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Madecassic acid attenuates sepsis-associated acute lung injury by regulating the PI3K/AKT/mTOR pathway to mediate anti-inflammatory, antioxidant and anti-apoptotic effects

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Abstract: **Background**: Sepsis-induced acute lung injury (ALI) is a critical illness with a high mortality rate. Madecassic acid (MA), a pentacyclic triterpenoid extracted from *Centella asiatica*, exhibits multiple biological activities, but its role in sepsis-associated ALI remains poorly elucidated. **Objectives**: The aim of this study was to investigate the protective effect of MA on lipopolysaccharide (LPS)-induced ALI in mice and to elucidate its potential mechanisms in regulating inflammation, oxidative stress, apoptosis and the PI3K/AKT/mTOR signaling pathway. **Methods**: An ALI mouse model was established by intraperitoneal LPS injection. The mice were randomly divided into a sham operation group, an MA alone group, an LPS model group and an LPS combined with MA treatment group. The degree of lung injury was assessed via histopathological examination of the lungs and the lung wet/dry weight ratio; the levels of inflammatory factors (TNF-α and IL-6) and oxidative stress markers (MPO, MDA, SOD and GSH-Px) in the bronchoalveolar lavage fluid (BALF) were measured; and the expression of apoptosis-related proteins and PI3K/AKT/mTOR pathway activation in the lung tissues were detected via Western blotting. **Results**: MA treatment significantly reduced LPS-induced lung tissue injury, edema and inflammatory cell infiltration; decreased the levels of proinflammatory factors (TNF-α and IL-6); improved oxidative stress parameters (decreased MPO and MDA levels and increased SOD and GSH-Px levels); inhibited apoptosis (downregulated Bax and cleaved caspase-3 expression and upregulated Bcl-2 expression); and inhibited the phosphorylation of PI3K, AKT and mTOR. **Conclusion**: MA attenuates sepsis-associated ALI through anti-inflammatory, antioxidant and anti-apoptotic effects and this mechanism is related to inhibiting the activation of the PI3K/AKT/mTOR signaling pathway. MA has the potential to be a therapeutic agent for sepsis-associated ALI.

Keywords: Acute lung injury; Apoptosis; Madecassic acid; Oxidative stress; PI3K/AKT/mTOR signaling pathway; Sepsis

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INTRODUCTION

Acute lung injury (ALI) and its severe form, acute respiratory distress syndrome (ARDS), are significant causes of high morbidity and mortality in critically ill patients (Liu *et al.*, 2025; Al-Husinat *et al.*, 2025; Vaughn *et al.*, 2024). The COVID-19 pandemic has further highlighted the global burden of ALI/ARDS (Ma *et al., 2025*). Sepsis is the primary cause of ALI/ARDS and its core mechanism lies in the dysregulation of the host response to infection, which in turn triggers a wide range of inflammatory responses, oxidative stress and apoptosis in the lung microenvironment (Qiao *et al.*, 2024; Barkat *et al.*, 2025). Despite an in-depth understanding of its pathogenesis, current treatments for sepsis-associated ALI are still based on supportive measures and effective pharmacological interventions are urgently needed (Fu *et al.*, 2026).

The pathological cascade in ALI involves complex cellular and molecular interactions, including NLRP3 inflammasome activation, the disruption of pulmonary vascular endothelial integrity and the recruitment of inflammatory cells such as neutrophils (Chung *et al*., 2024; Luo *et al*., 2025). Recent studies have explored the therapeutic potential of natural compounds for targeting these pathways. Several phytochemicals have been demonstrated to alleviate ALI by inhibiting inflammatory signaling pathways and protecting alveolar-capillary barrier function (Shen *et al*., 2024; Yang *et al.*, 2025).

The PI3K/AKT/mTOR signaling pathway plays a critical role in regulating cell survival, inflammatory responses and metabolic processes (Jiang *et al.*, 2025). The activation of this pathway can inhibit apoptosis, reduce oxidative stress and alleviate inflammatory responses in experimental lung injury models (Ni *et al.*, 2025; Pan *et al.*, 2023). In addition, the PI3K/AKT/mTOR axis is critical for maintaining endothelial barrier function and its dysfunction is closely associated with vascular hyperpermeability in ALI (Wang *et al.*, 2024; Zhao *et al.*, 2024). Thus, this pathway has emerged as an important therapeutic target in ALI.

