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Original Article

Coptisine improves sepsis-induced acute kidney injury by inhibiting ferroptosis

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ABSTRACT — Sepsis-associated acute kidney injury (SA-AKI) is a life-threatening complication characterized by high morbidity and mortality. However, effective pharmacological therapies are currently unavailable. Ferroptosis, an iron-dependent form of regulated cell death, plays a pivotal role in the pathogenesis of SA-AKI. Coptisine, a natural isoquinoline alkaloid derived from *Coptis chinensis*, has demonstrated anti-inflammatory and antioxidant effects, but its specific role in SA-AKI remains to be elucidated. In this study, we investigated the protective effects of Coptisine against SA-AKI and the underlying mechanisms involved. Using a cecal ligation and puncture (CLP) mouse model, our study revealed that administering Coptisine significantly alleviated renal injury and inflammation, decreased oxidative stress, and inhibited ferroptosis in kidney tissues. In vitro studies showed that Coptisine suppressed LPS-induced ferroptotic injury in HK2 cells. Nevertheless, this protective effect was reversed by Nrf2 knockdown or iron supplementation. Mechanistically, Coptisine upregulated the levels of Nrf2 and GPX4, resulting in reduced ROS, MDA, and Fe^{2+} levels, while enhancing GSH content. Collectively, our findings indicate that Coptisine alleviates sepsis-induced AKI by inhibiting ferroptosis through the activation of the Nrf2 signaling pathway, highlighting its potential as a therapeutic agent for SA-AKI.

Key words: Coptisine, Sepsis-associated acute kidney injury, Ferroptosis, Nrf2 signaling pathway, Oxidative stress

INTRODUCTION

Sepsis is a life-threatening condition marked by organ dysfunction due to an uncontrolled response to infection, and it remains one of the primary causes of mortality in critically ill patients (Bellomo and Jones, 2025). Among its various complications, acute kidney injury (AKI) is one of the most prevalent and severe, occurring in nearly 50% of sepsis cases and significantly elevating the risk of death and long-term health complications (Baker and Cantley, 2025). Sepsis-associated acute kidney injury (SA-AKI) is defined by the simultaneous or subsequent onset of AKI in the context of sepsis. Its pathogenesis is driven by a complex interaction of inflammatory, oxidative, and hemodynamic mechanisms (Zhao *et al*., 2025). Despite substantial advancements in supportive care, effective pharmacological treatments for SA-AKI remain elusive, highlighting the urgent need for novel therapeutic strategies.

Recent studies have underscored the significance of ferroptosis, an iron-dependent form of regulated cell death characterized by lipid peroxidation, as a key factor contributing to the impairment of renal tubular epithelial cells in the context of AKI (Lai *et al*., 2025). Unlike apoptosis and necrosis, ferroptosis is primarily driven by iron overload, reactive oxygen species (ROS) accumulation, and the depletion of glutathione peroxidase 4 (GPX4) (Ren *et al*., 2023). Research has demonstrated that inhibiting ferroptosis can alleviate renal injury and promote recovery in various models of AKI, including those induced by sepsis (Zheng *et al*., 2024). An essential factor in the suppression of ferroptosis is nuclear fac-

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tor erythroid 2-related factor 2 (Nrf2), a vital transcription factor that regulates cellular antioxidant responses (Zheng *et al*., 2024). Activation of the Nrf2 signaling pathway enhances the expression of antioxidative genes such as GPX4, which helps to mitigate, oxidative damage, and iron-dependent cell death.

Coptisine, a protoberberine alkaloid extracted from *Coptis chinensis*, is recognized for its anti-inflammatory, antioxidative, and antimicrobial properties (Zhou *et al*., 2024). In renal diseases, Coptisine has shown protective effects by modulating the PI3K/Akt and Nrf2 pathways, thereby reducing oxidative stress, inflammation, and mitochondrial dysfunction (Liu *et al*., 2022). Previous studies have shown that Coptisine alleviates diabetic nephropathy and renal damage associated with hyperuricemia (Zhai *et al*., 2020). Furthermore, our preliminary investigations revealed that Coptisine inhibits lipopolysaccharide (LPS)-induced inflammation and apoptosis in lung epithelial cells, thereby improving outcomes in sepsis-related lung injury (Huang *et al*., 2023). Nonetheless, the therapeutic potential of Coptisine in SA-AKI remains unexplored.

In this study, we aimed to investigate the effects of Coptisine on alleviating SA-AKI and uncover the underlying mechanism behind these effects. We employed both *in vivo* (cecal ligation and puncture mouse model) and *in vitro* (LPS-induced HK2 cell model) methods to comprehensively assess renal function, inflammation, oxidative stress, and ferroptosis. Our findings may provide valuable insights into the therapeutic efficacy of Coptisine in managing SA-AKI.

MATERIALS AND METHODS

Animal model and treatment

Male C57BL/6 mice (20–25 g) were maintained under standard laboratory conditions. SA-AKI was induced through CLP. The mice were randomly divided into four groups (n = 6 per group): Sham, CLP, CLP + Coptisine (20 mg/kg), and CLP + Coptisine (40 mg/kg). Coptisine (Beyotime, S2340, Shanghai, China) was dissolved in sterile saline and administered intraperitoneally 1 hr after CLP. After 24 hr, blood and kidney tissues were collected for subsequent analysis. Ethical approval was obtained from the Ethics Committee of Experimental Animals of Nantong University.

