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Isoegomaketone alleviates inflammatory response and oxidative stress in sepsis lung injury

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KEYWORDS
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Abstract
Background: Sepsis is a life-threatening condition characterized by acute organ dysfunction, which frequently leads to acute lung injury (ALI) in approximately 40% of cases. Isoegomaketone (IK) is a constituent of essential oil found in *P. frutescens*, known for its diverse biological properties, including anti-inflammatory and antitumor effects. However, the regulatory impact of IK on ALI in the context of sepsis remains poorly understood.
Methods: Pathological alterations in lung tissues were assessed using hematoxylin and eosin staining. Enumeration of total leukocytes and neutrophils in bronchoalveolar lavage fluid (BALF) was performed using a hematocytometer, while the levels of interleukin (IL)-6, IL-1β, IL-10, and IL-17 in BALF were quantified using enzyme-linked immunosorbent serological assay. In addition, the levels of malondialdehyde (MDA), myeloperoxidase (MPO), superoxide dismutase (SOD), and glutathione (GSH) in lung tissues were assessed using respective commercial kits; cell apoptosis was evaluated using the terminal deoxynucleotide transferase-mediated dUTP nick end-labeling assay, and protein expressions were determined through Western blot analysis.
Results: Our findings revealed that cecal ligation and puncture (CLP) treatment in mice induced severe lung injury, characterized by increased lung injury scores, significant bleeding, neutrophil infiltration, and alveolar edema. However, treatment with IK at a dose of 10 mg/kg ameliorated CLP-induced lung injury, while IK dose of 5 mg/kg showed no significant effect. Additionally, IK treatment at 10 mg/kg reduced CLP-induced inflammation by decreasing levels of IL-6, IL-1β, IL-10, and IL-17. Furthermore, IK at 10 mg/kg attenuated CLP-induced oxidative stress by modulating levels of MDA, MPO, SOD, and GSH. Moreover, IK treatment with a dose

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of 10 mg/kg activated the nuclear factor erythroid 2-related factor 2–heme oxygenase-1 (Nrf2–HO-1) pathway by enhancing the protein expressions of Nrf2 and HO-1.
Conclusion: This study demonstrates that IK could mitigate the inflammatory response and oxidative stress associated with sepsis-induced ALI, supporting IK as a promising therapeutic agent for the treatment of sepsis-associated ALI.
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Introduction

Sepsis is a medical condition characterized by a dysregulated host response to infection, leading to severe organ dysfunction and serving as a prominent global cause of mortality.[1-3] Among the affected organs, the lungs are particularly vulnerable, with sepsis causing acute lung injury (ALI) in 40% of cases, often resulting in a staggering mortality rate of 70–90%.[4] ALI is marked by acute inflammation, compromised endothelial barrier function, and damage to the alveolar epithelium, often leading to the accumulation of protein-rich pulmonary interstitial edema and the infiltration of immune cells into the alveolar space.[5] Despite the development of various therapeutic approaches, such as mechanical ventilation, hormonal therapy, and fluid management for ALI, the mortality rate remains high in sepsis patients who develop ALI complications.[6] Therefore, it is imperative to seek effective therapeutic agents that can mitigate lung inflammation and oxidative stress and attenuate lung injury as potential treatment strategies for ALI.

Isoegomaketone (IK) is an important constituent of the essential oil found in *P. frutescens*, possessing a diverse range of biological properties, including anti-inflammatory, antitumor, and anti-infection activities, among others.[7-9] For instance, in mice models of arthritis, IK treatment was shown to effectively reduce inflammatory cell infiltration and development of edema.[10] Additionally, IK can modulate the reactive oxygen species (ROS)/p38 mitogen-activated protein kinase–nuclear factor erythroid 2-related factor 2 (MAPK–Nrf2) pathway, leading to increased expression of heme oxygenase-1 (HO-1) in RAW264.7 cells.[11] Moreover, IK promotes the healing of skin wounds by activating the MAPK–extracellular signal-regulated kinase (MAPK/ERK) pathway.[12] Furthermore, research has indicated that IK exhibits favorable pharmacokinetic characteristics, bioavailability, and acceptable toxicity profiles.[8,9] Importantly, bioinformatics and network analyses have revealed that the target genes of IK are closely associated with various biological processes, including inflammation, bacterial and viral infections, atherogenesis, and tumor formation.[13] However, the regulatory effects of IK and its related pathways on the progression of ALI in sepsis have not been investigated.

