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ORIGINAL ARTICLE

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# *Alpinia officinarum Hance* extract relieved sepsis-induced myocardial ferroptosis and inflammation by inhibiting lncRNA MIAT/TRAF6/NF-κB axis

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**Abstract**
Sepsis is generally triggered by a dysfunctional host response to infection, and it can result in life-threatening organ dysfunction. *Alpinia officinarum Hance* (AO) exhibits regulatory functions in some diseases. However, whether AO extract (AOE) plays a promoting role in sepsis-triggered myocardial injury is unclear. This study was aimed at investigating the regulatory effects of AOE on myocardial ferroptosis and inflammation in sepsis, and the regulation effects on the lncRNA MIAT/TRAF6/NF-κB axis. Lipopolysaccharide (LPS) was used to treat mice for establishing an in vivo sepsis model. The pathological changes in heart tissues were observed through hematoxylin-eosin (HE) staining. The levels of CK-MB, cTnl, MDA, SOD, IL-1β, IL-18, IL-6, and TNF-α in serum were detected through enzyme-linked immunosorbent assay (ELISA). The level of $Fe^{2+}$ was assessed, and the protein expressions (ACSL4, GPX4, TRAF6, p-P65, and P65) were examined through western blot. The expressions of lncRNA MIAT and TRAF6 were measured through real-time quantitative polymerase chain reaction (RT-qPCR). Our results demonstrated that AOE treatment ameliorated sepsis-triggered myocardial damage by reducing the disordered cardiomyocytes, the destroyed sarcolemma, and the CK-MB and cTnl levels. In addition, AOE treatment inhibited sepsis-induced myocardial ferroptosis and inflammation by regulating $Fe^{2+}$, ACSL4, GPX4, IL-1β, IL-18, IL-6, and TNF-α levels. Moreover, the improvement effect of AOE was strengthened with the increase in the dose of AOE (25, 50, 100 mg/kg). It was also revealed that AOE treatment retarded the lncRNA MIAT/TRAF6/NF-κB axis. Rescue assays manifested that overexpression of MIAT reduced the cardioprotective

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effect of AOE. In conclusion, AOE relieved sepsis-induced myocardial ferroptosis and inflammation by inhibiting lncRNA MIAT/TRAF6/NF-κB axis. These findings may provide a potential therapeutic drug for the treatment of sepsis.


## Introduction

Sepsis is usually caused by exaggerated immune responses to pathogen-stimulated infections.[1-3] In spite of significant advancements in monitoring and support technology for treating severe patients, sepsis remains one of the leading causes of death.[4-6] Sepsis-induced cardiomyopathy (SIC) is a common complication of sepsis. It encompasses inflammation disorder, impaired autophagy, calcium regulation disorder, oxidative stress, mitochondrial dysfunction, apoptosis injury, and myocardial fibrosis.[7-9] The proactive approaches that have been adopted to relieve the progression of SIC are often insufficient. Therefore, there is an urgent need to find effective drugs or bio-targets to alleviate the progression of SIC.

In recent years, traditional Chinese medicine has gained prominence in treating sepsis-stimulated heart diseases. For instance, Irisin reduces inflammation-stimulated pyroptosis and relieves sepsis-triggered cardiac dysfunction.[10] Furthermore, apigenin retards the sphingosine kinase 1/sphingosine 1-phosphate signaling pathway to alleviate heart injury in sepsis.[11] Puerarin modulates mitochondrial autophagy to weaken lipopolysaccharide (LPS)-triggered H9C2 cell injury in sepsis.[12] In addition, piceatannol directly suppresses JAK2 to ameliorate sepsis-triggered myocardial dysfunction.[13]

*Alpinia officinarum Hance* (AO) is an herbaceous plant of the ginger family. It is mainly found in tropical and subtropical Asia.[14,15] AO is widely used in traditional medicine and as nutritional supplements, and AO extract (AOE) has been used to treat multiple diseases. For example, AOE suppresses the production of inflammatory factors in lipopolysaccharide (LPS)-treated macrophages.[16] In addition, AOE is also used to treat osteoporosis, as it reduces the percentage of osteoclast circumference.[17] Besides, AOE also modulates the MAPK signaling pathway to exhibit anti-helicobacter pylori-related gastritis.[18] However, the regulatory effects of AOE on SIC progression is unclear.