Cell culture and treatments

Human renal proximal tubular epithelial cells (HK2) were sourced from ATCC (Manassas, VA, USA) and cultured in DMEM/F12 medium (Gibco, 11330032, USA) supplemented with 10% fetal bovine serum (Gibco, 10099141) at 37°C in 5% CO_2. For *in vitro* experiments, HK2 cells were pretreated with Coptisine (Beyotime, S2340, Shanghai, China) for 2 hr at designated concentrations before stimulation with LPS (Beyotime, ST1720, Shanghai, China; 10 μg/mL, 24 hr). To induce ferroptosis, Fe-citrate (100 μM) was co-administered with LPS for 24 hr. Ferrostatin-1 (Fer-1, 2 μM) was added 1 hr before LPS administration and maintained throughout the 24 hr treatment. For Nrf2 knockdown, cells were transfected with siRNA targeting human Nrf2 (si-Nrf2; sequence: 5′-GCAUUGAGACUACCAUGAUTT-3′) using Lipofectamine 3000 (Invitrogen) for 48 hr before LPS/Coptisine treatment. Knockdown efficiency was validated by Western blot.

Histological analysis

Kidney tissues were fixed in 4% paraformaldehyde, then embedded in paraffin, and sectioned at 4 μm using a Leica RM2235 microtome (Leica Microsystems, Germany). The sections were stained with hematoxylin and eosin (H&E) following standard protocols, and the resulting slides were examined using a Nikon Eclipse E100 light microscope (Nikon, Japan).

Renal function analysis

Serum blood urea nitrogen (BUN) and creatinine (Cr) levels were measured using commercial kits (Beyotime, C013-2 and C011-2, Shanghai, China).

Quantitative real-time PCR (qPCR)

Total RNA was extracted using TRIzol reagent (Invitrogen, 15596026, USA). cDNA synthesis was performed using the Beyotime Reverse Transcription Kit (D7168, Shanghai, China) under the following conditions: 42°C for 30 min, followed by 85°C for 5 min. qPCR was conducted using SYBR Green Master Mix (Beyotime, D7260) on a QuantStudio 5 Real-Time PCR System (Applied Biosystems, USA). The cycling conditions were set as follows: 95°C for 30 sec, followed by 40 cycles of 95°C for 5 sec and 60°C for 30 sec. Melt curve analysis was performed to confirm specificity of the results. The following primers were utilized: TNF-α: Forward 5′-CAGGCGGTGCCTATGTCTC-3′, Reverse 5′-CGATCACCCCGAAGTTCAGTAG-3′; IL-6: Forward 5′-AGTTGCCTTCTTGGGACTGA-3′, Reverse 5′-CAGAATTGCCATTGCACAAC-3′; IL-1β: Forward 5′-GCAACTGTTCCTGAACTCAACT-3′, Reverse 5′-ATCTTTTGGGGTCCGTCAACT-3′;β-actin: Forward 5′-GGCTGTATTCCCCTCCATCG-3′, Reverse 5′-CCAGTTGGTAACAATGCCATGT-3′.

Relative gene expression was calculated using the 2^−ΔΔCt method.

Enzyme-linked immunosorbent assay (ELISA)

Kidney homogenates were prepared and analyzed for TNF-α, IL-6, and IL-1β using ELISA kits (Beyotime, PT512, PT518, PT517, Shanghai, China) according to the manufacturer's instructions. Protein concentrations were normalized before quantification.

Biochemical assays

The levels of malondialdehyde (MDA), glutathione (GSH), and ferrous iron (Fe^{2+}) in kidney and cell lysates were assessed using specialized detection kits (Beyotime, S0131S for MDA, S0053 for GSH, and S0381 for Fe^{2+}). All values were normalized to account for total protein concentration measured by BCA protein assay (Beyotime, P0010, Shanghai, China).

DHE Staining for ROS detection

Frozen kidney sections or HK2 cells were incubated with 10 μM dihydroethidium (DHE, Beyotime, S0063) in PBS for 30 min at 37°C in the dark. The nuclei were counterstained with DAPI (Beyotime, C1002). Fluorescence images were captured using a Zeiss LSM 880 confocal microscope (Carl Zeiss, Germany) with excitation/emission at 518/605 nm for DHE and 358/461 nm for DAPI. Fluorescence intensity was quantified utilizing ImageJ software (NIH, USA) with threshold-adjusted regions of interest (ROIs).

Western blotting

Protein samples were separated via SDS-PAGE and subsequently transferred to PVDF membranes (Millipore, ISEQ00010). The membranes were blocked and incubated overnight at 4°C with primary antibodies: anti-GPX4 (Abcam, ab125066, 1:1000, UK); anti-Nrf2 (Abcam, ab62352, 1:1000, UK); anti-TNF-α (Abcam, ab6671, 1:1000, UK); anti-IL-6 (Abcam, ab9324, 1:1000, UK); anti-IL-1β (Abcam, ab9722, 1:1000, UK); anti-β-actin (Abcam, ab8226, 1:5000, UK). After washing, the membranes were incubated with HRP-conjugated secondary antibodies (Beyotime, A0208, 1:5000), and the signals were visualized using ECL substrate (Beyotime, P0018S). Densitometric analysis was performed with ImageJ software.

Statistical analysis

All experiments were repeated at least three times. Data were expressed as mean ± SD. Statistical comparisons among multiple groups were performed using one-way ANOVA followed by Tukey's post hoc test. A *P*-value < 0.05 was considered statistically significant.

