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Activation of SIRT1 signaling pathway by clove improves cognitive dysfunction in septic mice

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Abstract
Clove is a kind of food spice, which can be used as food flavoring additive. In this work, we looked at clove's impact and underlying mechanism on cognitive impairment in infected mice. By using the open field test, Morris water maze, ELISA technique, kit method, and qPCR method, the biochemical and molecular biological indices of mice were identified. Clove component composition was established using HPLC. The findings demonstrated that clove might enhance mouse survival rates in comparison to the model group and could also lengthen driving distances, standing and combing periods, target quadrant duration, and crossing periods. In the hippocampus of infected mice, clove can lower levels of TNF-α, IL-6, IL-1β, and MDA while increasing SOD and CAT activity. In the hippocampus of infected animals, clove additionally increased the mRNA expression of SIRT1 and FOXO1 and decreased the mRNA expression of NF-B and p53. Animal studies revealed that clove's impact was comparable to dexamethasone in that it might help septic mice with cognitive impairment. The analysis revealed that rutin, isoquercitrin, ferulic acid, dihydroquercetin, and quercitrin were all present in clove. It is clear that clove can help septic mice with cognitive impairment by triggering SIRT1 through its active components.

Keywords: clove; SIRT1; functional food; sepsis; HPLC.

Practical Application: Clove is a high-grade spice used in food, and it has certain biological activity. This study confirmed that cloves can enhance the antioxidant capacity of experimental animals, and can play its role in inhibiting sepsis by regulating the SIRT1 signaling pathway, indicating that cloves can be used not only as spices, but also as health food or health food additives.

1 Introduction

Sepsis is a type of systemic inflammation brought on by an unbalanced host response to infection. It is closely related to the pathophysiological alterations of numerous systems and organs and results in systemic inflammatory network effect, gene polymorphism, immune dysfunction, coagulation dysfunction, tissue injury, and abnormal responses of the body to various infectious pathogenic microorganisms and their toxins (Rimmelé & Kellum, 2011). The most common causes of mortality in ICU patients are sepsis and its sequelae, with a case fatality rate between 30% and 70% (He & Chen, 2016). Sepsis survivors have been shown to have long-term cognitive damage, including memory loss, focus problems, and general cognitive decline. 70% of sepsis patients may experience subsequent central nervous system impairment (Honselmann et al., 2015). Sepsis lowers a patient's quality of life, increases the risk of dementia and neurological illnesses, and is very taxing on the patient's family. Empirical antibiotic therapy is typically used in the early stages of sepsis since it is hard to immediately get the findings of a bacterial culture. However, the administration of antibiotics can result in drug overuse and antibiotic resistance (Singla et al., 2015). Dexamethasone is an adrenocortical hormone that is frequently used to treat sepsis and has good anti-inflammatory, anti-allergic, and anti-toxic effects. However, it can also have side effects like mental symptoms, emotional instability, and edema (Fratoni et al., 2020), so it is used as a positive control in this study. Finding active compounds with fewer side effects for the treatment and adjuvant therapy of sepsis is of utmost importance since, despite the fact that medications for the treatment of sepsis can already play a certain role, they all have side effects to a certain amount.

Clove is a kind of high-grade spice in food. Because of its strong aroma and pungent taste, clove is often used for food seasoning, especially for meat and bread. It is a unique seasoning for Christmas food in Europe and the United States, and is often used as an auxiliary material for cooking flavor dishes, stewed dishes and pickles in Asian countries (Sary et al., 2022). Because of its strong fragrance, cloves were also used to cover up bad breath, and were not used as chewing gum in ancient China. The health effects of cloves have antibacterial and anti-inflammatory, analgesic, anticancer, antioxidant, antidepressant, hypoglycemic, deworming, antiseptic, anti-caries and other effects (Li et al., 2021).

Clove has antioxidant, anti-inflammatory and bactericidal effects, and existing studies have shown that it has no toxicity and adverse effects, so it has the potential to be used as an intervention and adjuvant therapy for sepsis (Chen et al., 2022). Based on

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these factors, this study conducted pertinent experiments to determine how clove affected the improvement of cognitive impairment in infected mice. SIRT1 has been demonstrated to be intimately related to sepsis and is a crucial nicotinamide adenine dinucleotide-dependent protein lysine deacetylase that controls stress responses, inflammatory signaling, apoptosis, and cell senescence (Jin et al., 2021). The improvement of cognitive impairment in infected mice can be attributed to SIRT1 activity (Mai et al., 2021). In this investigation, we also looked at the mechanism behind clove's anti-sepsis effects. We first observed that clove can improve the cognitive dysfunction of septic mice by activating SIRT1 through the development of animal models. We then used a variety of experimental techniques, including molecular biology, to analyze its mechanism of action in accordance with the results of clove components.

