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Effect of beta-glucan in lung damage secondary to experimental obstructive jaundice

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Background/aims: *This study aimed at investigating the protective effects of beta-glucans on the lungs in obstructive jaundice.* ***Methods:*** *In total, five groups -Sham (1), control (2) and treatment groups (3,4,5)- were established; each comprising randomly selected seven Wistar Albino rats. Beta-glucan was given after choleduct ligation in Group 3 while it was given before and after the choleduct ligation in Group 4. As pre-treatment beta-glucan was given before ligation in Group 5. Beta-glucan was administered in a single dose of 50 mg/kg/day by gavage for a ten-day period. Superoxide dismutase, and myeloperoxidase levels in serum; malondialdehyde, lipid hydroxyperoxidase and glutathione levels in lung tissue; lactate dehydrogenase levels in bronchoalveolar lavage fluid were measured.* ***Results:*** *The blood polymorphonuclear leukocytes level was highest in the control group and lower in the sham and treatment groups. Serum superoxide dismutase and tissue glutathione values were significantly higher in Groups 3 and 4 ($p \leq 0.04$) whilst Groups 3 and 4 did not differ from each other. In Groups 3 and 4 malondialdehyde, lipid hydroxyperoxidase, and myeloperoxidase values were significantly lower. However, Groups 3 and 4 did not differ for malondialdehyde or lipid hydroxyperoxidase values. Lactate dehydrogenase level in the bronchoalveolar lavage fluid was significantly lower in all of the treatment groups (Groups 3,4,5) ($p \leq 0.008$). When compared to the control group, it was observed that lung damage was much more limited in the treatment groups ($p < 0.001$).* ***Conclusion:*** *This study suggests that beta-glucan exhibits protective effect in pulmonary tissue against oxidative damage in obstructive jaundice.*

Key words: Obstructive jaundice, beta-glucan, lung damage, oxidative damage, antioxidants

Deneysel tıkanma sarılığında beta-glukanın akut akciğer hasarına etkisi

Amaç: *Bu çalışmada, beta-glukanın deneysel tıkanma sarılığı modelinde akciğer üzerine koruyucu etkisinin araştırılması amaçlandı.* ***Yöntem:*** *Her biri rastgele seçilmiş yedi Wistar Albino rattan oluşan, Sham (1), kontrol (2) ve tedavi grupları (3,4,5) olmak üzere toplam beş grup oluşturuldu. Beta-glukan Grup 3'e koledok ligasyonundan sonra, Grup 4'e ligasyondan önce ve sonra verildi. Grup 5'e ise ön tedavi olarak ligasyondan önce verildi. Beta-glukan uygulaması, 50 mg/kg/gün şeklinde tek doz halinde gavaj yoluyla on gün boyunca gerçekleştirildi. Serumda süperoksit dismutaz, myeloperoksidaz; akciğer dokusunda malondialdehit, lipid hidroperoksidaz, glutatyon; bronkoalveoler lavaj sıvısında laktat dehidrogenaz ölçümleri ile histopatolojik değerlendirilme yapıldı.* ***Bulgular:*** *Kan PNL düzeyi, kontrol grubunda en yüksek iken sham ve tedavi gruplarında düşük idi. Kontrol grubu ile karşılaştırıldığında serum süperoksit dismutaz ve doku glutatyon düzeyleri Grup 3 ve 4'te belirgin yüksek iken ($p \leq 0.04$) Grup 3 ile 4 arasında farklılık gözlenmedi. Grup 3 ve 4'te malondialdehit, lipid hidroperoksidaz, myeloperoksidaz değerleri belirgin düşük idi. Bununla birlikte Grup 3 ile 4 arasında malondialdehit ve lipid hidroperoksidaz değerleri farklı değildi. Bronkoalveoler lavaj sıvısındaki LDL değerleri tüm tedavi gruplarında (Grup 3,4,5) anlamlı derecede düşük idi ($p \leq 0.008$). Kontrol grubu ile karşılaştırıldığında akciğer hasarının tedavi gruplarında oldukça sınırlı olduğu tespit edildi ($p < 0.001$).* ***Sonuç:*** *Bu çalışma, tıkanma sarılığında beta-glukanın akciğer dokusunda oksidatif hasara karşı koruyucu etkiye sahip olduğunu göstermektedir.*

