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ORIGINAL RESEARCH

Curcumin exerts anti-inflammatory, antioxidant and anti-ferroptotic effects through the Nrf2/HO-1 pathway to protect cardiomyocytes against sepsis

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Abstract

This study explores the therapeutic effect of curcumin on H9c2 rat cardiac myoblasts *in vitro* sepsis model and its potential mechanisms. At first, Cell viability was measured using Cell Counting Kit 8 (CCK-8) and Cell-Light 5-ethynyl-2-deoxyuridine (EdU) staining, and inflammatory factors tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), interleukin 1β (IL-1β), oxygen species (ROS), malondialdehyde (MDA), superoxide dismutase (SOD), glutathione (GSH) and Fe^{2+} were calculated by ELISA and kits. Western blotting was used to quantitatively analyze nuclear factor erythroid 2-related factor 2 (Nrf2), heme oxygenase-1 (HO-1), glutathione peroxidase 4 (GPX4) and Acyl-CoA synthetase long-chain family (ACSL4) expression differences. Knocking down Nrf2 to study whether curcumin acts through the Nrf2/HO-1 pathway. The results show that curcumin significantly improved cell viability in lipopolysaccharide (LPS)-induced H9c2 cells ($p < 0.01$). Curcumin also significantly reduced inflammatory factor levels in LPS-induced cardiomyocytes ($p < 0.001$). Curcumin down-regulated ROS and MDA levels ($p < 0.001$), and up-regulated SOD and GSH levels ($p < 0.001$). A decrease in both Fe^{2+} content and protein expression of ACSL4 ($p < 0.001$), and increased protein expression of glutathione peroxidase 4 (GPX4) ($p < 0.001$) were observed with curcumin. By knocking down Nrf2 curcumin's therapeutic effect against LPS was eliminated. So curcumin can inhibit LPS-induced oxidative stress, inflammation and ferroptosis in cardiomyocytes by regulating Nrf-2/HO-1 signaling.

Keywords

Cardiomyocytes; Curcumin; Sepsis; Nrf2/HO-1; Ferroptosis; Oxidative stress; Inflammation

1. Introduction

Sepsis is a disease caused by infection, usually accompanied by a severe systemic inflammatory response. This results in organ and high mortality, especially in the elderly [1]. Sepsis is susceptible to the heart. Approximately half of sepsis patients suffer cardiac diseases, resulting in heart failure and hypotension [2, 3]. Cardiovascular disease is a general term for many diseases, including coronary heart disease, congenital heart disease, cerebrovascular disease, *etc.* [4]. Worldwide, cardiovascular disease is the leading cause of death, with high incidence rates [5]. Additionally, ferroptosis has been identified as a key mechanism in the pathogenesis and progression of cardiomyopathies, including those caused by sepsis, cardiac rhythm disorders and diabetes [6]. Therefore, to improve outcomes and prognoses for sepsis, novel drugs that target myocardial damage and ferroptosis are urgently needed.

Modern medicine is increasingly relying on natural compounds due to their relative safety, success, and low side effects. Curcumin, derived from *Curcuma longa* roots, is a natural polyphenol with antioxidant, anti-inflammatory and anti-cancer properties [7, 8]. Its therapeutic efficacy against cancer, ferroptosis-induced myocardial damage, neurological disorders, and many other diseases has been demonstrated [9–12]. Studies have confirmed that curcumin induces ferroptosis by activating autophagy in lung cancer, as well as enhancing its therapeutic effects [13]. Curcumin promotes nuclear translocation of nuclear factor erythroid 2-related factor 2 (Nrf2), increases heme oxygenase-1 (HO-1) expression, reduces excessive dissipation of glutathione peroxidase 4 (GPX4), and inhibits glucose-induced cardiomyocyte ferroptosis [14]. Curcumin reduces inflammation and oxidative stress in sepsis-induced myocardial damage [15, 16]. However, curcumin has rarely been reported to treat sepsis-induced myocardial injury, and its mechanism remains unclear.

We studied whether curcumin regulates Nrf-2/HO-1 in a sepsis model and reduces ferroptosis-induced myocardial injury. To elucidate curcumin's therapeutic mechanism on sepsis-induced myocardial injury, we used an *in vitro*

sepsis model administered with LPS to study its protective mechanism.

2. Methods

2.1 Cell culture

Experimental cells were rat H9c2 cardiomyocytes (Shanghai, China) cultured in high glucose Dulbecco's modified minimal medium (DMEM, Gibco, USA) with 10% fetal bovine serum (10500-64, Gibco, Carlsbad, CA, USA) and 1% penicillin-streptomycin (15140-122, Gibco, Carlsbad, CA, USA) in an incubator (37 °C, 5% CO_2).

