®, and COPD with diabetes + bitter almond oil (BAO). Treatments were administered orally once daily for 15 days. Clinical parameters were tracked throughout, and biochemical changes in serum and lung tissue were assessed at study completion using ELISA-based assays.

**Results.** Prolonged tobacco smoke exposure induced interstitial fibrosing alveolitis in rats, with marked weight loss and mortality in the COPD + diabetes group. Alloxan further aggravated hyperglycemia, reduced insulin levels, and elevated lung injury markers (SP-A, SP-D, KL-40, Neutrophil elastase). Herbion® treatment moderately improved clinical and biochemical parameters, reducing glucose and inflammatory proteins. Bitter almond oil demonstrated a stronger effect, lowering hyperglycemia by nearly 40%, enhancing insulin, and significantly reducing SP-A, SP-D, KL-40, and elastase levels.

**Conclusions.** Bitter almond oil exhibited comparatively greater therapeutic efficacy than Herbion®, suggesting its potential as a plant-derived adjunct in mitigating metabolic lung injury.



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| **Keywords:** | Chronic Obstructive Pulmonary Disease; Diabetes Mellitus; Plant Oils; Prunus amygdalus |

**Short title:** Diabetes-Associated Interstitial Pneumonia and Therapeutic Correction

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**Introduction.** The current strategy of the World Health Organization (WHO) is aimed at the primary, secondary, and tertiary prevention of chronic non-communicable diseases (NCDs), including chronic obstructive pulmonary disease (COPD) and diabetes mellitus (DM) [10]. According to the concept of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [17], COPD is a condition with significant extrapulmonary systemic manifestations such as DM, cachexia, obesity, dyslipidemia, skeletal muscle dysfunction, osteoporosis, osteopenia, arterial hypertension, ischemic heart disease, sleep apnea syndrome, cor pulmonale, pulmonary hypertension, kidney damage, lung cancer, anxiety disorders, and depression, which significantly aggravate the course of the disease. At the same time, there is a considerable global increase in the number of patients with DM [1, 2]. The combination of these socially significant diseases reflects the emergence of new pathologies characteristic of the current century. Components of DM, on the one hand, and impaired bronchial patency and reduced pulmonary function, on the other, may mutually potentiate each other [1, 2]. A key aspect in the pathogenesis of both COPD and DM is the concept of chronic persistent systemic inflammation, which leads to functional and structural changes in other organs and systems [10]. The increase in the incidence of metabolic syndrome among patients with COPD may be associated with a higher prevalence of obesity, decreased physical activity, smoking, corticosteroid use, as well as with important pathological mechanisms inherent in this condition—such as inflammation, oxidative stress, and hypoxia. The main factors contributing to COPD progression in the presence of these comorbidities are insulin resistance and dyslipidemia [22].

Idiopathic pulmonary fibrosis (IPF), characterized by fibrotic transformation of the pulmonary parenchyma—primarily in older individuals—progresses with the development of respiratory failure and is accompanied by the accumulation of inflammatory and immune effector cells. This often contributes to the formation of pathological extracellular matrix in the distal airways, alveolar walls, and interstitium [1, 3, 5]. The potential effects of pulmonary and extrapulmonary cellular functions in pulmonary fibrosis are associated with their ability to produce a wide range of biologically active substances possessing pro-inflammatory, fibrotic, immunosuppressive, and angiogenic properties.

In recent years, new therapeutic approaches for IPF have been actively explored, including modulation of pulmonary and extrapulmonary cellular functions, which is considered one of the most promising strategies. Experimental studies on the correction of pulmonary and extrapulmonary cell functions in small laboratory animals with induced pulmonary fibrosis have demonstrated the effectiveness and safety of plant-derived preparations. Nevertheless, many questions remain regarding the use of herbal preparations from locally sourced raw materials.

In this context, **the aim of the present study was**, based on the assessment of biochemical parameters of lung tissue in rats with interstitial pulmonary fibrosis combined with alloxan-induced diabetes, to evaluate the effectiveness of vegetable oils in preventing the development of interstitial lung lesions.

