

# Effects of Auraptene on Myocardial Injury Secondary to Acute Lung Injury: An Experimental Study

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## ABSTRACT

**Objective:** Acute lung injury (ALI) is caused by an imbalance between pro-inflammatory and anti-inflammatory cytokines as well as oxidants and antioxidants. These imbalances and the resulting hypoxemia can affect various cells, especially the myocardium. Auraptene is known for its antioxidant and anti-inflammatory effects. The aim of this study was to determine whether auraptene can be used to treat both ALI and myocardial injury secondary to ALI.

**Methods:** The study was conducted with 24 ALI and 16 sham rats. Zero hour: Blood sampling, followed by the 150µl saline (sham) or LPS (ALI) intratracheally. 24. Hour: Blood and organs sampling, followed by euthanize of the animals. The collected material was used for serum TNF-α, troponin T (TnT), pro-brain natriuretic peptide (BNP) and histologic examinations.

**Results:** TNF-α levels were significantly lower in the LPS+auraptene group than in the LPS group (p=0.007). Increased pulmonary lymphocyte, neutrophil, hemorrhage and, fibroblast and histiocyte scores in LPS-induced ALI were significantly reduced by the use of auraptene (p<0.001, p=0.003, p=0.006 and, p=0.001, respectively). The BNP and TnT values in the LPS auraptene group were significantly lower compared to the LPS group (p=0.046 and, p=0.045, respectively). Histologically, cardiac degeneration, disorganization, congestion and inflammation scores were significantly lower in the LPS+Auraptene group than in the LPS group (p=0.005, p=0.006, p=0.002 and, p=0.036, respectively).

**Conclusions:** This study showed that ALI can lead to myocardial injury. Our results also suggest that auraptene, which suppresses inflammation, can be used to treat both ALI and myocardial injury secondary to ALI.

**Keywords:** Auraptene, acute lung injury, myocardial injury, TNF-α, BNP, troponin T

## INTRODUCTION

Acute respiratory distress syndrome (ARDS) is one of the most important causes of respiratory failure. It has been proven by studies that 2.7-5.8 percent of patients in pediatric intensive care units have ARDS. Despite the availability of facilities, the mortality rate for patients with ARDS varies between 5.7% and 13% [1,2]. Due to these characteristics, studies on pathophysiology and treatment of ARDS continue to increase.

Acute lung injury (ALI) refers to experimental models in preclinical research that mimic some aspects of ARDS. ALI models correspond to mild ARDS according to the current Berlin definition [3]. In the first phase of ALI, the alveolar epithelium and vascular endothelial cells are damaged due to factors such as cytokine storms and oxidative stress. This leads to increased permeability, resulting in interstitial and intra-alveolar edema that disrupts gas exchange, which in turn leads to hypoxemia [4]. All these changes can also affect various organs other than the lungs. One of the most important target organs in sepsis is the heart. Cytokines alter the complement immune response, apoptosis and energy metabolism; the disruption of microcirculation and endothelial dysfunction caused by these changes impair myocardial oxygen utilisation [5,6]. These changes at the cellular level lead to ventricular dysfunction, which causes increased morbidity and mortality in ALI [7]. This type of dysfunction can exacerbate pulmonary oedema and impair gas exchange, making both cardiac and pulmonary treatment more difficult [8]. Currently, lung-protective ventilation, optimisation of fluid status, selective use of vasoactive agents and advanced support measures such as ECMO are considered in the treatment of ARDS when conventional measures fail [3].

Auraptene is a coumarin derivative that contains a geranyl group instead of phenolic hydrogen. In addition to its other properties, there has been evidence of Auraptene's anti-inflammatory, immunomodulatory, and antioxidant effects [9-11]. We

hypothesized that auraptene could mitigate both pulmonary and cardiac injury via its antioxidant and anti-inflammatory properties.

## MATERIAL AND METHODS

The protocol of this study was approved by the local ethics committee for animal experiments (Ethics Committee for Animal Research at Bolu Abant İzzet Baysal University. Date: May 11, 2022, Protocol: (2022/15)). Adult male Wistar rats (200 - 250 g, 6 - 8 weeks old) were used in this study. The rats were obtained from our University Experimental Animal Application and Research Center. The Universal Declaration of Animal Rights was followed in the planning of the rats' care and all surgical procedures. Standard laboratory conditions, including 50-70% relative humidity, 19±2°C room temperature, 12-hour light/dark cycle, were used to maintain rats, which received a standard diet and water ad libitum. The study was in accordance with the ARRIVE guidelines.

A total of 40 rats were randomly divided evenly into 5 groups (n=8).

**a. Control group (sham+vehicle) (n=8):** In this group, 150 µl of phosphate-buffered saline (PBS) was administered intratracheally, and 0.2 ml of vehicle solution (1% DMSO in PBS) was administered intraperitoneally (IP) 60 min later. The intratracheal tract was opened in accordance with the literature [12,13]. Anesthesia of 90mg/kg ketamine with 10 mg/kg xylazine were used to make an incision in the midline of the neck, which was visualized by dissection and inserted into the trachea, resulting in the opening of the intratracheal tract. After instillation of the intratracheal, the incised area was closed with a 3/0 suture.

**b. Model group (lipopolysaccharide (LPS)+vehicle) (n=8):** In this group, rats were administered 150 µl of LPS (5 mg/kg) through the intratracheal, and 60 min later, 0.2 ml of the vehicle solution (1% DMSO in PBS) was administered through the IP. Santa Cruz Biotechnology (Dallas, TX, USA) provided the LPS (E. coli O55:B5) for this experiment.

**c. LPS Auraptene group (LPS+auraptene) (n=8):** Rats in this group were administered 150 µl of LPS (5 mg/kg) through the intratracheal, and 60 minutes later, 0.2 ml of auraptene (10 mg/kg) was administered through the IP [14]. The positive effects of auraptene at a dose of 10 mg/kg are shown in the study by Arabi et al [14]. The auraptene used in this study was obtained from Cayman (Michigan, USA).

### Main Points

- The acute lung injury also led to damage to the myocardium. Caution is required in this condition, which can increase mortality.
- Aureptene could be a therapeutic target to alleviate both the acute lung injury and the secondary damage to the myocardium.