In this study, we discovered that IK alleviated inflammatory response and oxidative stress in sepsis-triggered ALI by modulating the Nrf2–HO-1 pathway, thus relieving lung injury and thereby providing novel perspectives for sepsis-mediated ALI treatment.

Materials and methods

Mice model

Male C57BL/6 mice, aged 8–10 weeks, bought from Vital River Laboratory Animal Technology Co. Ltd. (Beijing, China), were used to establish a sepsis mouse model. These mice were maintained under standard conditions, with ad libitum access to food and water, housed in an artificial 12-h light–dark cycle environment at 25°C and 50% humidity. The mice (n = 24) were categorized into four groups: Sham, cecal ligation and puncture (CLP), CLP+IK (5 mg/kg), and CLP+IK (10 mg/kg), with each group consisting of six mice. To induce sepsis, CLP surgery was performed as described previously.[14,15] After anesthesia using isoflurane (Sigma-Aldrich, St. Louis, USA), a 1-cm incision was caused in the abdominal region of the mice. The cecum was exposed, ligated with a sterile silk suture, and then punctured with a 20-gauge needle. Then, the cecum was repositioned, and the incision was closed. In the Sham group, identical procedures were conducted on mice but without CLP procedure. IK was purchased from Shanghai System Biochem Co. Ltd. (Shanghai, China), and IK treatment, administered at doses of 5 mg/kg or 10 mg/kg, was delivered via oral gavage for 3 days. Lastly, the mice were euthanized humanely through cervical dislocation, and blood and lung tissues were collected for subsequent experiments. Ethical approval was obtained from the Ethics Committee of the First Affiliated Hospital of Gannan Medical University. The animal experiment complied with the ARRIVE guidelines and in accordance with the National Institutes of Health guide for the care and use of laboratory animals.

Hematoxylin and eosin (H&E) staining

The collected lung tissues were immersed in 4% paraformaldehyde (Solarbio, Beijing, China), embedded in paraffin, sectioned into 4-μm thick slices, then subjected to H&E staining. The resulting images were examined under a light microscope (Olympus Corporation, Tokyo, Japan).[16]

To assess lung injury, a grading system based on criteria, such as alveolar edema, neutrophil infiltration, and bleeding, was used, with scores ranging from 0 to 4 (indicating normal to severe injury) as follows: 0: representing no discernible injury; 1: signifying injury affecting <25% of the field; 2: indicating injury spanning 25–50% of the field; 3: reflecting injury encompassing 50–75% of the field; and 4: showing injury extending >75% of the field. The total of these scores, with a maximum possible score of 12, yielded the total injury score.

Bronchial alveolar lavage fluid (BALF) analysis

The right lung was ligated, and the left lung was gently instilled with phosphate-buffered saline (PBS, 2 mL in total, administered in 0.5-mL increments) through a tracheal cannula. Subsequently, the PBS was slowly aspirated to recover BALF. The quantification of total leukocytes and neutrophils in BALF was conducted using a hematocytometer.[17]

Enzyme-linked immunosorbent serological assay (ELISA)

The levels of Interleukin (IL)-1β (ab197742; Abcam, Shanghai, China), IL-6 (ab222503), IL-10 (ab255729), and IL-17 (ab100702) in BALF were quantified using commercially available ELISA kits.[18]

Detection of malondialdehyde (MDA), myeloperoxidase (MPO), superoxide dismutase (SOD), and glutathione (GSH)

The levels of MDA (ab118970; Abcam, Shanghai, China), MPO (ab105136; Abcam), SOD (ab65354; Abcam), and GSH (ab65322; Abcam) in lung tissues were assessed utilizing commercial kits.[19]

Terminal deoxynucleotide transferase-mediated dUTP nick end-labeling (TUNEL) assay