Ferroptosis is an oxidative, stress-dependent cell death characterized by lipid peroxidation and iron accumulation.[19,20] The glutathione peroxidase 4 (GPX4) and acyl-CoA synthetase long-chain family 4 (ACSL4) are key players in ferroptosis.[21] However, the regulatory effects of AOE on ferroptosis is unclear.

In this study, the role of AOE and its associated regulatory network in SIC mice model was investigated.

## Materials and methods

### *Mice experiments*

The male C57BL/6 mice (n=36, 8 weeks old) were obtained from Vital River Laboratory Animal Technology Co., Ltd. (Beijing, China). LPS (10 mg/kg, Sigma-Aldrich, Merck KGaA, Germany) dissolved in saline was intraperitoneally injected into mice once to mimic the sepsis model.[22] The groups were randomly divided into six groups (six mice in each group): 1) Sham, 2) LPS, 3) LPS+25 mg/kg AOE, 4) LPS+50 mg/kg AOE, 5) LPS+100 mg/kg AOE, and 6) LPS+100 mg/kg+Ad-MIAT.

AOE (25, 50, and 100 mg/kg; purchased from Fufeng Sinuote Biotechnology, China, Shaanxi) dissolved in DMSO was intraperitoneally injected for 10 days. On day 11, mice were treated with LPS. The control group and the LPS group were treated with an equal volume of DMSO for 10 days. On day 11, LPS (10 mg/kg) dissolved in normal saline was intraperitoneally injected into the mice in the LPS group as well in the control group. Twelve hours later, all mice were euthanized, and their hearts were dissected.

All experimental procedures were in accordance with the National Institutes of Health Guidelines on the Care and Use of Laboratory Animals. Also, approval was obtained from the Institutional Animal Care and Use Committee of Tongji Medical College, Huazhong University of Science and Technology.

### *HE staining*

The heart tissues fixed in 4% paraformaldehyde (Solarbio, Beijing, CHN) were further embedded into paraffin. The heart tissues were cut into 4-μm sections, which were dyed with HE solution. Then, images were captured using a light microscope (Olympus Corporation, Tokyo, Japan).

### *Enzyme-linked Immunosorbent Assay (ELISA)*

The corresponding commercial ELISA kits including creatine kinase-MB (CK-MB, ab285231, Abcam, Shanghai, China), cardiac troponin I (cTnI, cat. no. 202108, R&D Systems China Co., Ltd, Shanghai, China), malondialdehyde (MDA, ab118970, Abcam), superoxide dismutase (SOD, ab285309, Abcam), TNF-α (ab208348, Abcam), IL-1β (ab197742, Abcam), IL-6 (ab222503, Abcam), and IL-18 (ab216165, Abcam) were used according to the manufacturer's instructions.

### *Detection of $Fe^{2+}$*

The $Fe^{2+}$ assay kit (E-BC-K304-S, Elabsciences, China) was used for measuring $Fe^{2+}$ level as per manufacturer's protocols. Briefly, the supernatant of heart tissues was added to the reagent containing iron reductase. Lastly, the optical density at wavelength 593 nm was inspected under the microplate reader.

### *Western blot*

Proteins were segregated from heart tissues using the RIPA buffer (Beyotime, Shanghai, China). Then, proteins were separated by 10% SDS-PAGE and transferred onto PVDF membranes (Beyotime, Shanghai, China). After blocking, the membranes were incubated with primary antibodies for 12 h at 4°C, followed by incubation with secondary antibodies (1/2000; ab7090; Goat Anti-Rabbit) for 2 h. Finally, the bands were evaluated using the chemiluminescence detection kit (Thermo Fisher Scientific, Inc.).

The primary antibodies included anti-acyl-CoA synthetase long-chain family 4 (ACSL4; 1/10000; ab155282; Rabbit; Abcam, Shanghai, China), glutathione peroxidase 4 (GPX4; 1/1000; ab125066; Rabbit), tumor necrosis factor receptor-associated factor 6 (TRAF6; 1/5000; ab40675; Rabbit), p-NF-kB p65 (1/1000; ab76302; Rabbit), NF-kB p65 (0.5 μg/mL; ab16502; Rabbit), and ß-actin (the internal reference, 1/5000; ab8227; Rabbit) antibodies.