**d. Dex group (LPS+dexamethasone) (n=8):** In this group, 150  $\mu$ l of LPS (5 mg/kg) was administered through the intratracheal, and 60 minutes later, 0.2 ml of dexamethasone (5 mg/kg) was administered through the IP [15]. The positive effects of dexamethasone at a dose of 5 mg/kg are shown in the study by Lee et al [15]. This group was used as positive control because dexamethasone has a therapeutic effect on LPS-induced ALI.

**e. Auraptene alone (sham+auraptene) (n=8):** In this group, 150  $\mu$ l of PBS was administered through the intratracheal, and 0.2 ml of auraptene (10 mg/kg dose) was administered 60 minutes later through the IP. The basal levels of relevant parameters were assessed using this group for the evaluation of auraptene's effect.

LPS and the treatments used in the groups were applied only once. All rats were anesthetized and euthanized intramuscularly with a 90mg/kg ketamine and 10 mg/kg xylazine combination 24 hours after IP administration. For biochemical analysis, 5 ml of blood was taken from the right ventricle of the rats and centrifuged at 3000  $\times$ g for 10 minutes at 4 °C. The blood was kept in Eppendorf tubes until the study was performed. After euthanizing the rats, the lungs and hearts were removed, and they were then soaked in 10% neutral buffered formalin and placed in paraffin blocks for histopathological examination. In the laboratory, under sterile conditions, all surgical procedures were carried out.

### Biochemical Assessments

Inflammatory and anti-inflammatory status were determined by analyzing the serum concentrations of TNF- and IL-10 [15,16]. Serum concentrations of total antioxidant status (TAS) were analyzed for antioxidant status [17]. Serum troponin T (TnT) and pro-brain natriuretic peptide (BNP) concentrations were analyzed for myocardial injury [18]. The rat ELISA test kits for TNF- $\alpha$  (Catalog no: NE06S139603), IL-10 (Catalog no: NE060114403), BNP (Catalog no: NE06S821103) and troponin T (Catalog no: NE06S836203) used in this study were obtained from Nepenthe Research Technologies (Nepenthe, Kocaeli, Turkey), and the rat ELISA kit for TAS (Catalog no: E1710Ra) was obtained from Bioassay Technology Laboratory (BT Lab, Shanghai, China). The measurements were performed in accordance with the instructions provided for using the kits that had been purchased.

### Histologic Evaluations

After being collected from the rats, the lung and heart tissues

were fixed with 10% formalin. To make the widest surfaces visible, the lung tissue was cut and traced, and then placed in paraffin blocks. Three-micron-thick sections were taken from the prepared paraffin blocks and stained with hematoxylin-eosin. Histological changes were detected using the imaging system (INFINITY 3 ANALYSE, Release 6.5) and light microscopy (Leica DM 2000 LED).

Lung and heart tissues were examined blindly by a pathologist congestion, hemorrhages, lipid-laden macrophage accumulations in the alveoli, bronchoalveolar proliferation (fibroblasts and histiocytes in the alveolar wall), lymphocytes surrounding the bronchi and vessels, abscess formation, and polymorphonuclear leukocyte infiltration in the alveolar spaces/bronchial lumen were all identified by pathological examination of the lung tissue. These findings were scored semiquantitatively on a scale of 0 to 4 [19].

When examining the cardiac tissue, areas of cytoplasmic vacuolization, degeneration, disorganization, inflammation, congestion, and hemorrhage in the vascular structures were scored semiquantitatively between 0 and 3 (0: no pathology, 1: mild (focal) pathology, 2: moderate (multifocal) pathology, and 3: severe (diffuse) pathology) [20].

### Statistical Analysis

The statistical analysis was conducted using SPSS 22.0. The mean  $\pm$  standard deviation is used to express the data. The homogeneity of variance was examined by Levene's test while the groups' conformance to a normal distribution was examined using the Shapiro-Wilk test. Since the data of the biochemical parameters (BNP, IL-10, TAS, TNF- $\alpha$  and TnT) exhibited homogeneous and normal distribution, they were analyzed with One-way ANOVA and post hoc Tukey tests. Lung and heart histological scores were analyzed with Kruskal–Wallis H test. Significant differences were defined as  $p < 0.05$ .

## RESULTS

### Biochemical Examinations

In our study, TNF- $\alpha$  levels were significantly different between the groups ( $p < 0.001$ ). There was a significant difference between the LPS and control groups in terms of TNF- $\alpha$  levels (87.9 $\pm$ 24.6 vs. 30.2 $\pm$ 4.2 pg/mL,  $p < 0.001$ ). The TNF- $\alpha$  levels in the LPS+dexamethasone group were significantly lower than those in the LPS group (40.5 $\pm$ 13.8 vs. 87.9 $\pm$ 24.6 pg/ml,  $p < 0.001$ ). The LPS auraptene group showed a significant decrease in TNF- $\alpha$

levels when compared to the LPS group ( $57.6 \pm 17.6$  vs.  $87.9 \pm 24.6$  pg/ml,  $p=0.007$ ) (Figure 1a).

