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Research Article
Gelsolin Attenuates Lipopolysaccharide-Induced Acute Lung Injury in Rats by Modulating TLR4/Myd88/NF-κB Signaling Pathway

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Abstract

Background and Objective: Gelsolin (GSN) is an important actin protein that can bind to actin and regulate the polymerization and depolymerization of actin. It is closely related to apoptosis, coagulation, immunity, tumour and inflammation. This study aimed to investigate the intervention effects and mechanism of GSN on LPS-induced ALI in rats. **Materials and Methods:** GSN of different concentrations (0.1, 0.3, 0.9 mg kg^{-1}) were used to treat LPS-induced ALI rats. Pathological changes of lung tissue and the contents of TNF-α, IL-6 and IL-1β in BALF, serum and lung tissue homogenate were measured by ELISA. The expressions of TLR4, MyD88, IRAK1, TRAF6, TAK1, IκBα and NF-κB p65 in lung tissue were detected at protein and gene levels by western blot and qRT-PCR. **Results:** The results showed that GSN markedly attenuated the histological alterations and suppressed the levels of TNF-α, IL-6 and IL-1β in BALF, serum and lung tissue homogenate. Furthermore, the expression of TLR4, MyD88, IRAK1, TRAF6, TAK1 and NF-κB p65 induced by LPS were markedly inhibited by GSN and the expression of IκBα increased at protein and gene levels. **Conclusion:** This study demonstrated that GSN attenuated LPS-induced acute lung injury in rats by modulating TLR4/MyD88/NF-κB signalling pathway.

Key words: Gelsolin, acute lung injury, lipopolysaccharide, TLR4/MyD88/NF-κB, signalling pathway

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Acute Lung Injury (ALI)/Acute Respiratory Distress Syndrome (ARDS) is a syndrome secondary to severe infection, shock, trauma and burns, which induces diffuse pulmonary interstitial and alveolar oedema of pulmonary capillary endothelial cells and alveolar epithelial cells, leading to acute hypoxic respiratory insufficiency or failure[1,2]. The clinical manifestations are progressive hypoxemia and respiratory distress and the pulmonary imaging manifestations were heterogeneous exudative lesions[3]. ALI is the most common type of acute respiratory failure with a high mortality rate of 32-50%[4,5]. Therefore, it has become the focus and difficulty of intensive care research.

Lipopolysaccharide (LPS), also called endotoxin, is a chemical component of the active tissue located in the cell wall of Gram-negative bacteria. It can directly activate alveolar macrophages and release a variety of inflammatory factors, leading to ALI[6]. The pathogenesis of LPS-induced ALI is complex, which is mainly due to the increase of pro-inflammatory factors and the release of inflammatory factors. When the pulmonary capillary endothelial cells and alveolar epithelial cells are seriously damaged, the active substances on the surface of the lung show a decreasing trend and the physiological function of the lung will be impaired[7]. A certain amount of Reactive Oxygen Species (ROS) will be released from injured pulmonary endothelial cells, which will lead to the imbalance of oxidation and antioxidation in the lung. A large number of proteins will directly enter the alveolar cavity, leading to pulmonary oedema and even respiratory failure[8]. At present, the main therapeutic drugs for LPS-induced ALI include glucocorticoids, adrenergic receptor agonists, antioxidants and traditional Chinese medicine[9-12].

Toll-Like Receptors (TLRs) are a family of receptors with pattern recognition function and their receptor families are highly conserved in evolution[13]. In the process of classic inflammation, TLR family members have to go through a very classic signalling pathway, which starts from the Toll/IL-1 receptor homologous region (TIR). TIR activates intracellular signal mediators, including IL-1R associated kinase (IRAK), TNFR-associated factor-6 (TRAF-6) and IκB-kinase (IκK) and then activate nuclear factor κB nuclear factor κB, NF-κB) to induce the expression of inflammatory factors[14,15]. A large number of studies have shown that the occurrence of LPS-induced ALI is related to NF-κB activation and then stimulate the cascade of inflammatory factors[16-19].

