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Original Article

Afzelin Prevents against Lipopolysaccharide-Induced Acute Lung Injury and Sepsis via Inhibiting the Inflammatory Mediators

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ABSTRACT

Background: One of the main causes of death in critical care units and a serious consequence of sepsis is Acute Lung Injury (ALI). Studies have shown that afzelin reduces inflammation and oxidative damage. However, the potential protective effects of afzelin's anti-inflammatory and antioxidative activities against Lipopolysaccharide (LPS)-induced ALI and sepsis remain unclear. **Materials and Methods:** Male Wistar albino rats were injected intraperitoneally with LPS (5 mg/kg) in order to develop an ALI model. The rats were split up into 3 groups: group I was the control group, group II was the LPS-treated control group, and group III was the Afzelin-treated group. **Results:** Increased levels of lung damage, inflammatory cytokines, MDA, NO, ROS, and W/D ratio were seen in the animals in group II. The animals in group II had lower antioxidant levels. Treatment with afzelin significantly decreased the amount of lung damage, inflammatory cytokines, MDA, NO, ROS, and the W/D ratio of the lungs in the LPS triggered rats. Furthermore, it raised the antioxidant content of the lung tissue. In the current study, nursing care for patients with acute lung disease emphasizes the importance of continuous monitoring, counselling, and providing essential support. However, further clinical trials are required to evaluate the safety and efficacy of these interventions. **Conclusion:** In summary, afzelin can ameliorate ALI induced by LPS through anti-oxidative and its anti-inflammatory effect.

Keywords: Acute lung injury, Lipopolysaccharide, Afzelin, Anti-oxidative, Anti-inflammatory.

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INTRODUCTION

Globally, acute inflammatory disorders continue to be the leading incidence of death in critical care units. They include sepsis and Acute Lung Injury (ALI), which are caused by either local or systemic inflammation. Sepsis and ALI, which harm many organs and tissues, are brought on by infections.[1] ALI is a disorder marked by sudden inflammation that impairs the lungs' epithelial and endothelial barriers. Among critically ill patients, ALI remains a substantial factor of illness and fatality. ALI is characterized by the production of pro-inflammatory, cytotoxic chemicals, increased transepithelial neutrophil movement, and a breakdown of alveolar-capillary membrane permeability. Morbidity and mortality in ALI are predicted by biomarkers on the epithelium and endothelium that are concerned in the inflammatory and coagulation pathways.[2]

ALI is a serious risk for patients with sepsis, a systemic inflammatory condition brought on by serious infections that affect several major organs, with the lung being the most susceptible. Bacteria, viruses, and other harmful microbes in the body are the cause of sepsis. Additionally, it is among the prevalent causes of mortality for individuals in critical condition. Sepsis continues to have a high morbidity and fatality rate.[3] Age, heredity, alcohol use, sepsis, trauma or numerous traumatic injuries, tobacco, post-lung transplantation, pneumonia, and other established risk factors can all contribute to the development of ALI and (Acute Respiratory Distress Syndrome) ARDS.[4] Acute Lung Injury (ALI) is a severe pulmonary condition associated with high morbidity and mortality rates. It is often triggered by infections, sepsis, or trauma, leading to significant respiratory dysfunction. ALI is recognized as one of the leading causes of death in critically ill patients, emphasizing the urgent need for effective therapeutic interventions and experimental models to study its pathophysiology.

The intricate relationship of circulating cellular components, soluble inflammatory mediators like Lipopolysaccharide (LPS), Interleukin (IL1β), and Tumor Necrosis Factor (TNF-α) on

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various pulmonary cellular targets is what causes the development of ALI/ARDS in sepsis. In response to infection or trauma, proinflammatory cytokines are overexpressed; alternatively, they might be a sign of ongoing cellular damage. Tumor Necrosis Factor (TNF)-α, IL-8, and IL-6 interleukins were demonstrated to be substantially predictive plasma levels of mortality at baseline and to be consistently higher.[5] A significant part of cell walls G-ve bacteria, Lipopolysaccharide (LPS), is essential for acute lung damage.[6] Immune system malfunction and inflammation can be brought on by lipopolysaccharide. LPS administrated rat models are used to understand the pathogenesis and prevention of ALI.[7] Despite current studies in this field, there are still no proven strategies to reduce the high fatality rate associated with ALI/ARDS. Finding new drugs and developing efficient ALI/ARDS treatment regimens are therefore crucial.

