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Protective effect of pristimerin against LPS-induced acute lung injury in mice

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ABSTRACT

Pristimerin (Pris) is a triterpenoid derivative obtained from Celastraceae and Hippocrateaceae families. This compound has been extensively tested for its potent anti-cancer activity against different types of tumors. However, its effects against acute lung injury (ALI) remain to be investigated. This study explored the efficacy of Pris to protect against lipopolysaccharide (LPS)-induced ALI and its possible pathways. Results have shown that Pris possesses potent protective activity against LPS-induced acute lung damage. It significantly decreased pulmonary edema as presented by significant decrease in lung W/D ratio and in protein content. Pris attenuated LPS-induced inflammatory cell infiltration into the lung tissue and suppressed the activity of myeloperoxidase in lung. LPS-induced histopathological lesions were significantly improved via Pris pretreatment. Pris exhibited not only inhibition of LPS-induced oxidative stress, but also enhancement of the suppressed antioxidant capacity of the lung tissue. The anti-inflammatory activity of Pris against LPS-induced ALI was clearly evident via attenuation of the levels of pro-inflammatory cytokines namely, tumor necrosis factor-α and interleukin-6. Similarly, Pris inhibited LPS-induced elevation of pro-apoptotic protein, Bax, and caspase-3. Pris also increased the diminished level of Bcl2 induced by LPS. Collectively, Pris exerted protective activity against LPS-induced ALI via anti-oxidant, anti-inflammatory and anti-apoptotic pathways.

1. Introduction

Acute respiratory distress syndrome (ARDS) is a leading cause of mortality in intensive care. This condition is characterized by overproduction of pro-inflammatory cytokines and the recruitment of inflammatory cell into the lung tissue leading to increased capillary permeability, diffuse pulmonary interstitial and alveolar edema. These changes contribute to acute lung injury (ALI) [1]. The pathophysiology of ARDS is somewhat complex and involves many pathogenic mechanisms in addition to cytokine-mediated inflammation. Recent evidence revealed the contribution of epithelial cell apoptosis in the progression of ARDS. The enhanced phagocytosis of apoptotic neutrophils could result in resolution of inflammation and repair during ARDS [2,3]. Lipopolysaccharide (LPS) is a component of cell wall of the Gram-negative bacteria that have been used to produce an experimental model of ALI in mice that clinically resembles ARDS [4,5]. Administration of LPS results in release of many cytokines such as tumor necrosis factor-α (TNF-α) and interleukins (ILs) which trigger inflammatory responses and induce alteration in the immune system function. Furthermore, LPS stimulates pro-apoptotic signals in different cell types including epithelial and endothelial cells leading to cellular apoptosis which is recognized now to play an important role in mediating LPS-induced ALI [6]. Till now, mechanical ventilation is the only effective therapy for ARDS. No specific and effective pharmacological intervention for ARDS is currently available [7]. Hence, there is a need to search for new therapeutics that could be used for the treatment of ARDS.

Pristimerin (Pris) is a natural quinone-methide triterpenoid derivative isolated from plants belonging to the Celastraceae or Hippocrateaceae families [8]. Pris was shown to possess many biological properties as anti-fungal [9], antibacterial [10] and antioxidant activity [11]. In the last few years, Pris has received attention because of its potent antitumor action. It can stop cell cycle progression and has potent anti-proliferative activity in multiple type of tumor cells [12,13]. Studies have tried to explore other therapeutic utilities of Pris based on its anti-inflammatory activity. It was demonstrated that Pris inhibits