Gelsolin (GSN) is an important component of the cytoskeleton. It can bind to actin and regulate the polymerization and depolymerization of actin and it is an important actin-binding protein[20,21]. Many studies have shown that GSN is closely related to apoptosis, immunity, tumour and inflammation[22-24]. At present, studies have found that GSN can improve the oxygenation of the ALI/ARDS animal model, inhibit the occurrence and development of the disease course and reduce mortality but its specific mechanism has not been completely elucidated.

This study aimed to explore the effect of GSN on LPS-induced ALI/ARDS and its possible mechanism, to provide an experimental basis for GSN to become a clinical therapeutic drug for ALI/ARDS or to develop a new type of drug targeting GSN.

MATERIALS AND METHODS

Study area: Part of this study was carried out in the Affiliated Hospital of Jinzhou Medical University, Jinzhou, China and the other part was carried out in Chinese PLA General Hospital, Beijing, China from March, 2020 to April, 2021.

Chemicals and reagents: LPS (Escherichia coli 055:B5) was provided by Sigma Chemical Co. (St.Louis, MO, USA). Mouse TNF-α, IL-6, IL-1β, MPO, MDA and SOD ELISA kits were purchased from Biyuntian Biotechnology Research Institute. TLR4, TRAF6, MyD88, IRAK1, TAK1, I κBα and NF-κB p65 polyclonal antibody IgG were purchased from Proteintech Group Inc. (Chicago, IL, USA).

Animals: Male SD rats were purchased from Liaoning Changsheng Biological Co., Ltd., weighing 200-230 g. The rats were reared in a clean light environment and the temperature was generally maintained at 22±3°C, the humidity was generally maintained at 50% and the light and dark lights alternated for 12 hrs.

Experimental design: Sixty mice were randomly divided into five groups as follows (n = 12): Control group, LPS group, LPS+GSN (0.1, 0.3, 0.9 mg kg^{-1}) groups. The rats of the LPS group and LPS+GSN (0.1, 0.3, 0.9 mg kg^{-1}) groups were given LPS of 2 mg kg^{-1} body weight by intratracheal instillation once a day for two consecutive days. GSN was given an intravenous injection one hour after the last intratracheal instillation of LPS. Rats in each group were killed 24 hrs after administration.

Determination of lung wet-to-dry weight ratio (W/D) and lung coefficient: The wet weight of the left lung tissue was accurately weighed, dried in an oven at 80°C for 24 hrs and

Table 1: Sequences of primers used for qRT-PCR

Gene	Strand	Sequence of the primer (5'-3')	Size (bp)
TLR4	Forward	CATGGATCAGAAACTCAGCAAAGTC	179
	Reverse	CATGCCATGCCTTGTCTTCA	
MyD88	Forward	TACAGGTGGCCAGAGTGGAA	119
	Reverse	GCAGTAGCAGATAAAGGCATCGAA	
IRAK1	Forward	CGGACTTCCACAGTTCGAGGTA	125
	Reverse	TGACCAGCAAGGGTCTCCAG	
TRAF6	Forward	TCATTATGATCTGGACTGCCCAAC	150
	Reverse	TTATGAACAGCCTGGGCCAAC	
TAK1	Forward	AGCAGAGTAGCTGCGGT	134
	Reverse	GAGGAGCTTGCTGCAGAT	
IκBα	Forward	GCTGAAGAAGGAGCGGCTACT	95
	Reverse	TCGTACTCCTCGTCTTTCATGGA	
NF-κB p65	Forward	AGTTGAGGGGACTTTCCCAGGC	124
	Reverse	TCAACTCCCCTGAAAGGGTCCG	
GAPDH	Forward	TGTGTCCGTCGTGGATCTGA	150
	Reverse	TTGCTGTTGAAGTCGCAGGAG	

dried to constant weight. The lung wet-to-dry weight ratio and lung coefficient were calculated according to the following Eq.:

$$W/D\ (\%) = \frac{\text{Wet weight of lung}}{\text{Dry weight of lung}} \times 100$$

$$\text{Lung coefficient} = \frac{\text{Wet weight of lung}}{\text{Weight of rat}} \times 100$$

Preparation of bronchoalveolar lavage fluid (BALF) and lung tissue homogenate: After the rats were anaesthetized with chloral hydrate, the blood was collected from the femoral artery of the rats and the rats were killed. The skin in the middle of the rat neck was cut to expose the trachea. The suture was used to ligate the right main bronchus and a small opening was cut transversely in the middle and lower part of the trachea. At this time, the catheter was inserted into the trachea from the small opening and tied with a suture. The left lung was lavaged with 4 mL normal saline twice to recover BALF. A small number of samples were taken and counted on the white blood cell counting disk under the microscope.