RESULTS

Coptisine mitigates renal injury in a murine model of sepsis-induced AKI

To evaluate the renoprotective effect of Coptisine in SA-AKI, we established a CLP-induced septic mouse model and assessed several renal function indicators. Compared to the sham group, serum BUN and creatinine levels were markedly elevated in the CLP groups. In contrast, treatment with Coptisine at doses of 20 mg/kg and 40 mg/kg resulted in a significant reduction of these levels (Fig. 1A–B). Histopathological analysis of kidney tissue conducted using H&E staining revealed structural damage such as tubular dilation and necrosis in the CLP group. However, these abnormalities were considerably less pronounced in mice treated with Coptisine (Fig. 1C). We further examined renal function and histopathological changes in a CLP mouse model treated with the ferroptosis inhibitor Ferrostatin-1 (Fer-1). Compared with the Sham group, CLP mice exhibited significantly elevated serum BUN and Cr levels, indicating considerable renal dysfunction (Fig. 1D-E). Administration of Fer-1 notably reduced both BUN and Cr concentrations, suggesting improved kidney function. Histological analysis revealed that CLP resulted in pronounced swelling of tubular epithelial cells, vacuolar degeneration, dilation of tubular lumens, and the formation of casts. In contrast, Fer-1–treated kidneys exhibited attenuated pathological changes, with improved preservation of tubular structure and reduced tissue damage (Fig. 1F). These findings suggest that Coptisine mitigates CLP-induced renal injury *in vivo*.

Coptisine modulates inflammatory cytokine expression in septic kidneys

To investigate the anti-inflammatory effect of Coptisine, the mRNA and protein levels of proinflammatory cytokines in renal tissues were measured. The CLP challenge resulted in a statistically significant increase of TNF-α, IL-6, and IL-1β transcripts, as determined by qPCR (Fig. 2A–C). Moreover, ELISA analysis confirmed that the protein levels of these cytokines were elevated in the CLP group, but significantly decreased following treatment with Coptisine (Fig. 2D–F). These results demonstrate that Coptisine effectively suppresses the inflammatory response in the kidneys of CLP-treated mice.