The *in situ* cell death detection kit (Roche, Basel, Switzerland) was used to evaluate cell death in lung tissues. Briefly, after treatment withTriton X-100 (0.1%), the lung tissues were incubated with TUNEL staining solution and 4′,6-diamidino-2-phenylindole (DAPI) in the dark for 1 h, following which the images were captured under fluorescence microscopy (Olympus, Japan).[20]

Western blot analysis

Protein isolation from lung tissues was conducted using radioimmunoprecipitation assay (RIPA) lysis buffer. The protein concentration was determined using the bicinchoninic acid (BCA) protein assay kit (Beyotime, Shanghai, China). Subsequently, 20 μg of proteins were separated via sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred onto a polyvinylidene difluoride membrane (PVDF; Sigma, St Louis, USA). Following a 2-h blocking step with 5% skimmed milk, the membranes were incubated with primary antibodies for 12 h, followed by incubation with secondary antibodies (1/1000; ab6721) for an additional 2 h. Finally, protein bands were visualized using the enhanced chemiluminescence system (Thermo Fisher Scientific, MA, USA) and analyzed using the Image J Software (version 1.46; National Institutes of Health).[21]

The primary antibodies used were as follows: Bax (1/1000; ab32503; Abcam, Shanghai, China), Bcl-2 (1/2000; ab182858; Abcam), β-actin (1 µg/mL; ab8226; Abcam), Nrf2 (1/1000; ab62352; Abcam), HO-1 (1/2000; ab52947; Abcam), and histone (1/1000; ab1791; Abcam).

Statistical analysis

All data were expressed as mean ± standard deviation (SD), and statistical analyses were performed using SPSS 20.0 (IBM Corp., Armonk, NY, USA). Group comparisons were conducted using either Student's *t*-test or one-way analysis of variance (ANOVA); $P < 0.05$ was considered statistically significant.

Results

Isoegomaketone lessened CLP-mediated lung injury

Initially, we determined that CLP treatment induced severe lung injury, characterized by elevated lung injury scores, along with notable neutrophil infiltration, bleeding, and alveolar edema (Figures 1A and B). However, in mice with sepsis, the administration of IK at a dose of 10 mg/kg ameliorated lung injury. Additionally, the increased total leukocytes and neutrophil counts in BALF following CLP treatment were mitigated by IK treatment at a dose of 10 mg/kg (Figures 1C and D). Comparatively, IK treatment at 5 mg/kg did not yield a significant effect. Thus, IK treatment could lessen CLP-induced lung injury.

Isoegomaketone reduced CLP-stimulated inflammation

Our findings revealed that the levels of proinflammatory factors, including IL-6, IL-1β, IL-10, and IL-17, were elevated following the CLP treatment. However, these inflammatory responses were mitigated following IK treatment at a dose of 10 mg/kg (Figures 2A-D), indicating that IK treatment effectively reduced the inflammation induced by CLP.

Isoegomaketone weakened CLP-triggered oxidative stress

Next, we examined markers related to oxidative stress, including MDA and MPO levels. Both MDA and MPO levels were elevated following CLP treatment; however, these changes were alleviated with IK treatment at a dose of 10 mg/kg (Figures 3A and B). Additionally, levels of SOD and GSH, which were decreased after CLP treatment, were restored by IK treatment at the same dose (10 mg/kg; Figures 3C and D). Overall, IK treatment effectively mitigated the oxidative stress triggered by CLP.

Isoegomaketone ameliorated CLP-induced apoptosis

Moreover, we evaluated cell apoptosis in the lung tissues of mice. Using the TUNEL assay, we observed an increase in cell apoptosis following CLP treatment, which could be