The lung tissue of rats was removed and washed in PBS. The lung tissue was quickly homogenized on ice with a tissue grinder. The lung tissue homogenate of rats was placed in a centrifuge tube and centrifuged at 7000 g for 10 min, packed separately and stored in a refrigerator at -70°C.

ELISA assay: The levels of inflammatory cytokines TNF-α, IL-1β and IL-6 in BALF, serum and lung tissues and the levels of MPO, MDA and SOD in lung tissues were detected by ELISA kits according to the manufacturer's instructions.

Histological analysis: The right middle lobe of the rat lung was removed and the obtained lung tissue was fixed in 10% formaldehyde solution for 24 hrs. The right hilum of the rat lung was obliquely cut through the hilum of the lung on the sagittal plane. The lung tissue with a thickness of 5 mm was dehydrated, embedded in paraffin, sectioned and stained with HE staining g to observe the damage by light microscopy.

Western blot: Total proteins of lung tissues were obtained using lysis solution. The protein concentration was measured by the bicinchoninic acid (BCA) method. The 20 μg protein was separated on 10% SDS-PAGE and transferred to PVDF membranes. The membranes were incubated with primary antibodies that recognized TLR4, MyD88, IRAK1, TRAF6, TAK1, IκBα, NF-κB p65 and GAPDH. Then the membranes were incubated with HRP-conjugated secondary antibodies. The band intensity was quantified by Image J software.

Quantitative real-time PCR (qRT-PCR): Total RNA was isolated using Trizol from the frozen lung of rats. cDNA synthesis was performed using a PrimeScript™ RT Reagent Kit according to the manufacturer's instructions. cDNA was amplified with specific primers using a Fast SYBR™ Green Master Mix and a Step One Plus™ RT-PCR System. Results were assessed using the $2^{-\Delta\Delta Ct}$ method. Primers used for analyses are listed in Table 1.

Statistical analysis: Statistical analyses were performed using the SPSS 24.0 software. The data were expressed as the Mean±SD. Multiple comparisons were evaluated by one-way analysis of variance (ANOVA) with Dunnett's post-test. Statistical significance was accepted at $p<0.05$ or $p<0.01$.

RESULTS

Effect of GSN on histopathological changes: The results of HE staining in lung tissue of rats in each group are shown in Fig. 1. In the control group, the alveolar structure was complete, the alveolar cavity was clear and complete and there was no obvious oedema and inflammatory cell infiltration in the alveolar septum in Fig. 1a. In the LPS group in Fig. 1b, the alveolar structure was destroyed, the alveolar