### *RT-qPCR*

RNAs from heart tissues were isolated through the TRIzol reagent (Invitrogen, USA). The SuperScript™ II Reverse Transcriptase Kit (Invitrogen, USA) was used for reverse transcribing RNAs to cDNAs, and the SYBR Premix Ex Taq™ kit (Takara, Dalian, China) was used for qRT-qPCR. Lastly, the relative mRNA expression was measured using the $2^{-\Delta\Delta Ct}$ method.

The primer sequences were listed as follows:

*MIAT*:
F: 5′-AGA GAG GAC ATG AGG ACC CC-3′,
R: 5′-CCT ACC TCA CAG GGC TGT TG-3′;
*TRAF6*:
F: 5′-GCC GAA ATG GAA GCA CAG-3′,
R: 5′-CAG GGC TAT GGA TGA CAA CA-3′;
*GADPH*:
F: 5′-GCA CCG TCA AGC TGA GAA C-3′,
R: 5′-TGG TGA AGA CGC CAG TGG A-3′.

## Statistical analysis

The data were presented as mean ± standard deviation (SD). The statistical analysis was performed using GraphPad Prism Software 8 (GraphPad Software, USA). Each group comprised six mice. Statistical comparisons were made using the student's *t*-test or one-way analysis of variance (ANOVA) followed by post hoc Tukey's test between two or among more groups. $P<0.05$ was considered as significant difference.

## Results

### *AOE ameliorated sepsis-triggered myocardial damage*

The cardiomyocytes were disordered, and the sarcolemma was destroyed after LPS treatment. However, these pathological changes were alleviated with the increased dose of AOE (Figure 1A). In addition, the levels of CK-MB and cTnl were increased after LPS treatment, and they were attenuated by the AOE treatment (Figure 1B). These findings illustrated that AOE ameliorated sepsis-triggered myocardial damage.

### *AOE inhibited sepsis-induced myocardial ferroptosis*

The level of $Fe^{2+}$ was increased after LPS treatment, but this effect was attenuated by AOE treatment (Figure 2A).

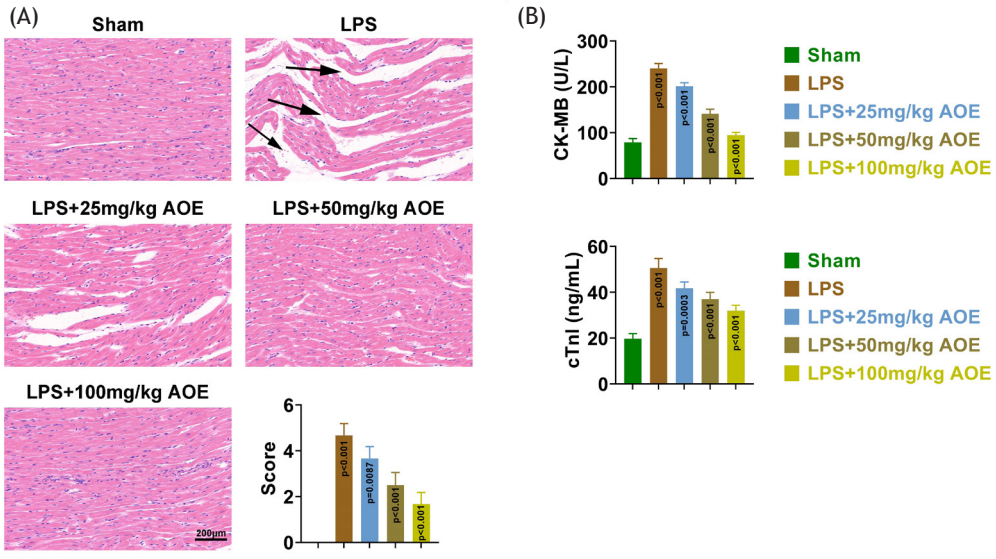


**Figure 1** *Alpinia officinarum Hance* extract ameliorated sepsis-triggered myocardial damage. Groups were divided into the Sham, LPS, LPS+25 mg/kg AOE, LPS+50 mg/kg AOE, and LPS+100 mg/kg AOE groups. (A) The pathological changes of heart tissues were observed through hematoxylin-eosin staining. (B) The levels of CK-MB and cTnl in serum were tested through ELISA.

