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Original Article

Isoliensinine Prevents against Lipopolysaccharide-induced Rat Acute Lung Injury and Sepsis via Inhibiting the Inflammatory Mediators

Lili Gao, Jie Qi*

Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Third Hospital of Shanxi Medical University, Tongji Shanxi Hospital, Taiyuan, CHINA.

ABSTRACT

Background: Novel pharmaceuticals have been largely derived from natural substances. Through this experimental study, we sought to assess the impacts of Isoliensinine (ILS) on Acute Lung Injury (ALI) and sepsis caused by Lipopolysaccharide (LPS) in rats. **Materials and Methods:** The rats were assigned to 3 different groups: control, LPS-induced and LPS+ILS. ILS exhibits a wet/dry weight ratio was measured. Blood Serum AST, ALT, ALP and hsCRP levels were measured. Also, levels of oxidative stress markers such as SOD, CAT, GPx and MDA were also analysed. ELISA was used to assess the quantities of inflammatory cytokine TNF-α, IL-1β, IL-6 and IL-10 and using a light microscope histopathological changes were examined. **Results:** ILS treatment dramatically enhanced lung tissue architecture while decreasing wet/dry weight ratio. It significantly inhibited the pro-inflammatory cytokine cascade. Group III (LPS+ILS) exhibited lower levels of ALT, AST, ALP and hsCRP. It has antioxidant properties by boosting the levels of SOD, CAT and GPx while decreasing MDA concentration. **Conclusion:** ILS has significant protective properties against LPS-induced lung damage as it lessens LPS-induced indications of lung injury while suppressing pro-inflammatory and oxidative stress markers. Thus, ILS could be a potential treatment for clinical ALI and sepsis. During the study, nurses emphasized the importance of monitoring vital signs, providing oxygen therapy, ensuring animal health, conducting ethical research and collecting accurate data for future research on ILS, which may have a potential for human use.

Keywords: Isoliensinine, Acute Lung Injury, Sepsis, Anti-Inflammatory, Lipopolysaccharide.

Correspondence:
Dr. Jie Qi
Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Third Hospital of Shanxi Medical University, Tongji Shanxi Hospital, Taiyuan-030032, CHINA.
Email: 13485322327@163.com

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INTRODUCTION

Globally, acute inflammatory disorders continue to be the leading cause of death in intensive care units. Examples of these diseases include sepsis and Acute Lung Injury (ALI), which are brought on by local or systemic inflammation. Sepsis and ALI are caused by infection, resulting in damage to various organs and tissues.[1] ALI is a fatal condition with a substantial mortality and morbidity rate brought on by burns, ischemia-reperfusion, sepsis and viral pneumonia. Changes in histopathology include diffuse lung alveolar infiltration, edema of the lungs, apoptosis and hyaline membrane formation.[2] End-stage renal failure is brought on by sepsis, an uncontrollably high level of host response to infection. As the most vulnerable organ, the lung is the first to be affected by sepsis, with acute cases occurs most frequently.[3] ALI includes the gradual activation of several inflammatory signaling pathways. Increased permeability of the capillaries and reduced endothelial function are the outcomes of the production of cytokines and inflammatory mediators that harm pulmonary capillary endothelial cells either directly or indirectly.

Lack of a specific and efficient treatment for ALI has resulted in extremely high rates of morbidity and mortality despite decades of dedicated efforts to address this illness. Consequently, it is critical to look into the pathogenic mechanisms behind ALI and create preventative measures. Lipopolysaccharide (LPS), a significant pathogenic component in ALI, can cause a severe inflammatory response and lung injury due to infiltration caused by inflammatory leukocytes.[4] The increased neutrophil concentration and proinflammatory cytokines generated result in diffuse pulmonary injury in the alveoli. Thus, minimizing inflammation caused by LPS is an exceptionally effective method to lessen the effects of ALI.[5] At the beginning of ALI, LPS activates the innate immune response and therefore is regarded as the primary microbial inducer of inflammation and is a key agent of sepsis.[6]

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Overexpression of pro-inflammatory cytokines is linked to inflammatory cell infiltration and inflammation, which are important in the pathophysiology of ALI and are also largely accountable for the emergence of tissue damage. LPS stimulates the release of proinflammatory cytokines like TNF-α, IL-1β and IL-6.[7] These cytokines are mostly produced by inflammatory cells and are present in high amounts in the lung. This stimulation of cytokine response accelerates the destruction of tissues present in the lung.[2] This damages the alveolar-capillary membrane and leads to pulmonary edema, hypoxia and respiratory failure. Furthermore, the inflammatory response causes an increase in Reactive Oxygen Species (ROS), which plays a key role in LPS-induced ALI. Furthermore, emerging data suggests that apoptosis plays a role in the pathophysiology of LPS-induced ALI.[8,9]