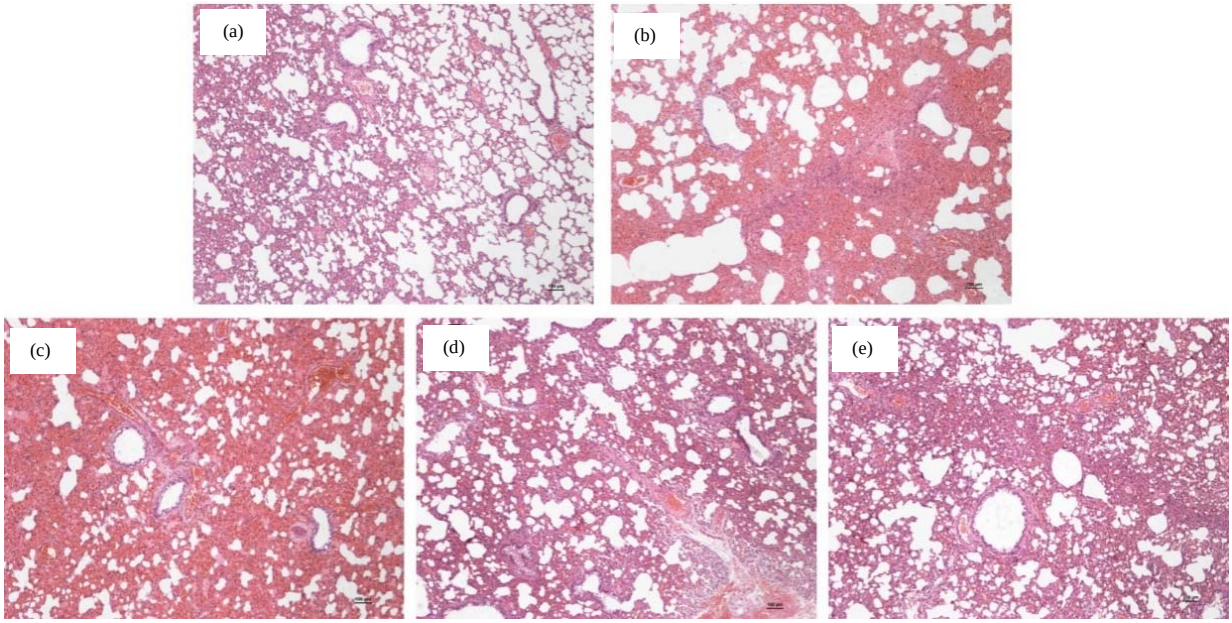

Fig. 1(a-e): Effects of GSN on histopathological changes in lung tissues in LPS-induced ALI rats, (a) Histological analysis of lung tissue section by HE staining in the control group, (b) Histopathological changes of lung tissues in LPS-induced ALI rats, (c) Effects of GSN (0.1 mg kg^{-1}) on histopathological changes of lung tissues in ALI rats, (d) Effects of GSN (0.3 mg kg^{-1}) on histopathological changes of lung tissues in ALI rats and (e) Effects of GSN (0.9 mg kg^{-1}) on histopathological changes of lung tissues in ALI rats

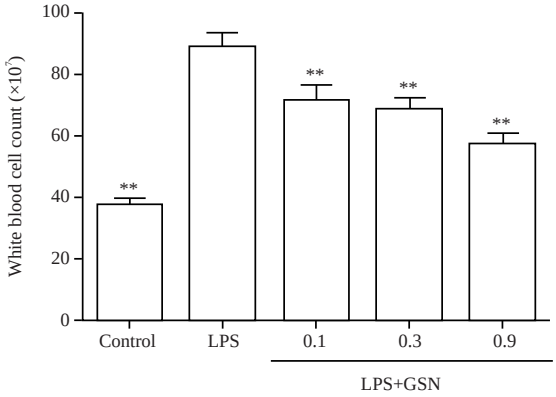

Fig. 2: Effect of GSN on the total number of white blood cells in BALF

**p<0.01 vs. LPS group

wall was diffusely thickened, there was obvious inflammatory cell infiltration and pulmonary interstitial oedema, which proved that the rat model of acute lung injury was established successfully. However, these pathological changes induced by LPS were significantly attenuated by GSN in Fig. 1(c-e). After intervention with different concentrations of GSN, the inflammatory exudation of lung tissue was significantly reduced, the leakage of red blood cells was significantly decreased, the alveolar structure was improved and the pulmonary interstitial oedema was alleviated. It can be seen that the inflammation of lung tissue was significantly reduced in the high concentration group of GSN (0.9 mg kg^{-1}) compared with the low concentration group of GSN (0.1 mg kg^{-1}).

Effect of GSN on lung wet-to-dry weight ratio (W/D) and lung coefficient: The effects of GSN on lung W/D and lung coefficient are listed in Table 2. Compared with the control group, the W/D and lung coefficient of the LPS group were significantly increased ($p<0.01$). However, 24 hrs after GSN injection, the lung W/D and lung coefficient of the LPS+GSN groups (0.3 and 0.9 mg kg^{-1}) were significantly lower than those of the LPS group ($p<0.05$, $p<0.01$).