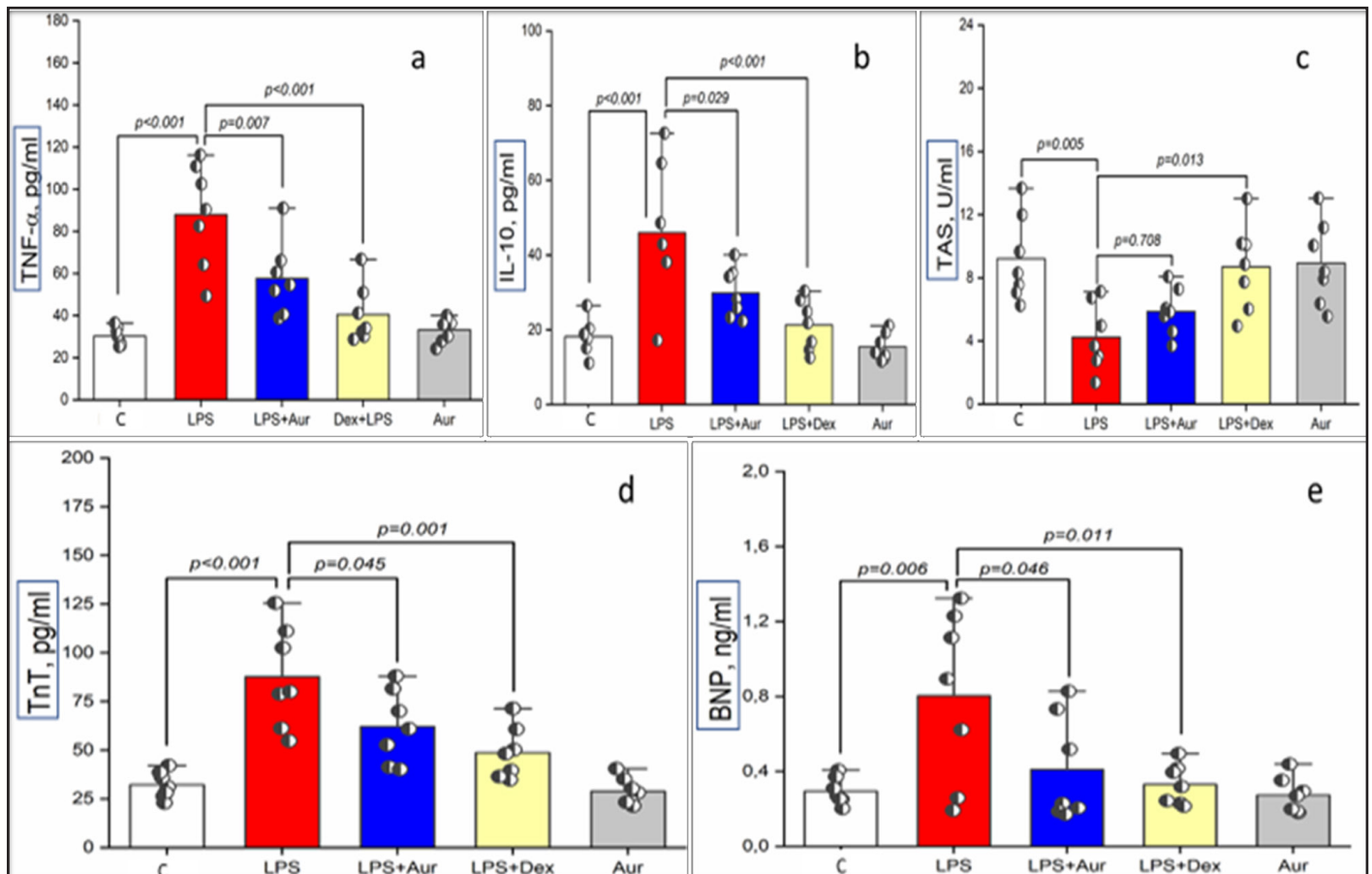
The groups' IL-10 levels differed significantly ( $p<0.001$ ). The IL-10 levels in the LPS and control groups differed significantly ( $45.9 \pm 18.3$  vs.  $18.2 \pm 4.7$  pg/mL,  $p<0.001$ ). IL-10 levels in the LPS+dexamethasone group were significantly lower than those in the LPS group ( $21.2 \pm 6.8$  vs.  $45.9 \pm 18.3$  pg/mL,  $p<0.001$ ). Additionally, the LPS+Auraptene group's IL-10 levels were noticeably lower than those of the LPS group ( $29.8 \pm 6.7$  vs.  $45.9 \pm 18.3$  pg/ml,  $p=0.029$ ) (Figure 1b).

The groups' TAS values differed significantly ( $p=0.001$ ). The TAS of the LPS and control groups differed significantly from one another ( $4.2 \pm 2.1$  vs.  $9.2 \pm 2.7$  U/ml,  $p=0.005$ ). Compared to the LPS group, the TAS levels in the LPS+dexamethasone group were noticeably higher ( $8.6 \pm 2.7$  vs.  $4.2 \pm 2.1$  U/ml,  $p<0.001$ ). However, there was no discernible difference in the TAS between the LPS+Auraptene group and the LPS group ( $5.8 \pm 1.4$

vs.  $4.2 \pm 2.1$  U/ml,  $p=0.708$ ) (Figure 1c).

The groups' TnT values differed significantly ( $p<0.001$ ). Troponin T levels varied significantly between the LPS and control groups ( $87.7 \pm 26.2$  vs.  $32.1 \pm 6.9$  pg/ml,  $p<0.001$ ). Troponin T levels in the LPS+dexamethasone group were significantly lower than those in the LPS group ( $48.7 \pm 13.4$  vs.  $87.7 \pm 26.2$  pg/ml,  $p=0.001$ ). Additionally, compared to the LPS group, the TnT values were considerably lower in the LPS+Auraptene group ( $62.1 \pm 18.7$  vs.  $87.7 \pm 26.2$  pg/ml,  $p=0.045$ ) (Figure 1d).

The groups' BNP values differed significantly ( $p=0.002$ ). The BNP levels of the LPS and control groups differed significantly ( $0.8 \pm 0.4$  vs.  $0.2 \pm 0.07$  ng/ml,  $p=0.006$ ). BNP levels in the LPS+dexamethasone group were significantly lower than those in the LPS group ( $0.3 \pm 0.1$  vs.  $0.8 \pm 0.4$  ng/ml,  $p=0.011$ ). Additionally, the LPS+Auraptene group's BNP levels were noticeably lower than those of the LPS group ( $0.4 \pm 0.2$  vs.  $0.8 \pm 0.4$  ng/ml,  $p=0.046$ ) (Figure 1e).



**Figure 1.** Variations in biochemical values between the groups (C: Control, LPS: Lipopolysaccharide, Aur: Auraptene, Dex: Dexamethasone,  $n=8$  for each group, One-way ANOVA).

