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Original Article

Magnolol reduces bleomycin-induced rodent lung fibrosis

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Abstract: Magnolol, a compound extracted from the Chinese medicinal herb *Magnolia officinalis*, has been proved to exert multiple pharmacological effects, including anti-oxidant and anti-inflammation activities. In this study, how it influenced bleomycin-induced lung fibrosis of rats was investigated. A single intratracheal instillation of bleomycin (5 mg/Kg, sacrificed 7 and 28 days post bleomycin instillation) caused body weight decrease and lung indices increase. Hodroxyproline content, myeloperoxidase (MPO) activity, tumor necrosis factor-α (TNF-α) and transforming growth factor-β (TGF-β) levels increased in the rat lung tissues after bleomycin administration, while superoxide dismutase (SOD) activity decreased in the rat lung tissues. Collagen were excessively deposited in rat lung tissues after bleomycin treatment. However, oral administration of magnolol (10 mg/Kg, 20 mg/Kg, 30 mg/Kg) apparently and significantly inhibited the fibrotic process. It partly reversed the bleomycin-induced increase of hydroxyproline content, MPO activity, TNF-α and TGF-β levels in the lung tissues, significantly inhibited the bleomycin-induced decrease of SOD activity, Excessive collagen deposition was also inhibited by magnolol administration. In summary, our results suggested that magnolol might be a potent anti-inflammatory and anti-fibrotic agent against bleomycin-induced lung fibrosis.

Keywords: Magnolol, lung fibrosis, tumor necrosis factor-α, transforming growth factor-β

Introduction

Inflammation plays an important role in the pathogenesis of interstitial pulmonary fibrosis. Bleomycin, a mixture of glycopeptides derived from *Streptomyces verticillus*, is known to produce pulmonary fibrosis in humans as well as in experimental animals. The molecular mechanisms of bleomycin in leading to pulmonary fibrosis are not yet clearly understood, but currently it is generally believed that superoxide radicals generated by bleomycin itself cause direct injury to epithelial or endothelial cells in the lung [1]. The initial lung injury induced by bleomycin may subsequently increase the influx of activated inflammatory cells into lung parenchyma [2]. The inflammatory cells (e.g., alveolar macrophages or polymorphonuclear cells) produce reactive oxygen species (ROS), and these ROS may greatly contribute to the pathogenesis of bleomycin-induced pulmonary fibrosis [1] .

Currently many treatments for idiopathic pulmonary fibrosis have been investigated, but the limited treatments mainly included anti-inflammatory, immunosuppressive, or anti-fibrotic methods, all of which showed no promising results in treating idiopathic pulmonary fibrosis [3]. Magnolol, a natural compound has been reported to have wide spectrum of biological effects including antioxidant [4-6], antithrombotic [7], antimicrobial [8], anti-allergic [9], antifungal [10], anti-inflammatory [11], and xanthine oxidase inhibition [12]. Moreover, magnolol exerted protective effects on lipopolysaccharide-induced acute lung injury in mice [13]. In this work we investigated the potential of magnolol to treat lung fibrosis using bleomycin-induced rat lung fibrosis model.

Materials and methods

Animals

All animal care and experimental procedures were performed according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Everything was done to minimize animal's suffering and only the num-

ber of animals necessary for producing reliable data were used.

Male Wistar Rats, 8 weeks old and weighing 200-240 g, were used in the experiments. They were purchased from Vital River Laboratories (Beijing, China). They were housed in an animal room maintained at a constant temperature (23 ± 1°C) and relative humidity (60 ± 5%) on an automatically controlled 12 h/12 h light/dark cycle (lights on at 07:00 h). Water and food were available *ad libitum*. All rats were allowed to acclimatize in our facility for one week before any experiments were started. The experimental design and procedures were approved by the Ethical Committee for Animal Care and Use at our hospital.