The experimental groups are as follows: (1) control; (2) 5 μg/mL LPS; (3) 5 μg/mL LPS + 10 μmol/L Curcumin (Sigma Aldrich, 8203540010, St. Louis, MO, USA); (4) 5 μg/mL LPS + 20 μmol/L Curcumin; (5) 5 μg/mL LPS + 40 μmol/L Curcumin. Treat the samples with LPS (5 μg/mL, Sigma-Aldrich, L2880, St. Louis, MO, USA) for 24 hours to construct an LPS-induced myocardial injury model [17].

2.2 Cell viability assay

Seed 1 $\times$ 10^4 cells per well in a 96-well plate. Add Cell Counting Kit 8 (CCK-8, CK04, Solarbio, Hangzhou, China) reagent after 24 hours of culture. Incubate cells for 1 hour. Use a microplate reader to detect absorbance at 450 nm. Repeat the experiment three times.

2.3 EdU incorporation assay

Staining cells with Cell-Light 5-ethynyl-2-deoxyuridine (EdU, RiboBio, R11053.2, Guangzhou, China) kit. Seed and incubate cells on glass slides with EdU for 12 hours. Fix and permeabilize the cells. Add and incubate the Apollo® reaction mixture under light-shielded conditions for 30 minutes. Finally, the cells were counterstained and observed with a laser scanning confocal microscope (Leica SP8, Leica, Wetzler, Germany).

2.4 ELISA

Detect each inflammatory factor's levels using interleukin 1β (IL-1β, P08505, MultiSciences, Hangzhou, China), interleukin 6 (IL-6, P05231, MultiSciences, Hangzhou, China), tumor necrosis factor-α (TNF-α, P01375, MultiSciences, Hangzhou, China), enzyme-linked immunosorbent (ELISA) kits.

2.5 Determination of ROS, MDA, SOD and GSH content

Measure oxygen species (ROS), malondialdehyde (MDA), superoxide dismutase (SOD) and glutathione (GSH) levels according to instructions (Beyotime, China). Lyse cells in lysis buffer. Mix the cell lysis supernatant and standard sample with the working solution and boil at 100 °C for 15 minutes. Test the cooled supernatant for absorbance data at 490 nm and 532 nm using a 96-well plate reader. Repeat the experiment three times.

2.6 Fe^{2+} concentration measurement

Iron content kit for measuring Fe^{2+} content. After 24 hours of 6-Hydroxydopamine (6-OHDA) incubation, collect cells for the assay. Wash cells in cold Phosphate Buffered Saline (PBS) and homogenize 10 to 15 times or sonicate on ice. Centrifuge the sample for 10 minutes to remove insoluble material and supernatant. Quantify Fe^{2+} levels by adding 5 μL of reagent per well. Add the iron probe and incubate the cells at 25 °C for 1 hour. Measure the absorbance at 593 nm with a microplate reader. Repeat the experiment three times.

2.7 Lentivirus transduction

Gene-Pharma (Shanghai, China) constructed Nrf2-specific short hairpin RNA (shRNA) with the target sequence GCAGTTCAATGAAGCTCAACT, and the new plasmid was named Nrf2-inhibited (Nrf2i). The random sequence TTCCCGAACGTGTCACGT was used as a negative control and was named NC. Cell transfections were performed with lentiviral particles in 6-well plates using Polybrene (Gene-Pharma) according to the manufacturer's instructions. Transfection was continued for 24 h, followed by recovery in complete medium for 24 h.

2.8 Western blot

Lyse protein in IP lysis buffer (P0013, Beyotime, Shanghai, China). After measuring the protein concentration, perform leveling. Separate the samples by SDS-PAGE and transfer them to a membrane. Separate, transfer, block then incubate the samples with primary antibodies including TNF-α (1:1000, ab183218, Abcam, UK), IL-6 (1:1000, ab233551, Abcam, UK), IL-1β (1:1000, ab216995, Abcam, UK), glutathione peroxidase 4 (GPX4, 1:1000, ab262509, Abcam, UK), Acyl-CoA synthetase long-chain family (ACSL4, 1:1000, ab155282, Abcam, UK), Nrf-2 (1:1000, ab137550, Abcam, UK) and HO-1 (1:1000, ab305290, Abcam, UK). Wash and incubate TBST with the secondary antibody (1:1000, cell signal technology) for 1 hour. Visualize the protein bands using a developer (Millipore, Massachusetts, USA). Finally, analyze the gray value using ImageJ software (1.8.0, National Institutes of Health, Bethesda, MD, USA).

2.9 Statistical analysis

Using GraphPad Prism V8.0 software (Motulsky, San Diego, CA, USA), the data were analyzed using a *t* test to compare the two groups. $p < 0.05$ was considered statistically significant.