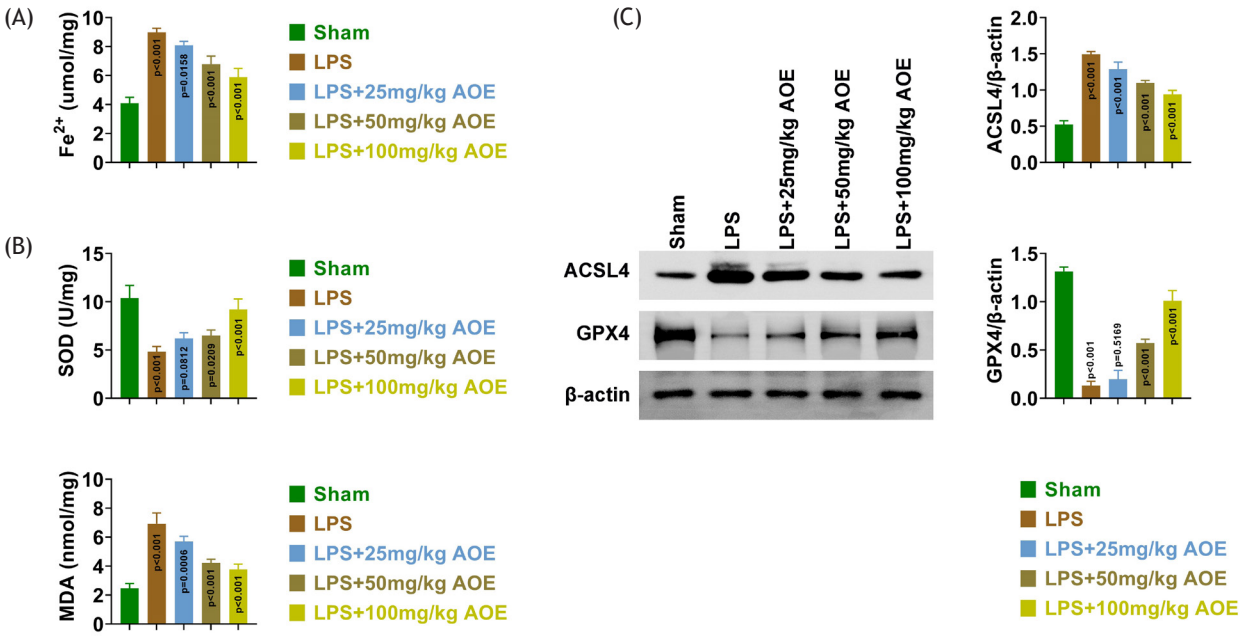


**Figure 2** *Alpinia officinarum Hance* extract inhibited sepsis-induced myocardial ferroptosis. Groups were divided into the Sham, LPS, LPS+25 mg/kg AOE, LPS+50 mg/kg AOE, and LPS+100 mg/kg AOE groups. (A) The $Fe^{2+}$ level was evaluated through the corresponding commercial kit. (B) The levels of MDA and SOD were examined through ELISA. (C) The protein expressions of ACSL4 and GPX4 were tested through western blot.

Furthermore, the SOD level was decreased, and the MDA level was increased after LPS treatment, which were reversed by AOE treatment (Figure 2B). Next, the important ferroptosis-related proteins ACSL4 (promote ferroptosis) and GPX4 (inhibit ferroptosis) were examined using western blot. The results showed that LPS treatment upregulated the expression of ACSL4 protein and down-regulated the expression of GPX4 protein. However, these effects were controlled by the AOE treatment (Figure 2C). Taken together, AOE inhibited sepsis-induced myocardial ferroptosis.

### *AOE suppressed sepsis-induced inflammation*

The levels of IL-1β, IL-18, IL-6, and TNF-α were all enhanced after LPS treatment, which were attenuated by the AOE treatment (Figure 3A-D). These data suggested that AOE suppressed sepsis-induced inflammation.

### *AOE retarded the lncRNA MIAT/TRAF6/NF-κB axis*

The expressions of lncRNA *MIAT* and *TRAF6* mRNA were both increased after LPS treatment, which were relieved by AOE treatment (Figure 4A). In addition, the protein expressions of TRAF6 and p-P65/P65 were also enhanced by LPS treatment, but these changes were offset by AOE treatment. In general, AOE retarded the lncRNA MIAT/TRAF6/NF-κB axis.

