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ORIGINAL ARTICLE

Protective effects of oridonin on the sepsis in mice

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Abstract This study aimed to investigate the protective effects of oridonin (ORI) on cecal ligation and puncture (CLP)-induced sepsis in mice. Male C57BL/6 mice weighing 22–30 g and aged 8–10 weeks were randomly assigned to three groups: Sham group, CLP group, or CLP plus ORI group. In the CLP group and ORI group, CLP was induced, and intraperitoneal injection of normal saline and oridonin (100 μg/kg) was conducted, respectively. The survival rate was determined within the following 7 days. The blood, liver, and lung were collected at 24 hours after injury. Hematoxylin–eosin staining of the lung, detection of lung wet-to-dry ratio, and serum cytokines (tumor necrosis factor [TNF]-α and interleukin [IL]-6), and examination of intraperitoneal and blood bacterial clearance were conducted to evaluate the therapeutic efficacy. Results showed that ORI treatment significantly reduced the lung wet-to-dry ratio, decreased serum TNF-α and IL-6, and improved liver pathology compared with the CLP group ($p < 0.05$). Moreover, the intraperitoneal and blood bacterial clearance increased markedly after ORI treatment ($p < 0.05$). The 7-day survival rate in the ORI group was also dramatically higher than in the CLP group ($p < 0.05$). Our findings indicate that ORI can attenuate liver and lung injuries and elevate bacterial clearance to increase the survival rate of sepsis mice.
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Conflicts of interest: All authors declare no conflicts of interest.

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Introduction

Sepsis is a syndrome, not a disease. It is an imprecise clinical diagnostic term used to describe patients who have a continuum of abnormalities in organ function [1]. The worldwide incidence of sepsis is estimated to be 18 million cases per year [2]. Sepsis remains the most common cause of death in people who have been hospitalized, and between 20% and 50% of patients with sepsis die [3,4]. Furthermore, sepsis is associated with a reduced quality of life in those who survive their acute illness [5].

Unlike other major epidemic illnesses, treatment for sepsis is nonspecific and limited primarily to support organ function and consists of administration of intravenous fluids, antibiotics, and oxygen [6]. There are no approved drugs that specifically target sepsis. In recent years, increasing studies employ Traditional Chinese Medicine in the therapy of sepsis [7—9]. Oridonin (ORI) is a famous diterpenoid isolated from the Chinese medicinal herb *Rabdosia rubescens* which is also known as *dong ling cao* [10]. This compound has drawn attention for its remarkable apoptosis and autophagy-inducing activity in cancer therapy [11]. However, many prominent studies have proven that ORI possesses many other therapeutic effects, such as antiinflammatory, neuroprotective, antibacterial, and antineoplastic activities [12—14]. In this study, the protective effects of ORI on sepsis were investigated in a mouse model. Our results show that ORI treatment attenuates lung and liver injuries and enhances the survival rate of sepsis mice, which is due to the reduction in serum proinflammatory cytokines and increase in serum and peritoneal bacterial clearance.

Materials and methods

Animals and grouping

A total of 50 male C57BL/6 mice aged 8—10 weeks and weighing 22—30 g were purchased from the Experimental Animal Center of the Second Military Medical University. Mice were randomly assigned into three groups. In the Sham group ($n = 10$), mice received laparotomy without manipulation of the intestine; in the CLP group, mice received cecal ligation and puncture (CLP) followed by intraperitoneal injection of normal saline ($n = 10$ for survival analysis; $n = 10$ for biochemical analysis); in the CLP+ORI group, mice received CLP followed by intraperitoneal injection of ORI at 100 μg/kg ($n = 10$ for survival analysis; $n = 10$ for biochemical analysis). Animals were housed under controlled temperatures (23 ± 2°C) with 12 hours of light/dark cycles and given *ad libitum* access to food and water. This study was approved by the Ethics Committee of the Second Military Medical University.

Reagents

The following reagents were used in the present study: ORI (Lot number: 28957-04-2; Shanghai Yuanye Biotechnology Co., Ltd. China), hematoxylin—eosin staining kit (Wuhan Boster Biotechnology Co., Ltd. China), nutrient agar medium (Shanghai Tiancheng Biotechnology Co., Ltd. China), paraformaldehyde (Sinopharm Biochemical Reagents Company, Shanghai, China), mouse tumor necrosis factor-α (TNF-α), Quantikin Enzyme-Linked Immunosorbent Assay (ELISA) Kit (Cat: MTA00B), and mouse interleukin-6 (IL-6) Quantikin ELISA Kit (Cat:M6000B; R&D Systems Inc., MN, USA).

Animal model of sepsis

CLP was employed to induce sepsis in mice. Briefly, following isoflurane anesthesia, the cecum was exposed after a 1-cm-long midline incision was made. The cecum was ligated ~15 mm proximal to the cecal pole with a 5/0 Prolene thread without stricture of the ileocecal valve. The ligated cecum was then punctured once with a 22-gauge needle. The cecum was slightly compressed until a small drop of stool appeared. The abdominal wall was closed, and fluid resuscitation was conducted with subcutaneous injection of 1 mL of normal saline after surgery. In the CLP group, mice received intraperitoneal injection of normal saline immediately after surgery; in the CLP+ORI group, mice received intraperitoneal injection of oridonin at 100 μg/kg immediately after surgery.

Detection of serum cytokines

At 24 hours after surgery, mice were deeply anesthetized with 10% chloral hydrate at 0.3 mL/100 g and sacrificed. Blood was collected from the heart, and serum was collected after centrifugation. Serum contents of TNF-α and IL-6 were detected with corresponding ELISA kits according to the manufacturer's instructions.

Pathological examination

At 24 hours after surgery, mice were anesthetized, and the liver and lung were collected, fixed in 4% paraformaldehyde, and embedded in paraffin and sectioned. Hematoxylin—eosin staining was performed to evaluate the liver and lung injuries.

Detection of lung wet-to-dry lung weight ratio

At 24 hours after surgery, animals were sacrificed and the left lungs were collected and weighed after removing water on the lung (wet weight). The lung was then heated at 60°C for 72 hours until the lung weight remained stable. The lung was weighed (dry weight). The wet to dry (W/D) weight ratio was calculated.

Detection of bacterial clearance

At 24 hours after CLP, mice were anesthetized with 2.5% isoflurane. Mice were fixed on a table and anesthesia was maintained with 2.5% isoflurane. The skin of the abdomen was cut open (0.5 cm) in the midline after thorough disinfection. Blood (200 μL) was collected by sterile puncture of the left cardiac ventricle with a syringe, transferred into a sterile tube and stored at 4°C. Then, laparotomy was

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