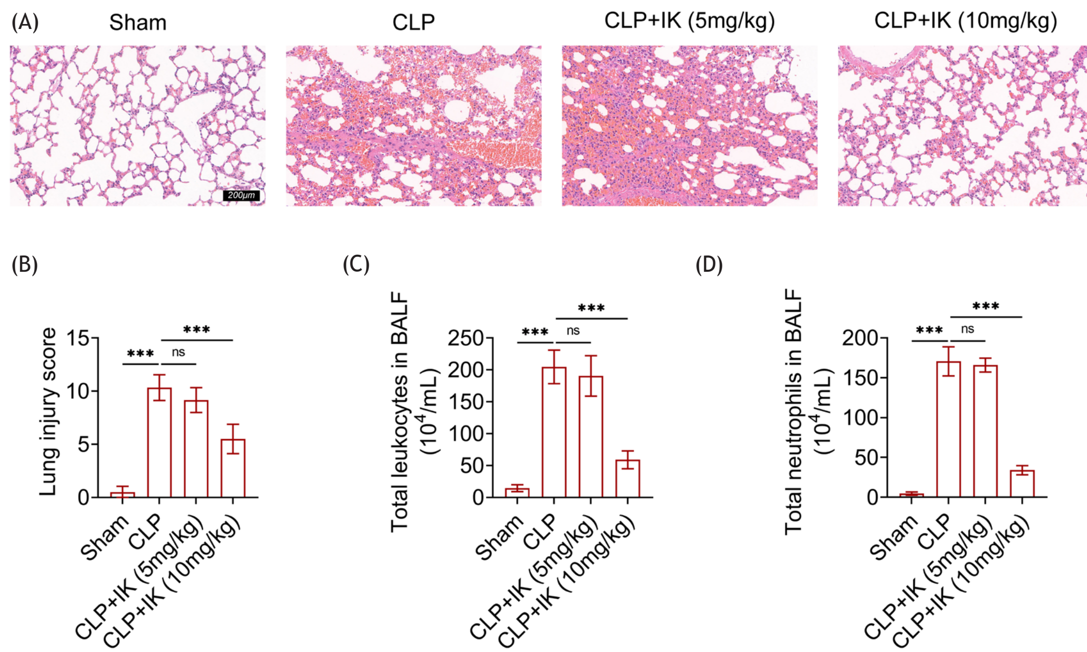

Figure 1 Isoegomaketone attenuated CLP-induced lung injury. Mice were allocated in groups categorized as Sham, CLP, CLP+IK (5 mg/kg), and CLP+IK (10 mg/kg). (A) Lung tissue pathology was confirmed through H&E staining. (B) Verification of lung injury score. (C) Total leukocytes in BALF were counted using a hematocytometer. (D) Total neutrophils in BALF were counted using a hematocytometer. ***P < 0.001.