Madecassic acid (MA) is a pentacyclic triterpenoid isolated from *Centella asiatica* that has received much

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attention because of its anti-inflammatory, antioxidant and anti-apoptotic properties (Lin *et al.*, 2023). MA has been shown to inhibit NF-κB activation and regulate the PI3K/AKT signaling pathway in skeletal muscle disease models (Fu *et al.*, 2022) while exhibiting antibacterial activity against pathogens such as *Staphylococcus aureus* (Wei *et al*., 2023). *In-silico* analysis also revealed potential interactions with SARS-CoV-2 targets, suggesting broader therapeutic implications (Ganguly *et al.*, 2023). However, studies on whether MA exerts a lung-protective effect in sepsis-associated ALI and whether its protective mechanism involves the PI3K/AKT/mTOR pathway are lacking. In view of the central role of this pathway in regulating cell survival and the inflammatory response, this study proposes that MA may synergistically regulate inflammation, oxidative stress and apoptosis by regulating the PI3K/AKT/mTOR signaling pathway, thereby alleviating LPS-induced ALI in mice.

MATERIALS AND METHODS

Animals and groups

SPF eight-week-old C57BL/6 mice (weighing 25 ± 5 g) were selected and maintained under controlled environmental conditions (temperature, 25 ± 2 °C; humidity, 55 ± 5%; alternating 12-hour light–dark cycle) with free access to food and water. All experimental procedures were approved by the Ethics Committee of Shanghai Pudong New Area People's Hospital (approval number: 2022-D-62) and conducted in strict accordance with the institution's relevant guidelines. After 1 week of adaptive feeding, the mice were randomly divided into 4 groups (8 mice in each group): the sham operation group (sham), the madecassic acid alone group (MA), the lipopolysaccharide model group (LPS) and the lipopolysaccharide combined with madecassic acid group (LPS + MA). ALI models were established via a single intraperitoneal injection of LPS (10 mg/kg; L2630; Sigma-Aldrich) (Han *et al.*, 2023). MA (T2758; TargetMol) dissolved in physiological saline containing 1% DMSO was administered intraperitoneally at a dose of 100 mg/kg, 1 hour and 15 minutes before LPS injection; this dose was determined based on previous studies (Cabrera-Rivera *et al.*, 2022; Du *et al.*, 2024). The sham and LPS groups were injected with an equal volume of vehicle at the corresponding time points. Twenty-four hours after LPS treatment, the mice were sacrificed by carbon dioxide inhalation and lung tissues and bronchoalveolar lavage fluid (BALF) were collected for subsequent analysis.

Histopathological examination of the lung

The right upper lobe was fixed in 4% paraformaldehyde, embedded in paraffin, cut into 5-μm sections and stained with hematoxylin-eosin (H and E, HE-3-500, KOHYPATH). Pathological changes, such as alterations in the alveolar structure, inflammatory cell infiltration and pulmonary edema, were observed under a light microscope (E100, NIKON, Japan). A semiquantitative scoring system (0–4 points, with higher scores representing more severe injury) was used to assess the degree of lung tissue injury and the scoring was independently performed by two pathologists who were blinded to the experimental groups. Five high-power fields (400×) were randomly selected from each section for observation and the mean score was calculated.

Lung wet/dry weight ratio determination

The lung tissues were removed from the mice and weighed to determine the wet weight. The tissues were then dried in an oven (YD-B, SPI, Shanghai, China) at 60℃ to a constant weight, after which the dry weight was measured. The lung wet-to-dry weight ratio was calculated to assess the extent of pulmonary edema, with higher ratios indicating greater fluid accumulation.

Inflammatory factor testing

The TNF-α (EK282EG, MultiSciences) and IL-6 (EK206, MultiSciences) levels in the BALF were measured using ELISA kits and the procedures were performed according to the manufacturer's instructions. The absorbance was measured using a microplate reader (Multiskan FCT, Thermo Scientific, USA) and the concentrations were determined from the standard curves generated.