2 Materials and methods

2.1 Clove extraction

200 g of freeze-dried clove (Bozhou Guqingtang Pharmaceutical Co., Ltd., Bozhou, Anhui, China) was mixed with 70% ethanol at a mass ratio of 1:20 and extracted at 60 °C for 3 h. Then slowly pouring the extract into a glass column filled with FL-3 macroporous resin, removing the filtrate after the first resin treatment, eluting with 70% ethanol until the resin becomes colorless, collecting the eluted solution with a beaker, and carrying out rotary distillation on the rotary eluted solution to obtain the clove extract.

2.2 Animal experiments

In the laboratory animal rearing environment, which had a temperature control set at (21 ± 2) °C, a humidity control set at (55 ± 2)%, and a light/dark cycle of 12 h, 50 male ICR mice (Chongqing Medical University, Chongqing, China) aged 10 weeks were fed adaptively for one week. They received unlimited amounts of food and liquids. After being separated into groups of 10 mice each, 50 mice were randomly assigned to the normal group, model group, low concentration of clove (clove-L), high concentration of clove (clove-H), and dexamethasone group. Other mice were given cecal ligation and puncture treatments to cause sepsis, with the exception of the normal group (Ferreira et al., 2017). Ketamine (15 mg/kg) and xylazine (7.5 mg/kg) intraperitoneal injections were used to anesthetize the test animals. A 2 cm incision was made in the mouse's midline to expose the cecum following iodophor cleaning. The feces were carried to the cecum, ligated with 5/0 acrylic thread, and attached beneath the ileocecum's connecting rod, however they were unable to impede the intestines. An 18-gauge needle was used to pierce the cecum ten times, and it was then gently massaged until a little drop of excrement emerged. The incision was stitched up after the cecum was moved back into the abdominal cavity. Every day, 0. 2 mL of saline was administered intraperitoneally and intragastrically to the mice in the normal group and the model group, respectively. Intragastrically, mice in the clove-L and clove-H groups received daily doses of 50 mg/kg and 100 mg/kg of clove extract, respectively. The mice in the dexamethasone group received daily intragastric injections of 0.2 mL saline and intraperitoneal injections of dexamethasone at a dosage of 1.0 mg/kg intraperitoneally. The experiment lasted one week. Every day, the mice's survival was checked, and for a full week, the study of survival was done. The mice were murdered by having their necks severed a week later, and the tissues and entire blood were taken out for future use.

2.3 Open-field experiment

The mice were individually placed in a box of length × width × depth (100 cm × 100 cm × 50 cm), and the total driving distance (m), standing times and grooming times of the mice within 5 min were carried out by using a video tracking system (Sun et al., 2010).

2.4 Morris water maze experiment

A black circular pool that was 150 cm in diameter and split into 4 visual quadrants and contained water that was 24 °C consisted of the Morris water maze gadget. In the middle of the third quadrant, 2 cm beneath the water's surface, a circular platform with a diameter of 10 cm was positioned. The mice were put in a pool facing a wall for 4 days straight, and each rat entered the water from each of the four quadrants in turn and in the same sequence. Mice that took longer than 60 s to locate the platform were guided and given permission to stay there for 10 s. The latency was measured as the amount of time the mice took to find the platform. On day 5, in the absence of a plateau, the mice's time spent in the target quadrant and the number of times they crossed it were counted (Nunez, 2008).

2.5 ELISA experiment

Split, 1:9 homogenized mouse hippocampus tissue was centrifuged for 15 min at 3000 rpm from 4 °C saline. According to ELISA guidelines (Shanghai Wellbio Technology Co., Ltd., Shanghai, China), the supernatant was separated, and the levels of TNF-α, IL-6 and IL-1β were found.

2.6 Oxidative stress analysis

Split mouse hippocampus tissue was immediately converted into a 1:9 homogenate using room temperature normal saline. According to the guidelines (Shanghai Wellbio Technology Co., Ltd., Shanghai, China), the levels of MDA, SOD, and CAT activity were all observed.

2.7 qPCR experiment

After gathering and homogenizing mouse hippocampus tissue, TRIzol™ was used to extract the RNA, which was then diluted to 1 μg/L. To create a cDNA template, reverse transcribe 1 μL of the diluted RNA solution using the reverse transcription kit's instructions. The relative gene expression was calculated using the $2^{-\Delta\Delta Ct}$ method, using GAPDH as the internal reference expression, using 1 μL of cDNA template, 10 μL of SYBR Green PCR Master Mix, 1 μL of upstream and downstream primers, and 7 μL of sterile distilled water (MedChemExpress, Shanghai, China). The reaction was run at 95 °C for 60 s, followed by 40 cycles of 15 s each at 55 °C, 95 °C, and 55 °C (Agilent Mx3000P, Palo Alto, CA, USA) (Hu et al., 2022; Long et al., 2022).