### *Overexpression of MIAT reduced the cardioprotective effect of AOE*

Rescue assays were further performed. Our results showed that the decreased expressions of TRAF6 and p-P65/P65 mediated by AOE treatment in LPS mice were mitigated by overexpression of MIAT (Figure 5A). Moreover, the reduced levels of CK-MB and cTnl mediated by AOE treatment in LPS mice were offset by overexpressing MIAT (Figure 5B-C). The decreased $Fe^{2+}$ level mediated by AOE treatment in LPS mice was enhanced by MIAT upregulation (Figure 5D). Also, the increased SOD level and decreased MDA level mediated by AOE treatment in LPS mice were reversed by overexpression of MIAT (Figure 5E). In short, overexpression of MIAT inhibited the cardioprotective effect of AOE.

## Discussion

SIC seriously threatens human life, and it is important to have more reliable drugs to treat it. AO ameliorates some diseases,[16-18] but the regulatory effects of AOE on the progression of SIC is unclear. In this study, LPS (10 mg/kg) was used to treat mice to establish an in vivo sepsis model. Results demonstrated that AOE treatment ameliorated sepsis-triggered myocardial damage by reducing the disordered cardiomyocytes, the destroyed sarcolemma, and the CK-MB and cTnl levels.

Ferroptosis and inflammation do play a role in the progression of sepsis-induced heart diseases. For instance, tectorigenin reduces Smad3 expression so as to repress

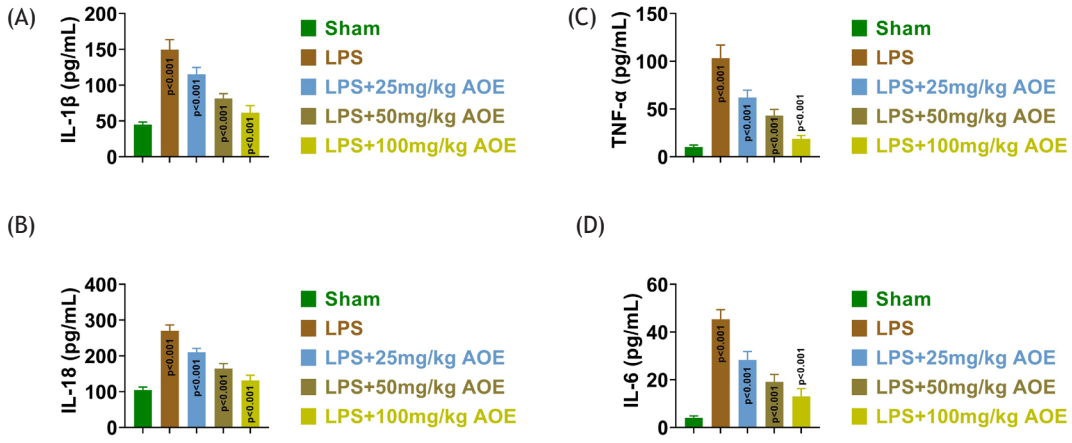


**Figure 3** *Alpinia officinarum Hance* extract suppressed sepsis-stimulated inflammation. Groups were separated into the Sham, LPS, LPS+25 mg/kg AOE, LPS+50 mg/kg AOE, and LPS+100 mg/kg AOE groups. (A–D) The levels of IL-1β, IL-18, IL-6, and TNF-α were determined through ELISA.