Anahtar kelimeler: Tıkanma sarılığı, beta-glukan, akciğer hasarı, oksidatif hasar, antioksidanlar

INTRODUCTION

Obstructive jaundice (OJ) is associated with the development of bacterial translocation and endotoxemia. Furthermore, inhibition of the hepatic phagocytic and anti-endotoxic functions is obser-

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ved (1-4). The resulting bacterial translocation and endotoxemia aggravate the inflammatory response. Thereby, the increased level of free oxygen radicals (FOR) may cause oxidative damage and multiple organ dysfunction, including dysfunction of the lungs (5-8). The accumulation of stimulated inflammatory cells in the small airways and interstitial region of the lungs results in damage to the alveolar epithelium and microcirculation, as well as in alveolar and interstitial edema. The continuation of this process results in acute respiratory distress syndrome (ARDS) (9,10).

Beta-glucans are known as potent immunostimulants. They have the capability of affecting both natural and adaptive immunity (11). When soluble beta-glucans are ingested through the oral route, they are absorbed from the gastrointestinal tract and pass into the systemic circulation, and are bonded competitively to the receptors on monocytes and neutrophil leukocytes. Owing to their potent stimulatory effect on macrophages, they increase the cytotoxicity and phagocytic capacity of macrophages (12). Literature reports indicate that beta-glucans exhibit antioxidant, antiviral, antibacterial, and antifungal activities, and have an ameliorative effect on wounds (13-19).

The present study was aimed at investigating the protective effect of beta-glucans on the lungs using an experimental OJ model.

MATERIALS AND METHODS

The Experimental Animals Ethics Board of Abant Izzet Baysal University approved this experimental study. Thirty-five adult Wistar Albino male rats, weighing 300-350 g, constituted the material of the study. All rats were housed and fed as stipulated in the relevant legislation.

In total, five groups were established, each comprising seven rats selected randomly. The groups were subjected to the applications described below:

Group 1 (Sham group, n=7): The choledochus was explored and the abdomen was closed without ligation of the choledochus. Physiological saline (PS) was administered by postoperative gavage for a period of 10 days.

Group 2 (Control group, n=7): The choledochus was explored and ligated. Following ligation, PS was administered by gavage for 10 days.

Group 3 (Choledochus ligation + Beta-glucan group, n=7): The choledochus was explored and ligated. Following ligation, beta-glucan was administered by gavage for 10 days.

Group 4 (Beta-glucan + Choledochus ligation + Beta-glucan group n=7): Beta-glucan was administered for 10 days as pre-treatment. On the 11th day, laparotomy was performed for the exploration of the choledochus. Following the ligation of the choledochus, beta-glucan was administered by gavage for another 10 days.

Group 5 (Beta-glucan + Choledochus ligation, n=7): Beta-glucan was administered for 10 days as pre-treatment. On the 11th day, laparotomy was performed for the exploration of the choledochus. Following the ligation of the choledochus, PS was administered by gavage for another 10 days.

The beta-glucan suspension was prepared by dissolving *Saccharomyces cerevisiae*-derived beta-glucan microparticles (Immuneks 50 mg cap., Mustafa Nevzat, Istanbul) in PS. The suspension was administered in a single dose of 50 mg/kg/day by gavage.

In the present study, Groups 3, 4 and 5 were defined as the treatment groups. Groups 4 and 5 were established so as to compare the efficacy of the increased immunopotency by the use of beta-glucan prior to ligation and the efficacy following the continued use post-ligation.

The experimental OJ model was established by means of the ligation of the choledochus twice at a distance of a few millimeters using 4/0 silk.

Surgical Technique

The experimental animals were put under general anesthesia by the combined intramuscular administration of 50 mg/kg ketamine HCl (Ketalar 50 mg/ml, Eczacibasi, Istanbul) and 10 mg/kg xylazine HCl (Rompun 20 mg/ml, Bayer, Istanbul).

All experimental animals were subjected to laparotomy along the midline (approximately 3 cm) incision under aseptic conditions for the exploration of the choledochus. In Group 1, the abdomen was closed without ligating the choledochus. In the other groups, the choledochus was ligated twice at a distance of a few millimeters with 4/0 silk. In all groups, relaparotomy and sternotomy were performed under general anesthesia on the 11th day post-ligation for the exploration of the abdomen and thorax. The rats were sacrificed by inducing cardiac arrest through bloodletting from the inferior vena cava. After sacrifice, the lungs were extracted.