Oxidative stress factor testing

In accordance with the kit instructions, the MPO (BC5715, Solarbio), SOD (BC5165, Solarbio) and GSH-Px (BC1195, Solarbio) activities and the MDA (BC6415, Solarbio) levels in the BALF were measured using a microplate reader (Multiskan FC, Thermo Scientific, USA).

Protein expression analysis

Total protein was extracted from the lung tissues and separated via SDS-PAGE before being transferred to membranes. The membranes were then incubated with the corresponding primary antibodies: Bax (2772, CST), Bcl-2 (3498, CST), cleaved caspase-3 (9661, CST), p-PI3K (4228, CST), PI3K (4292, CST), p-AKT (4060, CST), AKT (9272, CST), p-mTOR (2971, CST), mTOR (2972, CST) and GAPDH (2118, CST). Subsequently, the proteins were incubated with secondary antibodies and visualized via chemiluminescence. The gray values of the bands were analyzed using ImageJ software, normalized to GAPDH as an internal control and then used to calculate the relative protein expression levels.

Statistical analysis

The data are presented as mean ± SD and were evaluated using GraphPad Prism 9.0. Group comparisons were performed using one-way ANOVA with Tukey's post hoc test after the assessment of normality and homoscedasticity. A two-sided alpha of 0.05 was used.

RESULTS

Effects of MA on lung injury in ALI mice

The results of the H and E staining (Fig. 1A) revealed no significant abnormalities in the alveolar structures of the mice in the sham and MA groups. In the LPS group, severe lung injury, significant thickening of the alveolar walls, massive inflammatory cell infiltration and erythrocyte exudation were detected; these pathological changes were significantly improved after MA intervention. Compared with those in the sham group, the lung injury scores (Fig. 1B) and lung wet/dry weight ratios (Fig. 1C) were significantly greater in the LPS group; these parameters were significantly lower after MA intervention, suggesting that MA can reduce LPS-induced lung injury and pulmonary edema.

Effects of MA on inflammatory factors

The results of proinflammatory factor detection in the BALF (Figs. 2A and 2B) revealed that TNF-α and IL-6 levels were significantly higher in the LPS group than in the sham group, and that these cytokine levels decreased significantly after MA intervention. The results of the MA alone group did not significantly differ from those of the sham group, indicating that MA specifically inhibited LPS-induced inflammatory responses.

Effects of MA on oxidative stress factors

Compared with those in the sham group, the levels of oxidative stress markers in the BALF (Figs. 3A-D) showed that MPO activity and MDA content were significantly increased and SOD and GSH-Px activities were significantly decreased in the LPS group. These changes were significantly reversed after MA intervention. There were no significant differences between the sham group and the MA alone group, indicating that MA effectively alleviated LPS-induced oxidative stress injury in the lungs without affecting the basal redox status.

Effects of MA on apoptosis-related proteins

The Western blot results (Fig. 4) revealed that the expression of the pro-apoptotic proteins Bax and cleaved caspase-3 was significantly upregulated and that the expression of the anti-apoptotic protein Bcl-2 was significantly downregulated in the LPS group compared with the sham group; these changes were significantly reversed after MA intervention. MA alone did not significantly affect basal apoptotic signaling, indicating that MA inhibited LPS-induced apoptosis.

Effects of MA on the PI3K/AKT/mTOR signaling pathway

To investigate the underlying mechanism, the activation status of the PI3K/AKT/mTOR pathway was examined. The Western blot results (Figs. 5A and 5B) revealed that the expression levels of p-PI3K, p-AKT and p-mTOR significantly increased in the LPS group compared with those in the sham group, while the expression of total PI3K, AKT and mTOR did not significantly change; moreover, p-PI3K, p-AKT and p-mTOR expression significantly decreased after MA intervention. These results suggest that MA inhibits phosphorylation-mediated activation of the PI3K/AKT/mTOR pathway without altering total protein expression, which may be an important molecular mechanism by which MA attenuates LPS-induced lung injury.