A family of polyphenolic chemicals found in large quantities throughout the plant world are flavonoids. Kaempferol 3-O-rhamnoside, another term for afzelin, is a flavonoid component that is present in large amounts in a wide range of plant sources. Numerous research has confirmed afzelin's wide variety of activities, which include antibacterial, anti-inflammatory, antioxidant, and cytoprotective properties.[8] It was recently discovered that afzelin, which is relatively non-toxic to healthy cells, prevents the growth of lung cancer cells by triggering apoptosis.[9] In this study, nursing care in clinical application, new treatments, observed and providing support to sick person participating in clinical trials. Nurses can improve outcomes for patients. The current work used LPS-induced rat models to investigate the mechanism underlying afzelin's therapeutic influence on sepsis-induced acute lung injury. Our study provides evidence of the anti-inflammatory properties of afzelin in pulmonary damage, indicating that it may be a viable therapeutic target for the clinical treatment of ALI.

MATERIALS AND METHODS

Materials

Prior to the start of the trial, all chemicals, reagents, and kits were purchased commercially and made available.

Animals

Rats were obtained from the Approved Animal Centre with the necessary ethical approval for animal experimental study, and all applicable national rules and institutional policies for animal use and care were adhered to. Adult male Wistar albino rats weighing 200-250 g was obtained. With a 12-hr alternative dark and light cycle and a regulated temperature of 21±2°C and 45-55% R.H, the rats were housed in polycarbonate cages. The experimental animals were fed standard rat chow and provided unlimited accessibility to food and water. Rats were treated with the utmost attention and care.

Model of LPS-triggered ALI and sepsis

To induce ALI, rats were administered intraperitoneal injections of Lipopolysaccharide (LPS, 5 mg/kg; Sigma, St. Louis, MO, USA) or an equivalent volume of Normal Saline (NS) as a vehicle control. The protocol was optimized to induce ALI with minimal mortality within 24 hr of LPS administration.

Grouping and treatment

All rats were allocated into 3 groups such as control, LPS, and LPS+Afzelin (each group had 6 numbers of rats).

Group I comprised of a control group that had normal rats who received 100 µL of normal saline. Group II included rats that had been stimulated with LPS. Group III included rats that had been stimulated with LPS and treated with Afzelin (30 mg/Kg). Following the research, the rats were sedated using a combination of ketamine and xylazine, and samples of lung tissue and blood were taken for analysis.

Wet to dry weight ratio

Pulmonary edema was assessed using the wet/dry weight ratio, or W/D ratio. Assessing the lung tissue promptly after collecting the right upper lung and using filter paper to remove any surface blood or moisture allowed us to estimate the Wet weight (W). The pulmonary tissue was assessed again to determine the Dry weight (D) following a 24-hr drying period at 80°C. These weights were used to compute lung tissue W/D ratios.[10]

Estimation of NO

The Griess test was used to measure the amount of NO produced in each of the treated groups using the previously mentioned methodology. On the last day of the experiment, all of the experimental animals were killed, and a heart puncture was used to draw blood. After blood collection, the blood was centrifuged at 700 RCF for duration of 10 min at temperature condition of 4°C in order to extract the plasma from the cellular component for NO detection. After homogenizing the tissues in 5 mM Tris-HCl buffer (pH 7.4) with 2 mM EDTA, the tissues were centrifuged for 5 min at 2000 g. Cu-coated calcium granules in glycine buffer at pH 9.7 transformed the nitrate to nitrite after the samples were deproteinized using Somogyi reagent. Using a spectrophotometer, samples were measured at 545 nm post a 45-min interaction with Griess reagent at the ambient temperature.