The upper lobe of the right lung was placed in 10% formaldehyde solution for histopathological evaluation. The lower and mid-lobes of the right lung were maintained at

-80°C for the measurement of oxidative damage and antioxidative potential in their homogenates. The left lung and trachea were subjected to bronchoalveolar lavage (BAL). The BAL fluid was stored at -80oC until used for assessment.

Biochemical Analysis

Blood samples collected into EDTA-coated tubes were used for hemogram, and polymorphonuclear leukocyte (PNL) counts were determined. Blood samples collected into biochemical tubes were centrifuged at 3500 g for 15 minutes (min). The serum samples extracted were stored at -80°C until used. Serum superoxide dismutase (SOD) measurements were performed using a SOD assay kit (Catalogue no: 706002, Cayman Chemical Company, Ann Arbor, MI, USA), and serum myeloperoxidase (MPO) measurements were performed using a MPO enzyme immunoassay test kit (Catalogue no: BC-1129, BioCheck Inc, Foster City, CA, USA), both spectrophotometrically.

Measurements in Tissue Homogenates

The lower and mid-lobes of the right lung, which were maintained at -80°C after extraction, were homogenized and subjected to spectrophotometric measurements for malondialdehyde (MDA), lipid hydroperoxide (LPO) and glutathione (GSH) levels.

Malondialdehyde (MDA) measurements were performed using a Bioxytech MDA-586 kit (Catalogue no: 21044, Oxis Research, Burlingame, CA, USA), and LPO measurements were performed using a LPO assay kit (Catalogue no: 705003, Cayman Chemical Company, Ann Arbor, MI, USA). Furthermore, GSH measurements were made with a GSH assay kit (Catalogue no: 703002, Cayman Chemical Company, Ann Arbor, MI, USA). In SOD, GSH, MDA, LPO, and MPO measurements, a Thermo Scientific Wellwash 4 MK 2 (Thermo Scientific, MA, USA) was used for the washing of microplates, and a Biorad Benchmark Plus (Bio-Rad Laboratories Inc, CA, USA) was used for reading the microplates.

Examination of the BAL Fluid

The trachea and left lung were washed with injection of 5 cc of PS containing EDTA, applying minimal pressure so as to prevent tissue damage, and the fluid withdrawn was collected into a sterile container. This fluid was centrifuged at +4°C and 280 g for 10 min. A smear was prepared with a drop taken from the bottom layer of the fluid obtained by centrifugation, and the smear was stained with Giemsa dye. The remaining fluid was used for lactate dehydrogenase (LDH) measurement by an auto-analyzer.

Histopathological Evaluation

Sections prepared from the upper lobe of the right lung were stained with hematoxylin and eosin (H&E). Increase in connective tissue was evaluated by staining with Masson's trichrome under a light microscope. PNL infiltration, edema, hemorrhage, and degeneration of pulmonary structures were determined in pulmonary tissue, and histological scoring was performed (2). Normal pulmonary histology was scored as 0; slight leukocyte infiltration and capillary congestion as 1; mild leukocyte infiltration, perivascular edema, partial damage of pulmonary structures, and hemorrhage as 2; and intense and diffuse leukocyte infiltration, diffuse destruction of pulmonary structures and hemorrhage as 3.

Statistical Analysis

The data obtained was recorded using the SPSS 15.0 statistical software package. Statistical comparisons were made using the Mann-Whitney U test. $P<0.05$ was considered as statistically significant. Values were given as means and standard deviations (SD).

RESULTS

Histopathological Findings in the Pulmonary Tissue

Congestion of the pulmonary capillaries, hemorrhage, degenerated bronchiolar epithelium, and perivascular leukocyte infiltration were observed in the control group (Group 2). In some of the control subjects, hemorrhage was more diffuse, the bronchi and bronchioles contained many erythrocytes, and the epithelium of some of the bronchi and bronchioles had been lost (Figures 1, 2).

The treatment groups (Groups 3-5) did not exhibit severe hemorrhage or neutrophil infiltration, but displayed capillary congestion (Figures 3, 4). When compared to the control group, it was observed that damage was much more limited in the treatment groups ($p=0.001$, $p<0.001$ and $p<0.001$, respectively). The severity of damage did not differ between the treatment groups (Table 1).