Effect of GSN on the total number of white blood cells in BALF: The total number of white blood cells in BALF of control and LPS groups were 37.16±2.22 and 88.51±5.10.Compared with the control group, the total number of white blood cells in the LPS group was significantly increased ($p<0.01$). The total number of white blood cells in BALF of 0.1, 0.3 and 0.9 mg kg^{-1} GSN intervention groups were 71.24±5.48, 68.26±4.02 and 56.73±4.05, respectively. After the injection of GSN, the total number of white blood cells in the BALF was significantly decreased ($p<0.01$) and there was a dose-effect relationship in the degree of reduction in Fig. 2.

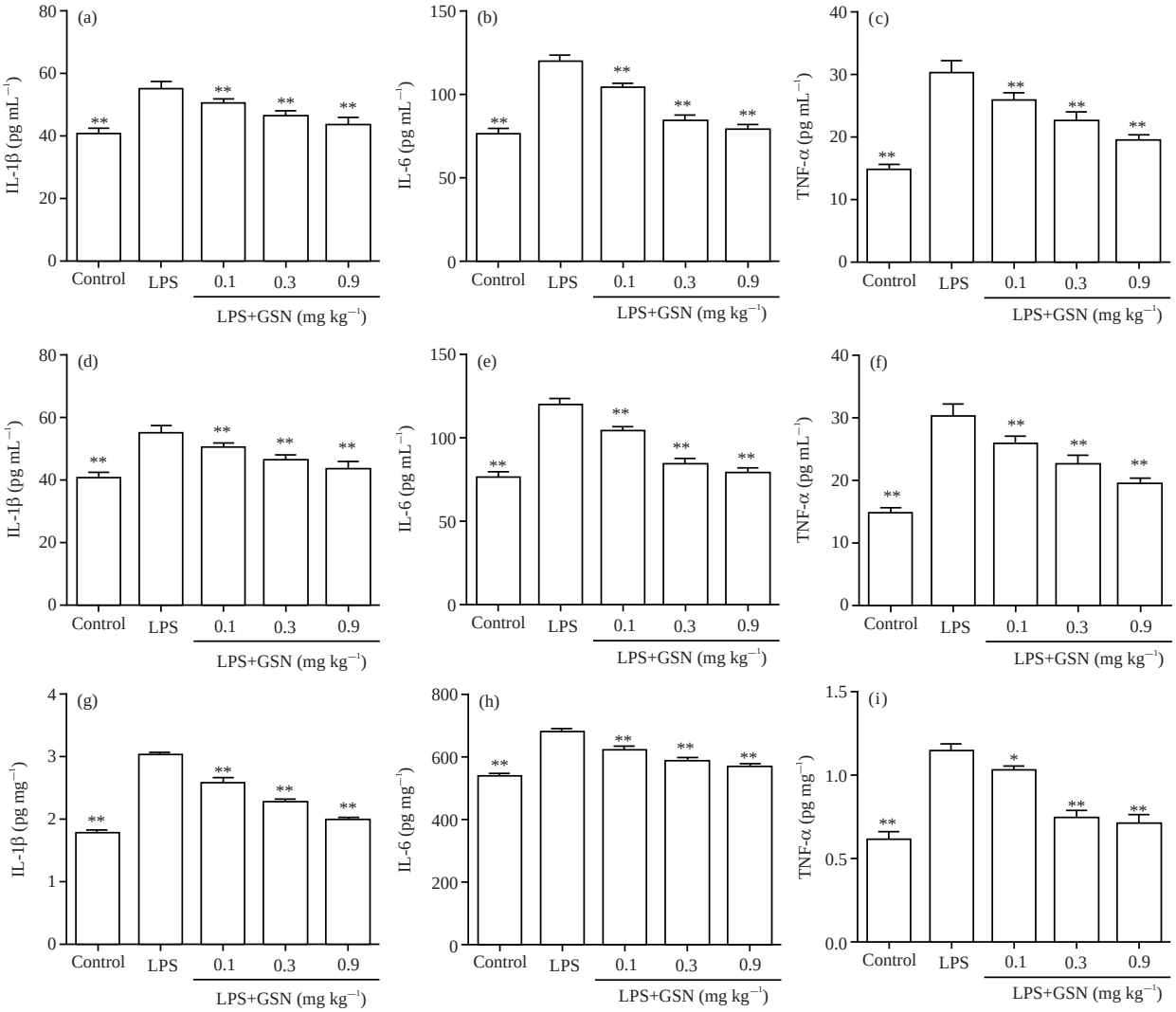

Fig. 3(a-i): Effect of GSN on levels of inflammatory cytokine in BALF, serum and lung tissue, (a) IL-1β in BALF, (b) IL-6 in BALF, (c) TNF-α in BALF, (d) IL-1β in serum, (e) IL-6 in serum, (f) TNF-α in serum, (g) IL-1β in lung tissue and (h) IL-6 in lung tissue

Effect of GSN on level of TNF-α in lung tissue, *p<0.05 vs. LPS group, **p<0.01 vs. LPS group