Experimental model of bleomycin-induced lung fibrosis

Rats were randomized into 5 groups: saline-treated control group (group 1), bleomycin-treated group (group 2), magnolol-treated group (group 3, 4, 5). Each group had 8 animals. Animals in group 3, 4, 5 were respectively treated with 10, 20, 30 mg/kg/daily of magnolol during the induction of lung fibrosis by bleomycin until the end of the experiment. Single dose of bleomycin (5.0 mg/kg body weight in 1.0 ml phosphate buffered saline, Taihe Pharmaceutical, Tianjin, China) was injected into the animals' lung intratracheally. Control animals received the same volume of intratracheal saline instead of bleomycin. Magnolol (dissolved in deionized water; National Institute for the Control of Pharmaceutical and Biological Products, Beijing, China) was given orally through feeding tube. The day of bleomycin injection was considered as day 0 and the body weight of the animals was recorded every 3-4 days.

Biochemical assays

At the end of the treatment the rats were sacrificed and the lungs were removed, weighed, washed twice with cold saline and then was divided into 2 parts: the right part fixed in 10% formalin solution was used for histological examination and the left one was used for biochemical assay and cytokine detection.

The lung tissues were homogenized as 10% homogenate in 0.9% saline by homogenizer on ice. Then centrifugation was performed, and the supernatant was saved at -20°C for future assays. The determination of superoxide dismutase (SOD) activity, myeloperoxidase (MPO) activity, and hydroxyproline levels were done according to the manufacturer's manuals (Nanjing Jiancheng Bioengineering Institute, Nanjing, China).

Lung histological assays

Lung specimens were fixed in 10% formalin solution for 24 h, dehydrated in ethyl alcohol, and embedded in paraffin. Sections of 5 μm were stained with hematoxylin and eosin (H and E) and Masson trichrome for histological evaluation of lung injury and fibrosis by light microscopy.

ELISA assays

The TNF-α and TGF-β levels in the lung tissues were determined using commercially available ELISA kits of each cytokines. The level of TNF-α was determined using ELISA kit from AssayPro (St.Charles, Missouri, USA). TGF-β level was assayed using a TGF-β ELISA kit (TGF-β E max ImmunoAssay System; Promega Corp., Madison, Wisconsin).

Statistical analysis

Statistical analysis was performed using SPSS 13.0 software (SPSS Inc. Chicago, Illinois, USA). Values were showed as mean ± SD. Statistical differences between groups were analyzed through one-way analysis of variance (ANOVA), followed by post-hoc multiple comparison tests (LSD). Difference with $P < 0.05$ was considered as statistically significant.

Results

Effects of magnolol on body weight increase and lung indices of rats with bleomycin-induced lung fibrosis

Compared with control rats, bleomycin-treated rats showed a gradual decrease in body weight and at day 7-11 after bleomycin injection the body weight came to the lowest level, which could be significantly and concentration-dependently inhibited by magnolol administration (**Figure 1A**).

Lung index [weight of wet lung (mg)/body weight] was employed to evaluate the effects of