## Histological Investigations

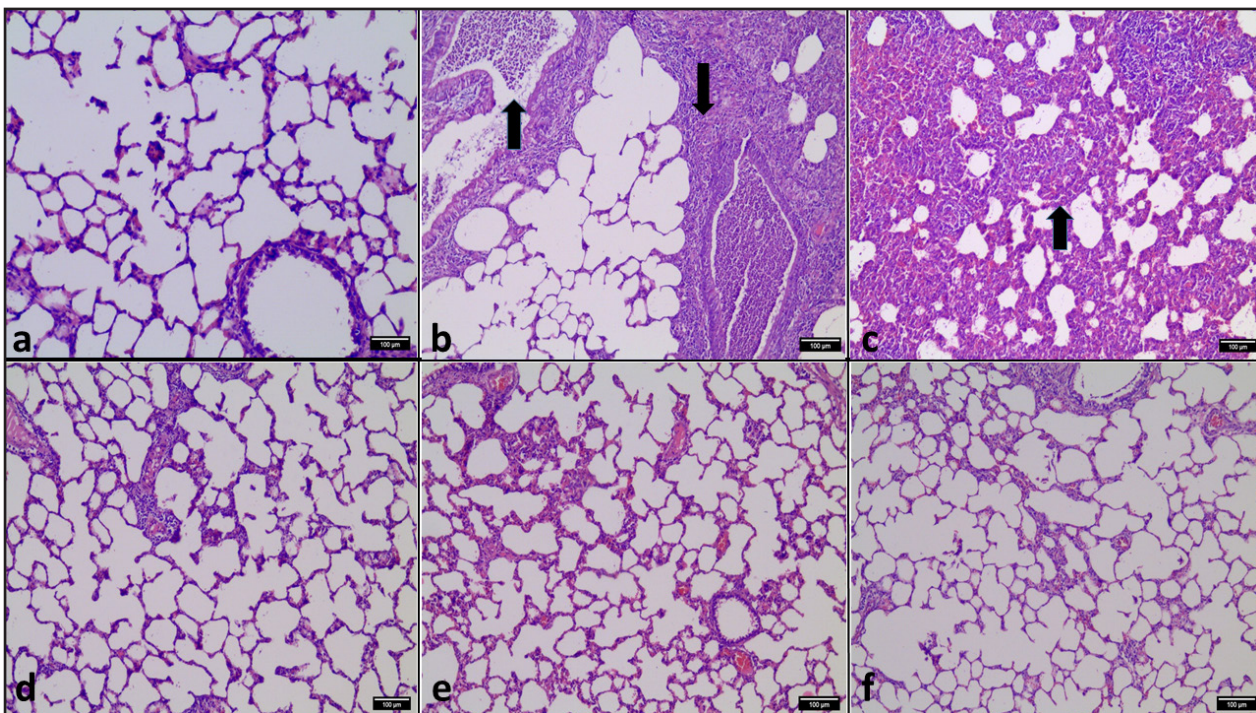
### Pulmonary Histologic Examinations

First, a histologic examination of acute lung injury (ALI) was performed. The groups' pulmonary lymphocyte scores differed significantly from one another ( $p < 0.001$ ). The lymphocyte ratings of the LPS and control groups differed significantly ( $1.5 \pm 0.53$  vs.  $3.12 \pm 0.35$ ,  $p < 0.001$ ) (Figure 2a, 2b). Compared to the LPS group, the LPS+dexamethasone group's lymphocyte scores were noticeably lower ( $2 \pm 0.57$  vs.  $3.12 \pm 0.35$ ,  $p = 0.002$ ) (Figure 2f). Additionally, the LPS+auraptene group's lymphocyte counts were noticeably lower than those of the LPS group ( $1.57 \pm 0.78$  vs.  $3.12 \pm 0.35$ ,  $p = 0.002$ ) (Figure 3a) (Figure 2d, 2e).

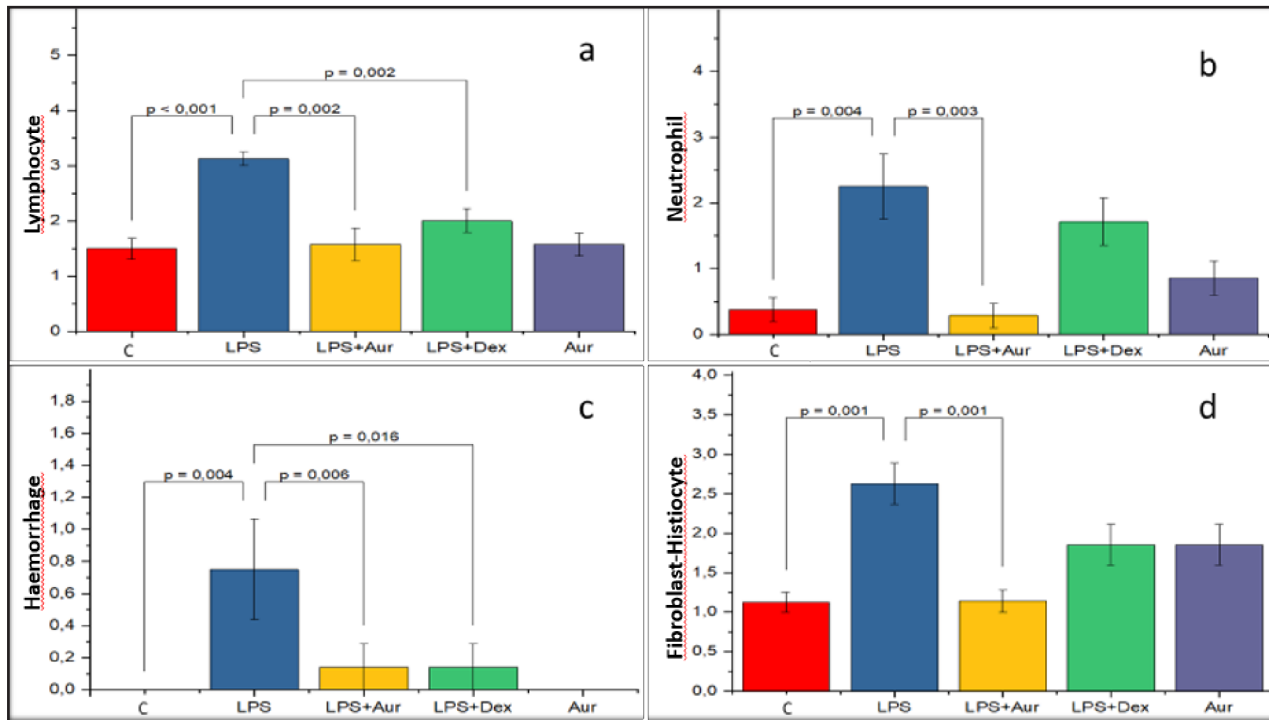
The groups' pulmonary neutrophil scores differed significantly from one another ( $p < 0.001$ ). The neutrophil ratings of the LPS and control groups differed significantly ( $0.37 \pm 0.51$  vs.  $2.25 \pm 1.38$ ,  $p = 0.004$ ) (Figure 2a, 2b). Additionally, the LPS+auraptene group's neutrophil ratings were noticeably lower than those of the LPS group ( $0.28 \pm 0.48$  vs.  $2.25 \pm 1.38$ ,  $p = 0.003$ ). In contrast, neutrophil scores were not significantly different between the LPS+dexamethasone group and the LPS group ( $1.71 \pm 0.95$  vs.  $2.25 \pm 1.38$ ,  $p = 0.44$ ) (Figure 3b).