Table 2: Effect of GSN on lung wet-to-dry weight ratio (W/D) and lung coefficient in LPS-induced ALI rats

Groups	Dose (mg kg^{-1})	W/D	Lung coefficient
Control	-	4.37±0.06**	0.32±0.02**
LPS	-	4.85±0.09	0.46±0.03
LPS+GSN	0.1	4.71±0.08	0.41±0.02*
	0.3	4.62±0.05**	0.39±0.01*
	0.9	4.42±0.09**	0.36±0.02**

*p<0.05 vs. LPS group and **p<0.01 vs. LPS group

Effect of GSN on levels of inflammatory cytokine in BALF, serum and lung tissue: The levels of TNF-α IL-6 and IL-1β in BALF, serum and lung tissue of rats in different groups were detected by ELISA in Fig. 3. The results showed that the levels of TNF-α, IL-6 and IL-1β in BALF, serum and lung tissue of rats with ALI induced by LPS significantly increased (p<0.01 versus the control group), which indicated that LPS caused pulmonary inflammation in rats. After different concentrations of GSN (0.1, 0.3 and 0.9 mg kg^{-1}) were given, the levels of TNF-α, IL-6 and IL-1β in BALF and serum significantly decreased (p<0.01) in Fig. 3(a-f). Treatment with GSN markedly attenuated the content of TNF-α, IL-6 and IL-1β in lung tissue