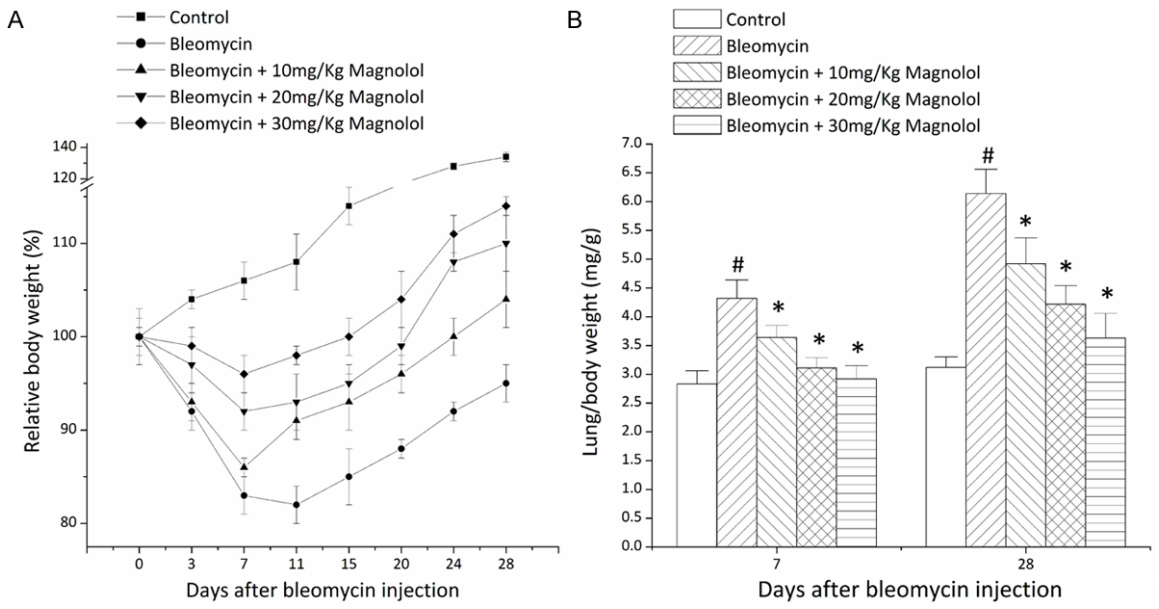

Figure 1. A. Effects of magnolol on body weight loss induced by bleomycin administration. Rats were randomized into weight-matched groups. The body weight on day 0 was considered as 100%. The relative body weight was calculated as percentage of that on day 0. Data were presented as mean ± SD (n = 8). The experiments were repeated three times independently with similar results. #$P < 0.05$ *vs* Control group; *$P < 0.05$ *vs* Bleomycin group. B. Effects of magnolol on lung index increase induced by bleomycin. Rats were sacrificed on day 7 and day 28 after bleomycin injection. Lung index was calculated as ratio of lung wight (mg) to body weight (g) of each rat. Values were expressed as mean ± SD (n = 8). The experiments were repeated three times independently with similar results. #$P < 0.05$ *vs* Control group; *$P < 0.05$ *vs* Bleomycin group.

magnolol on lung edema caused by bleomycin. As shown in **Figure 1B**, bleomycin treatment increased the lung indices of rats due to lung weight gain at day 7 and day 28 after bleomycin administration. The lung index increase could be greatly reversed by magnolol treatment in dose-dependent manner (**Figure 1B**).

Effects of magnolol on hydroxyproline content, superoxide dismutase (SOD) activity and myeloperoxidase (MPO) activity in rats with bleomycin-induced lung fibrosis

Hydroxyproline content has been widely used as indicator of lung fibrosis. In order to study the anti-fibrotic potential of magnolol, the hydroxyproline content were measured and compared between normal and bleomycin-treated rats. As illustrated in **Figure 2A**, at day 28 after bleomycin injection the lung hydroxyproline content increased significantly compared with control rats without bleomycin treatment. Meanwhile, administration of magnolol could dose-dependently inhibit bleomycin-induced increase of hydroxyproline content (**Figure 2A**).

As shown in **Figure 2B**, compared with control, bleomycin treatment greatly reduced SOD activity in lung tissues at day 28 after bleomycin injection, while administration of magnolol concentration-dependently alleviated the decrease of SOD activity in lung tissues caused by bleomycin. **Figure 2C** showed that MPO activity in lung tissues increased significantly at day 7 and day 28 after bleomycin administration. Meanwhile, magnolol treatment caused significant decrease in myeloperoxidase activity in dose-dependently (**Figure 2C**).

Effects of magnolol on TNF-α and TGF-β expression levels in lung tissues of rats with lung fibrosis

As shown in **Figure 3**, expression of TNF-α and TGF-β were determined to study the effects of magnolol on cytokines expression which were involved in lung fibrosis. We found that compared with control, TNF-α level was increased significantly in lung tissues at day 7 after bleomycin administration, while magnolol suppressed the increase of TNF-α level dose-dependently (**Figure 3A**).