As an effective method for inducing a therapeutically relevant type of ALI in animal studies, LPS is extensively used in preclinical experimental research. Scientific findings and epidemiological evidence suggest that food-derived substances and natural plant components can help avoid inflammation-mediated illnesses. In Asia, this embryo is frequently used as a flavoring agent in common dishes like soup and tea.[10] Therefore, it may be concluded that ILS is a competent choice for selecting "drug-like" molecules. Indeed, ILS has a wide range of beneficial therapeutic properties. It has demonstrated promise in the treatment of cardiovascular illness.[11] ILS treatment significantly reduces blood pressure, increases and improves functional and pathological alterations in the abdominal aorta in SHRs, implying that ILS has antihypertensive properties.[12] In a prior work, ILS inhibited antihypertensive and vascular smooth muscle growth via the PI3K/AKT pathway. We postulated that ILS may possess preventive properties against ALI and sepsis caused by Lipopolysaccharide (LPS) in light of these results. Despite substantial investigation into such activities, the specific effects of ILS on acute inflammatory illness and its intended target are not well understood. As a result, in the current investigation, we explored the curative properties of ILS and its fundamental target on LPS-induced rat models. In addition, we sought to determine if ILS might lessen the degree of lung edema, injury and oxidative stress in a rat model of ALI and sepsis caused by Lipopolysaccharide Stress.

Monitoring and supportive care included monitoring vital signs, providing oxygen therapy and managing fluid levels. Data collection and analysis involved maintaining detailed records, statistical analysis and post-study care. The study's findings could pave the way for further research into ILS potential in human medicine. Key nursing interventions include vigilant monitoring of animal health, adequate administration of treatments, ethical and humane treatment of laboratory animals and accurate data collection and analysis to support research findings.

MATERIALS AND METHODS

Materials

Isoliensinine and Lipopolysaccharides were procured from Sigma-Aldrich (USA). Inflammatory cytokines ELISA kits procured from Thermo fisher scientific, USA. Prior to the start of the trial, all chemicals, reagents and kits were purchased commercially and made available.

Animals

The applicable national regulations and institutional policies for animal use and care were followed and rats were acquired from the Approved Animal Center with the appropriate ethical approval for animal experimentation study. Male adult Wistar albino rats weighing between 200 and 250 g were acquired. The animals were housed in polycarbonate cages and kept under regulated room temperature of 21±2°C and 45-55% relative humidity, with a 12-hr light-dark cycle. The rodents were fed conventional rat chow and had unfettered access to water and food.[13]

Grouping and treatment

All rats were allocated into 3 groups such as Group I comprised of a control group that had normal rats who received 100 µL of normal saline in oral form twice a day via an intragastric tube (gavage) for 2 days. Group II included rats that had been stimulated with LPS (5 mg/kg). Group III included rats that had been stimulated with LPS and treated with ILS (10 mg/kg) (each group had 6 of rats).

Effects of ILS on the wet/dry weight ratio

To assess edema in the lungs, the W/D ratio known as the wet/dry weight ratio was determined. After gathering the right upper lung, the wet Weight (W) was calculated by weighing the lung tissue directly and any surface blood and moisture were removed with filter paper. After 24 hr of drying at 80°C, the lung tissue was once again weighed to assess the Dry weight (D). These weights were used to compute lung tissue W/D ratios.[3]

Effects of ILS on measurement of oxidative stress biomarkers

To assess MDA, CAT, SOD and GPx levels in lung tissue was collected, homogenized and centrifuged at 4°C and 1500g for 15 min before being dissolved in extraction buffer. The supernatant was tested for Malondialdehyde (MDA) using the thiobarbituric acid colorimetric method and Superoxide Dismutase (SOD) was identified using a yellow purine oxidase method. Additionally, in accordance with the manufacturer's recommendations CAT and GPx levels were found to quantify antioxidative enzyme activity in the lung tissue.[14]

Effects of ILS on Serum biochemical enzymes parameters

The enzyme levels of AST, ALT and ALP and high sensitivity C-Reactive Protein (hs-CRP) were measured using a biochemical assay and the Diagnostic Modular Analyzer. The results were quantified in units/liter for the enzymes and milligrams per liter for hs-CRP.[6]

Effect of ILS on cytokine levels of pro-inflammatory cytokines

Pro-inflammatory cytokines TNF-α, IL-1β and IL-6, as well as the anti-inflammatory cytokine IL-10 quantities were measured using commercially available ELISA kits. Although IL-6 and IL-10 were assessed in serum, TNF-α and IL-1β were evaluated in the lung tissue. Cytokine levels were estimated using standard curves and the results were reported in pg/mL.[2]

Histological Examination

Histopathological investigation was performed on a part of the right lung lobe. For 48 hr, the samples of lung tissue were kept in 10% neutrally treated formalin. Once the samples were fixed, they were washed with tap water, dried in graded ethanol, cleaned with xylene and coated with paraffin. After being sectioned at a thickness of 5 µm using a rotary microtome, the paraffin blocks were stained with H&E. Two pathologists who were not aware of the groups examined and rated histopathological changes. H&E-stained lung slides were used to grade the degree of intraalveolar edema, hemorrhage and neutrophil permeation. The scores ranged from 0-4 of which 0 indicated no negative impact, 1 had mild change, 2 with moderate symptoms, 3 notifying severe change and 4 being the representation of overpowering neurological impairment. The image analysis system and light microscope were used for all histopathology examinations.[2]

Statistical Analysis

The statistical analysis was performed using GraphPad Prism. A one-way ANOVA was performed to compare differences across groups. The student *t*-test was applied to compare the differences between the two groups. A statistically significant variation was defined as $p<0.05$ between the controls and induced animal groups.