2.8 HPLC

Weigh precisely 2 mg of the dried standard, add 2 mL of methanol to a consistent volume, and create a 1 mg/mL solution. In addition, a 0.5-1.0 mL amount of the sample solution was aspirated into an injection bottle using a disposable needle and filter membrane. The following were the chromatographic conditions: Agilentzorbax SB-C18 column (5 μm, 4.6 × 250 mm); 30 °C column temperature; methanol, acetic acid water, acetonitrile, and clean water as the mobile phase; 0.5 mL/min flow rate; 359 nm detection wavelength; and 10 μL injection volume (S3000 LC/IC,). The composition of the compound was then analyzed according to the chromatogram.

2.9 Statistical analysis

All experiments were carried out three parallel experiments to take the average, using SPSS23 statistical software for analysis, using the one-way ANOVA method to compare between groups, at the level of $P < 0.05$ to observe the significant differences between groups.

3 Results

3.1 Survival of mice with sepsis

No mice from the normal group passed away one week after sepsis induction, but 8 animals from the model group, 6 mice from the clove-L group, 4 mice from the clove-H group, and 3 mice from the dexamethasone group did (Figure 1). Clove and dexamethasone can lower the death rate of septic mice as compared to the model group.

3.2 Cognitive impairment in mice with sepsis

The overall driving distance, standing durations, grooming times, target quadrant time, and crossing times of mice in the model group were much shorter than those of the normal group, whereas the latency time was noticeably longer (Figure 2). Clove-L, clove-H, and dexamethasone considerably increased total distance traveled, periods spent standing and grooming, times spent in the target quadrant, times spent traversing the area, and greatly decreased latency time when compared to the model group. Clove-H and dexamethasone group had the least cognitive impairment.

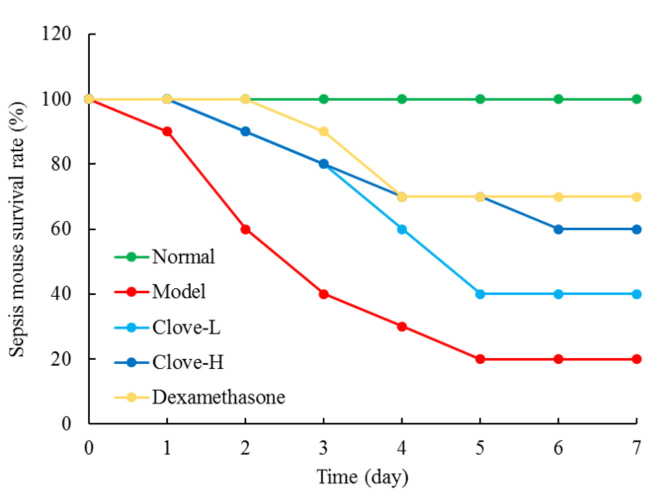

Figure 1. Survival of septic mice in different groups.

3.3 Inflammatory reaction in hippocampus of mice

Figure 3 shows that the levels of the inflammatory cytokines TNF-α, IL-6, and IL-1β were greatest in the mice from the model group and lowest in the animals from the normal group. The levels of TNF-α, IL-6, and IL-1β in the hippocampus of infected mice could be significantly reduced by clove-L, clove-H, and dexamethasone, with clove-H and dexamethasone having the greatest impact. This could bring the levels of TNF-α, IL-6, and IL-1β in the hippocampus of infected mice closer to those in normal mice.

3.4 Oxidative stress in hippocampus of mice

The mice in the normal group had the strongest SOD and CAT activity in the hippocampus, while the amount of MDA was the lowest (Figure 4). In contrast, the mice in the model group displayed the reverse tendency, with the highest level of MDA and the lowest activity of SOD and CAT. Dexamethasone had a somewhat larger impact than clove-H in bringing the activity of SOD, CAT, and the amount of MDA in the hippocampus of mice closer to that of the normal group.

3.5 Mouse hippocampal mRNA expression

Figure 5 shows that whereas NF-κB and p53 had considerably greater mRNA expression than the other groups, SIRT1 and FOXO1 had significantly lower mRNA expression in the hippocampus of infected mice (the model group). In the hippocampus of infected mice, clove-L, clove-H, and dexamethasone were able to up-regulate the mRNA expression of FOXO1, SIRT1, and down-regulate the mRNA expression of NF-κB, p53. The effects of clove-H and dexamethasone were larger than those of clove-L.

3.6 Composition of clove

The trial outcomes revealed that clove contains rutin, isoquercitrin, ferulic acid, dihydroquercetin, and quercitrin, a total of five components, according to HPLC analysis (Figure 6). And that content of rutin was the high.