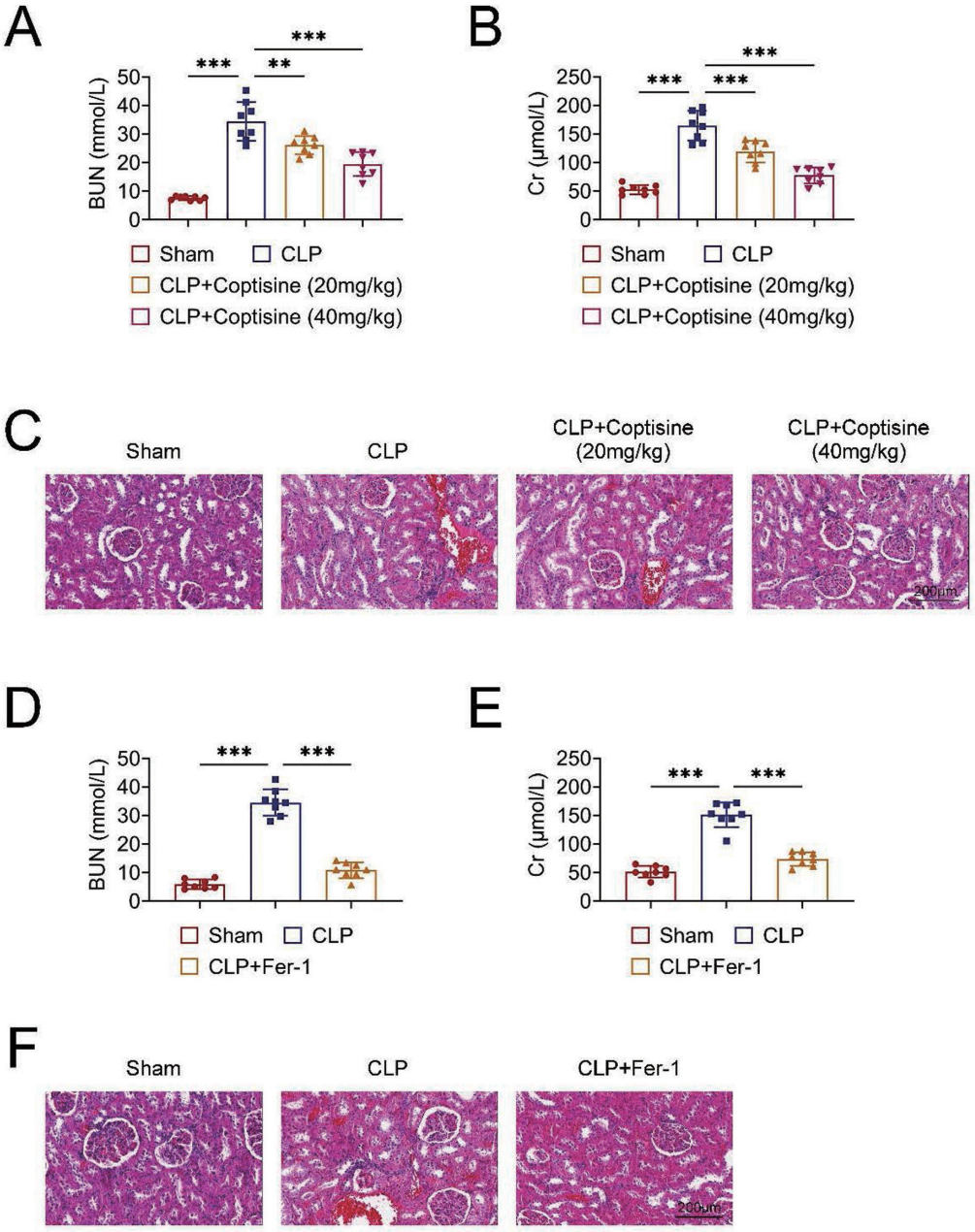

Fig. 1. Coptisine Attenuates Renal Injury in CLP-Induced Septic Mice. (A-B) Blood urea nitrogen (BUN) (A) and serum creatinine (Cr) (B) levels were measured in mice from the sham, CLP, CLP+Coptisine (20 mg/kg), and CLP+Coptisine (40 mg/kg) groups. (C) Representative hematoxylin and eosin (H&E) staining images of kidney tissues collected from each group. Scale bar = 200 μm. (D-E) Serum blood urea nitrogen (BUN) (D) and creatinine (Cr) (E) levels in the Sham, CLP, and CLP+Fer-1 groups. (F) Representative hematoxylin and eosin (H&E) staining images of kidney tissues from each group. CLP resulted in severe tubular injury, including tubular dilation, epithelial cell swelling, and cast formation, whereas Fer-1 treatment mitigated these changes. Scale bar = 200 μm. Data are shown as mean ± SD. Statistical analysis was performed using one-way ANOVA with post hoc tests. $^{**}P < 0.01$, $^{***}P < 0.001$.

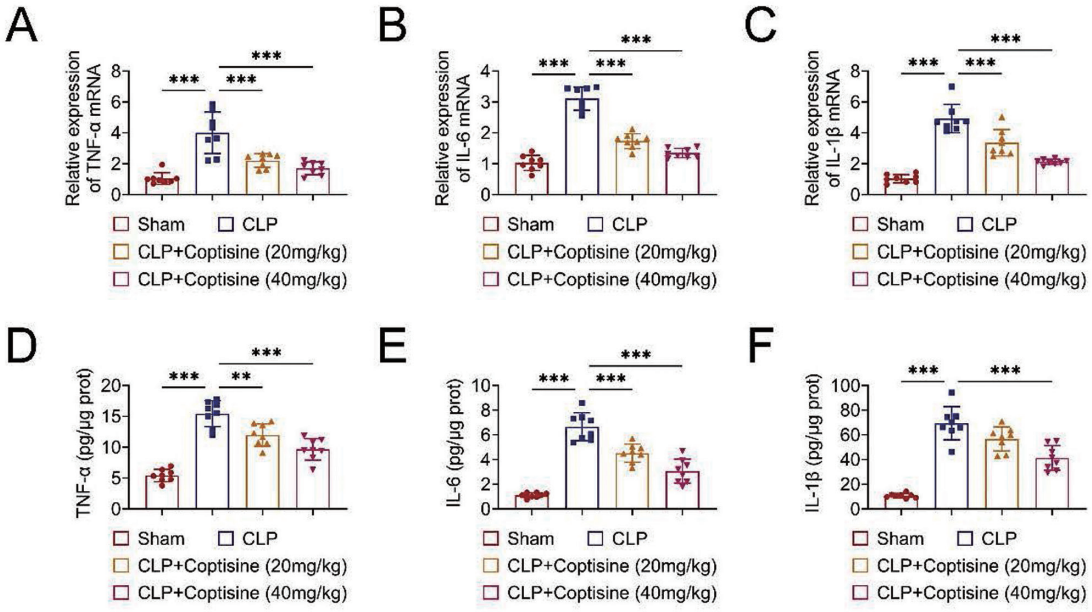

Fig. 2. Coptisine Reduces Renal Inflammation in CLP-Induced Septic Mice. (A-C) mRNA expression levels of TNF-α (A), IL-6 (B), and IL-1β (C) in kidney tissues were measured by quantitative PCR. (D-F) ELISA showed the protein levels of TNF-α (D), IL-6 (E), and IL-1β (F) in kidney tissues. Mice were divided into four groups: sham, CLP, CLP+Coptisine (20 mg/kg), and CLP+Coptisine (40 mg/kg). Data are presented as mean ± SD. Statistical analysis was performed using one-way ANOVA with appropriate post hoc tests. $^{**}P < 0.01$, $^{***}P < 0.001$.

Coptisine affects ferroptosis-related biochemical parameters in septic kidneys

To investigate the involvement of ferroptosis in the observed renal injury and to evaluate whether Coptisine exhibits anti-ferroptotic effects, a range of biochemical markers was analyzed. DHE staining revealed an increase in ROS levels in the kidneys of CLP mice, which were significantly attenuated by Coptisine treatment (Fig. 3A). CLP also led to elevated MDA and Fe^{2+} levels, accompanied by a reduction in GSH, all of which were reversed with Coptisine administration (Fig. 3B–D). In addition, Western blot analysis showed that Coptisine upregulated the expression of GPX4 and Nrf2 proteins, which had been downregulated by CLP (Fig. 3E–F). Together, these results indicate that Coptisine inhibits ferroptosis in septic kidneys.

Coptisine counteracts LPS-induced ferroptosis in HK2 cells

To evaluate the protective effect of coptisine against ferroptosis in renal tubular epithelial cells, HK2 cells were stimulated with LPS in the presence or absence of coptisine, or Fe-citrate. CCK-8 assay demonstrated that coptisine at concentrations up to 10 μg/mL showed no significant cytotoxicity; whereas at 20 μg/mL, it resulted in a slightly reduced cell viability (Fig. 4A). LPS exposure markedly increased MDA levels and decreased GSH levels, indicating enhanced lipid peroxidation and oxidative stress (Fig. 4B-C). Treatment with coptisine significantly reduced MDA accumulation and restored GSH levels in a dose-dependent manner. Conversely, he addition of Fe-citrate counteracted the antioxidant effects of coptisine. DHE fluorescence imaging further confirmed that LPS-induced ROS production was substantially attenuated by coptisine and Fer-1. In contrast, the presence of Fe-citrate nullified the protective effect of coptisine on ROS levels (Fig. 4D-E). Furthermore, Western blot analysis revealed that LPS markedly reduced GPX4 protein expression, a key regulator of ferroptosis. Treatment with coptisine restored GPX4 levels in a concentration-dependent manner (Fig. 4F). However, this restoration was eliminated when Fe-citrate was co-administered. Collectively, these results suggest that coptisine mitigates LPS-induced ferroptosis in HK2 cells by reducing oxidative damage and preserving GPX4 expression. These results confirm that Coptisine protects HK2 cells from