RESULTS

Effects of ILS on the wet/dry weight ratio

According to the findings presented in Figure 1, rats that were exposed to LPS possessed a greater W/D ratio than control. This suggests the existence of inflammatory cell infiltration and lung edema. However, group III had a lower W/D ratio than group II.

Effects of ILS on measurement of oxidative stress biomarkers

Figure 2 (a-d) the level of MDA in the lung tissue of the LPS group was found to be significantly higher in comparison to that of the control group. On the other hand, the levels of SOD, CAT and GPx were significantly decreased in the LPS group. In contrast, the lung tissue of the LPS+ILS group exhibited significantly reduced levels of MDA in contrast to the LPS induced rats. Moreover, the expression of SOD, GPx and CAT in the lung tissue of the LPS+ILS group was significantly increased.

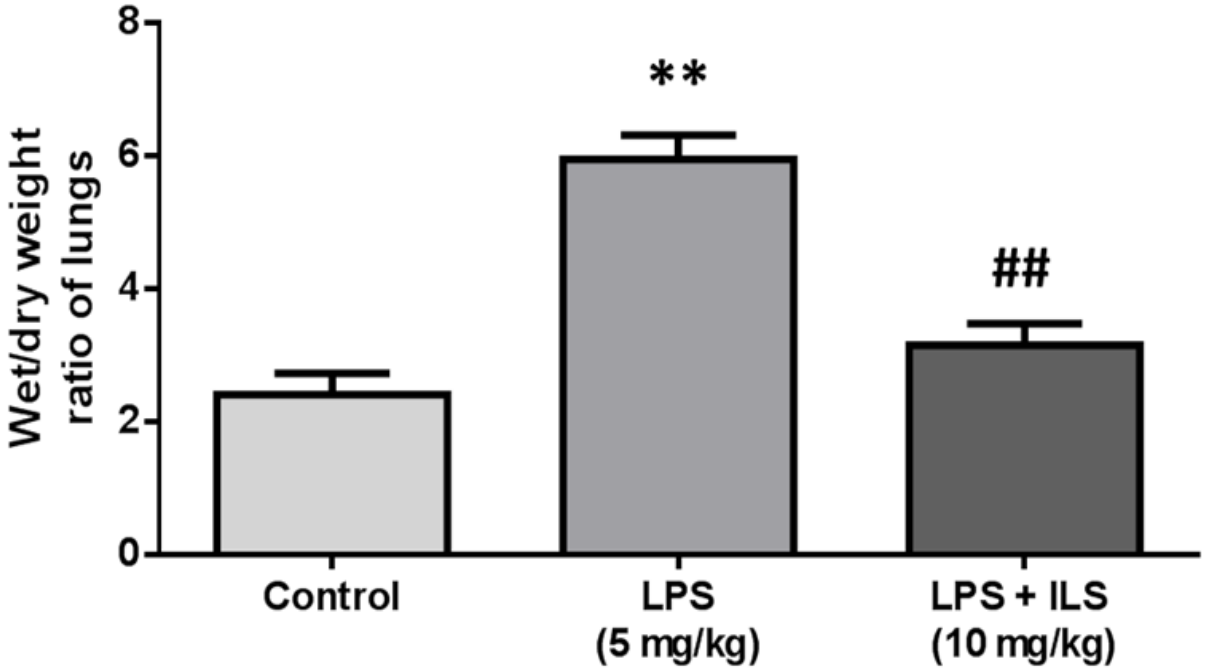

Figure 1: ILS lowered the lung W/D ratio in rats with LPS-induced ALI. The data is shown as mean±S, with $^{**}p<0.05$ compared to the control group and $^{\#\#}p<0.05$ compared to rats treated with LPS.