Estimation of oxidative stress in lung tissues

Tissue from the left lung was collected. To determine the levels of CAT, MDA, and SOD, the obtained tissue was homogenized, centrifuged for duration of 15 min at 4°C and 1500 g, and then dissolved in extraction buffer. The thiobarbituric acid colorimetric approach was used to test the supernatant for Malondialdehyde (MDA), and a yellow purine oxidase method was used to identify Superoxide Dismutase (SOD).[10] Additionally, it was found that,

in accordance with the manufacturer's recommendations, SOD and CAT levels assess the antioxidative enzyme activity in the lung tissue.[11]

Estimation of inflammatory cytokines

Inflammatory cytokines TNF-α, IL-1β, and IL-6 were measured using commercially available ELISA kits. Although IL-6 were assessed in serum, IL-1β and TNF-α were evaluated in the lung tissue. Using a microplate spectrophotometer, cytokine levels were estimated using standard curves and the results were reported in pg/mL.[12]

Histoarchitecture analysis

Lungs were preserved in formaldehyde solution for 24 hr before being fixed in PFA solution to demonstrate the histological changes brought on by LPS. The tissues were then cut into 5 µm sections and stained with haematoxylin and eosin using conventional histology methods. Under an optical microscope, the tracheal and lung tissues were inspected, and pictures were captured.

Statistical analysis

The mean±SD (n=6) was used to represent the results from the triplicate testing. The statistical analysis was conducted using GraphPad Prism. A one-way ANOVA was used to assess the variations between the groups. The two groups' differences were compared using the student t-test. When the difference between the control and induced animal groups was $p<0.05$, it was considered statistically significant.

RESULTS

Effect of Afzelin on wet/dry ratio

Figure 1 represents the effect of Afzelin on wet/dry ratio of the rat's lungs exposed to LPS. It indicates that rats exposed to LPS had a higher W/D ratio than the control group. This implies the presence of pulmonary edema and inflammatory cell infiltration. But compared to group II, group III's W/D ratio was smaller.

Effect of Afzelin on the NO level

Figure 2 depicts the effect of afzelin on the levels of NO in the lung tissue and the plasma of the animals. In both lung tissue and plasma, it was shown that the LPS-treated animals had higher levels of NO than the control group. Animals treated with afzelin in (group III) had a considerable decrease in the level of NO compared to the LPS treated animals in the plasma and in the lung tissue.

Effects of Afzelin on measurement of oxidative stress biomarkers

Figure 3 shows the effect of afzelin on the oxidative stress biomarkers. It was found that the LPS group's lung tissue had a much greater amount of MDA than the control groups. Conversely, the LPS group exhibited a considerable drop in SOD and CAT levels. MDA levels in the lung tissue of the LPS+afzelin group were significantly lower than those in the LPS-induced animals. Additionally, the LPS+afzelin group's lung tissue showed noticeably higher levels of SOD and CAT expression.

Effect of Afzelin on inflammatory cytokine levels

Figure 4 represents the effect of afzelin on inflammatory cytokines level in LPS induced animals. Compared to the control group, the lung tissue of animals that were exposed to LPS showed noticeably greater expression levels of TNF-α, IL-1β, and IL-6. However, in contrast to the LPS-treated rats, the LPS+afzelin-treated animals showed a substantial decrease in TNF-α, IL-1β, and IL-6 expression.

Effect of Afzelin on histoarchitecture

The lung tissue architecture for each group has been shown in Figure 5. The findings showed that the control animals and the animals treated with afzelin (group III) did not exhibit any obvious pathological abnormalities. However, the animals treated with LPS (group II) showed obvious congestion and a high number of neutrophils and macrophages, indicating severe lung damage. However, animals treated with afzelin showed a substantial decrease in lung damage.