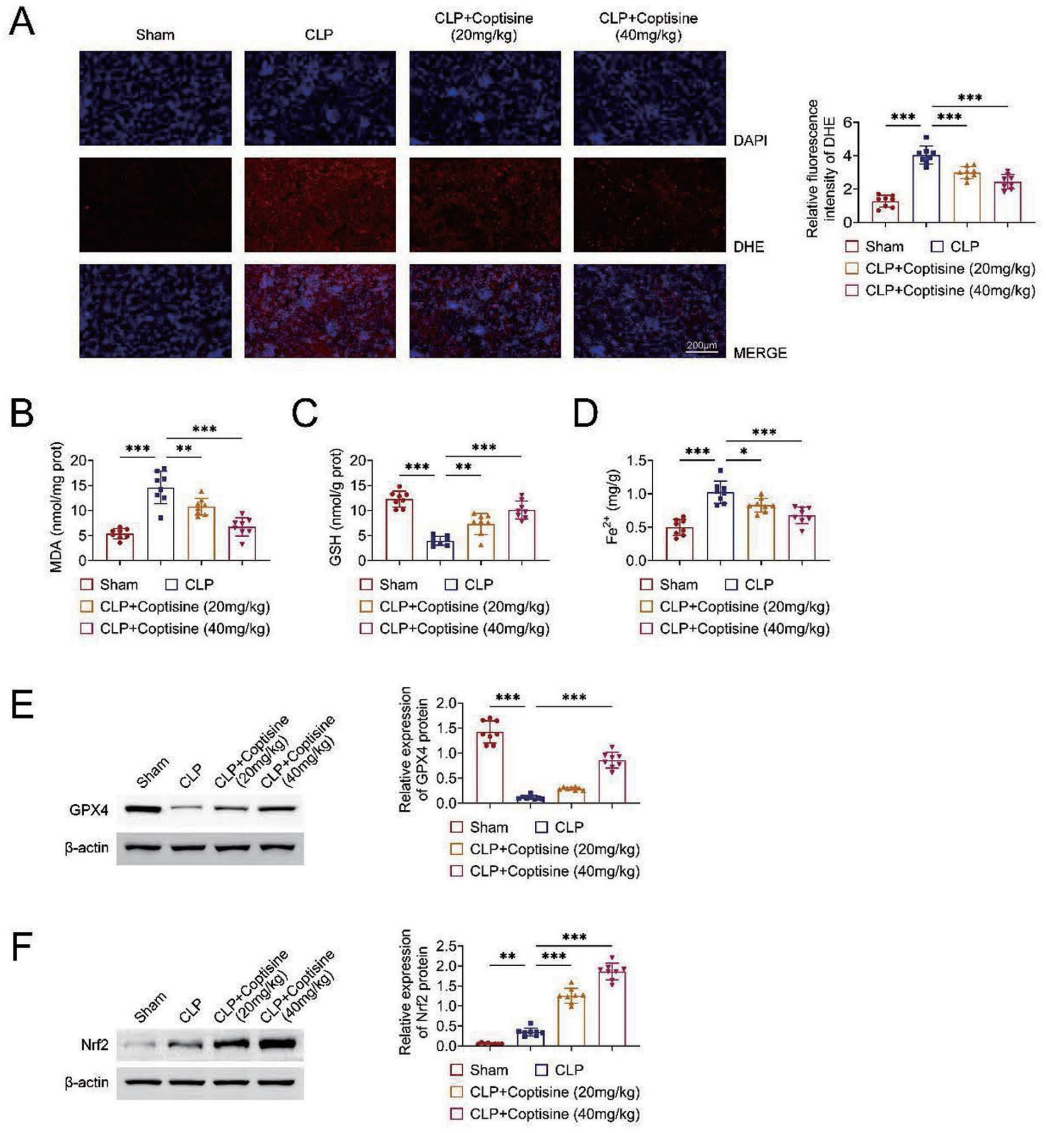

Fig. 3. Coptisine Inhibits Ferroptosis in the Kidneys of CLP-Induced Septic Mice. (A) Representative DHE fluorescence staining of kidney sections from mice in each group. Nuclei were counterstained with DAPI. Scale bar = 200 μm. (B-D) Quantification of malondialdehyde (MDA, B), glutathione (GSH, C), and ferrous iron (Fe^{2+}, D) levels in kidney tissues. (E-F) Western blot analysis and quantification of GPX4 (E) and Nrf2 (F) protein expression in renal tissues. β-actin was used as a loading control. Mice were divided into four groups: sham, CLP, CLP+Coptisine (20 mg/kg), and CLP+Coptisine (40 mg/kg). Data are expressed as mean ± SD. Statistical analysis was conducted using one-way ANOVA followed by post hoc tests. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

LPS-induced ferroptosis.