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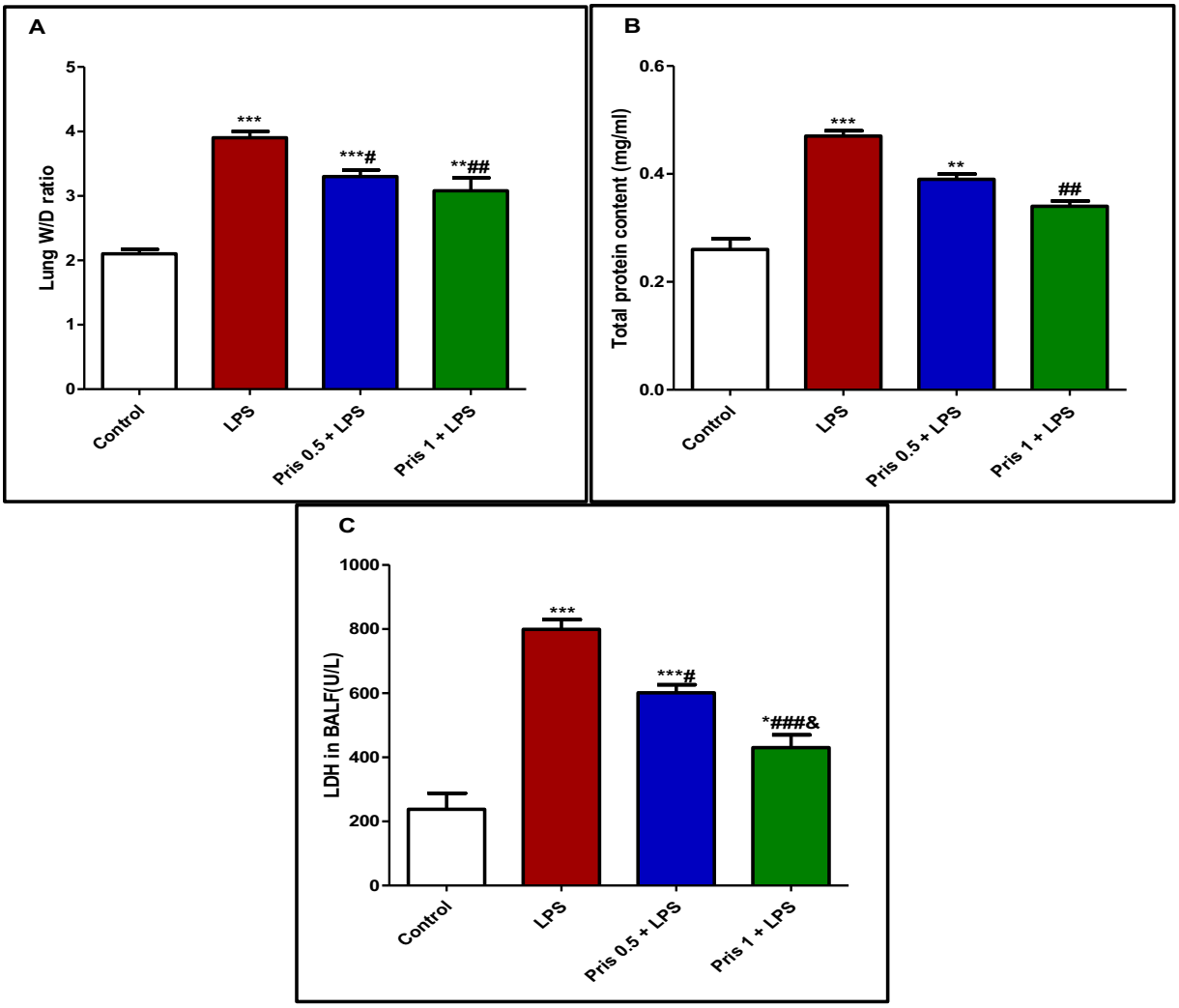

Fig. 1. Pris ameliorated LPS-induced elevation of a) Lung W/D ratio b) Protein content and c) Lactate dehydrogenase (LDH) activity in BALF.
Mice were administered Pris at two different dose levels (0.5 and 1 mg/kg, IP) once daily for 5 days prior to LPS injection (10 mg/kg, IP). Samples were collected 24 h after LPS injection.
Values are the mean ± S.E. ($n = 8$).
$^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs control group; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ vs LPS group; $^{\&}P < 0.05$ vs Pris 0.5+ LPS group (one way ANOVA followed by Tukey-Kramer's multiple comparisons test).

inducible nitric oxide synthase (iNOS), which is an important enzyme that induces inflammation via the release of nitric oxide (NO) [14,15]. More recently, it was shown that Pris exerts potent anti-inflammatory activity in LPS-stimulated murine macrophage RAW cells via inhibition of nuclear factor kappa-B (NF-κB) activation and subsequently suppression of the release of inflammatory cytokines such as TNF-α and ILs [16]. Similarly, Hui et al. [17] reported that Pris can block NF-κB activation and its translocation in LPS-stimulated THP-1 cells. However, the effect of Pris against LPS-induced ALI has not been tested yet. Hence, this study was targeted to evaluate the ability of Pris to protect against LPS-induced ALI and to provide the possible mechanisms for these effects.

2. Materials and methods

2.1. Chemicals and reagents

Pris was bought from Tocris (Bristol, UK) and dissolved in DMSO. LPS (*Escherichia coli* serotype O111:B4) was purchased from Sigma-Aldrich (St. Louis, MO, USA). On the day of experiment, LPS was freshly prepared in normal saline. Other chemicals and reagents were of highest purity.

2.2. Animals

Male Swiss albino mice (18–25 g) were obtained from Faculty of Pharmacy, Mansoura University. Animals were kept in standard cages and allowed free access to food and water under standard condition of temperature (25 °C) and dark/light cycle. Experimental protocol was approved by the Ethical Committee of Faculty of Pharmacy, Mansoura University which closely adapts the NIH guidelines.

2.3. Experimental design

Mice were randomly assigned into 4 experimental groups (each of 8 mice). Animals were treated according to the following regimen:

Group 1. Control group where mice received the vehicle once daily for 5 days.

Group 2. LPS group where mice received a single intraperitoneal injection of LPS (10 mg/kg).

Groups 3 and 4. Mice were administered Pris at two different dose levels (0.5 and 1 mg/kg, IP) once daily for 5 days prior to LPS challenge.