DISCUSSION

ALI is an inflammatory condition that impairs arterial oxygenation by causing lung edema and an impairment of alveolar-capillary membrane integrity.[13] Increased pro-inflammatory cytokine levels, decreased antioxidant enzymes, reduced gaseous exchange, substantial neutrophilic infiltration, and limited pulmonary vascular permeability are the core features of ALI.[14] Acute bacterial illnesses that result in pneumonia or sepsis can

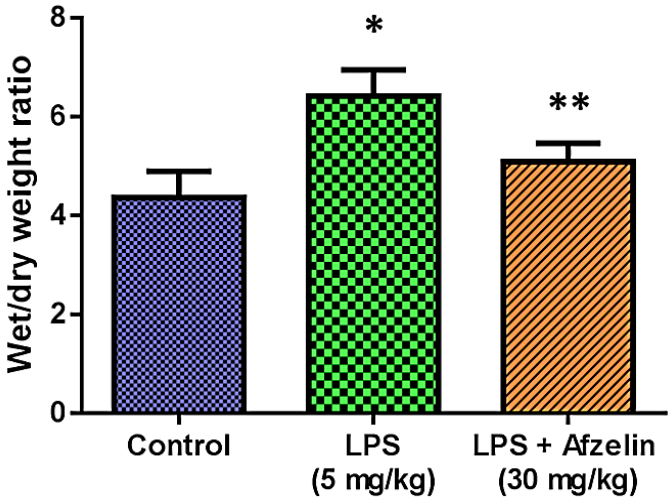

Figure 1: Effects of Afzelin on the wet/dry weight ratio of lungs of rats exposed to LPS. *p<0 .05 compared to the control group; **p<0.05 compared to the LPS group.

induce significant inflammatory lung damage, which can lead to Acute Lung Injury/Inflammation (ALI) in chronically ill patients. Primary causes of ALI (6-42%) are sepsis. The pulmonary innate immune system is a key player in the pathophysiology of ALI, depending on the host's age, sex, and the etiology of ALI/ARDS.[15]

LPS, a major constituent of the outer membrane of G-ve bacteria, can infiltrate the bloodstream and cause inflammatory reactions that might cause shock or even death. LPS administered intraperitoneally is a widely employed model of ALI in animals. The mouse model's expression of LPS-induced ALI symptoms closely resembles the disease seen in humans.[16] Afzelin, also called kaempferol 3-O-rhamnoside, is a naturally occurring flavonol glycoside that is generated from kaempferol and is present in a variety of plant species. According to research, it possesses strong neuroprotective, anticancer, antibacterial, anti-inflammatory, antidiabetic, and cardioprotective properties.[17] Results from earlier research show that three flavonoid components obtained from *H. cordata*, including afzelin, have the potential to be used therapeutically to treat LPS induced lung inflammatory disease for the first time.[18]

The study indicated that giving LPS significantly increased the wet/dry weight ratio, indicating the presence of lung edema and inflammatory cell infiltration, which is in line with another research.[12] As a result, afzelin showed noticeably more activity in