**Materials and Methods.** The experimental studies were conducted in the scientific laboratory of Tashkent Medical University. All animal experiments were performed in compliance with O‘zDSt 2762:2018 (Good Laboratory Practice, GLP) standards [4]. Animal procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of Tashkent Medical University. A total of 50 male albino outbred rats weighing 150–200 g were used. Interstitial pneumonia was induced by

chronic exposure to tobacco smoke in a special Kurlandsky chamber for 2.5 months [6]. The animals were housed under standard vivarium conditions with natural light and free access to food and water [6].

The Kurlandsky chamber, designed for modeling chronic tobacco smoke exposure, ensures controlled and reproducible inhalation exposure for laboratory animals, particularly rats. In this chamber, Pall Mall cigarettes (Uzbekistan) containing 0.7 mg nicotine were burned to ash. The burning process lasted 20–30 minutes, during which the concentration of tobacco smoke increased, followed by a 30–40-minute plateau phase with a slight gradual decrease. After each procedure, the chamber was ventilated. Smoking sessions were conducted once daily for 75 consecutive days. Inhalation of tobacco smoke caused airway irritation and lung inflammation in the rats. Clinical signs of pneumonia – such as altered respiratory rate, coughing, and possible nasal or airway discharge – were assessed after smoke exposure. During the experimental period, one rat died on day 21 of the study. The exposure system ensured controlled and reproducible inhalation conditions, engineering controls (closed chamber, dedicated exhaust and ventilation) and trained personnel were used to minimize exposure to staff.

After one month of smoke exposure, type 1 diabetes mellitus was induced in 30 rats by subcutaneous administration of alloxan solution at a dose of 170 mg/kg body weight, given twice. One month after the initiation of alloxan administration, the surviving animals were divided into groups to evaluate the efficacy of bitter almond oil (BAO). The reference drug was Herbion® (KRKA, Slovenia). The test substances were administered orally once daily for 15 days.

The rats were allocated into the following groups:

Group I – Intact rats, no experimental manipulations performed (n = 8);

Group II – COPD without treatment (2.5 months) (n = 10);

Group III – COPD + alloxan-induced diabetes without treatment (2.5 months), control group (n = 10);

Group IV – COPD + alloxan-induced diabetes + Herbion® (2.5 months), comparison group (n = 10);

Group V – COPD + alloxan-induced diabetes + bitter almond oil (2.5 months), main experimental group (n = 10).

Throughout the experiment, body weight, general condition, heart rate, and respiratory rate of the rats were monitored. At study termination, animals were euthanized by decapitation in accordance with the American Veterinary Medical Association (AVMA) Guidelines for the Euthanasia of Animals (2020 Edition). Death was confirmed by absence of respiration and corneal reflex prior to subsequent procedures. Blood was collected immediately for serum preparation and standard biochemical analyses (insulin concentration) performed on a HumaLuzer Primus 602828 biochemical analyzer (Germany) using manufacturer reagent kits. The levels of surfactant protein A, surfactant protein D, YKL-40 (chitinase-3-like protein 1, CHI3L1), and neutrophil elastase were determined by enzyme-linked immunosorbent assay (ELISA) from . The obtained data were processed using the STATISTICA software package, with statistical significance assessed by Student's paired t-test [9].

**Results and Discussion.** The conducted studies demonstrated that two months of exposure in the Kurlandsky chamber led to the development of interstitial fibrosing alveolitis, confirmed morphologically. The condition of the rats deteriorated sharply, with the onset of apathy, weight loss, and fur becoming dull and patchily lost. Body weight measurements in the experimental animals revealed a decreasing trend, whereas in the intact group it increased significantly—by 42.5%. In the COPD + alloxan-induced diabetes (AD) group, the administration of alloxan caused a further deterioration in the animals' condition, accompanied by polyphagia and polydipsia. Weight loss in this group amounted to 31.4% relative to the initial assessment, 55.7% compared with Group 1 values, and 33% compared with Group 2. Mortality in this group reached 30%.

Experimental pharmacotherapy with Herbion®

for 15 days contributed to a slight improvement in the condition of the rats. Weight loss amounted to 28.8% relative to the initial assessment, 51.1% compared with Group 1 values, and 25.9% compared with Group 2. No mortality was observed in this group. Experimental pharmacotherapy with bitter almond oil for 15 days also led to a slight improvement in the condition of the rats. Weight loss in this group was 21.9% relative to the initial assessment, 46.8% compared with Group 1 values, and 19.3% compared with Group 2. No mortality was observed in this group.