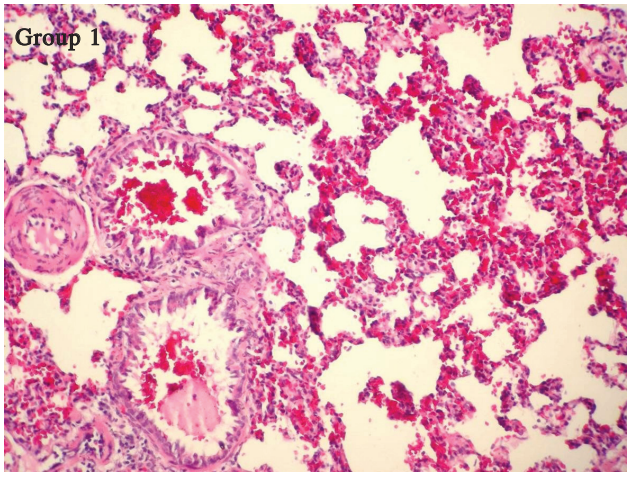

Figure 1. Erythrocytes and fluid accumulation observed in some bronchioles in Group 2, H&Ex10.

Results of the Biochemical Measurements:

Antioxidative parameters

Mean serum SOD values were significantly higher in Groups 3 and 4 (p=0.003 and 0.002, respectively) in comparison to the control group, while no statistically significant difference was determined in Group 5 (p=0.063). Similarly, tissue GSH values were significantly higher in Groups 3 and 4 (p=0.04 and p=0.002, respectively) when compared to the controls, while Group 5 did not differ significantly (p=0.655) (Table 2).

The comparison of the treatment groups demonstrated that serum SOD values were significantly higher in Groups 3 and 4 when compared to Group 5 (p=0.011 and 0.004, respectively), while Gro-

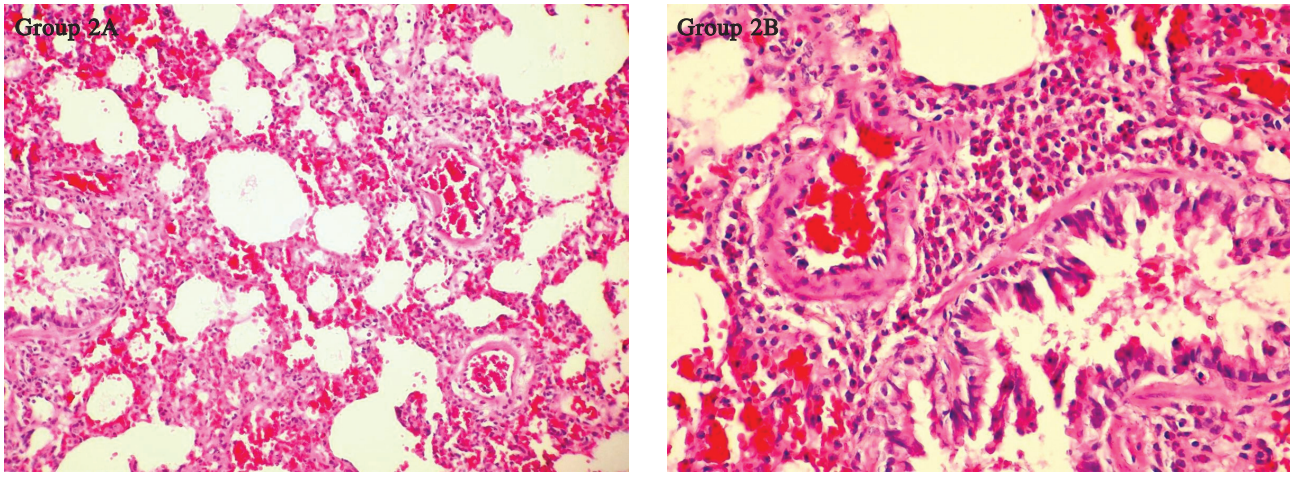

Figure 2. Conspicuous capillary congestion and hemorrhage in pulmonary tissue in Group 2 (A), H&E x20. Neutrophil infiltration at peribronchiolar, periarterial regions (B), H&E x40.