The groups' pulmonary hemorrhage scores differed significantly from one another ( $p = 0.002$ ). The hemorrhage scores of the LPS and control groups differed significantly ( $0 \pm 0$  vs.  $1.37 \pm 1$ ,  $p = 0.004$ ) (Figure 2c). Compared to the LPS group, the LPS+dexamethasone group's hemorrhage scores were noticeably lower ( $0.14 \pm 0.37$  vs.  $1.37 \pm 1$ ,  $p = 0.016$ ). Additionally, the LPS+Auraptene group's hemorrhage values were noticeably lower than those of the LPS group ( $0 \pm 0$  vs.  $1.37 \pm 1$ ,  $p = 0.006$ ) (Figure 3c).

The quantity of lung fibroblasts and histiocytes varied significantly between the groups ( $p = 0.001$ ). The fibroblast and histiocyte scores of the LPS and control groups differed significantly ( $1.12 \pm 0.35$  vs.  $2.62 \pm 0.74$ ,  $p = 0.001$ ) (Figure 2c). The LPS+Auraptene group's fibroblast and histiocyte scores were noticeably lower than those of the LPS group ( $1.14 \pm 0.37$  vs.  $2.62 \pm 0.74$ ,  $p = 0.001$ ). Conversely, there was no discernible difference in the fibroblast and histiocyte scores between the LPS+dexamethasone group and the LPS group ( $1.85 \pm 0.69$  vs.  $2.62 \pm 0.74$ ,  $p = 0.066$ ) (Figure 3d).



**Figure 2.** H&E-stained sections showing histological changes in lung tissue: (a) Control group, HEX100. (b) LPS group: inflammation and thickening of alveolar walls with significant lymphocyte and neutrophil infiltration, HEX100. (c) LPS group: hemorrhage and thickened alveolar walls with fibroblasts and histiocytes, HEX100. (d) LPS + Auraptene group, HEX100. (e) Auraptene group, HEX100. (f) Positive control (LPS + Dexamethasone) group, HEX100.



**Figure 3.** Pulmonary histological score differences between groups (C: Control, LPS: Lipopolysaccharide, Aur: Auraptene, Dex: Dexamethasone, n=8 for each group, Kruskal–Wallis H test).

The groups' pulmonary congestion scores differed significantly from one another ( $p < 0.001$ ). The congestion scores of the LPS and control groups differed significantly from one another ( $1.25 \pm 0.7$  vs.  $2.25 \pm 0.7$ ,  $p = 0.019$ ), while there was no significant difference between the other groups ( $p > 0.05$ ).

There was a significant difference between the groups in terms of pulmonary abscess scores ( $p = 0.003$ ), but this difference was only due to the difference between the LPS+dexamethasone and auraptene groups ( $0 \pm 0$  vs.  $1.28 \pm 1.11$ ,  $p = 0.009$ ), while there was no significant difference between the other groups ( $p > 0.05$ ).

There was no significant difference in pulmonary macrophage scores between the groups ( $p = 0.069$ ).

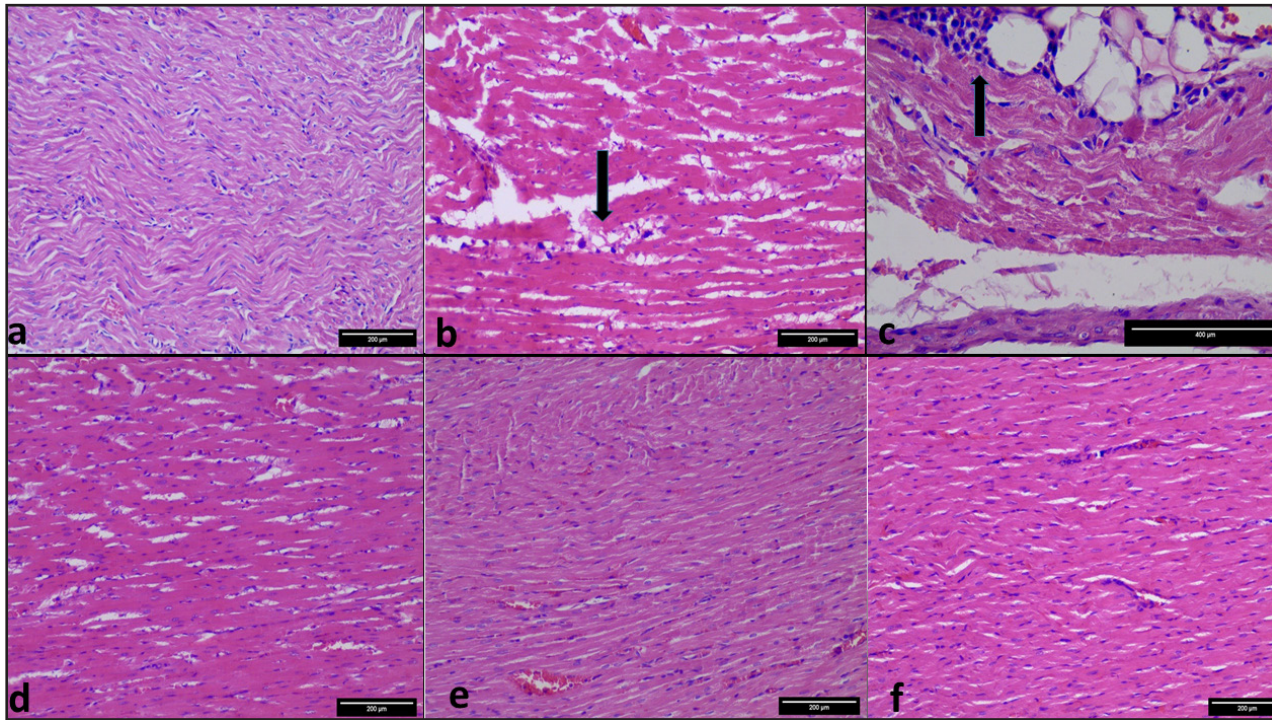
### Cardiac Histologic Examinations

At this stage, a histologic examination of the myocardial injury caused by ALI was performed. The groups' cardiac degeneration scores differed significantly from one another ( $p < 0.001$ ). The degeneration scores of the LPS and control groups differed significantly ( $0 \pm 0$  vs.  $1.25 \pm 0.46$ ,  $p < 0.001$ ) (Figure 4a, 4b). Compared to the LPS group, the LPS+dexamethasone group's degeneration scores were noticeably lower ( $0 \pm 0$  vs.  $1.25 \pm 0.46$ ,  $p < 0.001$ ) (Figure 4f). Additionally, the LPS+Auraptene group's