3. Result

3.1 Curcumin promotes proliferation in LPS-induced H9C2 cells

We detected the effects of different curcumin doses on rat cardiomyocyte viability using CCK-8 assay and EdU staining. Fig. 1a shows curcumin's chemical structural formula. In the Fig. 1b–d, LPS significantly reduces cell survival and proliferation. In LPS-induced cardiomyocytes, curcumin increased cell survival and proliferation dose-dependently.

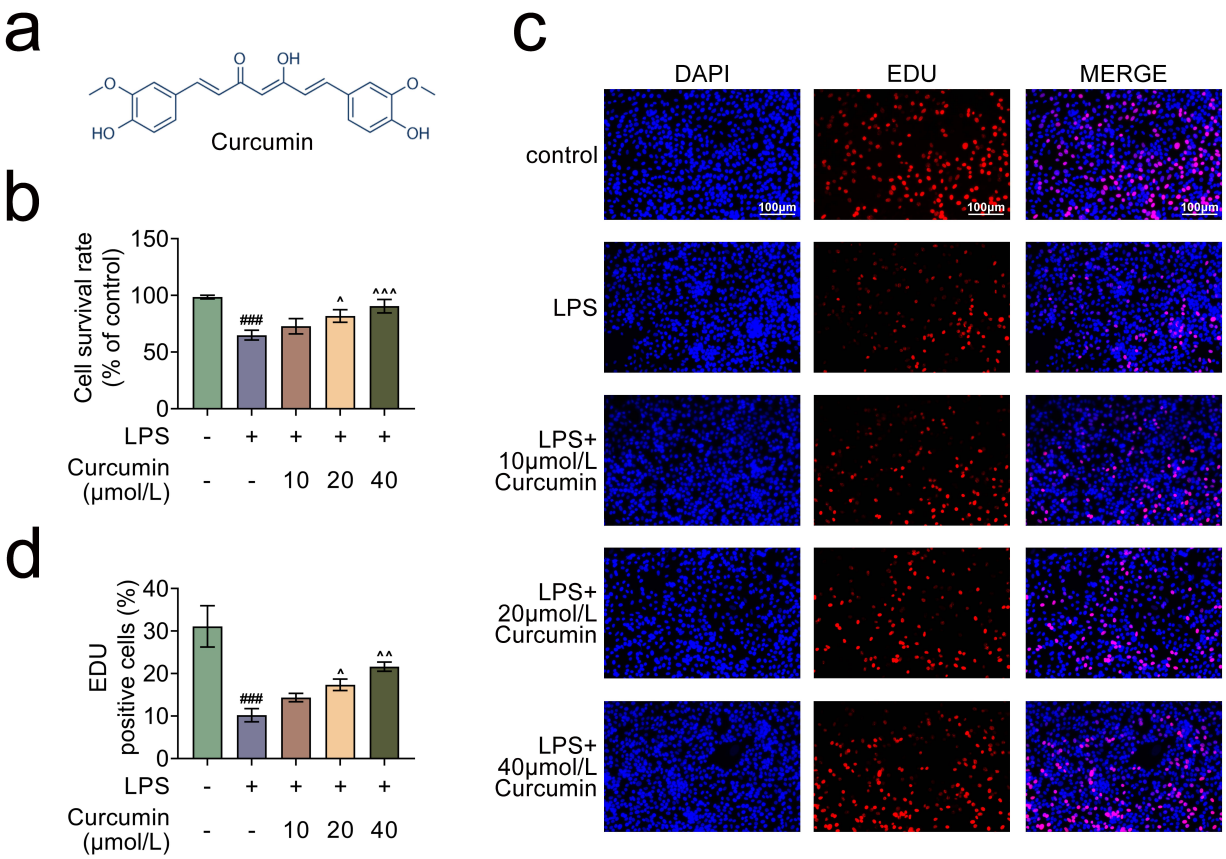

FIGURE 1. Curcumin increases cell viability and inhibits injury in cardiomyocytes exposed to LPS. (a) Curcumin chemical structural formula. (b) CCK-8 detects cell survival rates. (c) EdU staining diagram. (d) Cell proliferation was determined using EdU staining. Values are presented as mean ± SD. $^{###}p < 0.001$ versus control group. $^{\wedge}p < 0.05$, $^{\wedge\wedge}p < 0.01$, $^{\wedge\wedge\wedge}p < 0.001$ versus LPS group. n = 6. LPS: lipopolysaccharide; DAPI: 4′,6-diamidino-2-phenylindole; EDU: Cell-Light 5-ethynyl-2-deoxyuridine.