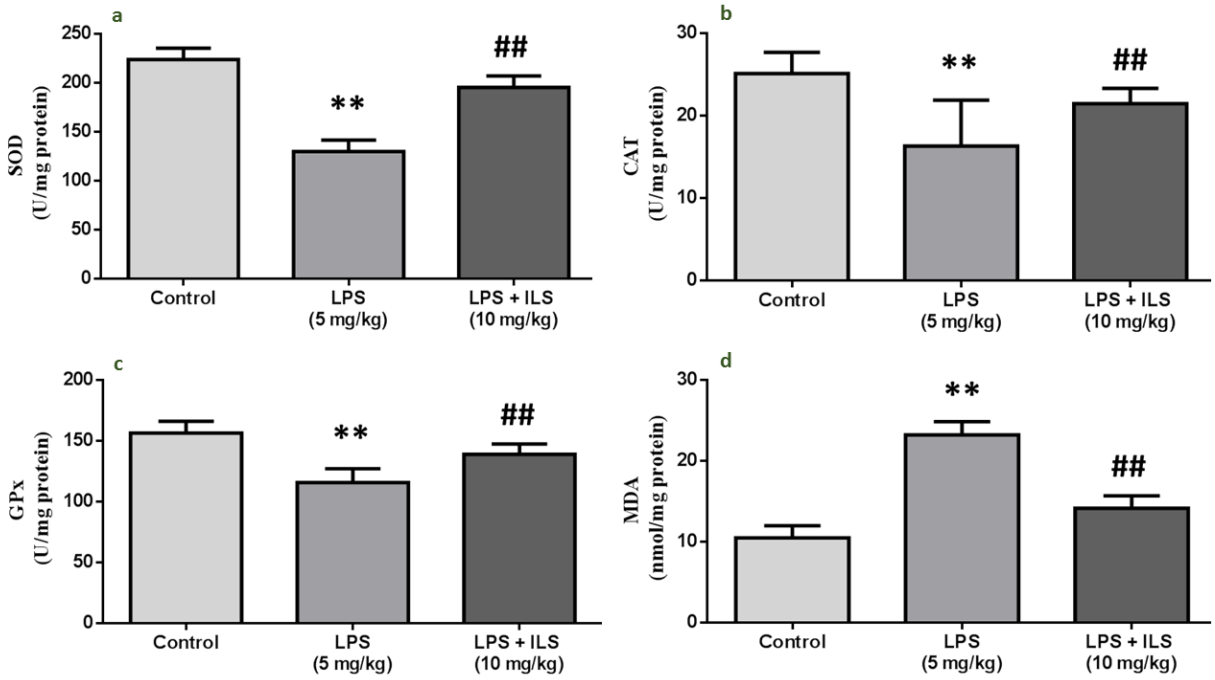

Figure 2: In lung tissue, expression of oxidative indicators. The data is shown as mean±SD. The LPS+ILS group showed higher levels of (a) SOD, (b) CAT and (c) GPx. In group III rats, however, the expression of (d) MDA was reduced. $^{**}p<0.05$ compared to control group; $^{\#\#}p<0.05$ compared to rats treated with LPS and vehicle.

Effects of ILS on Serum biochemical enzymes parameters

Figure 3 the LPS-induced group showed significantly higher levels of ALT, AST, ALP and hsCRP compared to the control group. The LPS induced+ ILS group showed substantial decreases in ALT, AST, ALP and hsCRP levels contrast to the LPS induced rats. The serum levels of ALT, AST, ALP and hsCRP differed only slightly between the control and ILS groups.

Effect of ILS on cytokine levels of inflammatory cytokines

Based on the aforementioned results, we looked into ILS possible ability to prevent inflammation in rats with ALI and sepsis caused by LPS. Thus, ELISA was used to measure the levels of TNF-, IL-1 β, IL-6 and IL-10. The LPS group showed significantly higher levels of TNF-α and IL-1β in lung tissue samples than the control group. Similarly, IL-6 levels in serum samples were higher in the LPS group than in the control group. In addition, LPS stimulation reduced IL-10 levels. ILS treatment significantly reduced the expression of TNF-α, IL-1β and IL-6 in the LPS+ ILS group in contrast to the LPS group. In addition, ILS therapy increased IL-10 levels in serum as compared to the LPS group Figure 4 (a-d).

Histological Examination

The control group's lung tissue had normal architecture and clean alveoli, with no congestion or edema visible under the microscope. In contrast, lung tissue from the LPS group showed a numerous infiltrating inflammatory cell, edema and thickening of alveolar wall. ILS significantly improved lung histology, alleviating negative effects like pulmonary edema Figure 5 (a-c). The lung injury score of group II increased considerably to that of group I. ILS significantly reduced the lung damage score in LPS-treated rats.

DISCUSSION

Despite advances in clinical treatment, acute inflammatory disorders continue to be the leading reason for death in critical care units across the globe. The foremost prevalent tissue harm caused by sepsis is ALI.[3] Oxidative stress, mitochondrial dysfunction and a dysregulated immunological response are the hallmarks of sepsis, a leading cause of death worldwide.[6] ALI, defined by an assortment of clinical characteristics (early onset of bilateral pulmonary infiltrates with hypoxemia in the absence of hydrostatic pulmonary edema), has a high incidence of 200,000 per year in the United States and a high overall fatality rate. ALI is caused by injury to both the vascular endothelium and the alveolar epithelium.[15] Sepsis is a difficult condition to treat. The heterogeneity of presentation, resemblance to other inflammatory conditions and disease duration make identification difficult and mortality stays high notwithstanding global efforts to improve treatment.[16]

A significant contributor to the pathophysiology of ALI and Acute Respiratory Distress Syndrome (ARDS), lipopolysaccharide is thought to be one of the major inducers of pulmonary inflammation and the release of proinflammatory cytokines across the lungs. A powerful inducer of sepsis and acute inflammation,

lipopolysaccharide-is regarded as the endotoxin that constitutes the outer membrane of bacteria.[2]

In other words, novel medicines must be created to improve clinical results. Anti-inflammatory medications, both steroidal and nonsteroidal have limited effectiveness in treating sepsis and ALI. The most common cause of death in intensive care units is still sepsis, which makes it difficult to treat. Despite this, more than 30 pharmaceutical candidates have been developed or are presently in the development stage for the treatment of sepsis. One potential approach to treating and preventing septic shock and its associated diseases is the intervention of the inflammatory response.[1] As a result, the ongoing study aimed to evaluate if ILS has anti-inflammatory and antioxidant properties in LPS-induced acute lung damage and septic rats.