Nrf2 is required for the anti-ferroptotic effect of coptisine

To determine the role of Nrf2 in the anti-ferroptotic action of Coptisine, siRNA specifically targeting Nrf2 was employed in HK2 cells. Western blot analysis confirmed effective knockdown of Nrf2, revealing that the Coptisine-induced elevation of Nrf2 levels was negated in the si-Nrf2 group (Fig. 5A). In the absence of Nrf2, Cop-

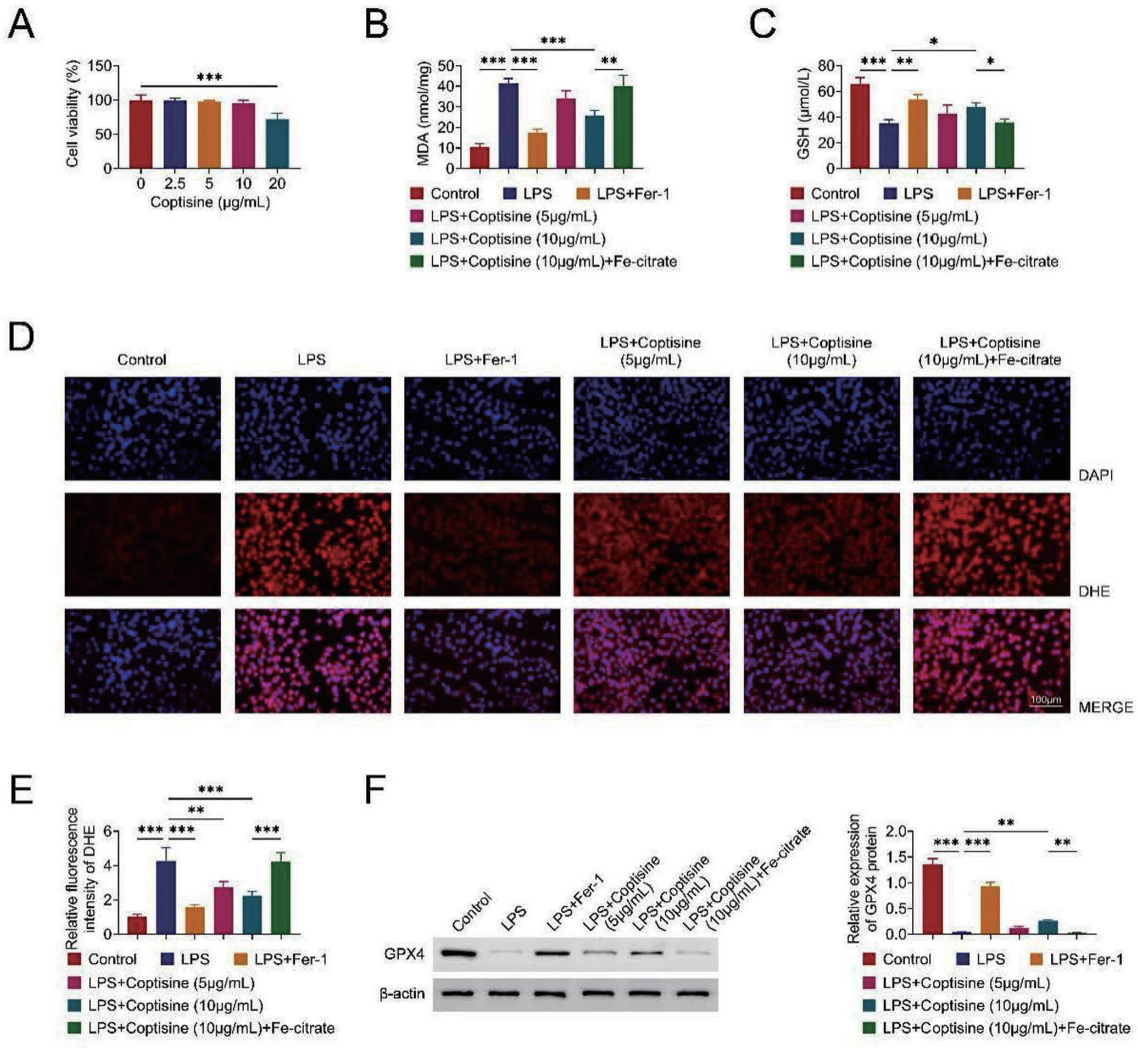

Fig. 4. Coptisine Suppresses LPS-Induced Ferroptosis in HK2 Cells *in vitro*. (A) Cell viability of HK2 cells treated with increasing concentrations of coptisine (0-20 μg/mL) for 24 hr, assessed by CCK-8 assay. (B-C) Quantification of malondialdehyde (MDA) content (B) and glutathione (GSH) levels (C) in HK2 cells under different treatments: Control, LPS, LPS+Fer-1, LPS+coptisine (5 μg/mL), LPS+coptisine (10 μg/mL), and LPS + coptisine (10 μg/mL) + Fe-citrate. (D) Representative DHE fluorescence staining images showing intracellular ROS levels. Nuclei were counterstained with DAPI. Scale bar = 100 μm. (E) Quantification of DHE fluorescence intensity from (D). (F) Western blot analysis of GPX4 protein expression and corresponding densitometric quantification in HK2 cells from the indicated groups. β-actin served as a loading control. Data are shown as mean ± SD. Statistical analysis was performed using one-way ANOVA with appropriate post hoc tests. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

tisine was ineffective in reducing MDA levels or restoring GSH content after exposure to LPS (Fig. 5B–C). Similarly, the upregulation of GPX4 by Coptisine was significantly diminished after Nrf2 silencing (Fig. 5D). These results indicate that the protective effect of Coptisine against ferroptosis is mediated via the activation of the Nrf2 pathway.