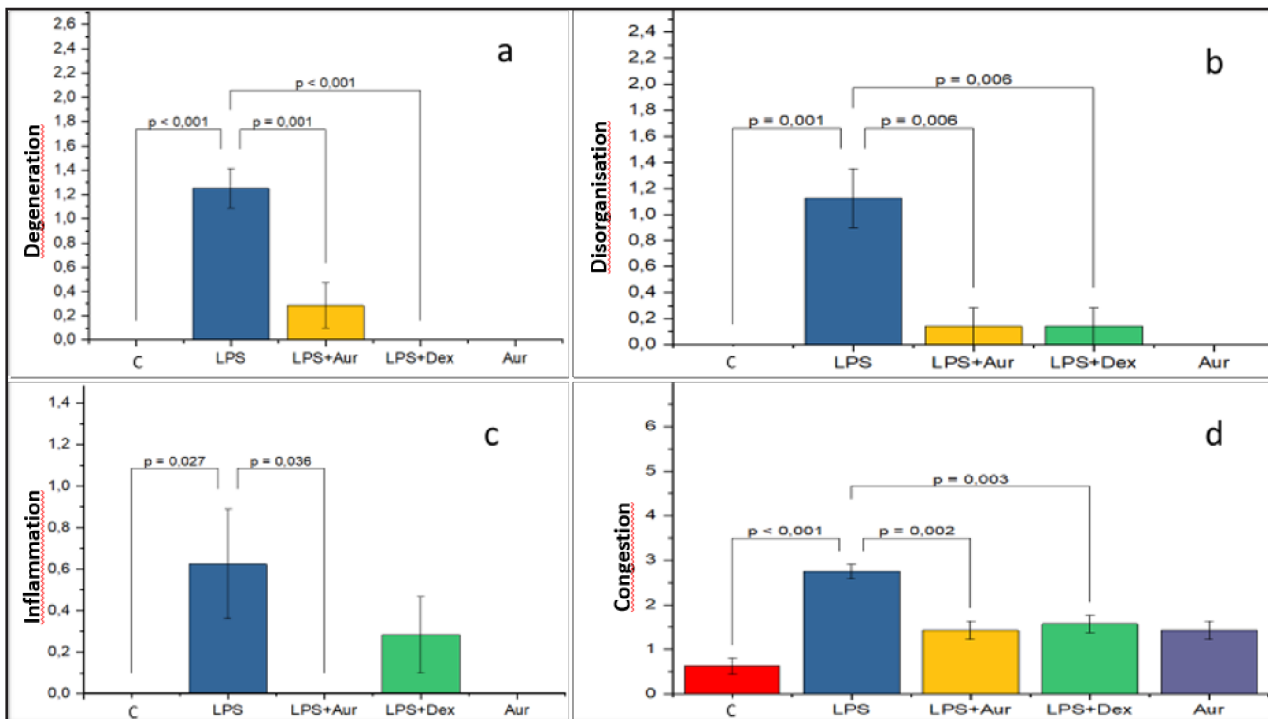
degeneration scores were noticeably lower than those of the LPS group ( $0.28 \pm 0.48$  vs.  $1.25 \pm 0.46$ ,  $p = 0.005$ ) (Figure 5a) (Figure 4d, 4e).

The groups' cardiac disorganization scores differed significantly from one another ( $p < 0.001$ ). There was a significant difference between the LPS and control groups in terms of disorganization scores ( $0 \pm 0$  vs.  $1.12 \pm 0.64$ ,  $p = 0.001$ ). Compared to the LPS group, the LPS+dexamethasone group's disorganization scores were noticeably lower ( $0.14 \pm 0.37$  vs.  $1.12 \pm 0.64$ ,  $p = 0.006$ ). Additionally, the LPS+Auraptene group's dysorganization scores were noticeably lower than those of the LPS group ( $0.14 \pm 0.37$  vs.  $1.12 \pm 0.64$ ,  $p = 0.006$ ) (Figure 5b).

The groups' scores for cardiac inflammation varied significantly from one another ( $p = 0.021$ ). The LPS and control groups' inflammation scores differed significantly from one another ( $0 \pm 0$  vs.  $0.62 \pm 0.74$ ,  $p = 0.027$ ) (Figure 5c). Compared to the LPS group, the LPS+Auraptene group's inflammation scores were noticeably lower ( $0 \pm 0$  vs.  $0.62 \pm 0.74$ ,  $p = 0.036$ ). In contrast, inflammation scores were not significantly different between the LPS+dexamethasone group and the LPS group ( $0.28 \pm 0.48$  vs.  $0.62 \pm 0.74$ ,  $p = 0.35$ ) (Figure 5c).



**Figure 4.** H&E-stained sections showing histological changes in the myocardium: (a) Control group, HEX200. (b) LPS group: muscle fiber degeneration and cytoplasmic vacuolization, HEX200. (c) LPS group: inflammation between muscle fibers, HEX400. (d) LPS + Auraptene group, HEX200. (e) Auraptene group, HEX200. (f) Positive control (LPS + Dexamethasone) group, HEX200.



**Figure 5.** Myocardial histological score differences between groups (C: Control, LPS: Lipopolysaccharide, Aur: Auraptene, Dex: Dexamethasone, n=8 for each group, Kruskal–Wallis H test).