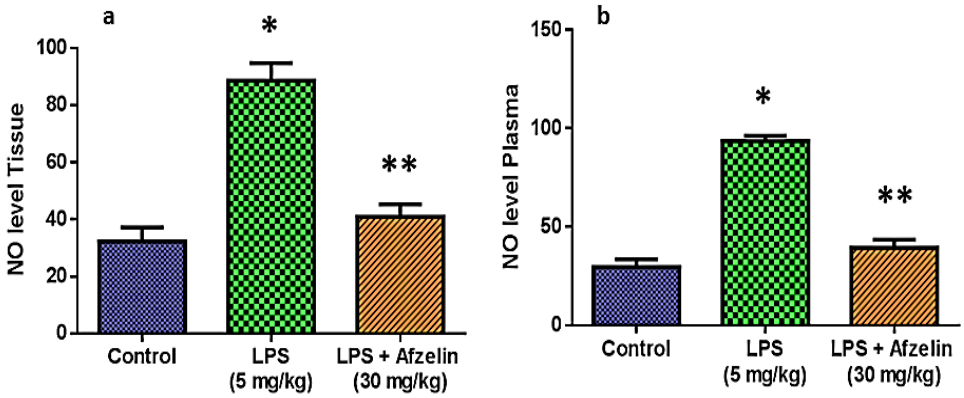

Figure 2: Effects of Afzelin on lung tissue and plasma levels of the following: (a) lung tissue Nitric oxide (b) plasma level Nitric oxide (nmol/100 mg). *p<0 .05 compared to the control group; **p<0.05 compared to the LPS group.

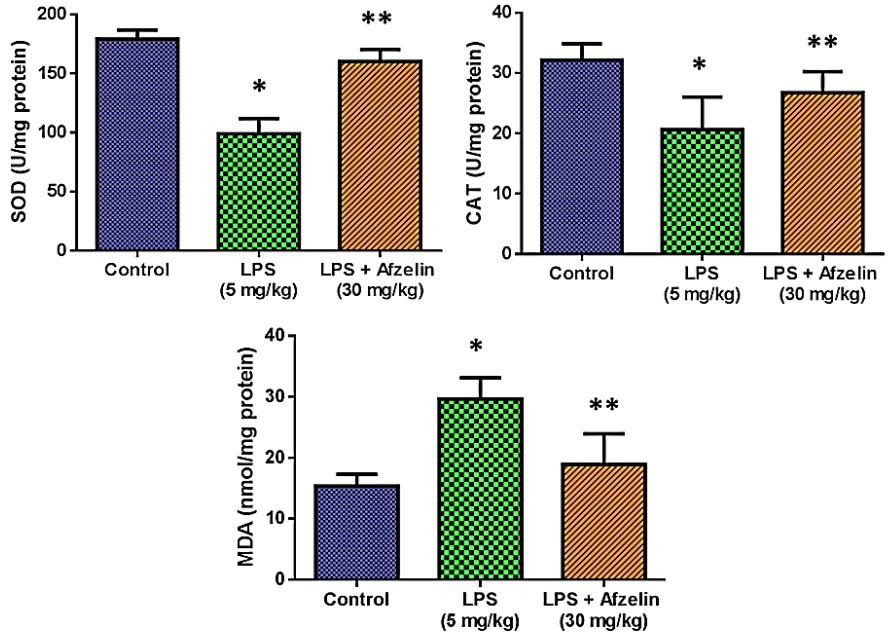

Figure 3: Effects of afzelin on lung tissue oxidative stress tests on Superoxide Dismutase (SOD), Catalase (CAT) and Malondialdehyde (MDA) in lung tissue. *p<0 .05 compared to the control group; **p<0.05 compared to the lps group.