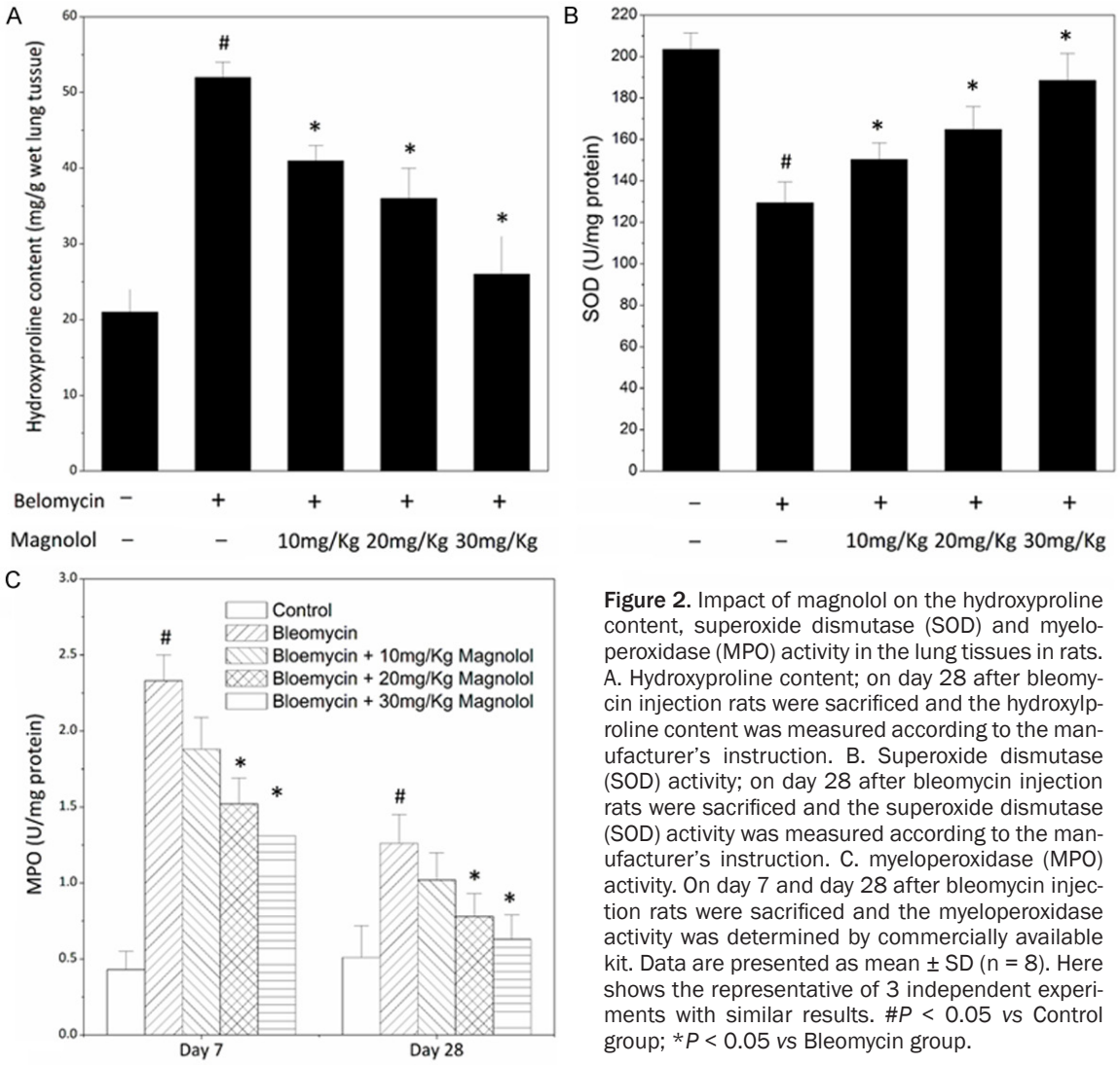

Figure 2. Impact of magnolol on the hydroxyproline content, superoxide dismutase (SOD) and myeloperoxidase (MPO) activity in the lung tissues in rats. A. Hydroxyproline content; on day 28 after bleomycin injection rats were sacrificed and the hydroxylproline content was measured according to the manufacturer's instruction. B. Superoxide dismutase (SOD) activity; on day 28 after bleomycin injection rats were sacrificed and the superoxide dismutase (SOD) activity was measured according to the manufacturer's instruction. C. myeloperoxidase (MPO) activity. On day 7 and day 28 after bleomycin injection rats were sacrificed and the myeloperoxidase activity was determined by commercially available kit. Data are presented as mean ± SD (n = 8). Here shows the representative of 3 independent experiments with similar results. #$P < 0.05$ *vs* Control group; *$P < 0.05$ *vs* Bleomycin group.

In contrast with control, bleomycin treatment also increased the TGF-β expression level in lung tissues at day 7 and day 28 after injection (**Figure 3B**). Administration of magnolol dose-dependently inhibited the increase of TGF-β expression level in lung tissues caused by bleomycin treatment (**Figure 3B**).

Effects of magnolol on lung fibrogenesis and alveolar inflammation in bleomycin-treated rats

At day 7 after bleomycin administration the rats were sacrificed and the lungs were removed for histological examination. The HE staining showed that intact lung architecture in the control group appeared (**Figure 4A**), and collapsed and narrow alveoli, marked thickening of the interalveolar septa, and dense interstitial infiltration by inflammatory cells in bleomycin-treated rats (**Figure 4B**). Masson trichrome staining showed an excessive collagen deposition in the lung tissues in bleomycin-treated rats (**Figure 4E**) compared with control rats (**Figure 4D**). Magnolol treatment prevented those changes in rats lungs administered with bleomycin (**Figure 4C** and **4F**).

Discussion

Magnolol, a compound extracted from the Chinese medicinal herb Magnolia officinalis, has been proved to exert multiple pharmacological effects. Previous researches showed that magnolol could provide cardiovascular protection [14, 15]. Magnolol also exerted neuro-