4 Discussion

Sepsis is a widespread, possibly deadly systemic condition that frequently causes unchecked inflammation, tissue destruction, and multiple organ failure. The most common reason for mortality in ICU patients is sepsis and its consequences (Hu et al., 2020). In a similar manner, this study discovered that clove might boost the effectiveness of dexamethasone while also increasing the survival rate of septic mice. One of the many organ dysfunctions brought on by sepsis is cognitive impairment, which has a major impact on the prognosis and survival of sepsis patients. The open field test and the Morris water maze tests were utilized in this experiment to measure the mice's capacity for movement and exploration and learning (Wang et al., 2022a). It was discovered

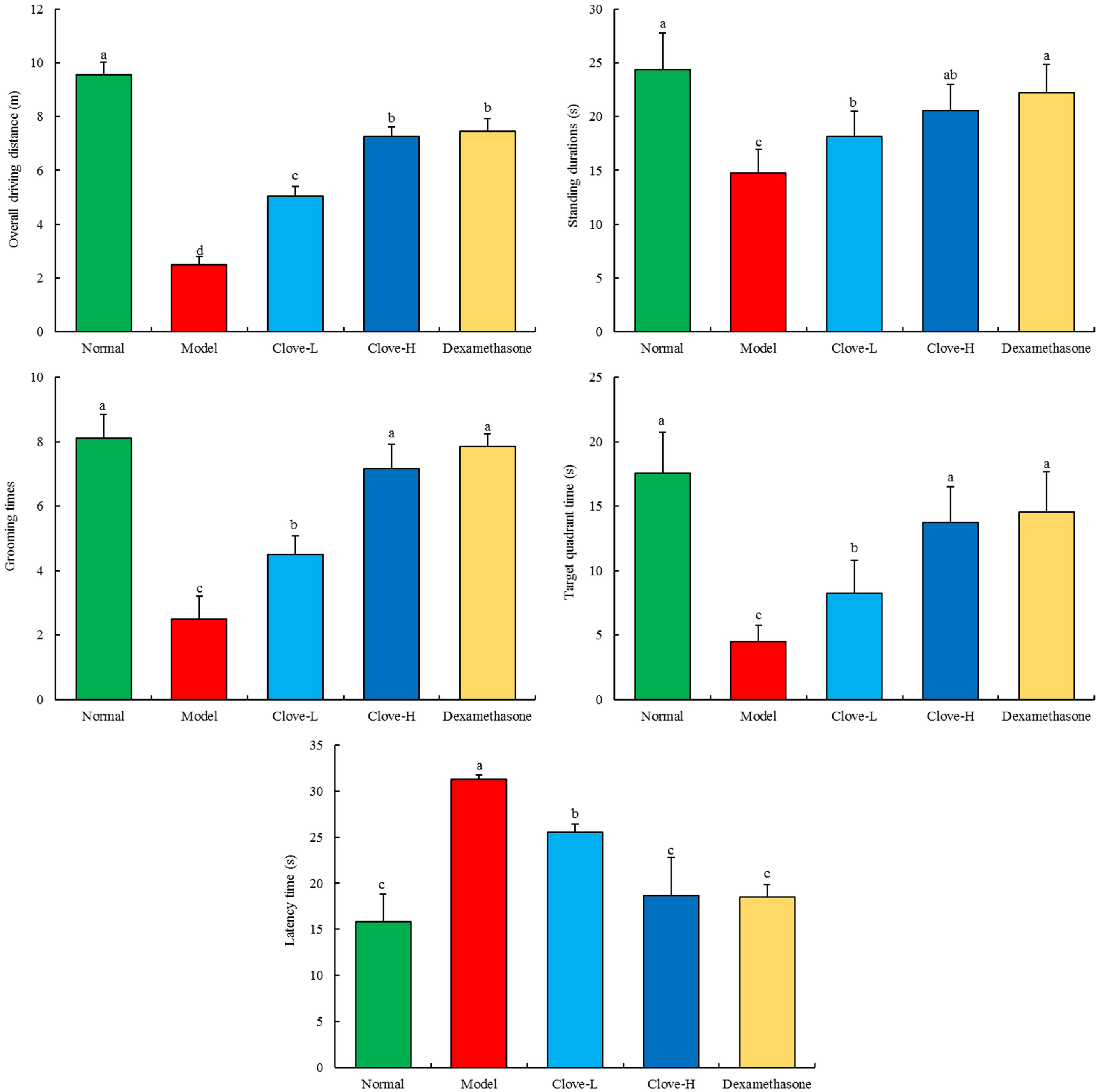

Figure 2. Cognitive impairment in septic mice. a-d: Indicates significant differences between groups of mice ($p < 0.05$).

that while clove might boost the activity, exploration ability, learning capacity, and cognitive ability of sick mice, these traits were all impaired in the septic mice. It is suggested that clove can improve the cognitive dysfunction in sepsis.