3.2 Curcumin inhibits the inflammatory response in LPS-induced H9C2 cells

ELISA and Western Blot detection of cardiomyocyte inflammatory responses. The content and protein expression of TNF-α, IL-6 and IL-1β in the LPS group were significantly higher than those in the control group. However, co-treatment of LPS and curcumin abolished the LPS-induced inflammatory response dose-dependently (Fig. 2a,b). Therefore, curcumin reduces LPS-induced inflammation in cardiomyocytes.

3.3 Curcumin inhibits oxidative stress in LPS-induced H9C2 cells

Sepsis is often accompanied by oxidative stress. Thus, we examined curcumin's effect on LPS-induced oxidative stress. LPS significantly increased ROS and MDA levels compared to the control group, but SOD and GSH levels showed opposite trends (Fig. 3). However, curcumin administration abolished these effects (Fig. 3). Therefore, curcumin alleviates LPS-induced oxidative stress damage in cardiomyocytes.

3.4 Curcumin inhibits ferroptosis in LPS-induced H9C2 cells

Our study examined whether curcumin affected ferroptosis using Fe^{2+} content, GPX4 and ACSL4 protein expression in LPS-induced cardiomyocytes as detection indicators. Compared with the control group, the LPS group's Fe^{2+} content and ACSL4 were higher (Fig. 4a,b). GPX4 was significantly reduced (Fig. 4c), and ACSL4 in the LPS group was higher (Fig. 4d). However, these effects can be abolished by curcumin administration dose dependently (Fig. 4a–d). Therefore, curcumin alleviates LPS-induced ferroptosis in cardiomyocytes.

3.5 Curcumin protects cardiomyocytes from LPS effects by regulating the Nrf-2/HO-1 signaling pathway

To prove that curcumin protects cardiomyocytes by regulating Nrf-2/HO-1, we knocked down Nrf2 in cardiomyocytes. TNF-α, IL-6, IL-1β levels were significantly higher than those in the LPS group after knocking down Nrf2 (Fig. 5a). ROS, MDA, Fe^{2+} levels were also significantly increased, while SOD and GSH levels were significantly reduced (Fig. 5b,c). At the same time, GPX4, Nrf2 and HO-1 proteins were reduced; TNF-α, IL-6, IL-1β, ACSL4 were significantly increased (Fig. 5d–f). Curcumin significantly abolished these effects. As a result, curcumin may exert a therapeutic effect on cardiomyocytes through the Nrf-2/HO-1 pathway.