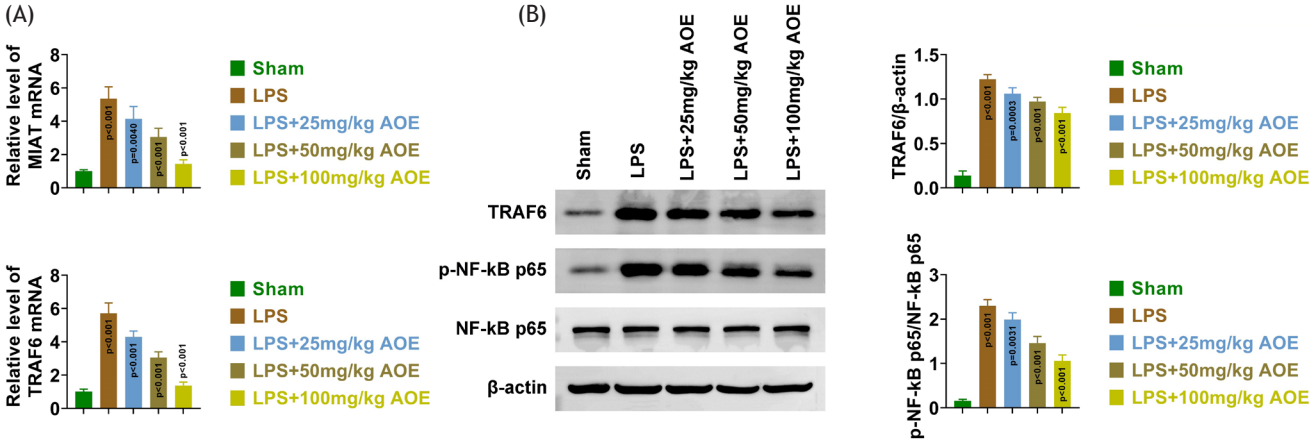


**Figure 4** *Alpinia officinarum Hance* extract retarded the lncRNA MIAT/TRAF6/NF-κB axis. Groups were separated into the Sham, LPS, LPS+25 mg/kg AOE, LPS+50 mg/kg AOE, and LPS+100 mg/kg AOE groups. (A) The mRNA expressions of *MIAT* and *TRAF6* were measured through RT-qPCR. (B) The protein expressions of TRAF6, p-P65, and P65 were examined through western blot.

sepsis-stimulated myocardial ferroptosis.[23] ANXA1sp affects SIRT3-mediated p53 deacetylation to relieve ferroptosis-stimulated cardiomyocyte death in sepsis-induced myocardial injury.[24] In addition, melanin nanoparticles relieve ferroptosis and inflammation in sepsis-induced myocardial injury.[25] Moreover, platelet-rich plasma alleviates inflammation and ferroptosis to improve LPS-triggered cardiac injury.[26] It has been found that galangin (extracted from AO) modulates the Nrf2/Gpx4 pathway to relieve myocardial ischemic reperfusion-triggered ferroptosis.[27] Similar to this report, our study demonstrated that AOE treatment inhibited sepsis-induced myocardial ferroptosis and inflammation. Moreover, the improvement effect of AOE was strengthened with the increased dose of AOE (25, 50, and 100 mg/kg).

A large number of studies have confirmed that long noncoding RNAs (lncRNAs) are involved in the occurrence and development of multifold diseases and transcriptional regulation.[28] LncRNA MIAT can accelerate inflammation and oxidative stress in sepsis-triggered cardiac injury by targeting the miR-330-5p/TRAF6/NF-κB axis.[29] Moreover, suppression of lncRNA MIAT regulates the NF-κB axis to improve sepsis-stimulated myocardial inhibition.[30] These findings indicate that lncRNA MIAT plays critical roles in sepsis-related heart disease. Studies have revealed that curcumin is one of the dominating components of AOE.[16] Curcumin reduces inflammation and improves the cardiac function in the SIC rat model.[31,32] In addition, curcumin can inhibit lncRNA MIAT to ameliorate atherosclerosis.[33,34] Therefore, we speculated that AOE may modulate lncRNA MIAT to alleviate LPS-triggered myocardial injury. In our study, we found that AOE treatment retarded the lncRNA MIAT/TRAF6/NF-κB axis. Lastly, rescue assays manifested that overexpression of MIAT reduced the cardioprotective effect of AOE.

In conclusion, we for the first time found that AOE relieved sepsis-induced myocardial ferroptosis and inflammation by inhibiting lncRNA MIAT/TRAF6/NF-κB axis. This study may reveal the potential future use of AOE as a drug for the treatment of SIC. Our study still has some limitations, such as the lack of cell model, human samples, and investigations into other cellular progressions. In the