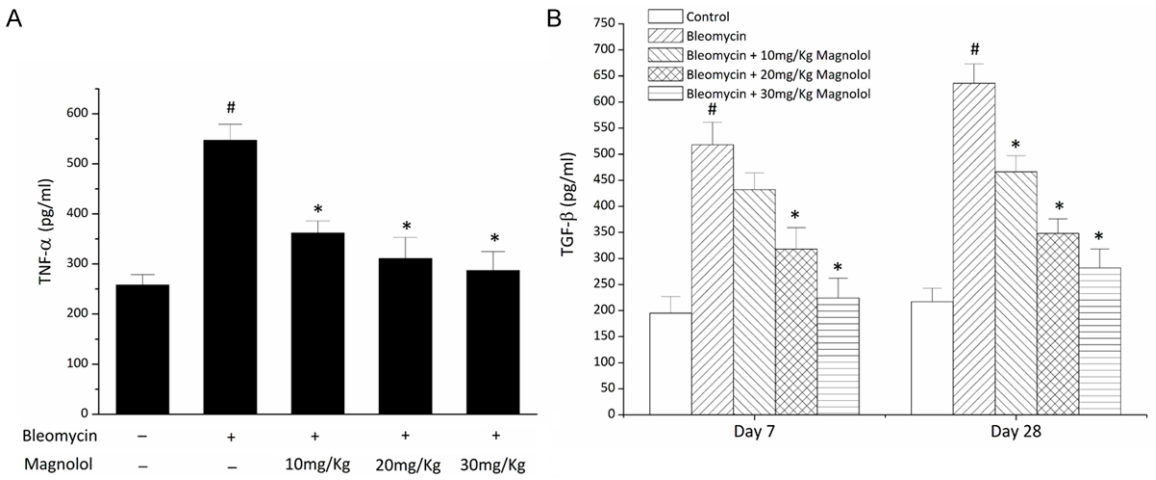

Figure 3. Influence of magnolol on TNF-α and TGF-β production in lung tissues of bleomycin-treated rats. A. TNF-α; Rats were sacrificed on day 7 and lungs were removed and homogenized. Supernatants were analyzed for TNF-α level. B. TGF-β. Rats were sacrificed on day 7 and day 28 after bleomycin injection. Lungs were removed and homogenized. After centrifugation the supernatants were assayed for TGF-β level. Values were expressed as mean ± SD (n = 8). Three independent experiments were performed with similar results. #$P < 0.05$ *vs* Control group; *$P < 0.05$ *vs* Bleomycin group.

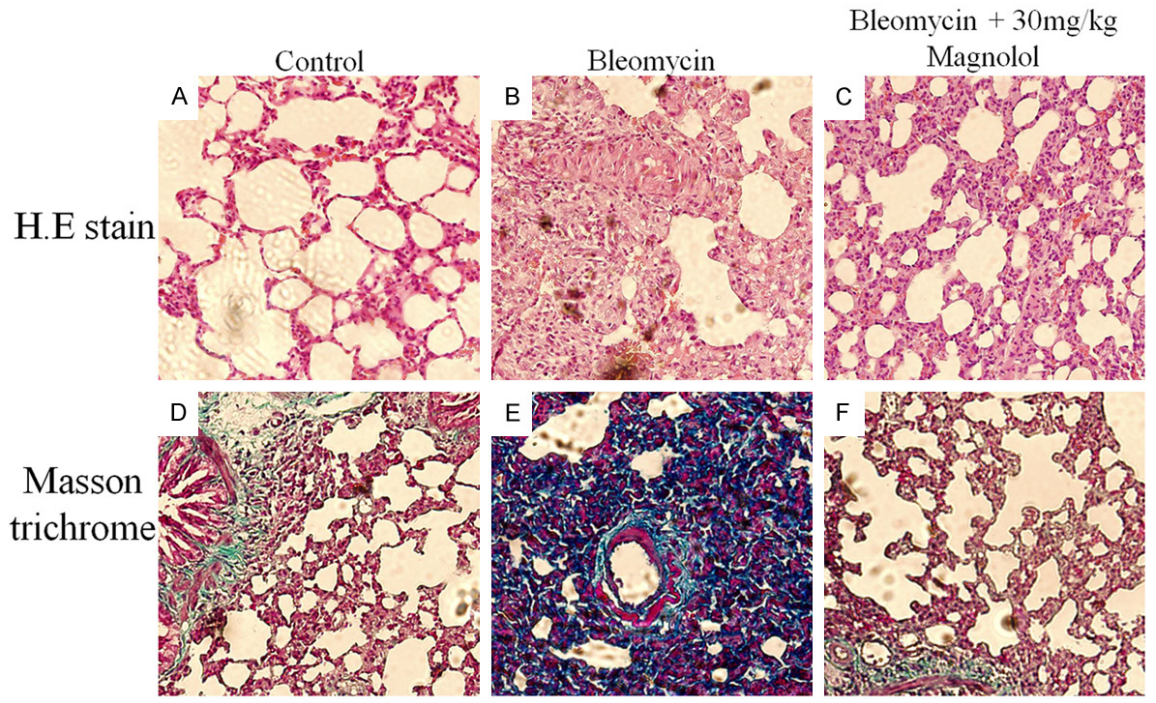

Figure 4. Photomicrographs of rat lung sections. Rats were sacrificed on day 7 after bleomycin injection. The lungs were removed, fixed in 10% formalin solution, dehydrated in ethyl alcohol and embedded in paraffin. Sections of 5 μm were stained with hematoxylin and eosin (H.E) and Masson trichrome. A-C. H.E stain; D-F. Masson trichrome stain. A, D. Control group; B, E. Bleomycin group; C, F. Bleomycin + 30 mg/Kg Magnolol treated group. (×200).