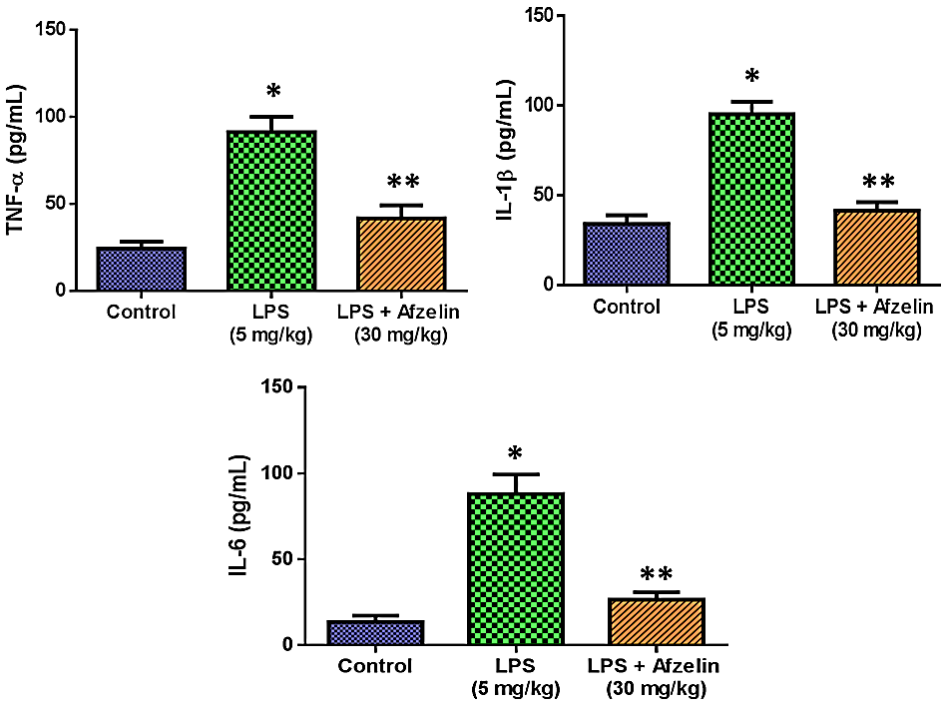

Figure 4: Effects of afzelin on analysis of lung tissue inflammatory cytokine assays. (a) TNF-α, (b) IL-1β and (c) IL-6. *p<0 .05 compared to the control group; **p<0.05 compared to the lps group.

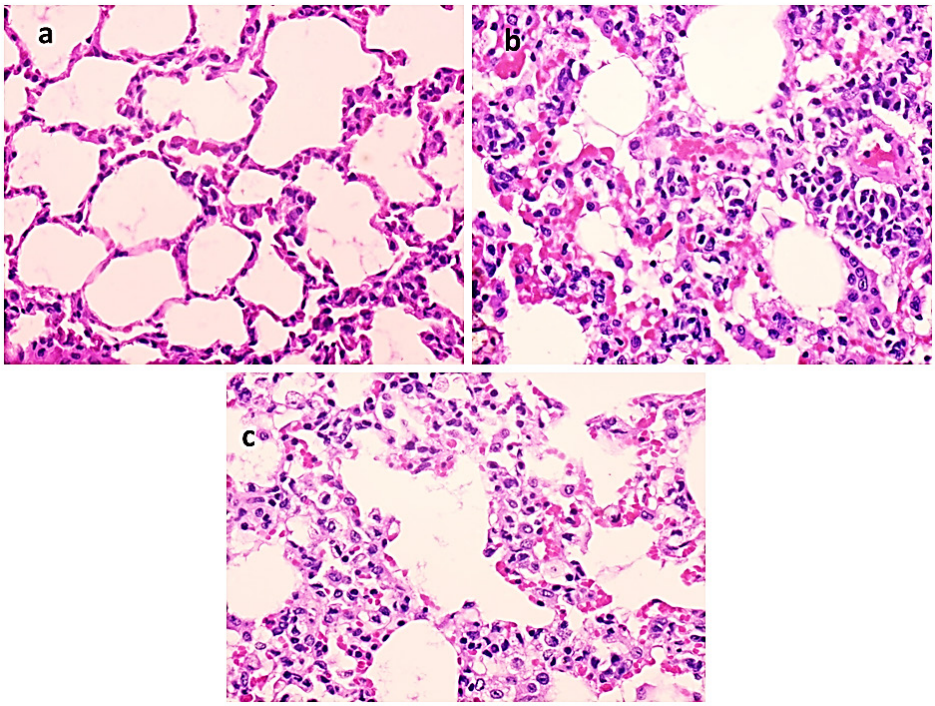

Figure 5: Histopathological Changes in Lung Tissue. Group I is normal control (a), Group II is LPS Induced (b), Group III is treatment LPS+Afzelin 30 mg/kg (c).

reducing the W/D ratio, and the LPS-induced rats showed elevated LPS levels. LPS has the innate capacity to raise the generation of ROS in lung tissue, which exacerbates the inflammatory response and causes damage to the lungs. ROS is necessary for the innate immune system to function, but excessive amounts of it can lead to harm to tissues, necrosis, and apoptosis.[19] As significant pro-oxidants, O_2, H_2O_2, NO, and XO are key contributors to the generation of ROS under different stressful conditions. As mentioned in the previous study, the level of NO increases upon LPS administration indicating oxidative stress condition.[20] As a

result, similar observation of found in the current study, where the level of NO was elevated in LPS treated animals. Afzelin treated animals showed decreased level of NO indicating the antioxidant property of afzelin.