DISCUSSION

In this study, it was revealed that madecassic acid significantly reduced LPS-induced acute lung injury in mice, as shown by the alleviation of pulmonary edema, inflammatory cell infiltration and histopathological damage. Its protective effect is closely related to the inhibition of proinflammatory factor release, the alleviation of oxidative stress and the inhibition of apoptosis. In addition, MA inhibited the phosphorylation and activation of the PI3K/AKT/mTOR signaling pathway, suggesting that this pathway may mediate the multiple protective effects of MA.

Inflammation and oxidative stress play key roles in the development of ALI (Cabrera-Rivera *et al.*, 2022; Joffre and Hellman, 2021). TNF-α and IL-6 are important proinflammatory factors and their overexpression exacerbates inflammation and tissue injury (Chen *et al.*, 2021). In this study, TNF-α and IL-6 levels in the BALF were significantly increased in the LPS group but decreased after MA treatment, indicating that MA has anti-inflammatory effects. Decreased MPO activity, a marker of neutrophil infiltration, further suggests that MA exerts anti-inflammatory effects by inhibiting immune cell recruitment (Lin *et al.*, 2024). Tests of oxidative stress markers revealed that MA reversed LPS-induced increases in MDA activity and decreases in SOD and GSH-Px activities, highlighting its antioxidant capacity (Yang *et al.*, 2016). These dual anti-inflammatory and antioxidant effects may be associated with the regulation of the PI3K/AKT/mTOR pathway (Yu *et al.*, 2026).

Apoptosis also plays an important role in ALI (Chen *et al.*, 2023). In this study, LPS upregulated Bax and cleaved caspase-3 expression and downregulated Bcl-2 expression, whereas MA reversed these changes. This suggests that MA attenuates apoptosis in the lung tissues and that its anti-apoptotic effect is associated with the regulation of the PI3K/AKT/mTOR pathway, which promotes cell survival (Xu *et al.*, 2024).

In this study, it was further revealed that the protective effect of MA in an ALI model was associated with specific inhibition of the PI3K/AKT/mTOR pathway. The phosphorylation of PI3K, AKT and mTOR in the lung tissues was significantly increased in the LPS group (while total protein expression was unchanged), suggesting that excessive activation of this pathway may exacerbate lung injury (Zhao *et al.*, 2024).