The groups' scores for cardiac congestion varied significantly from one another ( $p < 0.001$ ). The congestion scores of the LPS and control groups differed significantly from one another ( $0.62 \pm 0.51$  vs.  $2.75 \pm 0.46$ ,  $p < 0.001$ ). Compared to the LPS group, the congestion scores in the LPS+dexamethasone group were noticeably lower ( $1.57 \pm 0.53$  vs.  $2.75 \pm 0.46$ ,  $p = 0.003$ ). Additionally, the LPS+Auraptene group's congestion scores were noticeably lower than those of the LPS group ( $1.42 \pm 0.53$  vs.  $2.75 \pm 0.46$ ,  $p = 0.002$ ) (Figure 5d).

The groups' cardiac vacuolization scores differed significantly from one another ( $p = 0.045$ ). Only in terms of vacuolization scores did the LPS and control groups differ significantly ( $0 \pm 0$  vs.  $0.5 \pm 0.5$ ,  $p = 0.025$ ) (Figure 4b); there was no significant difference between the other groups ( $p > 0.05$ ).

The groups' scores for cardiac hemorrhage differed significantly from one another ( $p = 0.042$ ). Only in terms of cardiac hemorrhage scores did the LPS and control groups differ significantly ( $0 \pm 0$  vs.  $0.75 \pm 0.88$ ,  $p = 0.027$ ); there was no significant difference between the other groups ( $p > 0.05$ ).

## DISCUSSION

ALI is characterized by damage to the endothelial and epithelial barriers, exposing the alveoli to a cytokine storm and oxidative stress due to primary or secondary causes [21]. All of these are a result of severe inflammation mediated by key signalling pathways such as NF- $\kappa$ B, MAPKs and oxidative stress response pathways such as Keap1/Nrf2 [22,23]. Pulmonary disease mortality may be increased by secondary cardiac dysfunction due to infection, increased inflammation, endothelial dysfunction, an increased prothrombotic state, and increased cardiac oxygen demand [24,25]. Despite current technological advances, there is no treatment modality that can directly treat ALI, and the treatments used can be summarized as follows: suppression of the inflammatory response, enhancement of antioxidant activity, and protection from hypoxia [26,27]. The lack of effective treatment for ALI makes studies of both ALI and ALI-associated conditions valuable, and the knowledge gained from these studies will support the development of new methods to treat these conditions. Our study revealed that auraptene may be an alternative treatment for both ALI and ALI-related myocardial dysfunction.

The main proinflammatory cytokine that increases in ALI is TNF- $\alpha$  [15]; thus, we measured TNF- $\alpha$  levels to assess the

immune response at the site of inflammation. In our study, we found that TNF- $\alpha$  levels increased in ALI due to LPS. A histological increase in inflammation was also shown by increased levels of lung lymphocytes, neutrophils, hemorrhage, congestion, fibroblasts and histiocytes in the lungs. A cytokine storm triggered by T helper cells, respiratory dysfunction and hypoxemia are thought to be responsible for myocardial injury in ALI [28,29,30]. Failure to suppress the proinflammatory/anti-inflammatory cytokine storm and the resulting oxidative stress leads to the progression of ALI and the development of multiorgan failure [31]. Inflammation plays an important role in the development of sepsis-related cardiac dysfunction [32,33]. Studies have shown that elevated serum TnT and BNP levels are early indicators of myocardial injury and cardiac dysfunction [18]. In our study, elevated TNF- $\alpha$  was shown to cause myocardial injury in ALI through increased serum BNP and TnT levels, and these biochemical changes were confirmed by morphological changes in rat heart tissue.

Dexamethasone strongly suppresses the production and release of TNF- $\alpha$ . TNF- $\alpha$  is an important proinflammatory cytokine involved in numerous inflammatory and immune responses [34]. Dexamethasone exerts its anti-inflammatory effect by binding to intracellular glucocorticoid receptors. This complex inhibits NF- $\kappa$ B activation or directly suppresses gene transcription [35,36]. In our study, TNF- $\alpha$  levels were decreased by dexamethasone in ALI attributable to LPS, and this result was consistent with the literature [20]. A reduction in the lung's lymphocyte and hemorrhagic counts also indicated a reduction in inflammation. Dexamethasone has been shown to reduce biomarkers of myocardial damage. Dexamethasone protects myocardial cells from damage, particularly by suppressing systemic inflammation [37]. In our study, we found that dexamethasone reduced the levels of BNP and TnT, which are indicators of myocardial dysfunction. Histologically, the decrease in inflammation was also reflected in a decrease in the severity of cardiac degeneration, disorganization and congestion.

Studies have demonstrated that auraptene significantly lowers the blood levels of proinflammatory cytokines like TNF- $\alpha$  in inflammatory processes, making its ability to control inflammation one of its most significant benefits [38,39]. Experimental studies have shown that auraptene has an anti-inflammatory effect by reducing the NF- $\kappa$ B/MAPKs signalling pathways [40]. We measured TNF- $\alpha$  levels to evaluate the effects

of auraptene on proinflammatory cytokines in LPS-induced lung injury. In our study, TNF- $\alpha$  levels were reduced when auraptene was used to treat ALI caused by LPS. Histologically, auraptene significantly attenuated lung parenchymal damage.

Troponins are released when the heart muscle is injured. Given the known antioxidant and anti-inflammatory properties of auraptene, it is plausible that it could reduce myocardial injury in conditions where inflammation and oxidative stress play a role (e.g. ischaemia-reperfusion injury, inflammatory cardiomyopathy or myocardial damage associated with sepsis). If it mitigates such damage, a reduction in troponin levels would be an expected result [41]. Our study showed that treatment with auraptene in LPS-induced lung injury significantly decreased the levels of BNP and TnT, which are indicators of myocardial dysfunction, and decreased the production of proinflammatory cytokines, suggesting that auraptene may improve sepsis-induced myocardial dysfunction. These biochemical changes were confirmed by morphological changes in the heart tissue of rats were significantly alleviated by auraptene.

Anti-inflammatory procedures are necessary to avoid situations when the host is harmed by an excessive inflammatory response caused by a variety of factors. The most crucial factor in controlling inflammatory processes is the anti-inflammatory cytokine IL-10 [42]. After LPS injection, cytokine levels may fluctuate in different directions. There are publications reporting a decrease in IL-10 [16,43], while there are publications reporting the opposite increase [44,45]. The level of IL-10, the main anti-inflammatory cytokine, was found to increase in ALI caused by LPS. In our study, IL-10 levels were found to increase in ALI due to LPS, and histologic findings showed that pulmonary lymphocyte, neutrophil, hemorrhage, congestion, fibroblast, and histiocyte levels were increased in these images.