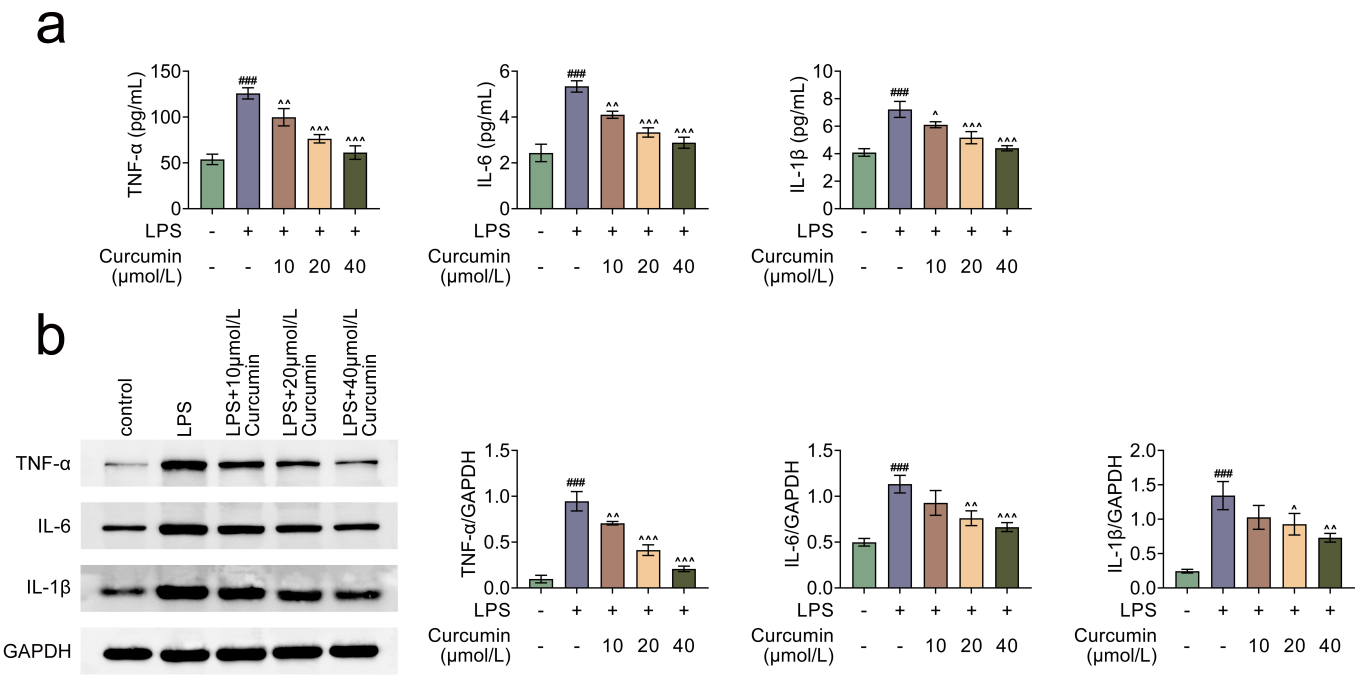

FIGURE 2. Curcumin inhibits inflammatory response in LPS-induced H9C2 cells. (a) Contents of TNF-α, IL-6, IL-1β in cells. (b) Expression levels of TNF-α, IL-6, IL-1β in cells. Values are presented as mean ± SD. $^{###}p < 0.001$ versus control group. $^{\wedge}p < 0.05$, $^{\wedge\wedge}p < 0.01$, $^{\wedge\wedge\wedge}p < 0.001$ versus LPS group. n = 3. TNF-α: tumor necrosis factor-α; IL-6: interleukin 6; IL-1β: interleukin 1β; LPS: lipopolysaccharide; GAPDH: glyceraldehyde-3-phosphate dehydrogenase.

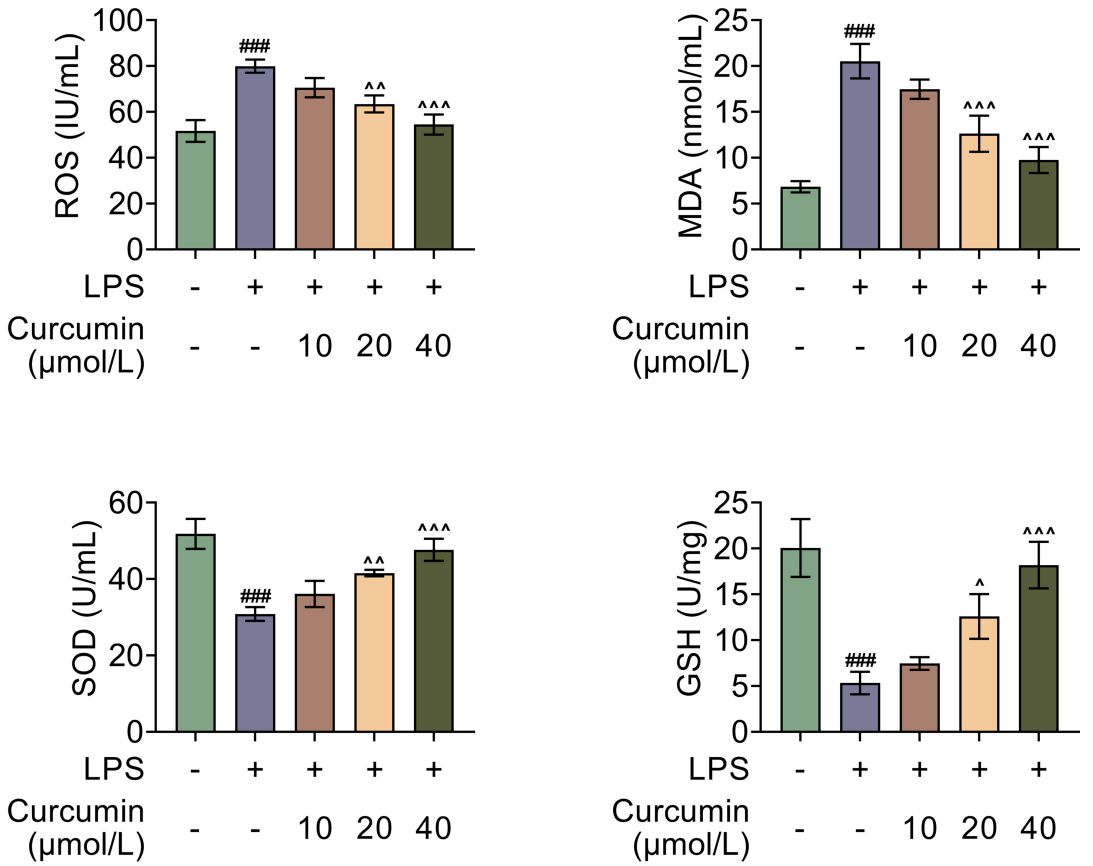

FIGURE 3. Curcumin inhibits oxidative stress in LPS-induced H9C2 cells. The kit detects the level of ROS, MDA, SOD and GSH. Values are presented as mean ± SD. $^{###}p < 0.001$ versus control group. $^{\wedge}p < 0.05$, $^{\wedge\wedge}p < 0.01$, $^{\wedge\wedge\wedge}p < 0.001$ versus LPS group. n = 3. ROS: Oxygen species; LPS: lipopolysaccharide; MDA: malondialdehyde; SOD: superoxide dismutase; GSH: glutathione.