Both *in vitro* and *in vivo* studies, ILS has demonstrated therapeutic effects in a variety of disorders. Following investigations, it was discovered that ILS could be extracted from all sections of the lotus, including the leaf, rhizome and seed. However, the composition of different alkaloids extracted from the same portion of the plant varies according on the origin and manner of lotus dissection. Thus, the data available validates ILS as a natural product with a variety of beneficial effects against various diseases. Additionally, due to its origin from an edible plant, it is safer than many compounds that are made chemically.[17]

In line with earlier research, the study discovered that the treatment of LPS significantly increased the ration of wet/dry weight, showcasing the presence of lung edema and inflammatory cell infiltration. After hesperetin treatment, the LPS with hesperetin group had a considerably lower W/D ratio than the LPS group.[2,18] Accordingly, the LPS-induced rats displayed increased LPS levels and ILS demonstrated significantly higher activity in lowering the W/D ratio than in earlier research. Disequilibrium between ROS and antioxidant defense mechanisms happens during sepsis and elevated ROS cause organ failure and cellular damage. The bulk of sepsis cases result from bacterial infection of the blood. Cell apoptosis and necrosis are ultimately caused by lipid peroxidation, which also deteriorates mitochondrial and cellular membranes. Changes in MDA levels, a consequence of lipid peroxidation and in the activity of SOD, which is crucial for scavenging ROS, are major indicators of how well the body is able to scavenge ROS and halt oxidative damage to lipids.[6,3] ILS antioxidant capacity is demonstrated in the current study by its effective rise in SOD, CAT and GPx activities as well as its decrease in MDA content.

Well-known markers of LPS-induced hepatic injury include elevated blood liver enzymes that show cellular leakage and loss of hepatocellular membrane function. According to the previous study, the sepsis group had higher AST, ALT and ALP concentrations in their serums. Elevated levels of serum hepatic marker enzymes suggest that LPS causes substantial liver damage by free radical generation, leading to increased leakage of intracellular enzymes.[6] In the present investigation, administering isoliensinine to septic rats resulted in a reduction in the parameters under investigation. This could imply that isoliensinine can mitigate the harmful effect of LPS on the liver. According to certain clinical states, CRP is a valid indicator of sepsis that may help with early identification of a serious bacterial infection and prognosis guidance. Elevated serum CRP levels are linked to an increased risk of organ failure and death.[19] Compared

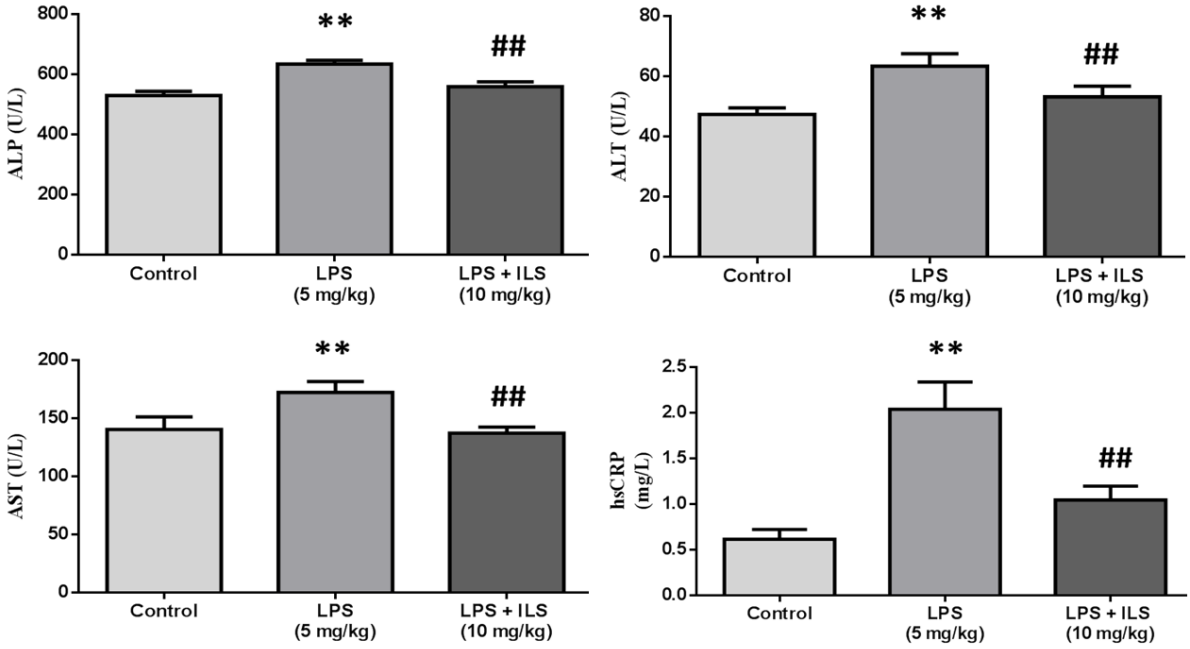

Figure 3: The effects of ILS on the serum biochemical enzyme parameters high sensitivity Creative protein ALP, ALT, AST and hsCRP. $^{**}p<0.05$ when compared to the control group; $^{\#\#}p<0.05$ when compared to rats treated with LPS.