Analysis of serum glucose levels showed that in animals with COPD there was only a tendency toward an increase (Table 1). In the COPD + alloxan-induced diabetes group, serum glucose levels increased significantly by 92.6% compared with the initial assessment. This value was 80.2% higher than in the intact group and 81.2% higher than in the COPD group.

**Table 1**

**Dynamics of Changes in Serum Glucose Levels (mmol/L) in Experimental Animals, M ± m**

| Animal Group | Initial assessment, n=10 | Final assessment, n=7-10 | P1 | P2 | P3 |
|---|---|---|---|---|---|
| Intact | 5,43 ± 0,22 | 5,61 ± 0,20 | >0,05 | | |
| COPD | 5,03 ± 0,27 | 5,58 ± 0,27 | >0,05 | >0,05 | |
| COPD+ AD | 5,25 ± 0,25 | 10,11 ± 0,45 | 0,001 | 0,001 | |
| COPD+ AD+ Herbion | 5,27 ± 0,19 | 8,30 ± 0,47 | 0,002 | 0,01 | 0,01 |
| COPD+ AD+ BAO | 5,10 ± 0,18 | 6,11 ± 0,24 | 0,05 | 0,05 | 0,05 |

Note: $P_1$ – significance compared with baseline level; $P_2$ – significance compared with intact group values; $P_3$ – significance compared with control group values. COPD – Chronic obstructive pulmonary diseae; AD – alloxan-induced diabetes; BAO – bitter almond oil.

Experimental pharmacotherapy of COPD + AD in rats with Herbion® over a 15-day period resulted in a 23% reduction in serum glucose levels compared with the values in the control group. However, this parameter remained elevated by 57.4% relative to the initial assessments, by 47.9% compared with the values in the intact group, and by 48.7% compared with the values in the COPD group.

A similar but more pronounced dynamic was observed in the group of rats with COPD + AD treated with bitter almond oil. Experimental pharmacotherapy of COPD + AD with bitter almond oil for 15 days led to a 39.6% reduction in serum glucose levels compared with the values in the control group. Nevertheless, the parameter remained elevated by 19.8% relative to the initial assessments, by 8.9% compared with the values in the intact group, and by 9.5% compared with the values in the COPD group.

Thus, the combination of such pathologies as COPD and AD leads to a more severe course of diabetes, accompanied by marked hyperglycemia. Experimental pharmacotherapy of COPD + AD in rats with either Herbion® or bitter almond oil reduced the severity of hyperglycemia. Bitter almond oil was more effective compared with Herbion®, decreasing blood glucose levels by 26.4% relative to the values in the Herbion®-treated group.

To confirm the hypoglycemic properties of the studied agents, we determined the serum insulin content in the experimental animals. The conducted studies showed that in intact animals, the serum insulin level was 118.5 ± 1.2

μU/mL. Induction of COPD in experimental animals led to a statistically insignificant increase in serum insulin to 124.7 ± 3.3 μU/mL, which, in our view, is associated with the adaptive reorganization of the animals' physiological systems. Administration of alloxan against the background of toxicant exposure caused a sharp decrease in serum insulin levels in rats. The values dropped by 37.4% compared with those of intact animals and by 40.5% compared with the COPD group, amounting to 74.2 ± 3.3 μU/mL. The mechanism of alloxan's toxic action on pancreatic β-cells is linked to increased generation of reactive oxygen species under conditions of low activity of antioxidant defense enzymes. This results in the destruction of cellular biomembranes, degradation, and suppression of their functional integrity. This coincides with a loss of glucose homeostasis control, impairment of the insulin-sensitive GLUT-4 transporter function, and the development of hyperglycemia.