DISCUSSION

Sepsis-induced acute kidney injury (SA-AKI) poses a significant clinical challenge due to its high incidence and limited therapeutic options currently available (Li *et al*., 2024). The complex pathophysiology of SA-AKI involves not only hemodynamic changes but also oxi-

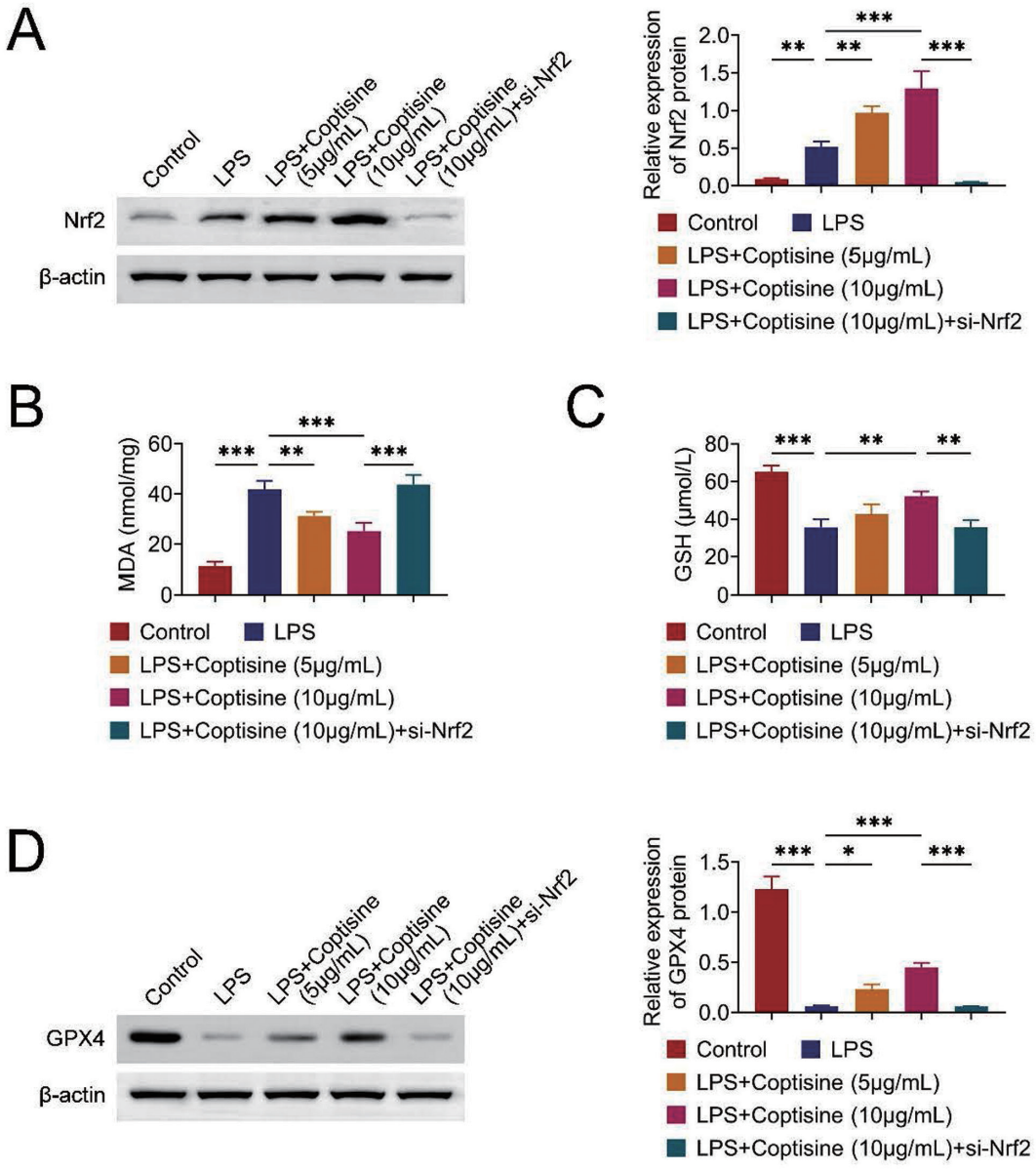

Fig. 5. Coptisine Alleviates Sepsis-Induced Ferroptosis via Activation of the Nrf2 Signaling Pathway. (A) Western blot analysis and quantification of Nrf2 protein expression in HK2 cells treated with LPS and Coptisine, with or without Nrf2 knockdown (si-Nrf2). β-actin served as a loading control. (B-C) Quantification of malondialdehyde (MDA, B) and glutathione (GSH, C) levels in HK2 cells under the indicated treatment conditions. (D) Western blot analysis and quantification of GPX4 protein levels. β-actin was used as a loading control. Experimental groups include: control, LPS, LPS + Coptisine (5 μg/mL), LPS + Coptisine (10 μg/mL), and LPS + Coptisine (10 μg/mL) + si-Nrf2. Data are presented as mean ± SD. Statistical analysis was conducted using one-way ANOVA with appropriate post hoc tests. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

dative stress, immune dysregulation, and various forms of regulated cell death. Consequently, identifying the molecular pathways that lead to kidney injury in sepsis is essential for the development of targeted therapies. In this study, we employed the cecal ligation and puncture (CLP) model, which is widely recognized for its ability to replicate the immunological and pathological features of human sepsis, to investigate the mechanisms underlying renal damage (Zhao *et al*., 2021). Our results revealed that Coptisine provides protective effects in septic kidneys, thus offering new insights into potential intervention strategies for SA-AKI.