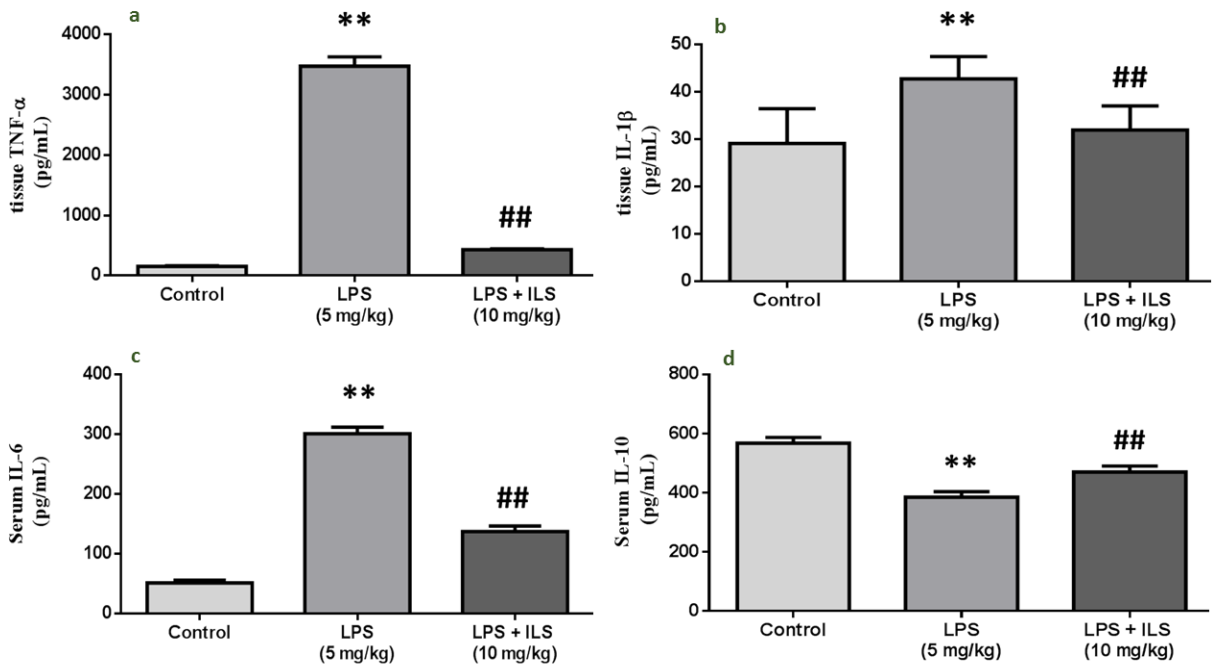

Figure 4: ILS effect on pro-inflammatory cytokine levels (a) TNF-a, (b) IL-1β, (c) IL-6 and anti-inflammatory cytokine levels IL-10 (d) was observed. TNF-α and IL-1β affect lung tissue and IL-6 and IL-10 in the serum. $^{**}p<0.05$ when compared to the control group; $^{\#\#}p<0.05$ when compared to rats treated with LPS.

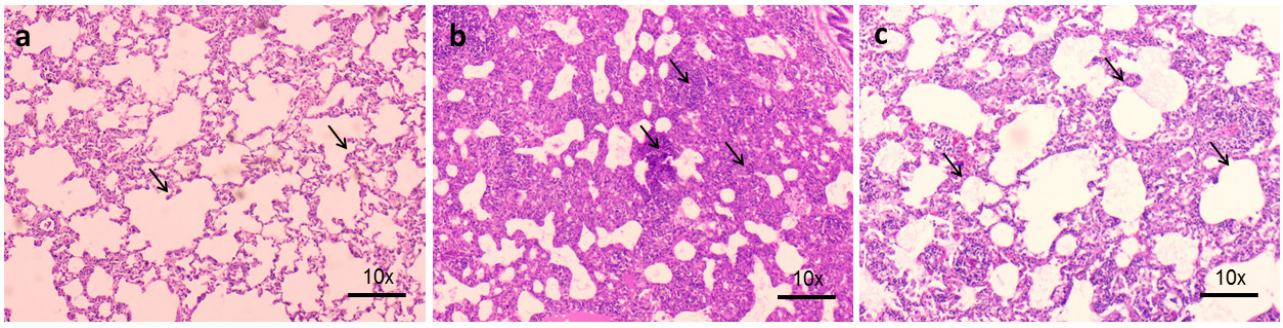

Figure 5: In LPS-challenged rats, ILS protects against lung damage. Lung sample preparation involved sectioning, staining with H&E (10x) and fixing in 10% formalin. The results demonstrate H&E staining of lung tissue slices from the (a) control, (b) LPS-induced and (c) LPS+ILS groups.

to control groups, septic rats in this study exhibited higher levels of hsCRP. Nonetheless, the LPS+ILS group's hsCRP was inhibited by ILS anti-inflammatory properties. Sepsis and ALI research has primarily focused on the innate immune system, with the concept of sepsis/ALI being seen as a hyperinflammation illness. Dysregulation of cytokines during acute inflammation is linked to sepsis and ALI, according to emerging data.