logical effects [16]. Lin YR's research illustrated that magnolol had antinociceptive actions [17]. Lee YK showed that magnolol protected against scopolamine-induced memory impairment [18]. Chen CR and his colleague proved that magnolol exerted antiepileptic effects via

the GABA/benzodiazepine receptor complex in mice [19]. Muroyama's study indicated that magnolol protected against MPTP/MPP(+)-induced toxicity via inhibition of oxidative stress in *in vivo* and *in vitro* models of Parkinson's disease [20]. Besides above actions, magnolol also has antitumor activities. It could induce tumor cell apoptosis [21, 22], inhibit tumor migration and invasion [23, 24], was a potential antitumor agent [25]. Recently, researchers found that magnolol could provide protective effects against acute lung injury induced by some insults [13, 26]. Magnolol attenuated the lung injury in hypertonic saline treatment from mesenteric ischemia reperfusion through diminishing iNOS [26]; Magnolol also inhibited lipopolysaccharide-induced acute lung injury by inhibiting toll-like receptor 4 (TLR4) mediated nuclear factor kappa B (NF-kappaB) and MAPKs signaling pathways [27, 28]. It could protect endothelial cells from apoptosis induced by oxidative stress [29]. Additionally, magnolol could also protect rats against sepsis [5, 30], which proved its anti-inflammation action. However, at present it is not still investigated that how magnolol affect lung fibrosis process.

In present study, we investigated the protective effects of magnolol on the pathogenesis of lung fibrosis using bleomycin-induced rat lung fibrosis model. Bleomycin injection could cause body weight increase, lung index decrease, progressive and significant inflammation, exacerbated fibrosis, and severe alveolar destruction in rat lungs. In addition, decrease of SOD activity, increase of MPO activity and hydroxyproline content, elevation of TNF-α and TGF-β1 levels were also observed in the rat lung tissues after bleomycin injection. However, magnolol treatment haltered the bleomycin-induced lung fibrosis and inflammation, inhibited the bleomycin-induced TNF-α and TGF-β1 increase and decrease of SOD activity. Overall, our results suggested that magnolol could provide a protective effect on bleomycin-induced rat lung fibrosis.

During the process of lung fibrosis induced by bleomycin, inflammation response, including leukocytes infiltration, played an important role. The infiltrated leukocytes could sustain the injury/repair processes induced by bleomycin [31, 32]. Myeloperoxidase (MPO) activity has been widely used as an index of leukocyte infiltration. In our study, we found that increase of MPO activity caused by bleomycin treatment could be greatly inhibited by magnolol administration, which indicated the inhibitory effects of magnolol on leukocyte infiltration in the process of lung fibrosis. Redox state and oxidant-antioxidant balance also played an important role in the pathogenesis of lung fibrosis [33, 34]. High level of oxidants increased the TGF-β production, enhanced fibrosis process [35], while antioxidants including SOD protected against fibrosis [36]. In present study, our results showed that magnolol administration significantly inhibited the loss of SOD activity induced by bleomycin injection, which proved the protective role in bleomycin-induced lung fibrosis.

TNF-α is an important inflammatory cytokine. It can promote inflammation response and subsequent fibrosis during bleomycin action. Previous study showed that depletion of TNF-α by antibody could attenuate bleomycin-induced lung injury [37, 38]. TGF-β is another important cytokine involved in fibrosis. It can induce collagen gene expression or synthesis by stimulating fibroblast proliferation [39-42]. In present study, the results showed that bleomycin injection increased the levels of TNF-α and TGF-β in the lung tissues, while administration of magnolol significantly inhibited the increase of TNF-α and TGF-β levels and kept it at basal level as that in the normal control.

Taken together, magnolol could provide protective effects against bleomycin-induced lung fibrosis of rats, which might be closely associated with its activities of anti-inflammation, antioxidant, and cytokine inhibition.

Disclosure of conflict of interest

None.

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