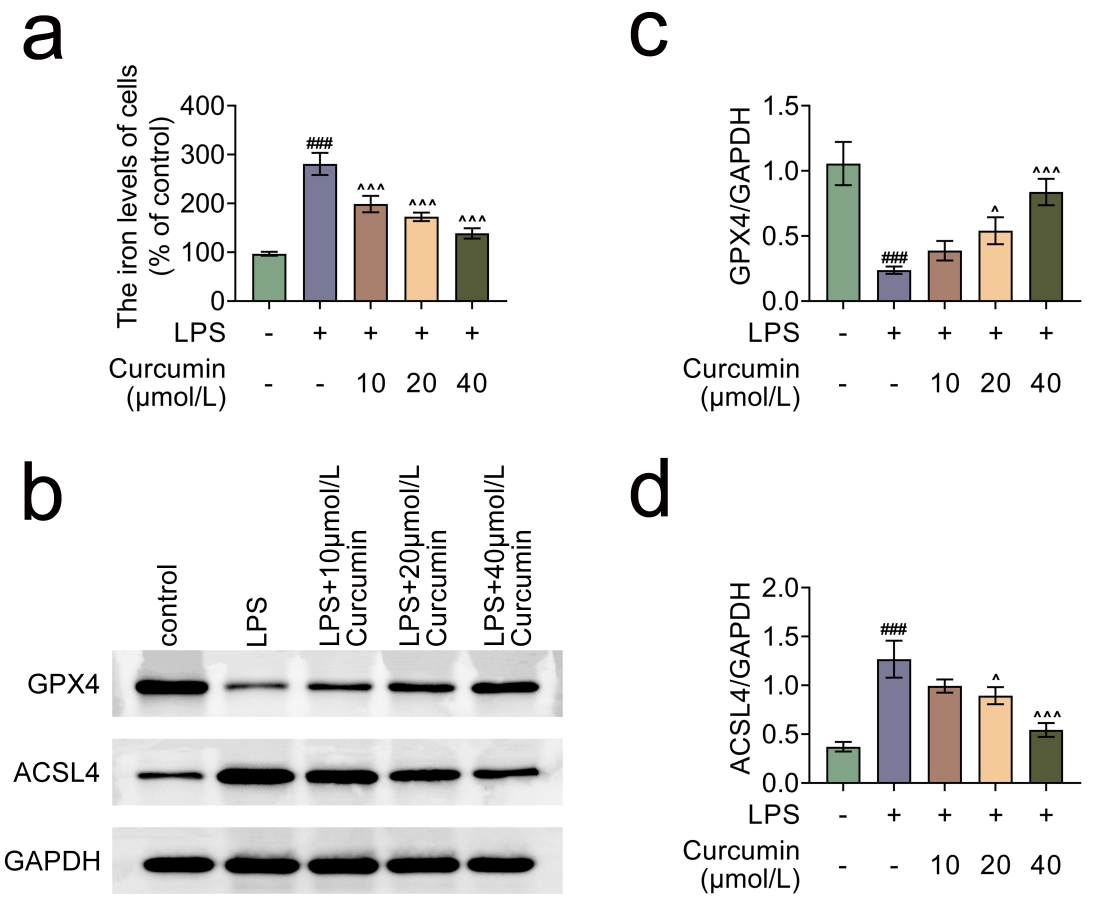

FIGURE 4. Curcumin inhibits ferroptosis in LPS-induced H9C2 cells. (a) Fe^{2+} content of cells. (b) Protein expression map of GPX4, ACSL4. (c) GPX4 protein expression levels. (d) ACSL4 protein expression levels. Values are presented as mean ± SD. $^{###}p < 0.001$ versus control group. $^p < 0.05$, $^{^^^}p < 0.001$ versus LPS group. n = 3. LPS: lipopolysaccharide; GPX4: glutathione peroxidase 4; GAPDH: glyceraldehyde-3-phosphate dehydrogenase; ACSL4: Acyl-CoA synthetase long-chain family.

4. Discussion

According to our research, curcumin is effective at treating LPS-induced myocardial injury due to its anti-inflammatory, antioxidant, and anti-ferroptotic properties. A knockdown of Nrf2 in the LPS model demonstrated that curcumin has a cardioprotective effect through the Nrf2/HO-1 pathway.