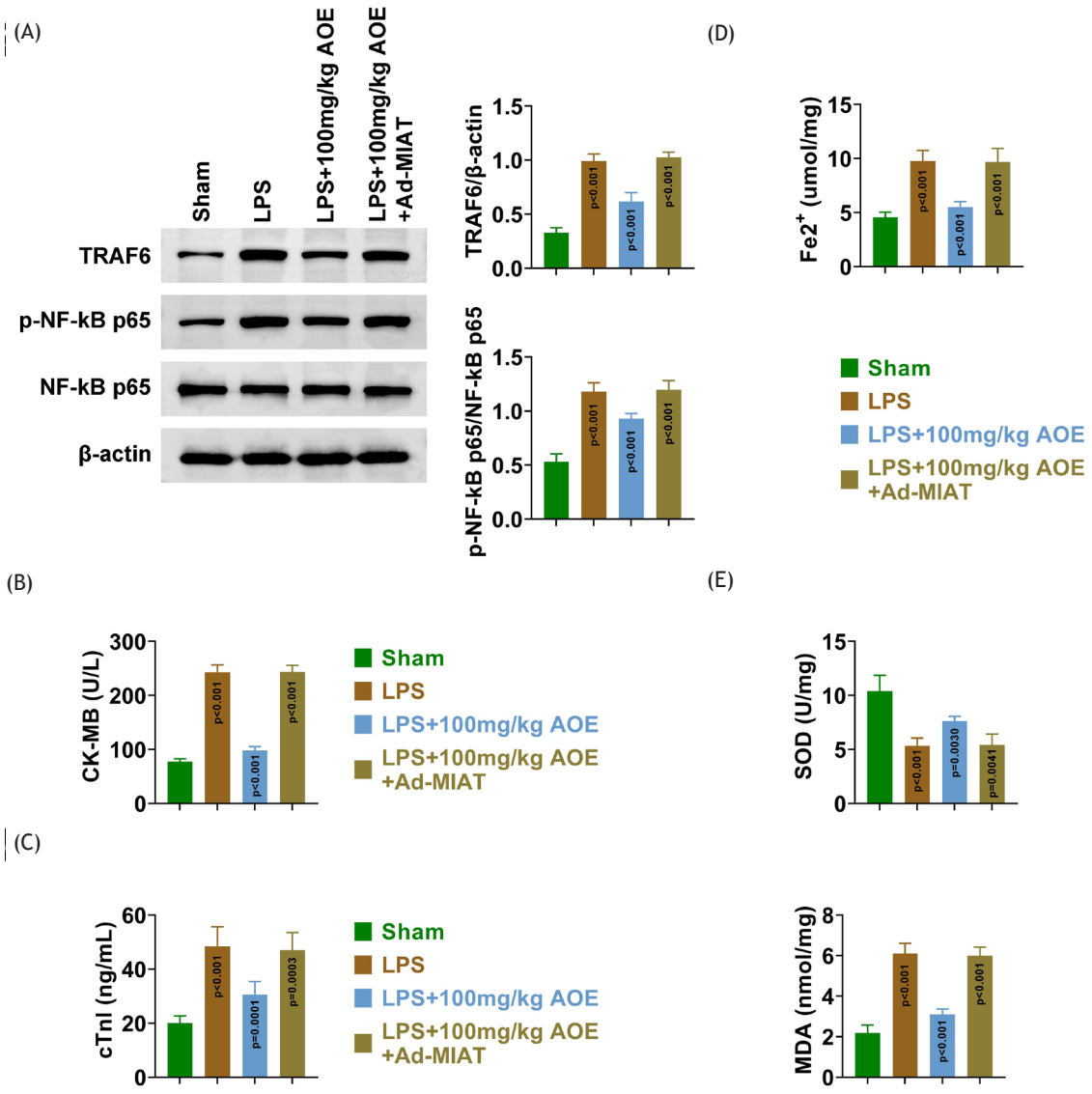


**Figure 5** Overexpression of MIAT reduced the cardioprotective effect of *Alpinia officinarum Hance* extract. Groups were separated into the Sham, LPS, LPS+100 mg/kg AOE, and LPS+100 mg/kg+Ad-MIAT groups. (A) The protein expressions of TRAF6, p-P65, and P65 were verified through western blot. (B) The level of CK-MB in serum was examined through ELISA. (C) The level of cTnI in serum was measured through ELISA. (D) The $Fe^{2+}$ level was tested through the corresponding commercial kit. (E) The levels of MDA and SOD were measured through ELISA.

future, more experiments will be conducted to explore other effects of AOE on the progression of SIC.

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## 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 during the present study are available from the corresponding author on reasonable request.

## Competing interests

The authors state that there are no conflicts of interest to disclose.

## Ethics approval

Ethical approval was obtained from the Institutional Animal Care and Use Committee of Tongji Medical College, Huazhong University of Science and Technology (Approval No.2020-073).

## Authors' Contribution

Conceptualization, methodology, and writing of original draft were performed by Yao Shi; formal analysis, resources, and investigation were the responsibility of Xiaobo Yang; formal analysis, visualization, and data curation were done by Hong Jiang; Project administration, supervision, and validation were performed by Shanxia Wu and Yan Hong; Validation, supervision, writing, review, and editing were performed by Wei Su and Xuan Wang. All authors read and approved the final manuscript.

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