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Ursolic acid improves survival and attenuates lung injury in septic rats induced by cecal ligation and puncture

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ABSTRACT

Background: Sepsis is characterized as a systemic inflammatory response syndrome during infection, which can result in multiple organ dysfunction and death. Ursolic acid (UA), a pentacyclic triterpene acid, has been reported to have potent anti-inflammatory and antioxidant properties. The aim of this study was to detect the possible protective effects of UA on sepsis-evoked acute lung injury.

Materials and methods: A rat model of sepsis induced by cecal ligation and puncture (CLP) was used. Rats were injected intraperitoneally with UA (10 mg/kg) after CLP, and then the survival was determined twice a day for 4 d. The protective effects of UA on CLP-induced acute lung injury were assayed at 24 h after CLP.

Results: The results revealed that UA treatment markedly improved the survival of septic rats, and attenuated CLP-induced lung injury, including reduction of lung wet/dry weight ratio, infiltration of leukocytes and proteins, myeloperoxidase activity, and malondialdehyde content. In addition, UA significantly decreased the serum levels of tumor necrosis factor-α, interleukin-6, and interleukin-1β, inhibited the expression of inducible nitric oxide synthase and cyclooxygenase-2 in the lung, which are involved in the productions of nitric oxide and prostaglandin E_2.

Conclusions: These findings indicate that UA exerts protective effects on CLP-induced septic rats. UA may be a potential therapeutic agent against sepsis.

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1. Introduction

Sepsis is a complex syndrome characterized by a systemic inflammatory response to severe infection, which can result in multiple organ dysfunction and even death [1,2]. Despite extensive therapeutic approaches, sepsis remains a leading cause of high mortality in intensive care units, as evidenced by approximately 215,000 deaths per annum in the United States [3,4]. Clinical and basic studies have demonstrated that the high mortality rate is closely related to sepsis-evoked

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severe complications, such as acute lung injury (ALI), acute respiratory distress syndrome, and acute kidney injury, among which ALI is the most common complication [1,5]. Hence, it is very important to search for novel and effective therapies for sepsis and septic complications.

Ursolic acid (UA) is a pentacyclic triterpenoid compound found in many plants, including *Ligustrum lucidum*, *Arctostaphylos uva-ursi*, and *Eriobotrya japonica*, which are widely used as traditional Chinese medicines [6]. Nowadays, UA has been reported to possess multiple biological activities, such as anti-inflammatory, antioxidant, and antitumor properties [7,8]. Previous studies have demonstrated the beneficial effects of UA on several experimental models of inflammation-related diseases, such as asthma [9], acute liver injury [10], cancer [11], arthritis [12], and colitis [13]. Moreover, a recent research showed that UA could attenuate lipopolysaccharide-induced ALI in a mouse model [14]. Because sepsis is an acute inflammatory disorder involving several organ systems dysfunction, an attempt to modify the excessive inflammatory response has been considered as one effective therapeutic target. In recent decades, there has been growing interest in the therapeutic use of natural components of plants to prevent such inflammatory disorders. Based on the previous findings, we hypothesized that UA, via its pleiotropic properties, may play a beneficial role in the treatment of polymicrobial sepsis.

In the present study, we investigated the protective effects of UA on lung injury and survival in a rat model of cecal ligation and puncture (CLP)-induced sepsis, and the primary mechanisms were involved.

2. Materials and methods

2.1. *Animals*

Male Sprague–Dawley rats (6–8 wk-old, weighing 200–250 g) were provided by the Experimental Animal Centre of China Medical University (Shenyang, China). All animals were housed in standard wire cages and provided with standard rodent chow and ultraviolet-sterilized tap water *ad libitum*. Rats were kept at a temperature of 22 ± 2°C and a relative humidity of 50%–60% for at least 3 d before the experiments throughout the study. All animal care and experiments were approved by the Institutional Animal Care and Use Committee of Liaoning Medical University.

2.2. *CLP-induced sepsis*

The rats were randomly divided into four groups as follows: sham group, CLP group, sham plus UA (10 mg/kg, intraperitoneally [i.p.]) group, and CLP plus UA (10 mg/kg, i.p.) group. Each group contained 20 rats. The CLP-induced sepsis model was performed according to as previously described [15]. Briefly, all rats were fasting but provided water *ad libitum* for 6 h before undergoing CLP surgery. After chloral hydrate anesthesia (350 mg/kg, i.p.), the abdominal region was disinfected and 1.5 cm incision was made, the cecum was then gently isolated with tightly ligation and punctured three times with an 18-gauge needle. Thereafter, the cecum was repositioned, and the abdomen was subsequently closed. For sham and UA group alone, rats underwent the same surgical procedures, but the cecum was neither ligated nor punctured. Saline (0.5 mL/10 g body weight) was given subcutaneously to rats for fluid resuscitation. For the UA treatment group, rats received intraperitoneal administration of UA (10 mg/kg) after CLP surgery. Rats in control and CLP groups were only given vehicle. One half of rats in each group were sacrificed at 24 h after CLP operation, the samples including blood, lung tissue, and bronchoalveolar lavage fluid (BALF) were collected for subsequent studies. The other half of rats were used to record the survival rate. Survival was monitored twice a day for 4 d ($n = 10$ in each group).

2.3. *Measurement of the lung wet/dry weight ratio*

The rat lungs were excised, immediately recorded the wet weight, and then placed in an incubator at 60°C for 72 h until the weight was unchanged and the dry weight was recorded. The ratio of the wet lung to the dry lung was calculated to assess tissue edema.

2.4. *Analysis of total protein concentration and cell count of the BALF*

BALF was obtained by washing the airways three times through a tracheal cannula with 1.5 mL of saline. BALF was centrifuged at 1500 rpm for 10 min at 4°C. The supernatant was harvested for total protein analysis using the BCA protein assay kit. Proteins were expressed in milligram protein per millileter BALF (Beyotime Institute of Biotechnology, Haimen, China). The bottom cell pellets were resuspended in phosphate-buffered saline (PBS) for the total cell counts using a hemacytometer, and differential cell counts were carried out with cytospins by the Wright–Giemsa staining method.

2.5. *Cytokines analysis*

Blood samples from different groups were centrifuged (1500 rpm, for 10 min, 4°C) to obtain the serums. The cytokine concentrations of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 in serums were determined by enzyme-linked immunosorbent assays (ELISA) using commercial kits specific for rat according to the manufacturer's instructions (USCN Life Science. Inc, Wuhan, China). Serum cytokine levels were expressed in picogram per millileter of serum analyzed.

2.6. *Measurement of myeloperoxidase and malondialdehyde*

To measure the myeloperoxidase (MPO) activity, the lung tissue samples were collected at 24 h after CLP, and then homogenized. The MPO activities in the lung homogenates were measured using a commercial MPO determination kit according to the manufacturer's instructions (Jiancheng Bioengineering Institute, Nanjing, China). The rest of the homogenate was centrifuged to obtain the supernatants, which were used to detect the levels of malondialdehyde (MDA) (Jiancheng Bioengineering Institute).

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