A number of possible pathways for sepsis-induced brain damage and cognitive impairment have been postulated, including excessive inflammation, oxidative stress, and severe neuronal death (Gao et al., 2017). The hippocampal region is crucial for learning, memory, emotion, endocrine, and visceral processes. This study's findings that septic mice had an increase in neuronal apoptosis are in line with earlier research (Huang et al., 2014). This study also discovered that clove might lessen this pathogenic alteration. The main causes of nerve cell apoptosis and necrosis are both oxidative stress and inflammatory ions (Pei et al., 2017). The major causes of neuronal death in sepsis are the emergence of oxidative stress and the production of proinflammatory cytokines (Huang et al., 2014). The pro-inflammatory factors TNF-α, IL-6, and IL-1β all have a significant impact on sepsis onset and incidence (Huang et al., 2022; Wu et al., 2022; Yang et al., 2022). MDA is a significant byproduct of oxidative damage, and SOD

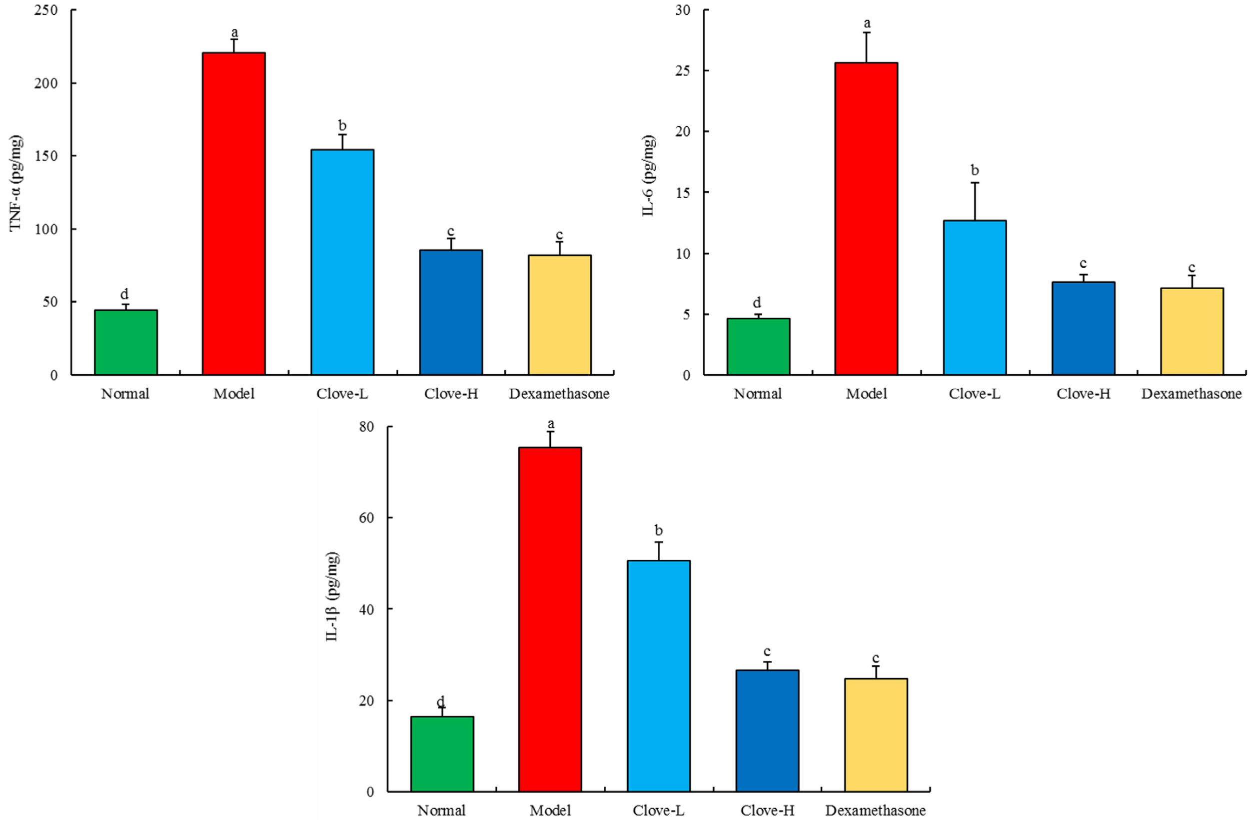

Figure 3. Inflammatory response in mouse hippocampus. a-d: Indicates significant differences between groups of mice ($p < 0.05$).