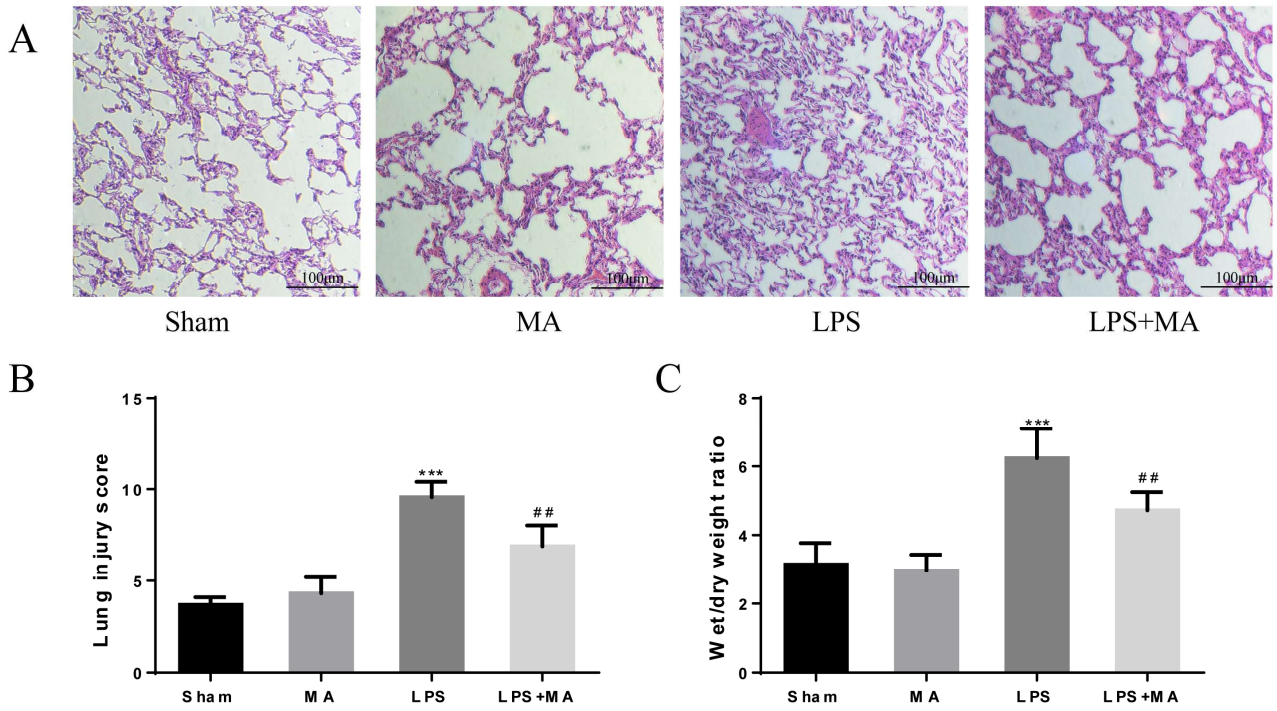

Fig. 1: Effect of MA on lung injury in LPS-induced ALI. (A) H and E staining (x 40); (B) Lung injury scores; (C) Lung wet-to-dry weight ratios. Comparisons vs sham: $^{***}P$<0.001, comparisons vs LPS: $^{\#\#}P$ <0.01.

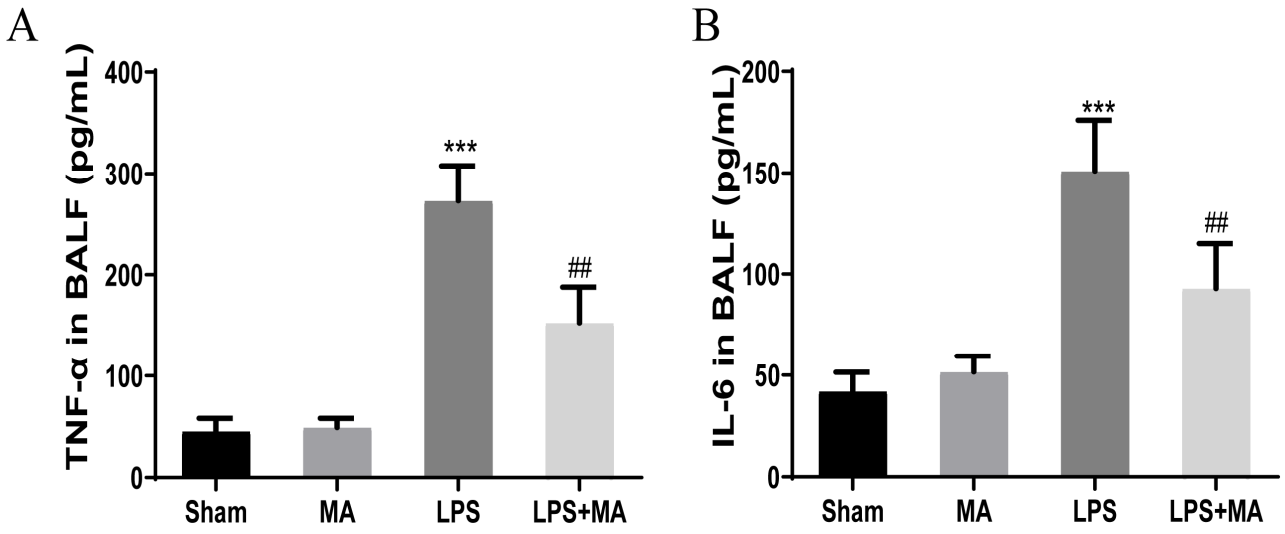

Fig. 2 Effect of MA on inflammatory mediators. (A) TNF-α concentration in BALF; (B) IL-6 concentration in BALF. Data are presented as mean ± SD, statistical comparisons were performed using one-way ANOVA followed by Tukey post hoc testing. Comparisons vs sham: $^{***}P$<0.001, comparisons vs LPS: $^{\#\#}P$<0.01.