IL-10 is recognized as an anti-inflammatory cytokine that is essential for resolving inflammation and keeping immune homeostasis. However, in certain conditions, high IL-10 levels can paradoxically indicate an ongoing severe inflammatory process or even lead to negative outcomes. In acute, severe inflammation, the body experiences an overwhelming increase in pro-inflammatory cytokines. In response, the immune system rapidly upregulates anti-inflammatory messengers such as IL-10 to dampen this destructive inflammation. Therefore, very high IL-10 levels in such scenarios are often an indicator of the severity of the original pro-inflammatory insult [46-48]. In conditions

such as sepsis, persistently elevated IL-10 levels have been consistently associated with increased morbidity and mortality. This is not necessarily because IL-10 causes death, but because its high levels indicate a systemic inflammatory response that is so severe that the body activates maximal anti-inflammatory countermeasures but still fails to contain the overall pathology [46-48]. It has been shown that CD8<sup>+</sup> T cells are stimulated by IL-10 to produce pro-inflammatory IFN- $\gamma$  [49].

Increased levels of IL-10 have also been considered to be the cause of myocardial damage. In our study, IL-10, the major anti-inflammatory cytokine that is elevated in ALI, was shown to cause myocardial injury with increased serum levels of BNP and TnT, and histologically, the increase in cardiac parameter levels were found to be indicative of this condition. It has been observed that IL-10 can have a negative effect on protective humoral immunity, leading to worse outcomes [50].

Previous studies have shown that IL-10 levels are decreased by dexamethasone [51]. Similar results were obtained in our study, and the histologic findings showed that lymphocyte and hemorrhagic scores decreased in these images.

In our study, the use of dexamethasone to treat myocardial dysfunction caused by elevated IL-10 levels improved biochemical and histological indicators of this dysfunction.

One of the most important effects of auraptene is its immunomodulatory activity. Auraptene decreases the levels of all cytokines involved in inflammatory processes [38]. In our study, when auraptene was used to treat myocardial dysfunction due to increased IL-10 levels, the levels of BNP and TnT, which are indicators of this dysfunction, decreased, and histological improvements were observed as shown in these conditions.

Oxidative stress results from increased oxidant and/or decreased antioxidant levels during inflammatory processes. This situation leads to damage to the cell structure. Antioxidants play a role in neutralizing increased oxygen free radicals under these conditions. When antioxidants are produced and consumed in response to oxidative stress, the total antioxidant status is evaluated using the TAS. Therefore, rather than being a straightforward sum of quantifiable antioxidants, the TAS is an integrated parameter [17,52]. In patients with ALI, increased oxygen free radicals and thus decreased TAS capacity cause contractile dysfunction, hypertrophy, and apoptosis in cardiomyocytes [53,54,55], resulting in decreased cardiac output. In our study, a decrease in TAS capacity was observed

in ALI caused by LPS. This decrease in TAS capacity caused histopathological changes in the lungs.

These increased oxygen free radicals disrupt the structure of proteins involved in the excitation and contraction of the heart, including calcium, sodium, potassium and sodium-calcium channels. This situation not only negatively affects the electrophysiology and contraction mechanism of cardiomyocytes but also may lead to an energy deficit by disrupting the function of proteins involved in energy metabolism [56,57]. Our study demonstrated that reduced TAS capacity in ALI caused myocardial damage by raising serum levels of BNP and TnT. These biochemical alterations were corroborated by morphological changes.

Dexamethasone is known to have a strong antioxidant effect [58]. In our study, dexamethasone was found to increase TAS capacity, which decreased in ALI due to LPS. This increase in TAS capacity contributed to a decrease in lymphocyte and hemorrhage scores in the lung.

In our study, it was shown that the levels of BNP and TnT, which are indicators of this dysfunction, could be suppressed when dexamethasone was used to treat myocardial dysfunction secondary to decreased TAS capacity. This increase in TAS capacity contributed to the decrease in histological changes of the heart.

Auraptene has been shown to strongly inhibit hydroxyl radicals. Auraptene promotes this effect by increasing the expression of superoxide dismutase, catalase and glutathione peroxidase genes. This change indicates the antioxidant potential of auraptene [9,11,59]. Although the increase in TAS with auraptene was not statistically significant in our study, the significant histological improvements observed in lung tissue suggest that the antioxidant activity of auraptene may contribute to its protective effect via mechanisms beyond the measurable TAS changes. On the other hand, studies have shown that in lung injury caused by LPS, expressions of the Keap1/Nrf2 signalling pathway were successfully regulated by auraptene treatment [60]. Our study showed that when auraptene was used in patients with myocardial dysfunction due to decreased TAS capacity, the levels of BNP and TnT, which are indicators of this dysfunction, were significantly decreased. These biochemical changes were confirmed by morphological changes in rat heart tissue. Experimental studies have shown that auraptene effectively

improves left ventricular function and reduces posterior wall thickness and perivascular fibrosis. Auraptene can suppress the activation of monocyte chemoattractant protein-1 mRNA levels, which is one of the most significant chemokines controlling monocyte and macrophage migration and infiltration, in addition to decreasing atrial natriuretic factor levels [61].

### Limitations

Our main limitation is the lack of more inflammatory markers in serum that can indicate cell injury. The other limiting factor of the present study is that the cardiac structure and function of the rats could not be assessed by echocardiography.

### CONCLUSIONS

This study suggested that myocardial injury may develop secondary to ALI, indicating that the underlying mechanism of myocardial injury should be further investigated. Furthermore, these results suggest that auraptene can be used in the treatment of ALI as well as in the treatment of myocardial injury resulting from ALI, due to its ability to suppress inflammation rather than its antioxidant properties. We believe that these results should be supported by clinical studies.

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**Conflict of Interest:** The authors have no relevant financial or non-financial interests to disclose.

**Informed Consent:** Data sets of this study are available from the corresponding author upon reasonable request.

**Ethical Approval:** The protocol for this study has been approved by the Ethics Committee for Animal Research at Bolu Abant İzzet Baysal University. Date: May 11, 2022 Protocol: (2022/15).

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