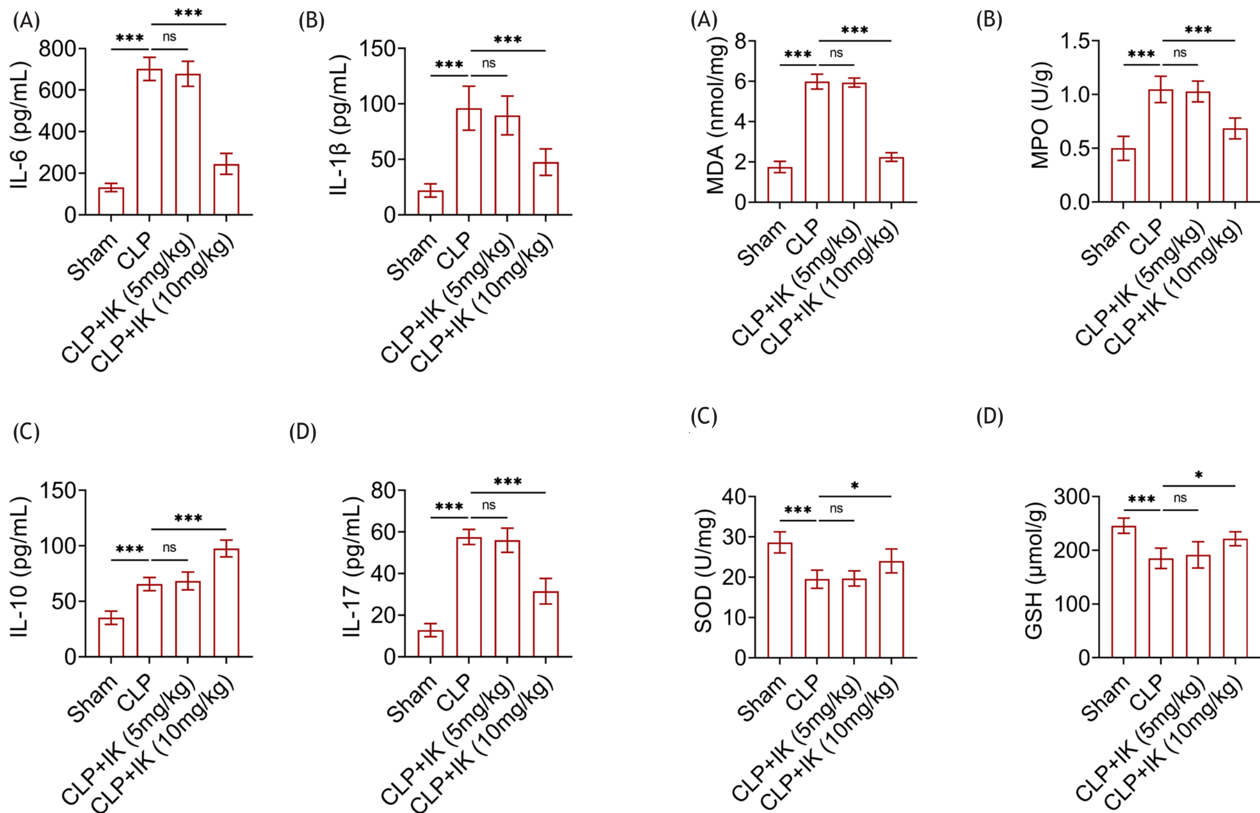

Figure 2 Isoegomaketone reduced CLP-stimulated inflammation. Mice were divided into Sham, CLP, CLP+IK (5 mg/kg), and CLP+IK (10 mg/kg) groups. Levels of (A) IL-6, (B) IL-1β, (C) IL-10, and (D) IL-17 in BALF were measured and quantified using ELISA. ***P < 0.001.

Figure 3 Isoegomaketone weakened CLP-triggered oxidative stress. The mice were divided into Sham, CLP, CLP+IK (5 mg/kg), and CLP+IK (10 mg/kg) groups, and the levels of (A) MDA, (B) MPO, (C) SOD, and (D) GSH in lung tissues were measured using corresponding commercial kits. *P < 0.05, ***P < 0.001.