MA intervention specifically inhibited phosphorylation in this pathway, suggesting it may act upstream of PI3K kinases or enhance phosphatase activity, thereby restoring pathway balance and reducing oxidative damage (Liu *et al.*, 2024). This mechanism is consistent with the known profile of PI3K/AKT/mTOR inhibitors and expands the anti-inflammatory molecular basis of MA (Xie *et al.*, 2025). Future validation of causality, in combination with inhibitors or gene regulation, could provide direct evidence supporting its use as a potential therapeutic strategy for ALI.

Limitations

This study has the following limitations: First, a prophylactic mode of administration was used, whereas clinical treatment is usually initiated after disease onset; thus, a post-treatment model is subsequently needed to better assess the potential for clinical translation.

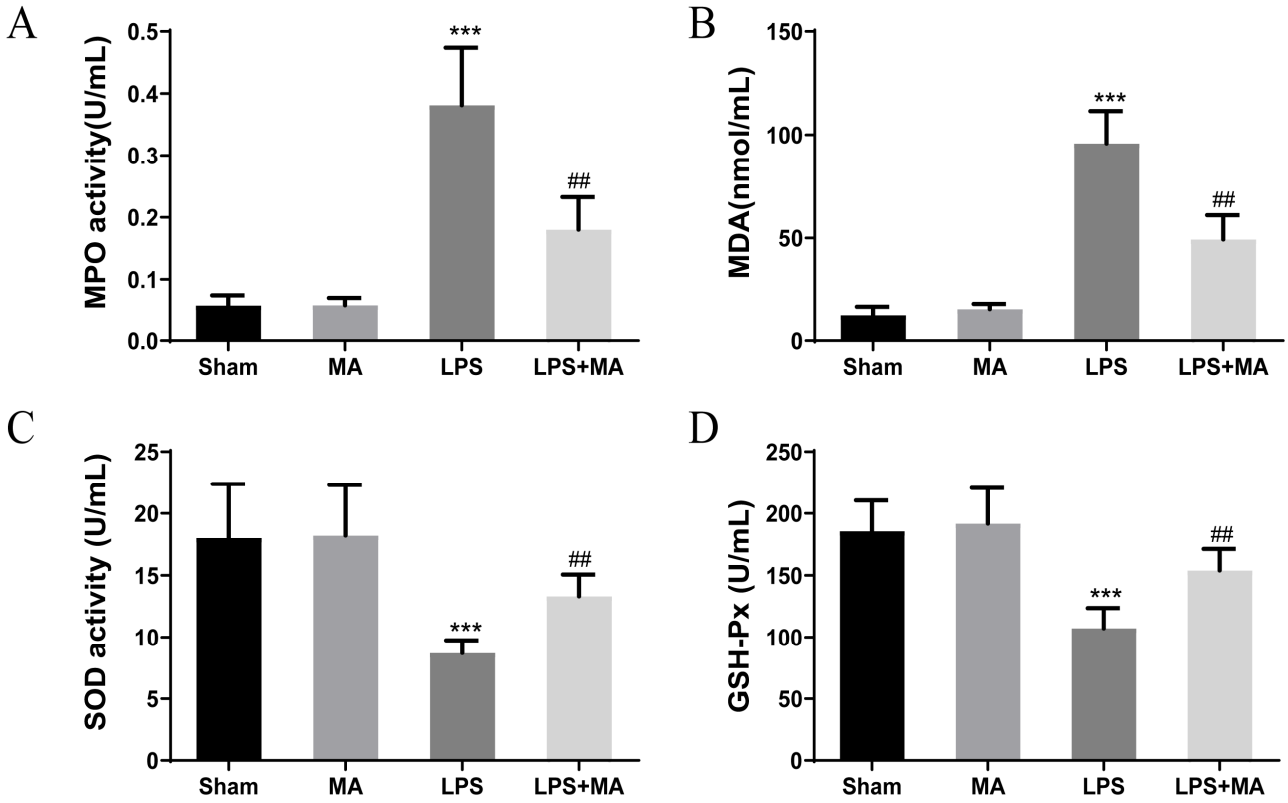

Fig. 3: Effect of MA on oxidative stress markers. (A) MPO activity; (B) MDA content; (C) SOD activity; (D) GSH-Px activity in BALF. Data are presented as mean ± SD, statistical comparisons were performed using one-way ANOVA followed by Tukey post hoc testing. Comparisons vs sham: $^{***}P<0.001$, comparisons vs LPS: $^{\#\#}P<0.01$.