Extreme oxidative stress and insufficient antioxidant defense cause lipid peroxidation, which produces aldehydic products like MDA and free fatty acids, also referred to as thibarbituric acid reactive chemicals.[21] In the previous study it was reported that in LPS induced ALI models, there was reduction in the amounts of CAT and SOD in lung tissue but elevated MDA level.[22] In the current study, the level of MDA was elevated and the SOD and CAT levels were reduced in the LPS treated animals indicating oxidative stress. On treatment with afzelin, the level of MDA was declined and the level of CAT and SOD were increased indicating the antioxidant property of afzelin. Among the proinflammatory cytokines, IL-1β, IL-8, IL-18, TNF-α, and IL-6 are the most promising potential molecular biomarkers to predict morbidity and mortality.[23] In ALI, the proinflammatory response is crucial. It is widely known that LPS may cause the synthesis of inflammatory cytokines, which may cause neutrophils to infiltrate lung tissues and start localized inflammatory reactions.[24] The level of IL-1β, TNF-α, and IL-6 was observed to be high in the LPS treated animals (group II) indicating inflammation of lung tissue. Afzelin treated exhibited low level of IL-6, TNF-α, and IL-1β, indicating the anti-inflammation activity of afzelin. In rats treated with LPS, our histological findings showed pathological lung damage, which was in line with the biochemical findings and those from previous studies. High levels of neutrophils and macrophages, together with clear congestion, were indicators of this damage. After receiving afzelin treatment, there was a notable decrease in histological changes.

CONCLUSION

Our results ultimately indicated that afzelin could shield the lung against acute lung damage brought on by sepsis and ALI in rats with LPS. Oxidative stress was decreased in LPS-treated rats by afzelin administration, which also raised antioxidant levels and decreased ROS. Afzelin medication also decreased levels of TNF-α, IL-6, and IL-1β, among other inflammatory mediators. Furthermore, the treatment of afzelin reduced MDA, NO levels, W/D ratio, and lung injury. Thus, the rats receiving afzelin are protected from the inflammation and oxidative stress caused by LPS. Nevertheless, further corroborative studies are needed to thoroughly comprehend the exact molecular mechanisms underlying the acute lung injury and sepsis of afzelin caused by lipopolysaccharide.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

SOD: Superoxide dismutases; **ALI:** Acute lung injury; **LPS:** Lipopolysaccharide; **ROS:** Reactive oxygen species; **ELISA:** Enzyme linked immunosorbent assay; **TNF:** Tumor necrosis factor; **IL:** Interleukin; **NO:** Nitric oxide; **EDTA:** Ethylenediaminetetraacetic acid; **H&E:** Hematoxylin and eosin; **NS:** Normal saline; **W/D:** Wet to dry; **MDA:** Malondialdehyde; **CAT:** Catalase; **ARDS:** Acute respiratory distress syndrome; **R.H:** Relative humidity.

SUMMARY

The ameliorative action of afzelin against LPS-triggered sepsis mediated ALI were thoroughly examined in this work. In the course of the study, it decreases the activity of MDA, NO, ROS, lung injury, and inflammatory cytokines, indicating the anti-inflammatory and anti-oxidative properties of afzelin. Additionally, there was a substantial increase in the level of antioxidant enzymes demonstrating afzelin's antioxidant properties. Thus, it is anticipated that afzelin will be utilized as a therapeutic drug to reduce the sepsis mediated acute lung injury.

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