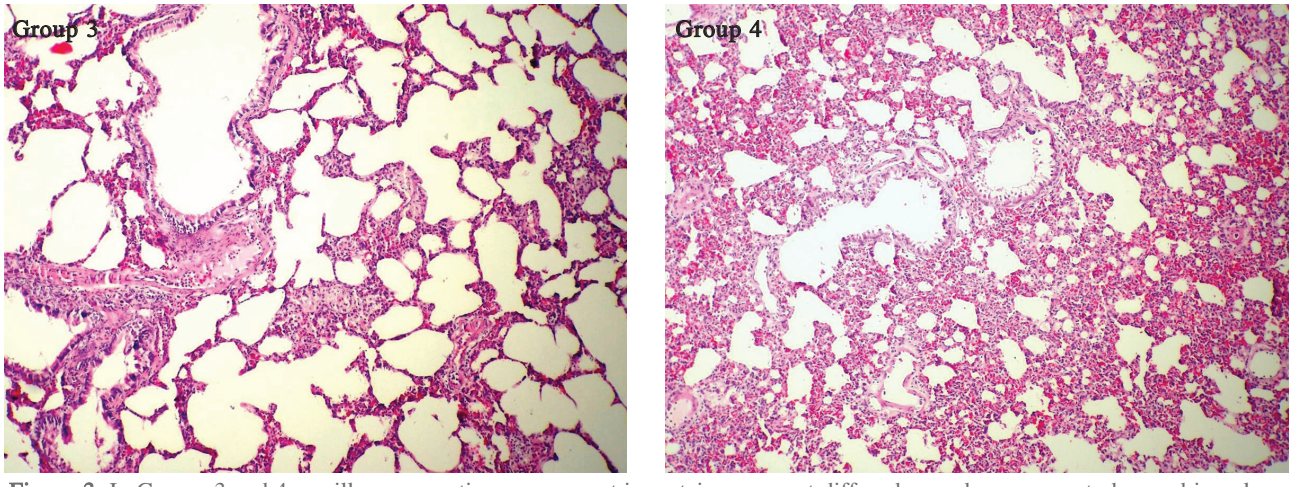

Figure 3. In Groups 3 and 4, capillary congestion was present in certain areas, yet diffuse hemorrhage was not observed in pulmonary tissue, H&E x10.

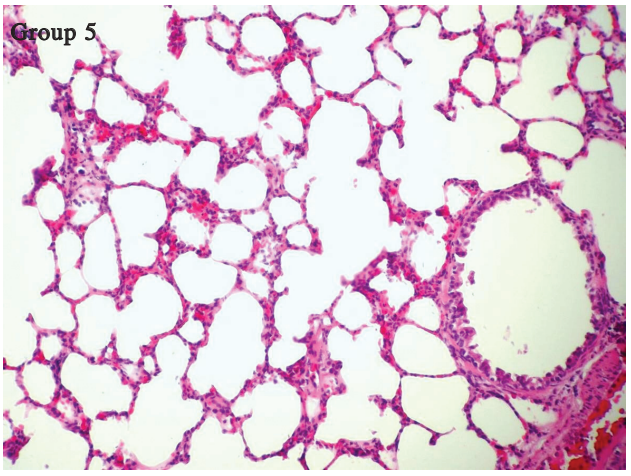

Figure 4. The pulmonary tissue of Group 5 was similar to that of Groups 3 and 4, H&E x10.

ups 3 and 4 did not differ from each other significantly (p=0.11). Tissue GSH values were significantly higher in Groups 3 and 4 compared to Group 5 (p=0.035 and p=0.018, respectively), but Groups 3 and 4 did not differ from each other significantly (p=0.406).

Oxidative damage parameters

When Groups 3 and 4 were compared to the control group, MDA values (p=0.025 and p=0.006, respectively), LPO values (p=0.004 and p=0.003, respectively) and MPO values (p=0.003 and p=0.002, respectively) were significantly lower. However, it was determined that the control group and Group 5 did not differ significantly from each other for MDA, LPO and MPO values (p=0.225, p=0.338 and p=0.073, respectively) (Table 3).

The comparison of the treatment groups demonstrated that, compared to Group 5, MDA values (p=0.003, p=0.002) and LPO values (p=0.004, p=0.006) in Groups 3 and 4, respectively, were significantly lower. However, Groups 3 and 4 did not differ significantly for MDA or LPO values (p=0.064 and 0.338, respectively). The distribution curve of serum MPO values was similar to those of MDA and LPO values. Nonetheless, MPO values were significantly lower in Group 4 compared to Groups 3 and 5 (p=0.002 and 0.002, respectively), while Groups 3 and 5 did not differ from each other significantly (p=0.141).