Sepsis is a reaction syndrome accompanied by systemic inflammation that leads to cardiac toxicity [18]. Lipopolysaccharides produced by Gram-negative bacteria are key to sepsis [19]. LPS signaling pathways have been identified as causing oxidative stress and inflammation in myocardial injuries caused by sepsis [20]. Various anti-inflammatory and antioxidant drugs are tested to determine how LPS damages the myocardium. Several studies have shown that many traditional Chinese medicines and their monomers have effective anti-inflammatory and antioxidant effects on cardiovascular diseases, including salidroside [21], Leonurine [22], *etc.*

Curcumin is a natural compound that has antioxidant and anti-inflammatory properties [23]. Studies have shown that curcumin improves drug-induced cardiotoxicity, hypertension, coronary heart disease, heart failure, *etc.* [24]. TNF-α, IL-1β and IL-6 are the major inflammatory mediators responsible for myocardial depression in sepsis [25]. Continuous ROS overproduction can lead to cell death. SOD's physiological activities on living organisms include anti-inflammatory and antioxidant functions. MDA is considered an indicator of lipid peroxidation. GSH is a key non-protein antioxidant that scavenges lipid peroxide free radicals [21]. Furthermore, our study confirmed this conclusion, as scholar Zhu [26] found that curcumin improves inflammation and oxidative stress in LPS-induced myocardial function. In CCK-8 experiments, curcumin promoted proliferation of LPS-treated cardiomyocytes; in WB and Elisa experiments, curcumin reduced the content and production of TNF-α, IL-1β and IL-6. At the same time, the kit test showed that curcumin inhibited ROS and MDA levels in LPS-treated cardiomyocytes and enhanced SOD and GSH levels. Accordingly, curcumin's therapeutic effects seem closely related to its anti-inflammatory and antioxidant activities.

Overactivation of lipid peroxidation leads to ferroptosis [27]. GPX4 and ACSL4 are thought to be important in ferroptosis [28]. Therefore, our study selected these two as ferroptosis monitoring indicators. Ferroptosis plays a role in a variety of cardiovascular diseases as well. Ferroptosis inhibitors improve various cardiovascular diseases [29]. Recent studies demonstrated that the ferroptosis inhibitor Ferrostatin-1 can effectively alleviate myocardial damage caused by sepsis by inhibiting ferroptosis [30]. To treat myocardial damage caused by sepsis, we believe inhibiting