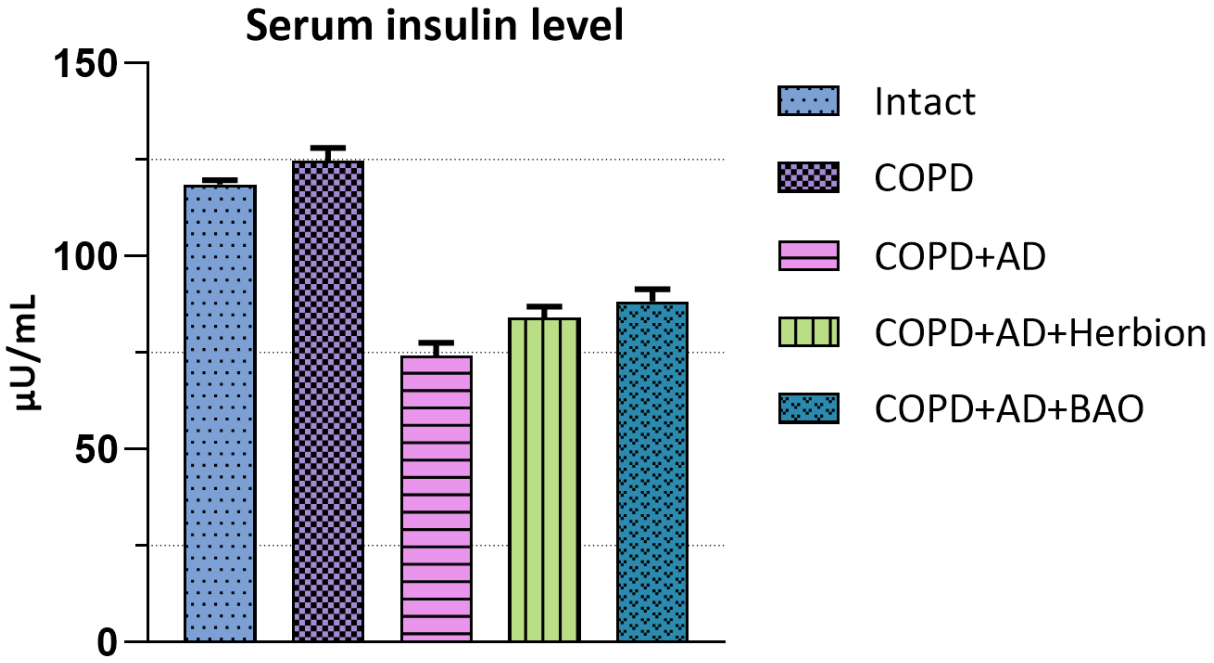


Figure – 1. Serum insulin content (μU/mL) in experimental animals. COPD – Chronic obstructive pulmonary disease; AD – alloxan-induced diabetes; BAO – bitter almond oil.

Experimental pharmacotherapy of COPD + AD with Herbion® for 15 days resulted in a moderate increase in serum insulin levels in this group of animals (see Fig. 1). We observed a 13.3% increase in insulin content compared with the COPD + AD group. However, these values remained 32.6% lower than in the COPD group and 29% lower than in the intact group.

Experimental treatment of COPD + AD with bitter almond oil also promoted an increase in serum insulin levels in rats, amounting to 19% relative to the COPD + AD group. However, as in the previous group, these values remained 29.2% lower than in the COPD group and 25.5% lower than in the intact group. It should be noted that the insulin-stimulating effect of bitter almond oil exceeded that observed in the COPD + AD group treated with Herbion® by 13.3%, which is likely attributable to the higher content of polyunsaturated fatty acids and other biologically active compounds in the bitter almond extract.

In recent years, several potential diagnostic and prognostic peripheral blood biomarkers characteristic of idiopathic pulmonary fibrosis (IPF) have been identified [8]. These include serum levels of matrix metalloproteinases, chemokine CCL-18, surfactant protein A, chitinase-like protein YKL-40, cell-free circulating DNA, periostin, osteopontin, and others [26, 31]. For example, Krebs von den Lungen-6 (KL-6) factor and alveomucin are produced by alveolar epithelial cells and type II pneumocytes. Elevated serum

levels of these proteins indicate damage to alveolar epithelial cells [1].