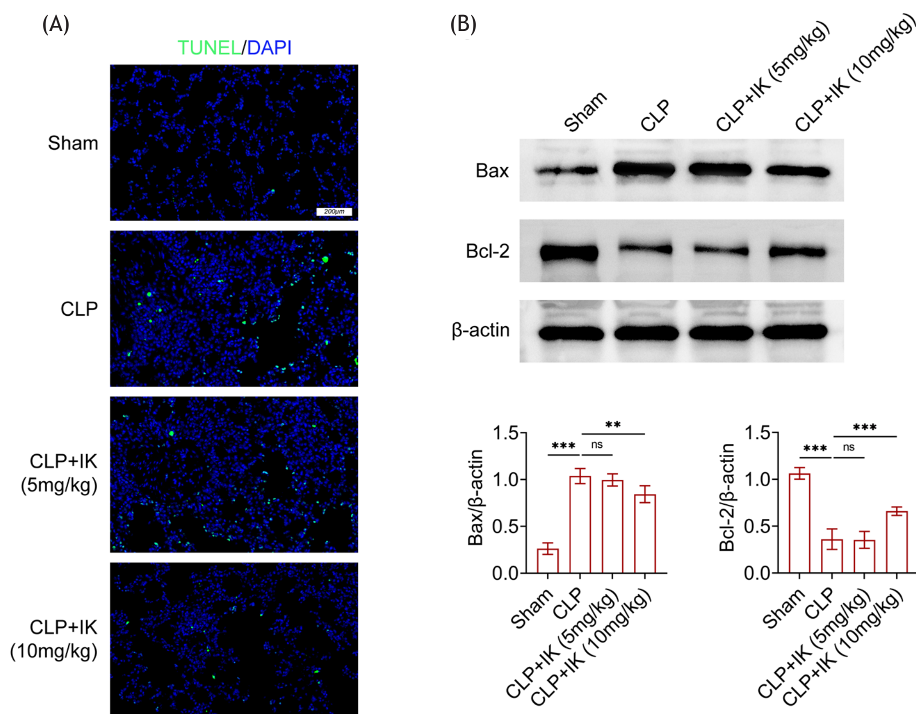

Figure 4 Isoegomaketone ameliorated CLP-induced apoptosis. The mice were divided into Sham, CLP, CLP+IK (5 mg/kg), and CLP+IK (10 mg/kg) groups. (A) Cell apoptosis was assessed through TUNEL assay. (B) Protein expressions of Bax and Bcl-2 were determined using Western blot analysis. $^{**}P < 0.01$, $^{***}P < 0.001$.

subsequently reduced following IK treatment at 10 mg/kg (Figure 4A). Furthermore, we observed an upregulation of Bax protein expression in lung tissues, while Bcl-2 protein expression was down-regulated after CLP treatment. These changes were reversed by IK treatment at 10 mg/kg (Figure 4B), indicating that IK treatment could ameliorate CLP-induced apoptosis.

Isoegomaketone provoked the Nrf2-HO-1 pathway

Lastly, we investigated the effects of IK on Nrf2-HO-1 pathway. The results indicated that Nrf2 protein expression increased following CLP treatment, and this effect was further enhanced after IK treatment at 10 mg/kg (Figure 5A). Additionally, HO-1 protein expression was enhanced after CLP treatment, and this enhancement was further potentiated by IK treatment at the same dose (Figure 5B). This indicating that IK treatment could activate the Nrf2-HO-1 pathway.

Discussion

Numerous extracts derived from Chinese herbs have been demonstrated to play a role in the progression of ALI, thereby alleviating lung injury in various contexts. For instance, artesunate has been shown to reduce cell apoptosis and pulmonary neutrophil infiltration in ALI induced by sepsis.[22] Similarly, glycyrrhizic acid has been discovered to modulate the PI3K/AKT/mTOR pathway, affecting autophagy and improving ALI stimulated by LPS.[23] Absinthin has been reported to regulate MIP-1α-induced inflammatory cell infiltration, thereby alleviating ALI triggered by LPS.[24] Isorhapontigenin has been shown to influence Nrf2 signaling, attenuating LPS-induced ALI.[25] Luteolin has been demonstrated to enhance IL-10 expression and reduce caspase-11-dependent pyroptosis, thus alleviating ALI triggered by LPS.[26] Additionally, loganin has been discovered to modulate macrophage polarization and reduce NLRP3 inflammasome activation, thereby improving LPS-induced ALI.[27] Interestingly, IK extracted from *P. frutescens* has been demonstrated to possess a wide range of biological properties to ameliorate various diseases.[10-12] However, the regulatory effects of IK on ALI in sepsis have remained unclear. In this study, our results revealed that CLP treatment in mice led to severe lung injury, characterized by higher lung injury scores, bleeding, neutrophil infiltration, and alveolar edema. In line with previous research, IK treatment at a dose of 10 mg/kg also demonstrated promising ability to lessen lung injury induced by CLP.

Inflammation and oxidative stress are pivotal processes in the pathogenesis of sepsis-induced ALI. Numerous studies have focused on mitigating inflammation and oxidative stress to ameliorate ALI progression. For example, sufentanil has been shown to reduce kininogen-1 (*KNG1*) gene expression in sepsis-induced ALI, thereby slowing down inflammation and oxidative stress.[28] Additionally, the suppression of estrogen-related receptor alpha (ERRα) has been linked to increased inflammation and oxidative stress, accelerating the onset of sepsis-mediated ALI.[29] Furthermore, nesfatin-1 has been demonstrated to modulate high mobility group box 1 protein (HMGB1) expression, leading to the alleviation of inflammation and oxidative stress and subsequently