Both inflammatory signaling and ferroptosis have emerged as pivotal elements in the progression of SA-AKI (Zheng *et al*., 2024). The excessive production of cytokines, such as TNF-α, IL-6, and IL-1β, disrupts renal microcirculation and induces tubular injury (Deng *et al*., 2024). Concurrently, ferroptosis which is a non-apoptotic, iron-dependent form of cell death driven by lipid peroxidation, plays a significant role in the deterioration of renal function (Dong *et al*., 2025; Shi *et al*., 2024). In our experiments, mice subjected to CLP exhibited elevated levels of inflammatory mediators and ferroptosis markers such as ROS, MDA, and Fe^{2+}, along with decreased GSH and GPX4. Treatment with Coptisine effectively modulated these indicators, suggesting its capacity to target both inflammatory and ferroptotic pathways in SA-AKI.

Coptisine, a natural alkaloid extracted from *Coptis chinensis*, is acclaimed for its diverse pharmacological activities, including antioxidative, anti-inflammatory, and antimicrobial properties (Xiao *et al*., 2024). Prior research has indicated that Coptisine can modulate cellular stress responses and inflammatory pathways (Nie *et al*., 2024). In our study, Coptisine notably attenuated kidney injury in CLP-treated mice and protected HK2 cells against LPS-induced ferroptosis. These protective effects were associated with decreased ROS levels, GSH and GPX4 restoration, and suppression of inflammatory cytokines. Our findings enhance the established pharmacological profile of Coptisine and suggest that it may play a role in modulating ferroptotic pathways, thereby promoting the survival of renal cells during sepsis.

There has been a growing interest in ferroptosis inhibitors as promising therapies for organ injury. Compounds such as Ferrostatin-1 have shown effectiveness in minimizing tissue damage in various preclinical models by inhibiting lipid peroxidation (Miotto *et al*., 2020; Scarpellini *et al*., 2023). In our *in vitro* studies, Ferrostan-1 effectively attenuated LPS-induced oxidative damage in HK2 cells. Additionally, Coptisine demonstrated similar efficacy in mitigating ferroptosis-associated injury, positioning it as a natural alternative with both anti-inflammatory and anti-ferroptotic properties. These findings emphasize the therapeutic potential of ferroptosis suppression in the context of septic kidney injury.

The transcription factor Nrf2 is vital for regulating responses to oxidative stress and providing resistance to ferroptosis (Kudo *et al*., 2020). By promoting the expression of antioxidant enzymes such as GPX4, Nrf2 activation helps to preserve redox balance and cellular viability. Our findings illustrated that Coptisine enhances Nrf2 expression in both *in vivo* and *in vitro* settings. Moreover, the knockdown of Nrf2 negated the protective effects of Coptisine on ferroptosis markers, suggesting that the observed renal protection is mediated through Nrf2-dependent signaling. This underscores Nrf2 as a key mediator of Coptisine's biological activity and highlights its potential as a therapeutic target in SA-AKI.

The observed increase in Nrf2 activation by coptisine during CLP/LPS stimulation may result from its direct interaction with upstream regulators of the Nrf2 pathway, such as KEAP1. Furthermore, coptisine may influence cellular redox balance, which aids in stabilizing Nrf2 and facilitating its translocation into the nucleus. Additionally, the structural properties of coptisine, particularly its isoquinoline backbone, may promote the induction of antioxidant genes by mimicking endogenous Nrf2 activators, thereby further strengthening the cytoprotective response against ferroptosis.

Our study demonstrates that coptisine effectively mitigates SA-AKI by inhibiting ferroptosis through the Nrf2 pathway. Notably, similar protective mechanisms have been identified in other organs. For instance, Liu *et al*. reported that coptisine alleviates hyperuricemia-induced liver injury by suppressing oxidative stress and inflammation via the PI3K/Akt and Nrf2 pathways (Liu *et al*., 2022). This aligns with our findings in renal tissues and highlights coptisine's broad organ-protective potential via conserved antioxidant mechanisms. However, our research advances this understanding by specifically linking coptisine to the regulation of ferroptosis within the context of sepsis, a connection that has not been previously explored. The convergence of coptisine's effects across various organs highlights its systemic therapeutic value. At the same time, its unique role in SA-AKI underscores the necessity for organ-specific mechanistic studies to optimize targeted therapies.

This study presents several limitations. Firstly, our investigation focused solely on the acute phase of injury, leaving longer-term outcomes, such as fibrotic progression or renal recovery, unexamined. Secondly, while our data suggest Nrf2 involvement, the upstream regu-

lators of this pathway in the context of Coptisine treatment remain to be elucidated. Additionally, the utilization of a single sex and cell type restricts the generalizability of our findings. Future research should incorporate diverse models, conduct broader mechanistic analyses, and explore the evaluation of combinatorial therapies to define the clinical applicability of Coptisine.

Conclusion

In summary, this study illustrates that Coptisine provides protection against sepsis-induced renal injury by modulating ferroptosis and inflammation via the activation of Nrf2 signaling. These results offer a mechanistic framework for targeting ferroptosis in SA-AKI and underscore the potential of Coptisine as a promising candidate for future drug development aimed at treating septic organ dysfunction.

Funding

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Conflict of interest

The authors declare that there is no conflict of interest.

Data availability

All data generated or analyzed during this study are included in this published article.

Author contributions

All authors contributed to the study conception and design. Material preparation and the experiments were performed by Yu Zhang. Data collection and analysis were performed by Junjun Huang and Xiaoyan Ji. The first draft of the manuscript was written by Ke Ren and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethical approval and consent to participate

Ethical approval was obtained from the Ethics Committee of Experimental Animal Center of Nantong University. The animal experiment complies with the ARRIVE guidelines and in accordance with the National Institutes of Health guide for the care and use of Laboratory animals.

Patient consent for publication

Not applicable.

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