The overabundance of pro-inflammatory cytokines, primarily TNF-α, IL-6, IL-1β, IL-12 and IL-8, leads to an immediate cellular and/or organic injury that develops into sepsis or ALI. Early detection and treatment of acute inflammatory illnesses is crucial, as they are often linked to lung harm. Anti-inflammatory candidates that suppress cytokine production, such as IL-6 and TNF-α, have shown promise in preventing and treating sepsis and ALI.[1,20] In LPS-stimulated rats, ILS inhibited the production of TNF-α, IL-1β and IL-6. It also boosted the levels of IL-10 in the group III rats. We found that ILS reduced pro-inflammatory expressions cytokines in an LPS-induced animal model, hence inhibiting inflammation.

The investigation revealed that the histological structure of lung tissue in the control group was nearly normal. In the LPS-induced group, we found lung deterioration, localized necrosis, mononuclear leukocyte infiltration and blood vessel congestion. Furthermore, lung tissue showed evidence of alveolar hemorrhage. ILS treatment of LPS-induced rats' lungs resulted in essentially normal alveolar structure. To summarize, alterations to the chemical structure and other rational decorating techniques can help modify the structure of ILS, making it a lead compound with greater curative effects for treating lung injuries. Our investigation found that ILS effectively decreased lung damage in LPS-induced rat models.

CONCLUSION

In a model of acute lung damage caused by lipopolysaccharide in rats, ILS improved histopathological changes, lung edema, inflammatory response targeting TNF-alpha, IL-6 and IL-1 beta, oxidative stress response and serum biochemical enzyme parameters. Together, these effects lessen lung damage and offer a theoretical basis for the therapeutic use of ILS to enhance prognosis in cases of acute lung injury and sepsis caused by lipopolysaccharide. Overall, our results correspond to ILS to enhance prognosis in cases of acute lung injury and sepsis caused by lipopolysaccharide and further investigation into the aforementioned framework may lead to the development of a potent acute lung injury and sepsis caused by lipopolysaccharide. Nevertheless, further corroborative studies are needed to thoroughly comprehend the exact molecular mechanisms underlying the acute lung injury and sepsis of ILS against caused by lipopolysaccharide

ETHICAL STATEMENT

The study was approved by the Ethics Committee of Shanxi Bethune Hospital, Taiyuan, China (YXLL-2023-288).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ELISA: Enzyme-linked immunosorbent assay; **SD:** Standard deviation; **ANOVA:** Analysis of variance; **GPx:** Glutathione peroxidase; **SOD:** Superoxide dismutase; **MDA:** Malondialdehyde; **CAT:** Catalase; **TNF:** Tumour necrosis factor; **IL:** Interleukin; **ROS:** Reactive oxygen species; **RNS:** Reactive nitrogen species; **LPS:** Lipopolysaccharide; **H&E:** Hematoxylin and eosin; **ALI:** Acute lung injury; **ARDS:** Acute respiratory distress syndrome; **DNA:** Deoxyribonucleic acid; **EB:** Evans blue; **CLP:** Cecal ligation and puncture; **BALF:** Bronchoalveolar lavage fluid; **AST:** Aspartate transaminase; **ALT:** Alanine transaminase ; **ALP:** Alkaline phosphatase; **hsCRP:** High-sensitivity C-reactive protein.

SUMMARY

Sepsis and acute lung injury caused by LPS have been reported to be considerably reduced by ILS by suppressing inflammatory markers. This natural compound's anti-inflammatory properties are derived from its ability to inhibit proinflammatory indicators. Additionally, ILS has been shown to enhance the survival rate of rats treated with LPS, indicating its potential in the treatment of sepsis and acute lung injury.