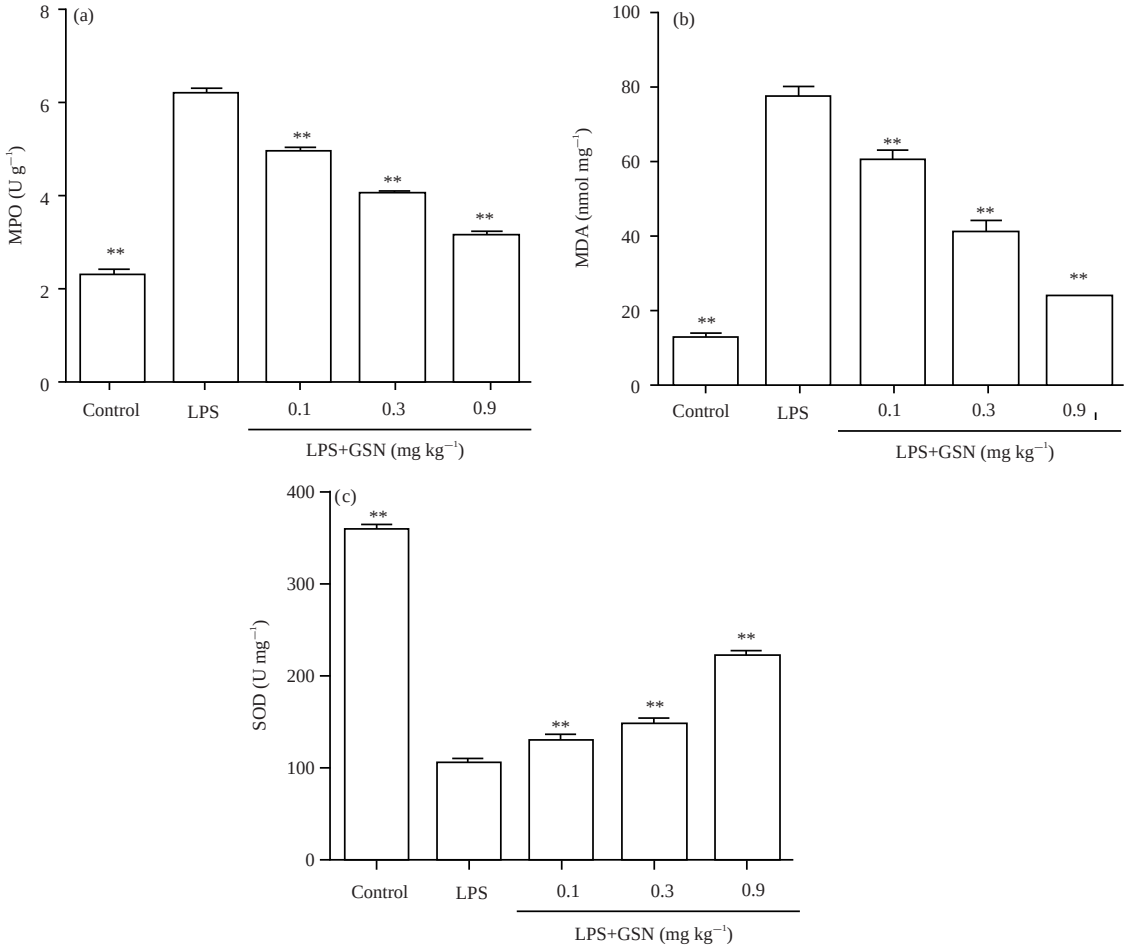

Fig. 4(a-c): Effect of GSN on levels of (a) MPO, (b) MDA and (c) SOD in lung tissue
**p<0.01 vs. LPS group

of rats (p<0.05, p<0.01) in Fig. 3(g-i). The data trend showed a certain dose-effect relationship, indicating that GSN can improve the inflammatory response of LPS-induced ALI in rats.

Effect of GSN on levels of MPO, MDA and SOD in lung tissue: As shown in Fig. 4, compared with the control group, MPO and MDA in lung tissue of LPS-induced ALI rats increased significantly (p<0.01), while SOD activity in lung tissue of LPS-induced ALI rats decreased significantly (p<0.01). After 24 hrs of GSN injection, MPO and MDA in lung tissue of LPS+GSN groups decreased significantly compared with the LPS group (p<0.01) in Fig. 4a and b, while SOD content increased significantly after GSN injection (p<0.01) in Fig. 4c. The data trend after treatment showed a dose-response relationship. Oxidative damage plays an important role in LPS-induced ALI rats, the results shown in Fig. 4 proved GSN could inhibit LPS-triggered oxidative stress.

Effect of GSN on the expressions of TLR and its downstream signal pathway proteins: As the TLR4/MyD88/NF-κB signalling pathway is a key regulator involved in the inflammatory process, explored the effect of GSN on the activation of the TLR4/MyD88/NF-κB pathway in lung tissue. The expressions of the TLR receptor and its downstream signal pathway proteins in lung tissue of each group are shown in Fig. 5. Compared with the control group, the protein expressions of TLR4, MyD88, IRAK1, TRAF6, TAK1 and NF-κB p65 in the LPS group significantly increased (p<0.01) Fig. 5(a-e) and g. Compared with the LPS group, the protein expressions of TLR4, MyD88, IRAK1, TRAF6, TAK1 and NF-κB p65 in LPS+GSN groups decreased in a dose-dependent manner(p<0.01) in Fig. 5a-c, e and g. When the concentration of GSN was 0.1 mg kg^{-1}, there was no significant difference in the expression of IRAK1 between the LPS+GSN and LPS groups. When the concentration of GSN was 0.3 and 0.9 mg kg^{-1}, the protein expression of IRAK1was significantly different from that of the LPS group (p<0.01) in Fig. 5d.