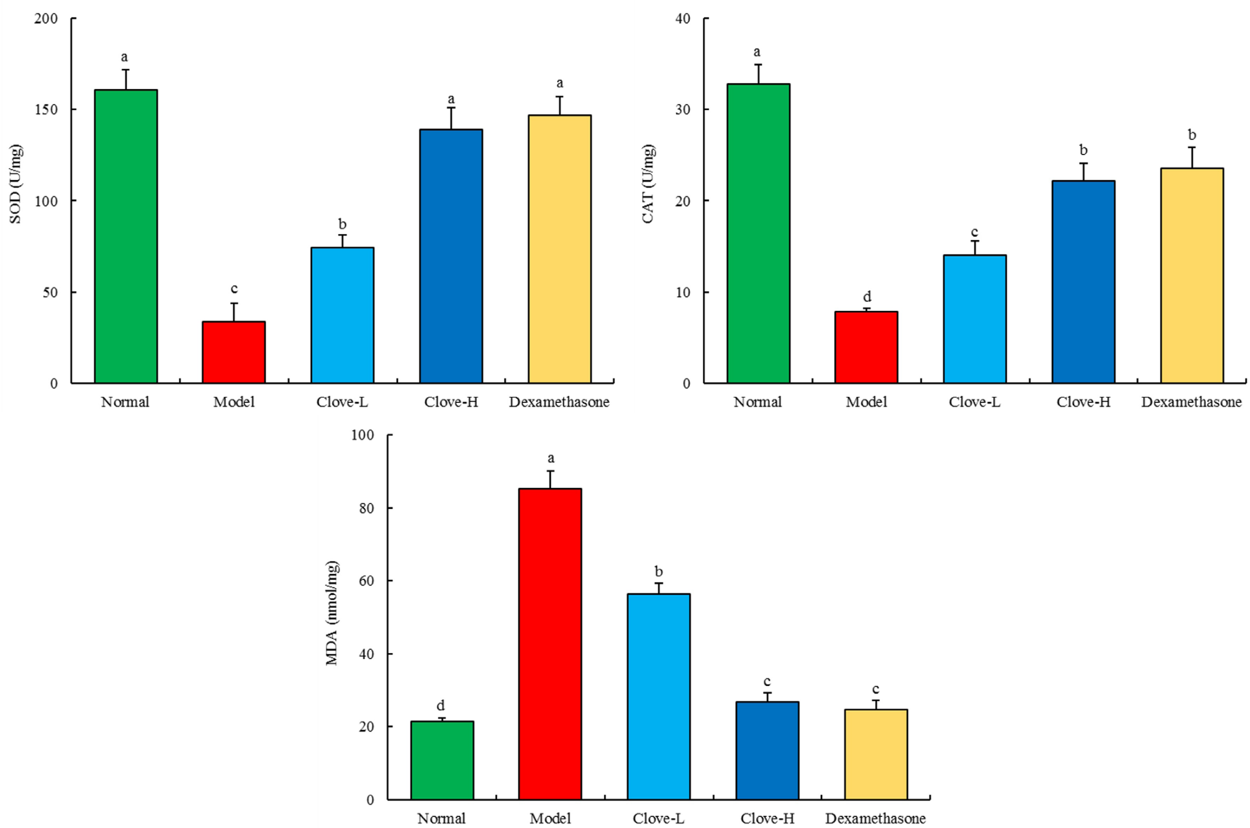

Figure 4. Oxidative stress in the mouse hippocampus. a-d: Indicates significant differences between groups of mice ($p < 0.05$).