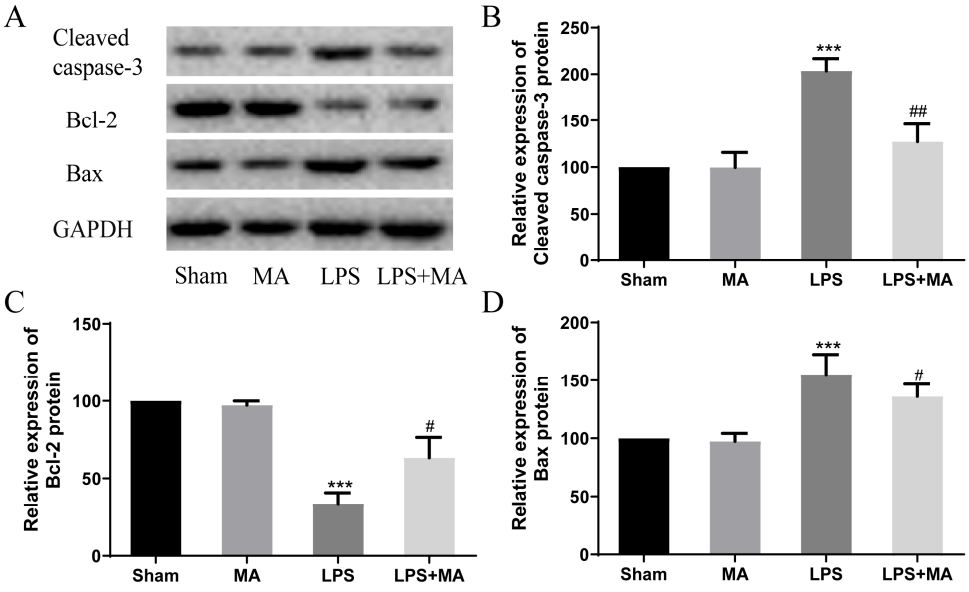

Fig. 4: Apoptosis-related protein expression by Western blot. Apoptosis-related protein expression by Western blot. (A) Representative Western blot analysis of Cleaved caspase-3, Bcl-2, and Bax proteins; (B) Quantitative analysis of Cleaved caspase-3 expression; (C) Quantitative analysis of Bcl-2 expression; (D) Quantitative analysis of Bax expression. Data are presented as mean ± SD and statistical comparisons were performed using one-way ANOVA followed by Tukey post hoc testing. Comparisons vs sham: $^{***}P < 0.001$, comparisons vs LPS: $^{\#}P < 0.05$,$^{\#\#}P < 0.01$.