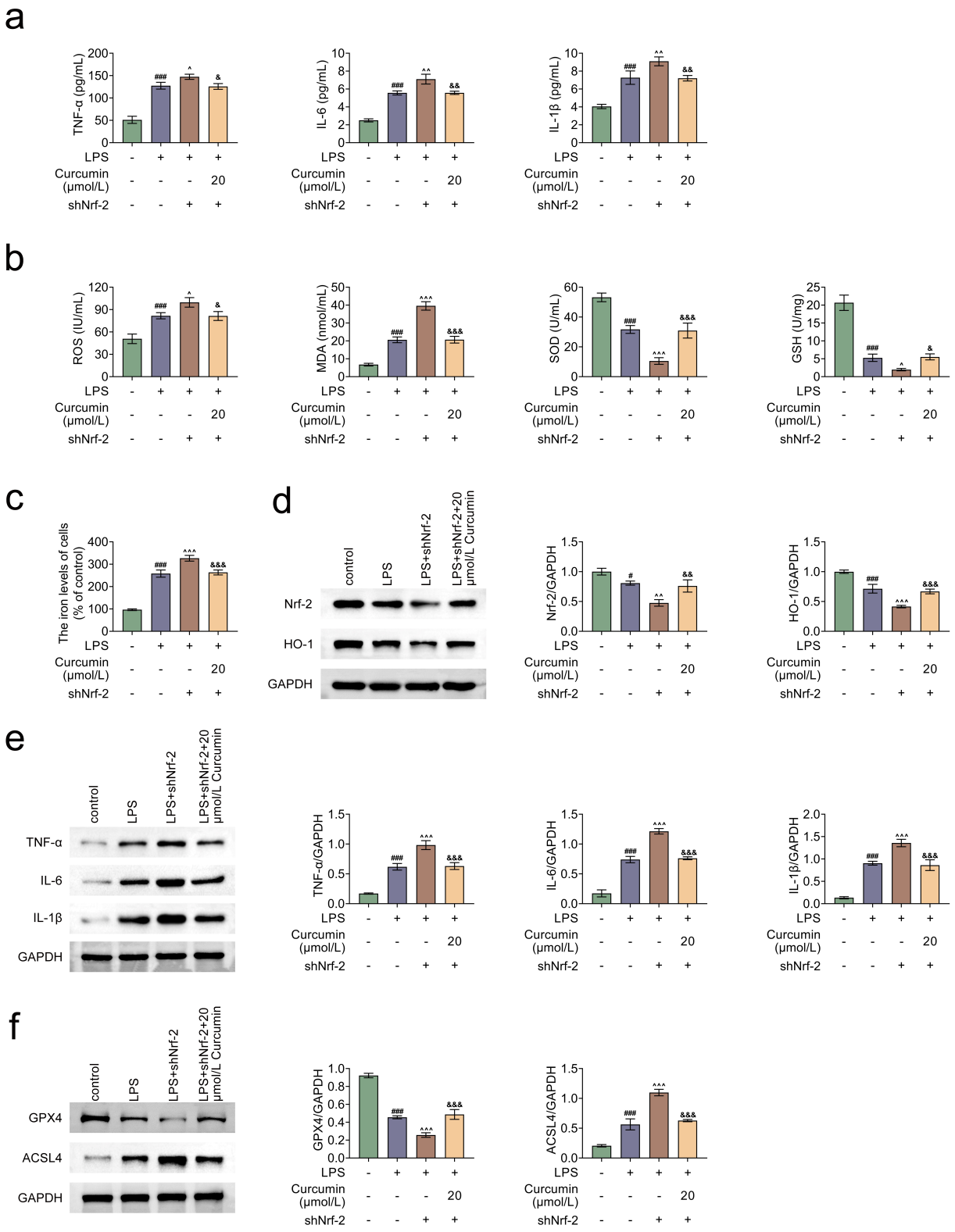

FIGURE 5. Curcumin protects cardiomyocytes from the effects of LPS by regulating the Nrf-2/HO-1 pathway. (a) Contents of TNF-α, IL-6, IL-1β in cells. (b) The kit detects the level of ROS, MDA, SOD and GSH. (c) Fe^{2+} concentration. (d) Protein expression of Nrf2 and HO-1. (e) Expression levels of TNF-α, IL-6, IL-1β in cells. (f) GPX4, ACSL4 levels. Values are presented as mean ± SD. $^{\#}p < 0.05$, $^{\#\#\#}p < 0.001$ versus control group. $^{\wedge}p < 0.05$, $^{\wedge\wedge}p < 0.01$, $^{\wedge\wedge\wedge}p < 0.001$ versus LPS group. $^{\&}p < 0.05$, $^{\&\&}p < 0.01$, $^{\&\&\&}p < 0.001$ versus LPS + shNrf-2 group. n = 3.

ROS: Oxygen species; MDA: malondialdehyde; SOD: superoxide dismutase; GSH: glutathione; GPX4: glutathione peroxidase 4; ACSL4: Acyl-CoA synthetase long-chain family; LPS: lipopolysaccharide; GAPDH: glyceraldehyde-3-phosphate dehydrogenase.

ferroptosis is key. Based on kit detection and WB, curcumin reduced LPS-induced cardiomyocyte Fe^{2+} content, reduced ACSL4, and enhanced GPX4. Our results are consistent with Zhang's study [14] that curcumin can improve myocardial infarction caused by ferroptosis. It is possible that curcumin's cardioprotective effects are due to its anti-ferroptotic activities.

Nrf2 is closely related to redox and ferroptosis, and activation of NRF2 plays a therapeutic role in sepsis-induced myocardial injury [31]. HO-1 inhibits cell apoptosis and redox, which are associated with ferroptosis [32]. Curcumin activates the Nrf2/HO-1 signaling pathway by inhibiting redox [33]. Therefore, we speculate that curcumin reduces LPS-induced inflammation, oxidative stress, and ferroptosis in cardiomyocytes by affecting the Nrf2/HO-1 pathway. In cardiomyocytes, knocking down Nrf2 exacerbated LPS-induced inflammation, oxidative stress and ferroptosis, whereas curcumin administration reversed these effects. Our study is consistent with Zhang's study [14] that curcumin improves myocardial infarction through Nrf. Curcumin exerts anti-inflammatory, antioxidant and anti-ferroptotic effects on LPS-induced cardiomyocytes *via* Nrf2/HO-1 signaling.

5. Conclusions

According to this study, curcumin appears to be a promising therapeutic compound for sepsis-induced myocardial injury. Curcumin may exert therapeutic effects through its pharmacological activities, including its antioxidant, anti-inflammatory, and antiferroptotic properties. Curcumin's therapeutic effects may also be attributed to the reduction of cellular inflammation, oxidative stress, and ferroptosis through activation of the Nrf2/HO-1 signaling pathway. These findings may provide an innovative treatment strategy for sepsis-induced myocardial injury. Curcumin needs further research *in vivo* and in clinical settings.

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.

AUTHOR CONTRIBUTIONS

YS and XBY—designed the research study. HJ—performed the research. SXW, YH and WS—analyzed the data. XW—wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGMENT

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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