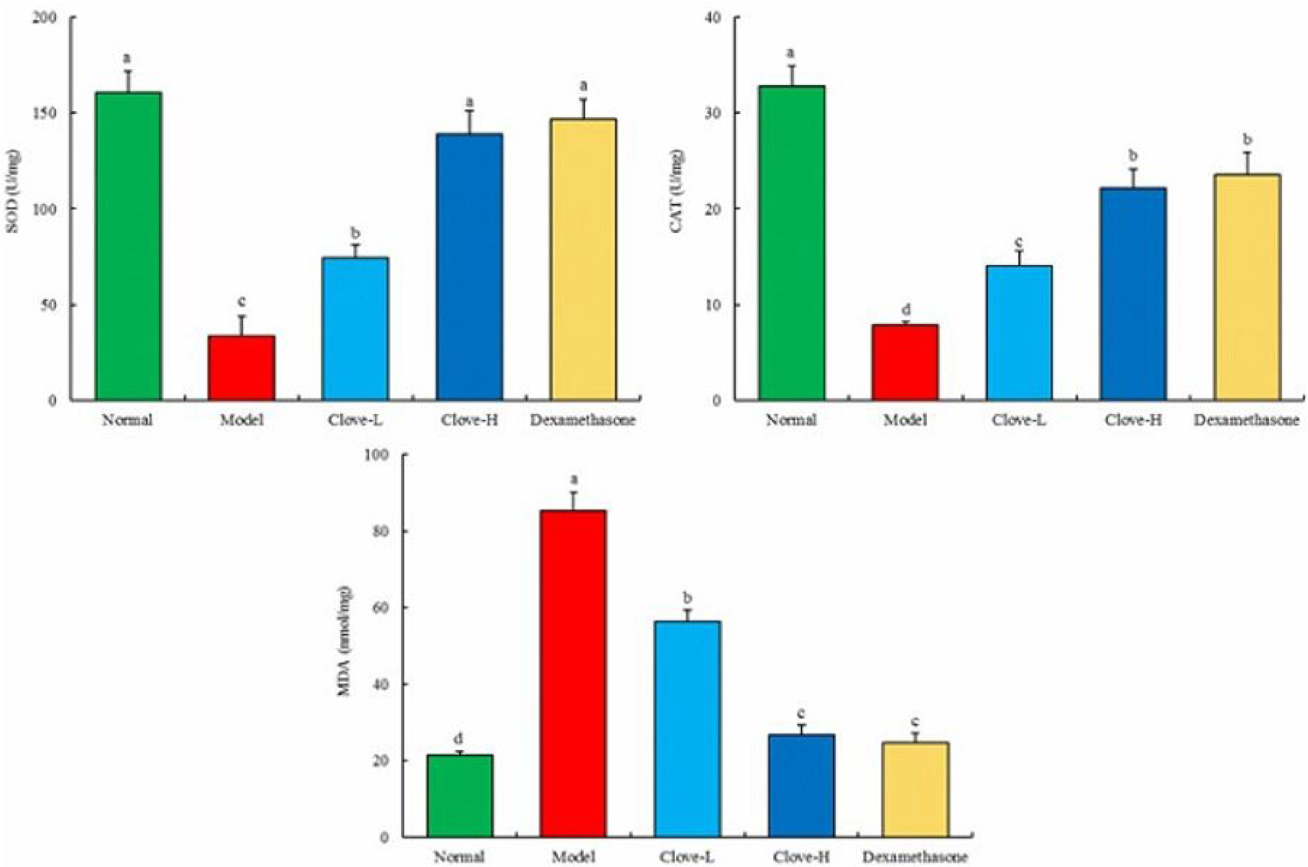

Figure 5. mRNA expression in mouse hippocampus. a-e: Indicates significant differences between groups of mice ($p < 0.05$).

and CAT are key antioxidant enzymes during oxidative stress (Yi et al., 2020). Therefore, reducing oxidative and inflammatory stress is a key therapy for sepsis-related cognitive impairment. By decreasing oxidative stress, inflammation, and apoptosis in animals, inflammation has been demonstrated to lessen the nephrotoxicity and neurotoxicity that colistin-induced toxicity causes (Dai et al., 2019). In the same sample study, it was discovered that clove significantly decreased the levels of TNF-α, IL-6, IL-1β, and MDA in the hippocampus of septic mice and increased the activities of SOD and CAT, suggesting that clove may be able to reduce oxidative stress and the inflammatory response in these animals.

The damage produced by sepsis to several organs, including the liver, kidney, and lung, is reduced when SIRT1 is activated because it reduces apoptosis, oxidation, and inflammatory ions (Li et al., 2022; Wang et al., 2022b). Numerous neurodegenerative disorders, ischemia damage, and traumatic brain injury have all been linked to SIRT1's neuroprotective effects (Nadtochiy et al., 2011). In this investigation, we discovered that clove may activate SIRT1, indicating that clove may help septic mice with their cognitive impairment by up-regulating SIRT1 expression. The deacetylation of downstream signaling proteins such FOXO1, p53, and NF-κB by SIRT1 is strongly associated to the antiapoptotic, antioxidant, and anti-inflammatory effects of SIRT1 activation (Ding et al., 2022). Animals' production of SOD and CAT, particularly SOD1 and SOD2, is thought to be regulated by FOXO1, a metabolic and antioxidant enzyme (Li et al., 2019). Direct deacetylation of FOXO1 by SIRT1 stimulates the expression of the gene that controls cytoprotection (Zhang et al., 2021). The function of p53 is closely related to tissue cells, and the regulation of p53 can control the inflammation and apoptosis of the body (Balthazar et al., 2021). The initial non-histone target of SIRT1 is p53, a strong pro-apoptotic transcription factor. SIRT1's deacetylation of p53 is linked to a decrease in p53 transcriptional activity, which inhibits apoptosis (Wang et al., 2021). By increasing the production of many proinflammatory cytokines like TNF-α, IL-6, and IL-1β, NF-κB activation contributes to the onset and progression of sepsis. SIRT1 has neuroprotective benefits via deacetylating NF-κB and inhibiting its activity (Elbaz et al., 2018). In this study, it was found that clove could control the cognitive dysfunction of septic mice by activating the expression of SIRT1, FOXO1 and affecting the expressions of NF-κB, p53. Additionally, clove downregulated the expression of NF-κB and Ac-p53 and upregulated the expression of SIRT1, FOXO1 in septic mouse models. By controlling the expression of SIRT1, it can also improve the intervention effect of dexamethasone on sepsis in mice.