REFERENCES

1. Cai X, Chen Y, Xie X, Yao D, Ding C, Chen M. Astaxanthin prevents against lipopolysaccharide-induced acute lung injury and sepsis via inhibiting activation of MAPK/NF-κB. Am J Transl Res. 2019;11(3):1884-94. PMID 30972212.
2. Kaya S, Kaya SA, Polat E, Erboğa ZF, Duran Y, Polat FR, *et al*. Protective effects of hesperetin on lipopolysaccharide-induced acute lung injury in a rat model. Turk J Thorac Cardiovasc Surg. 2020;28(2):359-68.
3. Wang Y, Yang W, Zhao X, Zhang R. Experimental study of the protective effect of simvastatin on lung injury in rats with sepsis. Inflammation. 2018;41(1):104-13. doi: 10.1007/s10753-017-0668-4, PMID 29022140.
4. Kumar V. Pulmonary innate immune response determines the outcome of inflammation during pneumonia and sepsis-associated acute lung injury. Front Immunol. 2020;11:1722. doi: 10.3389/fimmu.2020.01722, PMID 32849610.
5. Wu YX, Wang YY, Gao ZQ, Chen D, Liu G, Wan BB, *et al*. Ethyl ferulate protects against lipopolysaccharide-induced acute lung injury by activating AMPK/Nrf2 signaling pathway. Acta Pharmacol Sin. 2021;42(12):2069-81. doi: 10.1038/s41401-021-00742-0, PMID 34417573.
6. Bayraktar O, Tekin N, Aydın O, Akyuz F, Musmul A, Burukoglu D. Effects of S-allyl cysteine on lung and liver tissue in a rat model of lipopolysaccharide-induced sepsis. Naunyn-Schmiedebergs Arch Pharmacol. 2015;388(3):327-35. doi: 10.1007/s00210-014-1076-z, PMID 25480742.
7. Kamali AN, Zian Z, Bautista JM, Hamedifar H, Hossein-Khannazer N, Hosseinzadeh R, *et al*. The potential role of pro-inflammatory and anti-inflammatory cytokines in epilepsy pathogenesis. Endocrine, metabolic & immune disorders-drug targets (formerly current drug targets-immune, endocrine & metabolic disorders). 2021;21(10):1760-74.
8. Fouad AA, Albuali WH, Jresat I. Protective effect of naringenin against lipopolysaccharide-induced acute lung injury in rats. Pharmacology. 2016;97(5-6):224-32. doi: 10.1159/000444262, PMID 26872264.
9. Nova Z, Skovierova H, Calkovska A. Alveolar-capillary membrane-related pulmonary cells as a target in endotoxin-induced acute lung injury. Int J Mol Sci. 2019;20(4):831. doi: 10.3390/ijms20040831, PMID 30769918.
10. Ravichandran N, Suresh G, Ramesh B, Siva GV. Fisetin, a novel flavonol attenuates benzo (a) pyrene-induced lung carcinogenesis in Swiss albino mice. Food Chem Toxicol. 2011;49(5):1141-7. doi: 10.1016/j.fct.2011.02.005, PMID 21315788.
11. Yao M, Wu M, Yuan M, Wu M, Shen A, Chen Y, *et al*. Enhancing the therapeutic potential of isoliensinine for hypertension through PEG-PLGA nanoparticle delivery: A comprehensive *in vivo* and *in vitro* study. Biomed Pharmacother. 2024;174:116541. doi: 10.1016/j.biopha.2024.116541, PMID 38565063.
12. Yao M, Lian D, Wu M, Zhou Y, Fang Y, Zhang S, *et al*. Isoliensinine attenuates renal fibrosis and inhibits TGF-β1/Smad2/3 signaling pathway in spontaneously hypertensive rats. Drug Des Dev Ther. 2023;17:2749-62. doi: 10.2147/DDDT.S414179, PMID 37701045.
13. Zhao P, Zhou RU, Zhu XY, Hao YJ, Li N, Wang J, *et al*. Matrine attenuates focal cerebral ischemic injury by improving antioxidant activity and inhibiting apoptosis in mice. Int J Mol Med. 2015;36(3):633-44. doi: 10.3892/ijmm.2015.2260, PMID 26135032.
14. Lv H, Yu Z, Zheng Y, Wang L, Qin X, Cheng G, *et al*. Isovitexin exerts anti-inflammatory and anti-oxidant activities on lipopolysaccharide-induced acute lung injury by inhibiting MAPK and NF-κB and activating HO-1/Nrf2 pathways. Int J Biol Sci. 2016;12(1):72-86. doi: 10.7150/ijbs.13188, PMID 26722219.
15. Johnson ER, Matthay MA. Acute lung injury: epidemiology, pathogenesis and treatment. J Aerosol Med Pulm Drug Deliv. 2010;23(4):243-52. doi: 10.1089/jamp.2009.0775, PMID 20073554.
16. Lonsdale DO, Shah RV, Lipman J. Infection, sepsis and the inflammatory response: mechanisms and therapy. Front Med (Lausanne). 2020;7:588863. doi: 10.3389/fmed.2020.588863, PMID 33344475.
17. Cheng Y, Li HL, Zhou ZW, Long HZ, Luo HY, Wen DD, *et al*. Isoliensinine: a natural compound with "drug-like" potential. Front Pharmacol. 2021;12:630385. doi: 10.3389/fphar.2021.630385, PMID 33967765.
18. Kaur J, Rana P, Matta T, Sodhi RK, Pathania K, Pawar SV, *et al*. Protective effect of olopatadine hydrochloride against LPS-induced acute lung injury: via targeting NF-κB signaling pathway. Inflammopharmacology. 2024;32(1):603-27. doi: 10.1007/s10787-023-01353-3, PMID 37847473.
19. Duncan CF, Youngstein T, Kirrane MD, Lonsdale DO. Diagnostic challenges in sepsis. Curr Infect Dis Rep. 2021;23(12):22. doi: 10.1007/s11908-021-00765-y, PMID 34720754.
20. Matthay MA, Zemans RL, Zimmerman GA, Arabi YM, Beitler JR, Mercat A, *et al*. Acute respiratory distress syndrome. Nat Rev Dis Primers. 2019;5(1):18. doi: 10.1038/s41572-019-0069-0, PMID 30872586.

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