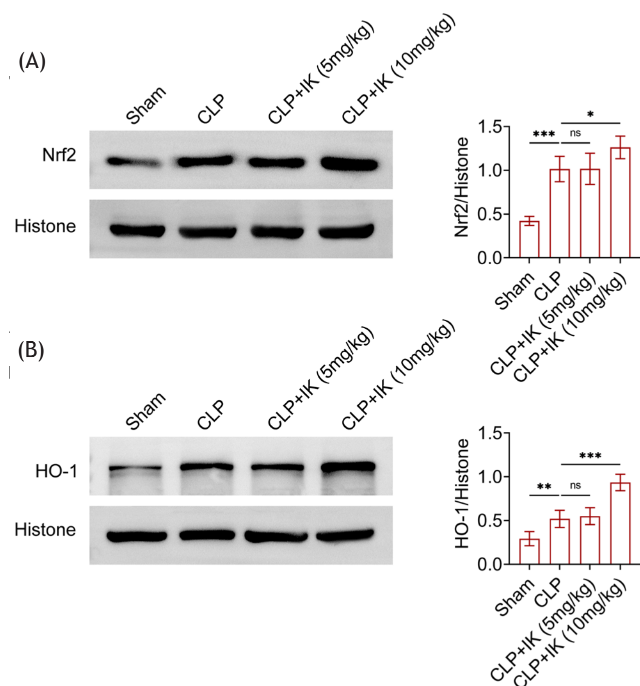

Figure 5 Isoegomaketone activated the Nrf2/HO-1 pathway. The mice were divided into Sham, CLP, CLP+IK (5 mg/kg), and CLP+IK (10 mg/kg) groups. (A) Nrf2 protein expression was examined by Western blot analysis. (B) HO-1 protein expression was measured using Western blot analysis. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

delaying the progression of ALI.[30] However, the regulatory effects of IK on inflammation and oxidative stress in sepsis-induced ALI have remained unclear. In the current study, we observed that IK treatment at a dose of 10 mg/kg effectively reduced CLP-induced inflammation, as evidenced by decreased levels of IL-6, IL-1β, IL-10, and IL-17. Furthermore, IK treatment at the same dose attenuated CLP-induced oxidative stress, as indicated by the modulation of MDA, MPO, SOD, and GSH levels.

The Nrf2/antioxidant response element (ARE) signaling pathway serves as a crucial endogenous antioxidant stress pathway.[31,32] Upon activation, Nrf2 is liberated from its interaction with Kelch-like epichlorohydrin-associated protein 1 (Keap1) and translocates to the nucleus, where it subsequently binds to ARE.[33] This complex formation further influences the expression of target genes, including HO-1.[34] Importantly, HO-1 plays a negative regulatory role in the inflammatory response and oxidative stress associated with ALI.[35,36] Moreover, the upregulation of HO-1 has been shown to reduce mortality in septic mice.[37,38] In this present study, we also investigated the regulatory effects of IK on the Nrf2–HO-1 pathway and observed that 10 mg/kg IK effectively stimulated the Nrf2–HO-1 pathway by enhancing the protein expressions of both Nrf2 and HO-1.

Conclusion

This study demonstrated that IK could mitigate inflammatory and oxidative stress responses in sepsis-induced ALI by modulating the Nrf2–HO-1 pathway, thereby alleviating lung injury. These findings suggested potential of IK as a therapeutic agent for ALI treatment. However, certain limitations prevailed, such as the absence of human samples and the investigation of other biological processes (autophagy, fibrosis, macrophage pyroptosis, and mitochondrial damage) in both *in vivo* and *in vitro* models. Future research is required to address these limitations and further explore IK's potential in ALI.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article. The datasets used and/or analyzed in the present study are available from the corresponding author upon reasonable request.

Competing Interests

The authors stated that there were no conflict of interest to disclose.

Author Contributions

All authors contributed to the study's conception and design. Yunwei Rao and Hai Lin conducted the experiments and prepared the material. Data collection and analysis were carried out by Huan Rao, Yunkun Rao, and Xiaoyuan Tang. The initial draft of the manuscript was written by Huimin Zuo and Ying Wang. All authors provided input and feedback on earlier versions of the manuscript. All authors have read and approved the final manuscript.

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