The primary objective of our study was to assess the condition of lung tissue under the combined influence of tobacco smoke intoxication and diabetes. For this purpose, we examined key biochemical parameters of the lungs: neutrophil elastase activity, serum levels of autoantibodies against surfactant proteins SP-A and SP-D, as well as lung protein KL-40. Our findings showed that the neutrophil elastase activity in the serum of intact rats was 4.2 ± 0.4 ng/mL (see Fig. 2). Prolonged exposure to tobacco smoke resulted in an 81% increase in neutrophil elastase activity compared with intact rats, reaching 7.6 ± 0.8 ng/mL ($P < 0.05$). This indicates activation of inflammatory processes in lung tissue and degradation of elastic fibers. Administration of alloxan against the background of COPD further exacerbated lung tissue damage. In this case, neutrophil elastase activity increased by 133.3% compared with intact rats and by 28.9% relative to the COPD group, amounting to 9.8 ± 1.1 ng/mL ($P < 0.05$). Based on these data, it can be concluded that hyperglycemia, in the context of a weakened immune system and chronic low-grade inflammation, contributes to further deterioration of both the respiratory and non-respiratory functions of the lungs. Moreover, the presence of persistent inflammation lowers insulin levels, creating a vicious cycle.

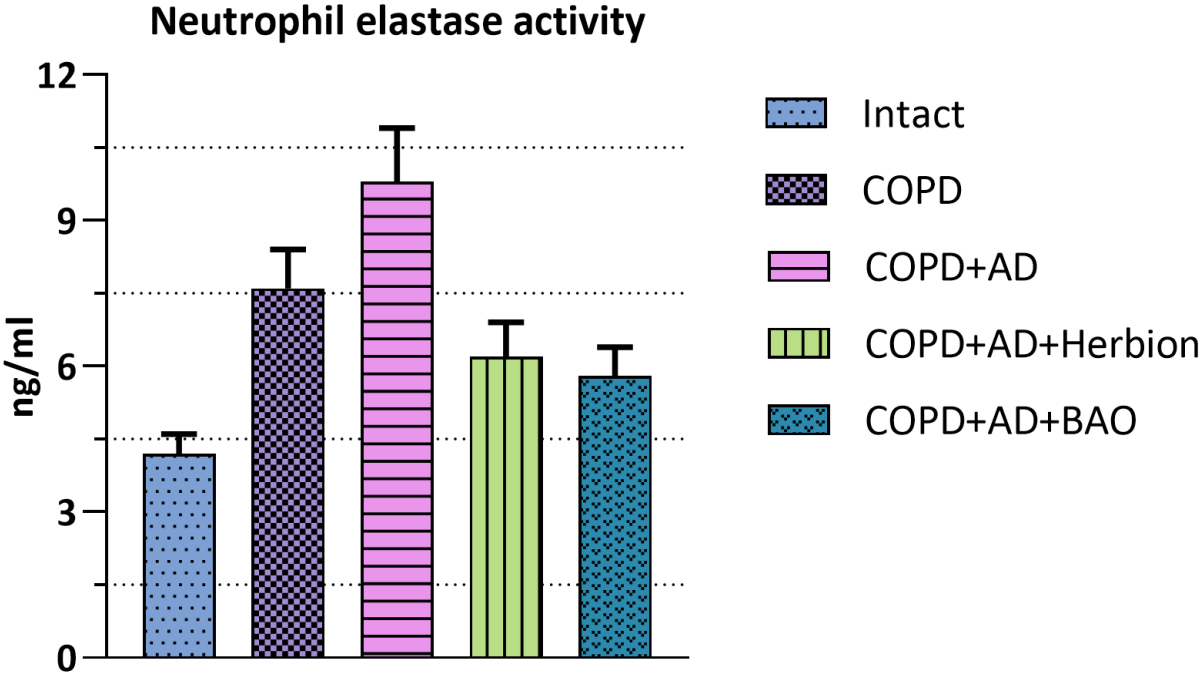


Figure – 2. Neutrophil elastase level (ng/ml) in the serum of experimental animals. COPD – Chronic obstructive pulmonary disease; AD – alloxan-induced diabetes; BAO – bitter almond oil.

Under such conditions, it is impossible to fully restore the lost functions. However, a healthy lifestyle incorporating natural antioxidants and bioflavonoids can, to some extent, improve pulmonary function. Indeed, administration of Herbion to rats with COPD+BA for 15 days contributed to a reduction in elevated neutrophil elastase activity (Fig. 2). Specifically, the neutrophil elastase concentration in the blood serum of experimental animals was 6.2 ± 1.2 ng/mL ($P < 0.05$), which is 36.7% lower than in the untreated group. This value was statistically significantly lower than that of the COPD group by 18.4%, yet still statistically significantly exceeded the values observed in intact rats by 47.6%.