Examination of the BAL fluid

Compared to the control group, LDH level in the BAL fluid was significantly lower in all of the treatment groups (Groups 3, 4, 5) (p=0.008, p=0.002 and p=0.003, respectively). The treatment groups did not differ from each other significantly. Interestingly, it was determined that the mean BAL LDH value of Group 4 did not differ greatly from the value of the sham group (p=0.08) (Table 4). The microscopic examination of the sediment of the BAL fluid demonstrated no major difference.

The blood PNL level was highest in the control group and lower in the sham and treatment groups. However, the treatment groups did not differ

Table 1. Histopathological scores of pulmonary tissue in the groups (mean±SD).

	Skor
Group 1	0.000±0.00
Group 2	2.43±0.53
Group 3	1.14±0.69
Group 4	0.57±0.53
Group 5	1.00±0.57

(SD: Standart deviation).

Table 2. Distribution of serum SOD and pulmonary tissue homogenate glutathione values, as antioxidative parameters, for the groups (meant±SD).

	SOD (U/ml)	Glutatyon (µM)
Group 1	0,132±0,2	40,496±3,94
Group 2	0,031±0,02	21,025±3,57
Group 3	0,079±0,01	29,923±4,88
Group 4	0,099±0,02	32,597±5,58
Group 5	0,050±0,02	23,020±5,41

SOD: Superoxide dismutase

Table 3. Distribution of MDA, LPO levels in pulmonary tissue homogenates and serum MPO levels, as oxidative damage parameters among groups (mean±SD).

	MDA (µM)	LPO (nM)	MPO (ng/ml)
Group 1	1,475±0,83	1,531±0,09	3,253±2,29
Group 2	7,731±2,21	4,012±1,13	17,611±3,56
Group 3	4,297±0,80	2,324±0,25	12,682±0,98
Group 4	3,538±0,81	2,204±0,44	9,860±1,79
Group 5	6,887±1,58	3,424±0,85	14,384±2,28

MDA: Malondialdehyde. LPO: Lipid hydroperoxidase.
MPO: Myeloperoxidase.

Table 4. LDH levels measured in the BAL fluid and the number of PNL in the blood (mean±SD.)

	LDH (IU/ml)	PNL (K/uL)
Group 1	8,285±0,48	6,394±1,48
Group 2	11,143±0,69	19,757±7,38
Group 3	9,714±0,75	31,285±11,49
Group 4	9,004±0,81	11,718±2,89
Group 5	9,285±0,75	17,527±4,34

LDH: Lactate dehydrogenase. PNL: Polymorphonuclear leukocytes.

significantly from each other. Interestingly, the highest PNL level was determined in Group 3. The PNL level of Group 4 was slightly higher than that of the sham group (p=0.561), but in Group 3 and Group 5 it was markedly higher (p≤0.027).

DISCUSSION

Obstructive jaundice (OJ) is known to induce several systemic effects. The prolonged healing of wounds, inhibition of RES, sepsis, and renal, cardiovascular and pulmonary failure can be listed among such effects. Endotoxemia and bacterial translocation are the major causes of the complicated pathophysiological changes observed in the case of OJ (1,2,5).

Uncontrollable inflammatory response and increased FOR may lead to multiple organ dysfunction, including the lungs, and in the ongoing process to death (1,4). Activated inflammatory cells, which accumulate in the small airways and interstitial area, increase the generation of reactive oxygen radicals, while decreasing the factors that eliminate these radicals from the environment. This process results in acute pulmonary damage and ARDS (9,10).

It has been reported that neutrophil adhesion constitutes a significant mechanism in the development of chronic pulmonary inflammation, and that this is related to the disturbance of the GSH redox equilibrium. Furthermore, the correlation of decreased GSH levels with apoptosis possibly linked to the pathogenesis of inflammatory pulmonary diseases has been demonstrated (9).

In the thesis study of Dinelek (20) titled "The efficacy of beta-glucan in preventing bacterial translocation in an experimental OJ model", it was determined that beta-glucan reduced bacterial translocation. This effect is significant in that it reduces the risk of the development of endotoxemia and the generation of FOR.