The rutin, isoquercitrin, ferulic acid, dihydroquercetin and quercitrin have antioxidant and anti-inflammatory effects (Khajevand-Khazaei et al., 2018; Bacanlı et al., 2014; Huang et al.,

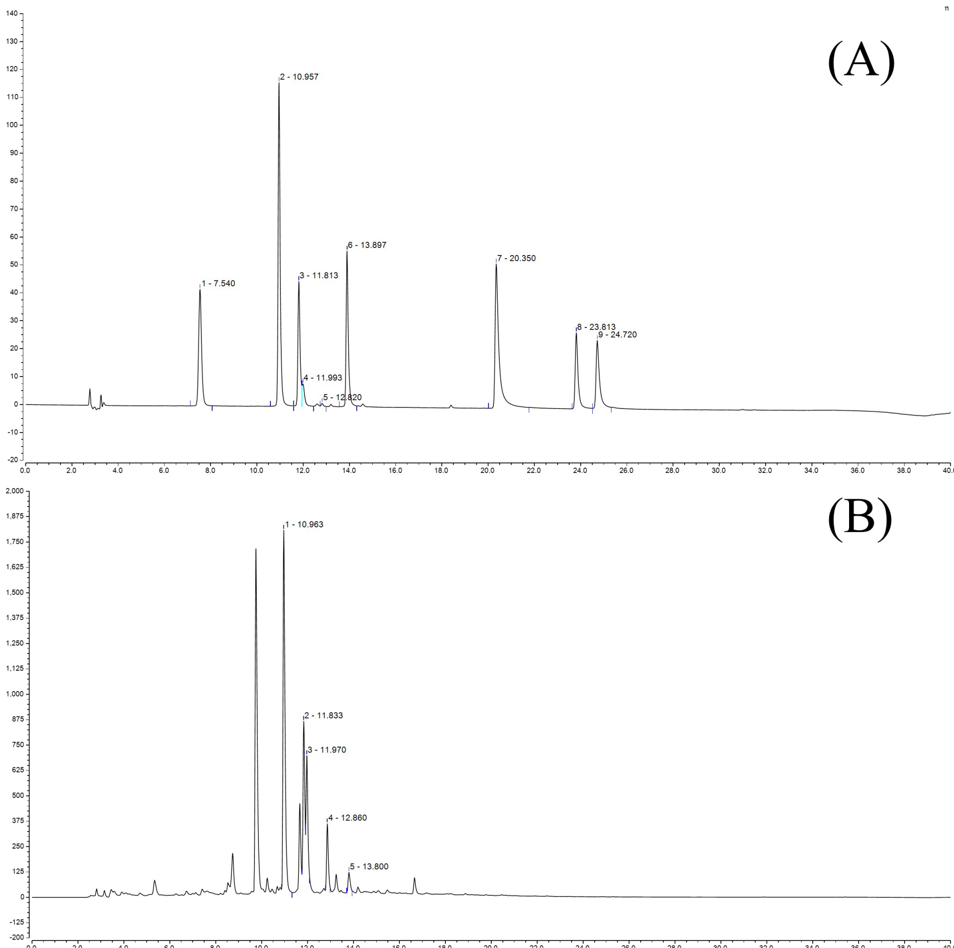

Figure 6. Compound composition of clove, (A) chromatogram of standards, 2: rutin, 3: isoquercitrin, 4: ferulic acid, 5: dihydroquercetin, 6: quercitrin (B) chromatogram of clove, 1: rutin, 2: isoquercitrin, 3: ferulic acid, 4: dihydroquercetin, 5: quercitrin.

2018). Among them, rutin and ferulic acid can effectively inhibit sepsis, and rutin is the most abundant chemical in cloves (Khajevand-Khazaei et al., 2018; Bacanlı et al., 2014). This study also shows that clove has an intervention effect on sepsis through the action of these nine active ingredients.

5 Conclusion

In conclusion, clove can improve the survival rate of septic mice by activating SIRT1, increase the ability of activity exploration and learning cognition in septic mice, lower the rate of nerve cell apoptosis, and reduce inflammation and oxidative stress response, which are closely related to the expression of FOXO1, NF-κB, and p53. These experimental findings offer baseline information for the use of clove as a health food to treat cognitive impairment in sepsis, but a more thorough investigation of the precise mechanism is still required.

Abbreviations

ELISA: enzyme linked immunosorbent assay. qPCR: quantitative polymerase chain reaction. HPLC: high performance liquid chromatography. TNF-α: tumor necrosis factor alpha. IL-6: interleukin 6. IL-1β: interleukin 1 beta. MDA: malondialdehyde. SOD: superoxide dismutase. CAT: catalase.

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