Experimental pharmacotherapy of rats with COPD+AD using bitter almond oil for 15 days resulted in a 40.8% reduction in neutrophil elastase activity in the blood serum compared with untreated animals, with a final value of 5.8 ± 1.1 ng/mL ($P < 0.05$). This value was also 23.7% lower than that of the COPD group. However, it still exceeded the values observed in intact rats by 30.1%. It should be noted that

the effectiveness of bitter almond oil exceeded that of Herbion by 7%.

Surfactant proteins play an important role in alveolar function. There are two types of surfactant proteins: SP-A and SP-D, with the latter being present at approximately ten times the concentration of the former. Determination of serum SP-A and SP-D levels in rats subjected to prolonged inhalation exposure to toxicants revealed a statistically significant increase of 1.58-fold and 1.25-fold, respectively, compared with intact rats (Table 2). In the COPD+AD group, this increase was even more pronounced: serum levels of SP-A and SP-D were 1.67-fold and 1.33-fold higher, respectively, compared with intact rats, and slightly exceeded those in the COPD group.

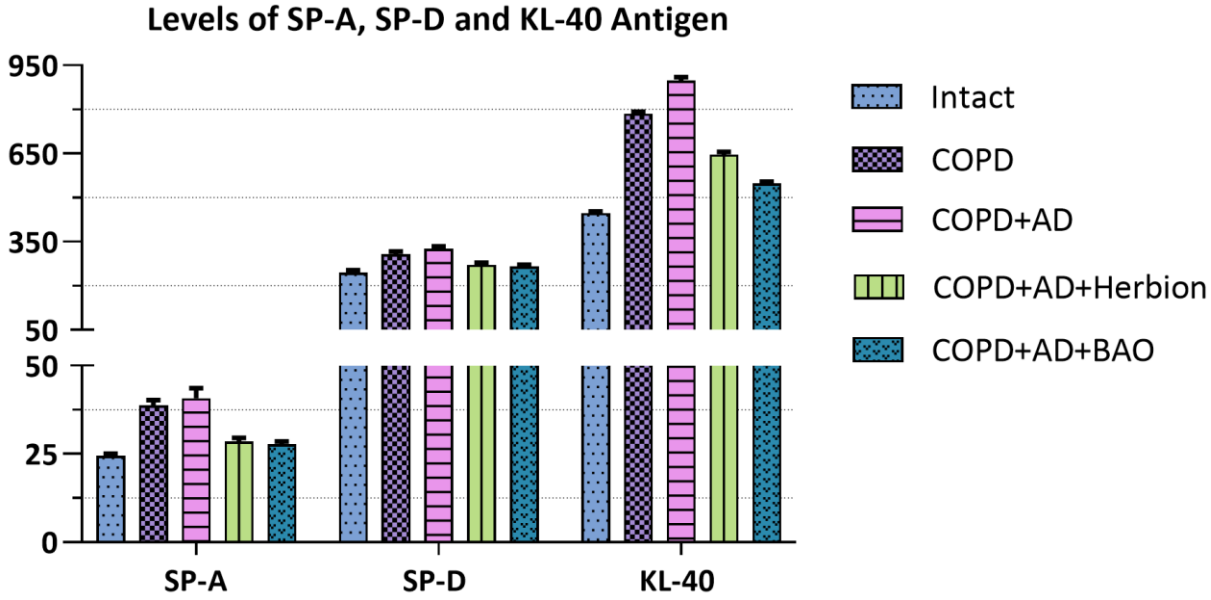


Figure – 3. Levels of Surfactant Proteins SP-A and SP-D and KL-40 Antigen in the Blood of Rats with Pneumonia under the Influence of the Investigated Drugs. COPD – Chronic obstructive pulmonary disease; AD – alloxan-induced diabetes; BAO – bitter almond oil.

Experimental pharmacotherapy of rats with COPD + AD using Herbion® for 15 days resulted in a decrease in serum levels of surfactant proteins SP-A and SP-D by 1.43-fold and 1.20-fold, respectively, compared with untreated COPD + AD animals. Relative to the COPD group, these decreases amounted to 1.38-fold and 1.13-fold, respectively. It should be noted that these values did not reach normal physiological levels, remaining 1.16-fold and 1.11-fold higher, respectively, than those of the intact group.

