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Salidroside rescued mice from experimental sepsis through anti-inflammatory and anti-apoptosis effects

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ABSTRACT

Background: Salidroside (SDS) is the main effective component of *Rhodiola rosea L* with a variety of pharmacologic properties. The objective of this study was to investigate the efficacy of SDS in the treatment of experimental sepsis in mice and explore the possible underlying action mechanisms.

Methods: Sepsis was induced in C57BL/6 male mice via cecal ligation and puncture (CLP). The animals were divided into three groups as follows: sham, CLP, and CLP plus SDS. SDS (50 mg/kg) was injected intraperitoneally 1 h after operation. Postoperative survival of the mice, bacterial clearance in blood and peritoneal lavage fluid, cytokine secretion in blood, and histology of lung were evaluated. In addition, apoptosis of immune cells in the spleen and thymus were examined, respectively.

Results: SDS administration prolonged the survival of the septic mice, inhibited the proinflammatory responses, and enhanced bacterial clearance. It also alleviated the pathologic changes in the lung and inhibited the apoptosis of immune cells in the spleen and thymus after CLP challenge.

Conclusions: SDS exerts a protective effect in CLP-induced sepsis by attenuating the proinflammatory responses, enhancing bacterial clearance, and preserving adaptive immunity. SDS may be a promising therapeutic strategy for the treatment of sepsis.

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1. Introduction

Sepsis is a systemic inflammatory response to infection and remains a major cause of death in critically ill patients [1]. It has been recognized that the septic host experiences a predominant proinflammatory response phase rapidly after infection and subsequently a prolonged period of immune suppression [2]. Recent studies [3,4] indicated that most patients with sepsis were prone to die during the later chronic immunosuppression phase. The underlying mechanisms of immunosuppression include apoptosis-induced apoptosis of T lymphocytes, production of anti-inflammatory cytokines, and the decreased antigen-presenting capacity of dendritic cells [5]. Thus, the development of new agents with potent anti-inflammatory effects and immunomodulatory properties is of paramount importance in sepsis therapy.

Salidroside (SDS) [2-(4-hydroxyphenyl)ethyl beta-D-glucopyranoside] is a phenylpropanoid glycoside extracted from the root of *Rhodiola rosea L* and has been used as a medicinal herb to protect erythrocytes against oxidative stress and improve resistance to fatigue [6]. Previous studies [7–10] demonstrated that SDS could restore the imbalance between cellular reactive oxygen species production and clearance by increasing of endogenous antioxidants and decreasing intracellular reactive oxygen species levels in various *in vitro* and *in vivo* studies. However, the exact active sites of SDS on cells remain unknown.

Lai *et al.* [11] found that SDS has protective effects on chronic intermittent hypoxia-induced, Fas-dependent, and mitochondria-dependent apoptotic pathways in the heart of mice. Xiao *et al.* [12] found that SDS protects *Caenorhabditis elegans* neurons from polyQ toxicity by reducing oxidative stress. In addition, SDS could promote erythropoiesis and upregulate the level of antioxidative enzymes glutathione peroxidase-1 and thioredoxin-1 to counteract oxidative stress in IL-5 dependent hematopoietic cell line [13]. Liu *et al.* [14] showed SDS protects septic rats from acute lung injury by upregulating peroxisome proliferator-activated receptor γ and attenuated the lipopolysaccharide-induced activation of nuclear factor kappa-light-chain-enhancer of activated B cells. Our previous study [15] found that SDS could attenuate concanavalin A-induced hepatitis via inhibiting proinflammatory cytokines and lymphocyte migration. However, whether SDS can provide protection against experimental sepsis remains unknown. Therefore, in this study, we used cecal ligation and puncture (CLP) in a murine model to investigate the protective effects of SDS and explore the possible underlying action mechanisms.

2. Material and methods

2.1. Animal preparation and treatment

All experiments were approved by the Institutional Animal Care and Use Committee of Changhai Hospital of the Second Military Medical University (CH20110617-11, Shanghai, China). Pathogen-free male C57BL/6 mice 8–10 wk-old (22–30 g) were purchased from the Animal Experimentation Center of Second Military Medical University. CLP-induced sepsis was performed as described previously [16]. Briefly, mice were anesthetized with sevoflurane, and the cecum was mobilized, ligated below the ileocecal valve, and punctured twice with a 22 gauge needle to induce polymicrobial peritonitis. The abdominal wall was closed in two layers. Sham-operated mice underwent the same procedure, including opening the peritoneum and exposing the bowel, but without ligation and needle perforation of the cecum. After surgery, the mice were injected with 1 mL physiologic saline solution for fluid resuscitation. All mice had unlimited access to food and water both preoperatively and postoperatively.

SDS (CAS 10338-51-9, purity >98%, molecular formula: C14H20O7, mol wt: 300.31) was purchased from Shanghai Ronghe Medicine Science and Technology Development Co, Ltd (Shanghai, China). The molecule structure of SDS is shown in Figure 1. Mice were randomized and divided into three groups as follows: sham, CLP, and SDS. SDS (50 mg/kg) was dissolved in 0.9% saline and administrated intraperitoneally (i.p.) 1 h after CLP to mice in the SDS group. Mice in the other groups were administrated with an equal volume of 0.9% saline.

2.2. Survival of septic mice

To observe survival, mice were randomized into three groups and subjected to laparotomy without CLP (sham group), laparotomy with CLP (CLP group), and laparotomy with CLP plus SDS administration (SDS group). A single dose of the broad spectrum antibiotic imipenem (25 mg/kg body weight) was administered subcutaneously 4–6 h after surgery. Mice were evaluated daily, and survival was recorded for 7 d. Knowing that a single dose of SDS at 1 h after CLP could improve the survival of septic mice in our preliminary experiment on survival, SDS was administered at 1, 24, and 48 h after the CLP challenge to see whether repeated administration of SDS could better improve the survival of the septic mice.

2.3. Evaluation of bacterial clearance

Bacterial loads in peritoneal cavity and blood were assessed to evaluate the bacterial clearance using the method

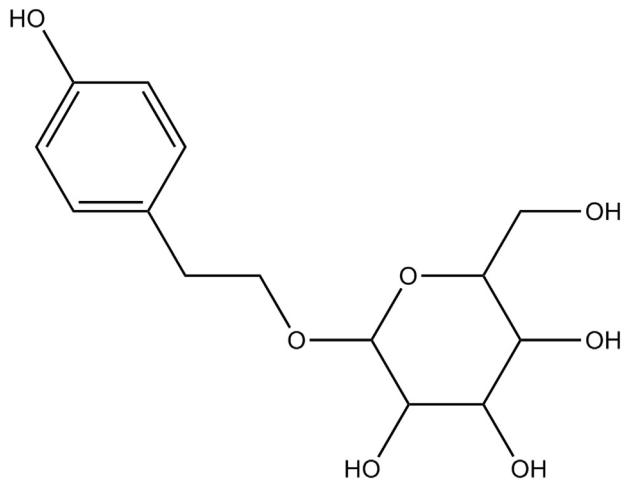

Fig. 1 – The molecular structure of SDS.