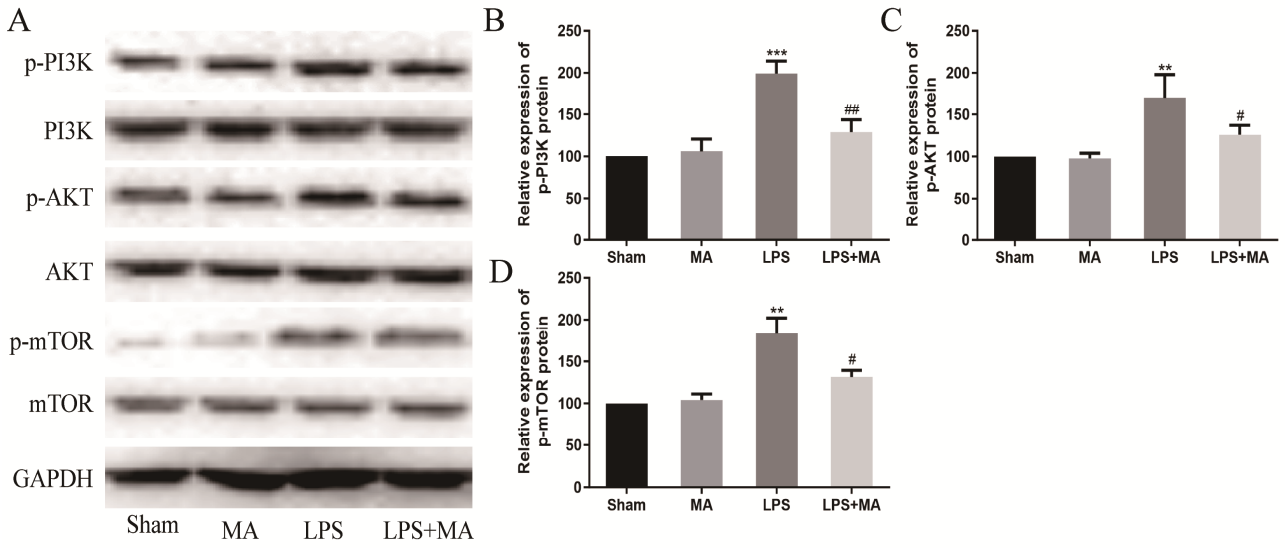

Fig. 5: Effect of MA on the PI3K/AKT/mTOR signaling pathway. (A) Representative Western blot analysis of PI3K/AKT/mTOR pathway proteins; (B) Quantitative analysis of p-PI3K expression; (C) Quantitative analysis of p-AKT expression; (D) Quantitative analysis of p-mTOR expression. Data are presented as mean±SD and statistical comparisons were performed using one-way ANOVA followed by Tukey post hoc testing. Comparisons vs sham: $^{**}P$ <0.01,$^{***}P < 0.001$, comparisons vs LPS: $^{\#}P < 0.05$, $^{\#\#}P < 0.01$.

Second, only the LPS-induced ALI model was used and no other sepsis models, such as CLP, were included; therefore, the protective effect of MA in other models needs to be verified. Third, no specific inhibitors or knockdown experiments were used to validate the importance of the PI3K/AKT/mTOR pathway and the current conclusions reflect only associations. Fourth, only a single dose of MA was used and a dose-response relationship with formal toxicity assessment was lacking. Fifth, apoptosis detection relied solely on Western blotting and lacked histological evidence, such as TUNEL staining. Sixth, the study was limited to the PI3K/AKT/mTOR pathway, and other signaling pathways (such as NF-κB and Nrf2) that may be involved in the lung-protective effect of MA were not explored; thus, its multi-targeted mechanism could be further elucidated using omics and network pharmacology methods.

CONCLUSION

In summary, MA attenuates LPS-induced acute lung injury by inhibiting inflammatory responses, oxidative stress and apoptosis, possibly by inhibiting the activation of the PI3K/AKT/mTOR signaling pathway. This study provides an experimental basis for the use of MA as a potential therapeutic agent for sepsis-associated ALI and its pathway dependence needs to be further clarified by dose-response assessment, time-course analysis and pharmacological inhibition in the future.

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Author's contributions
Jian Wan: Responsible for the conception and design of the study, as well as the drafting, review and editing of the manuscript. Zhen Han: Responsible for literature retrieval, data organization and statistical analysis and participated in the drafting of the initial manuscript, as well as the revision and validation of the content; Qian Zhang, Bo Cai, Rui Zhou and Tao Zhang: Jointly involved in data collection, data analysis and interpretation and provided critical feedback on the research content. All authors reviewed the results and approved the final version of the manuscript.

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Data availability statement
The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval
The experimental protocols were approved by the Ethics Committee of the People's Hospital of Pudong New Area (No. 2022-D-62). All animal experiments complied with the ARRIVE guidelines and were carried out in

accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments or the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978). This study was performed in adherence with the ARRIVE guidelines. See supplementary file for the ARRIVE checklist.

Conflict of interest

The authors declare no conflict of interest.

Supplementary data

https://pjps.pk/uploads/2026/08/SUP1788157149.pdf

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