Experimental pharmacotherapy of COPD + AD rats with bitter almond oil for 15 days led to reductions in SP-A and SP-D levels by 1.47-fold and 1.23-fold, respectively, compared with untreated COPD + AD animals. Relative to the untreated COPD group, these decreases were 1.40-fold and 1.16-fold, respectively. A tendency towards normalization of these parameters, approaching the values of the intact group, was observed. It should be emphasized that no substantial differences were found between the effects of Herbion® and bitter almond oil.

Determination of serum KL-40 antigen levels in rats with COPD revealed a significant 1.79-fold increase compared with the intact group (Table 2). Administration of alloxan against the background of COPD further elevated KL-40 antigen levels, showing a 2.02-fold increase relative to intact rats and a 1.15-fold increase compared with the COPD group, indicating that alloxan administration in COPD rats further aggravated lung injury. Experimental pharmacotherapy of COPD + AD for 15 days with Herbion® reduced the elevated serum KL-40 antigen levels by 1.39-fold compared with the untreated COPD + AD group, and by 1.21-fold relative to the COPD group. Nevertheless, these values still remained significantly higher than those of the intact group, exceeding them by 1.44-fold.

The use of bitter almond oil as a therapeutic

agent in COPD + AD produced a more pronounced effect. Specifically, it significantly reduced the elevated serum KL-40 antigen levels in COPD + AD rats by 1.64-fold compared with the untreated group, and by 1.43-fold relative to the COPD group. It should be noted that bitter almond oil demonstrated a stronger effect than Herbion®, as the difference between the two treatment groups was 1.18-fold. Nevertheless, the studied parameter still exceeded the values observed in intact rats by 1.23-fold.

Analysis of the obtained data indicates that Herbion® contains extracts of primrose root and thyme herb in a ratio of 1 : 3.3 [14]. The preparation is used as an expectorant in the complex therapy of inflammatory diseases of the respiratory tract accompanied by cough. Herbion® exhibits expectorant, anti-inflammatory, and antimicrobial properties, reduces mucus viscosity, and promotes its clearance from the respiratory tract.

In contrast, bitter almond oil is classified as a dietary supplement and is recommended as a natural source of bioactive compounds that help normalize gastrointestinal function. It contains a high proportion of fats, organic acids, tannins, and vitamins. Bitter almond oil is rich in omega-9 and omega-6 fatty acids, palmitic acid, B-group vitamins, as well as vitamins E and K, magnesium, calcium, zinc, and copper. It also contains phytosterols, tocosterols, and amygdalin. The oil exhibits anti-inflammatory, wound-healing, emollient, mild laxative, and anticonvulsant properties. It may be recommended for patients with gastric and duodenal ulcers, gastritis, nephritis, and chronic inflammatory diseases of the upper respiratory tract.

Thus, alloxan administration in the presence of pre-existing lung injury leads to further damage to pulmonary tissue, manifested by leakage of specific proteins into the bloodstream and activation of elastin fiber degradation in the alveoli. Compared with Herbion®, a widely used drug in pulmonology, bitter almond oil exerts a more pronounced therapeutic effect by reducing the levels of lung tissue proteins in the serum of experimental animals. It demonstrates the most notable beneficial impact, effectively normalizing markers of inflammation and lung tissue injury, which supports its potential use in pulmonology.

**Conclusions.** The experimental rat model of COPD combined with diabetes mellitus (COPD+DM) successfully reproduces the pathogenesis of inflammatory lung injury associated with metabolic disorders.

It was established that the combination of COPD and diabetes leads to a significant increase in biochemical markers of lung tissue injury—SP-A, SP-D, and KL-40—as well as inflammatory markers such as neutrophil elastase.

The administration of herbal preparations (Herbion® and bitter almond oil) exerted a statistically significant normalizing effect on biochemical parameters, reducing inflammation and glycemia, and improving lipid profile indicators.

Bitter almond oil demonstrated a more pronounced therapeutic effect compared with Herbion®, including normalization of glucose levels, reduction in the concentrations of inflammatory markers (SP-A, SP-D, KL-40, elastase), and enhancement of insulin production.

The biochemical findings support the potential of bitter almond oil as an accessible, effective, and safe plant-based agent for correcting pulmonary injury in the setting of metabolic diseases.

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