Superoxide dismutase (SOD) is a cellular antioxidant of critical importance, which is structurally a metalloenzyme and transforms the superoxide radical, generated in cases such as oxidative stress, into molecular oxygen and hydrogen peroxide. It is known that in OJ, SOD levels are reduced (21,22). Bayrak et al. (23) demonstrated that beta-glucan increased SOD levels and protected the kidneys from damage caused by reperfusion under conditions of renal ischemia-reperfusion. In the present study, it was observed that beta-glucan treatment increased SOD levels significantly in comparison to the control group.

Glutathione (GSH) is a major intracellular compound protective against destructive stimuli, including oxidative stress. It has been indicated in several literature reports that GSH levels are reduced in cases of OJ (6,24-27). In an experimental study, Şener et al. (28) detected that beta-glucan treatment reduced the damage caused by nicotine to the kidneys and urinary bladder, and significantly increased tissue GSH levels. In another trial conducted by the same researchers, the administration of beta-glucan increased tissue GSH levels and reduced damage in cases of liver toxicity caused by acetaminophen (29). In another study conducted by Şener et al. (30), it was reported that, in rats, beta-glucan reduced methotrexate-induced oxidative damage in internal organs and increased GSH levels significantly. Similarly, in the present study, it was ascertained that beta-glucan increased GSH levels in the pulmonary tissue significantly against pulmonary damage caused by OJ.

Lipid peroxidation is one of the major causes of the damage and destruction of the cell membrane (31). MDA is an end product of lipid peroxidation and its increased level is an indicator of oxidative damage. MDA level increases in OJ (6,24-27,32). In a study conducted by Şener et al. (14), in pulmonary damage resulting secondary to abdominal sepsis, beta-glucan reduced both MDA level and damage in the pulmonary tissue. In an experimental burn model studied by Toklu et al. (33), damage to the lungs and other distant organs was investigated, and it was determined that beta-glucan reduced tissue MDA level. Furthermore, Bayrak et al. (23) reported that beta-glucan reduced both organ damage caused by renal ischemia-reperfusion as well as tissue MDA level. Based on these findings, it is suggested that beta-glucan decreases lipid peroxidation. Accordingly, in the present study, it was also detected that beta-glucan decreased lipid peroxidation in the lungs, caused by OJ, and exhibited a protective effect against pulmonary damage.

Lipid peroxidase (LPO) is among the intermediate products of lipid peroxidation, and like MDA, it is an indicator of oxidative damage. In the present study, the low tissue level of LPO, similar to the MDA level, can be considered as an indicator of beta-glucan treatment preventing pulmonary damage.

It has been reported that, in OJ, neutrophil infiltration is observed in the liver and distant internal organs, and thereby, that MPO activity is increased (5,32,34). In an experimental study conducted by Şener et al. (35) in rats, in which pressure-induced ulcer was generated, it was determined that beta-glucan reduced the MPO level and organ damage. In the abdominal sepsis model studied by Babayigit et al. (36), beta-glucan reduced the MPO level and decreased damage to the internal organs, including the lungs. The present study also demonstrated that serum MPO level decreased significantly because of beta-glucan treatment. This also shows that in OJ, beta-glucan exhibits a protective effect against neutrophil infiltration.

To the authors' knowledge, there is no literature report available on examination of BAL fluid for the detection of pulmonary damage in cases of OJ. This study demonstrated that LDH levels reduced with beta-glucan treatment. It was also observed that the use of beta-glucan during the inflammatory process increased the number of PNL in the circulation, whilst the administration of beta-glucan prior to the development of OJ prevented the number of PNL in the blood circulation from increasing.

In the present study, it was determined that the administration of beta-glucan as pre-treatment neither increased antioxidant efficiency nor proved to be effective in preventing oxidative damage. It was also ascertained that the administration of beta-glucan as combined pre-treatment and treatment (Group 4), or for treatment purposes post-ligation, did not cause any significant change in antioxidative efficiency or oxidative damage. However, exceptionally, combined pre-treatment and treatment with beta-glucan further reduced BAL LDH and serum MPO level.

In conclusion, the findings obtained in the present study suggest that beta-glucan acts as a potent antioxidative agent in OJ and exhibits a protective effect in pulmonary tissue against oxidative damage. Owing to its immunostimulant effect, beta-glucan still has clinical use. It is considered that further clinical studies are required to prescribe beta-glucan as part of a standard treatment protocol with the aim to prevent pulmonary damage in cases of OJ.

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