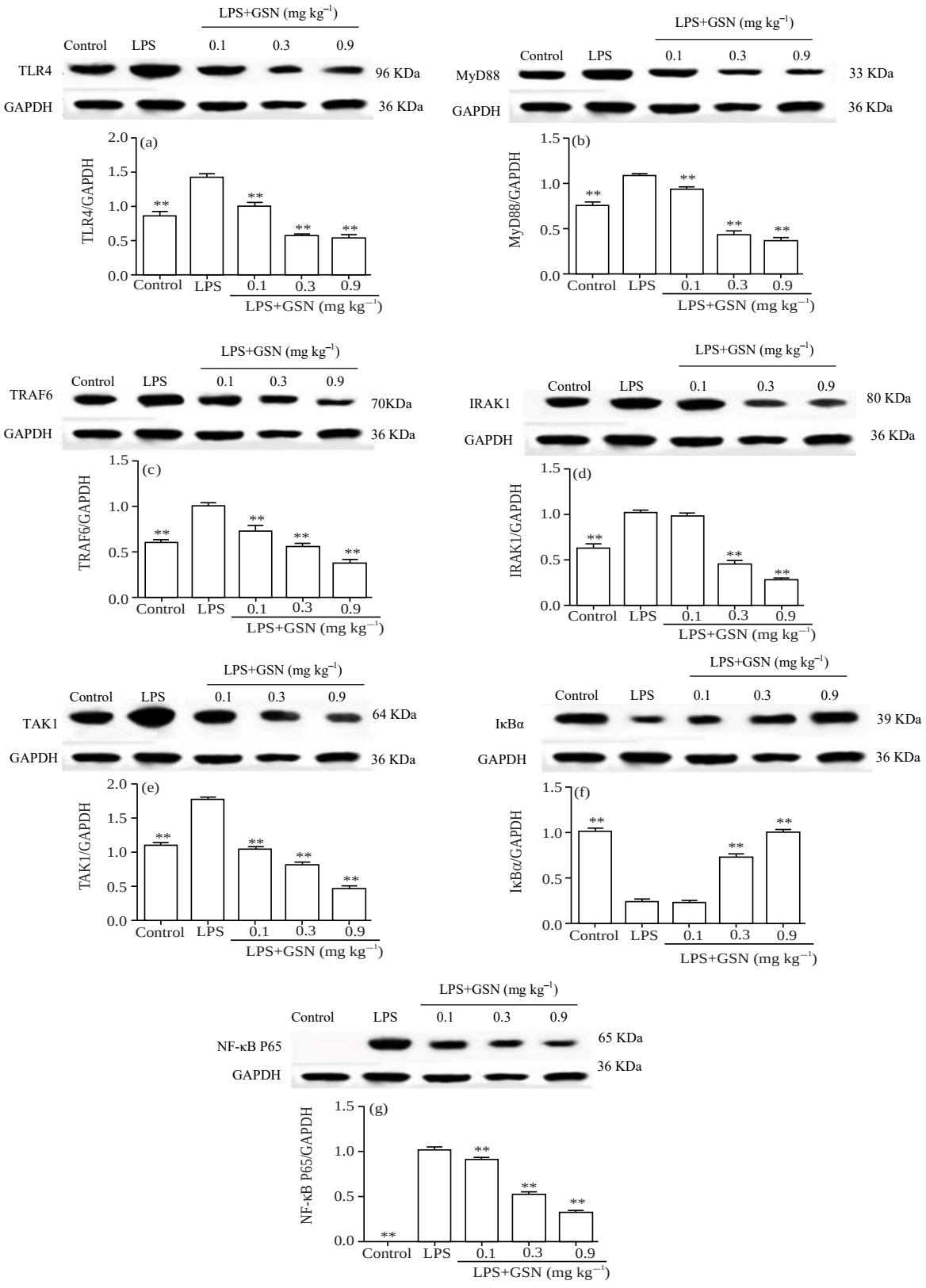

Fig. 5(a-g): Effect of GSN on the protein expression of (a) TLR4, (b) MyD88, (c) TRAF6, (d) IRAK1, (e) TAK1, (f) IκBa and (g) NF-κB p65 in lung tissue

**p<0.01 vs. LPS group

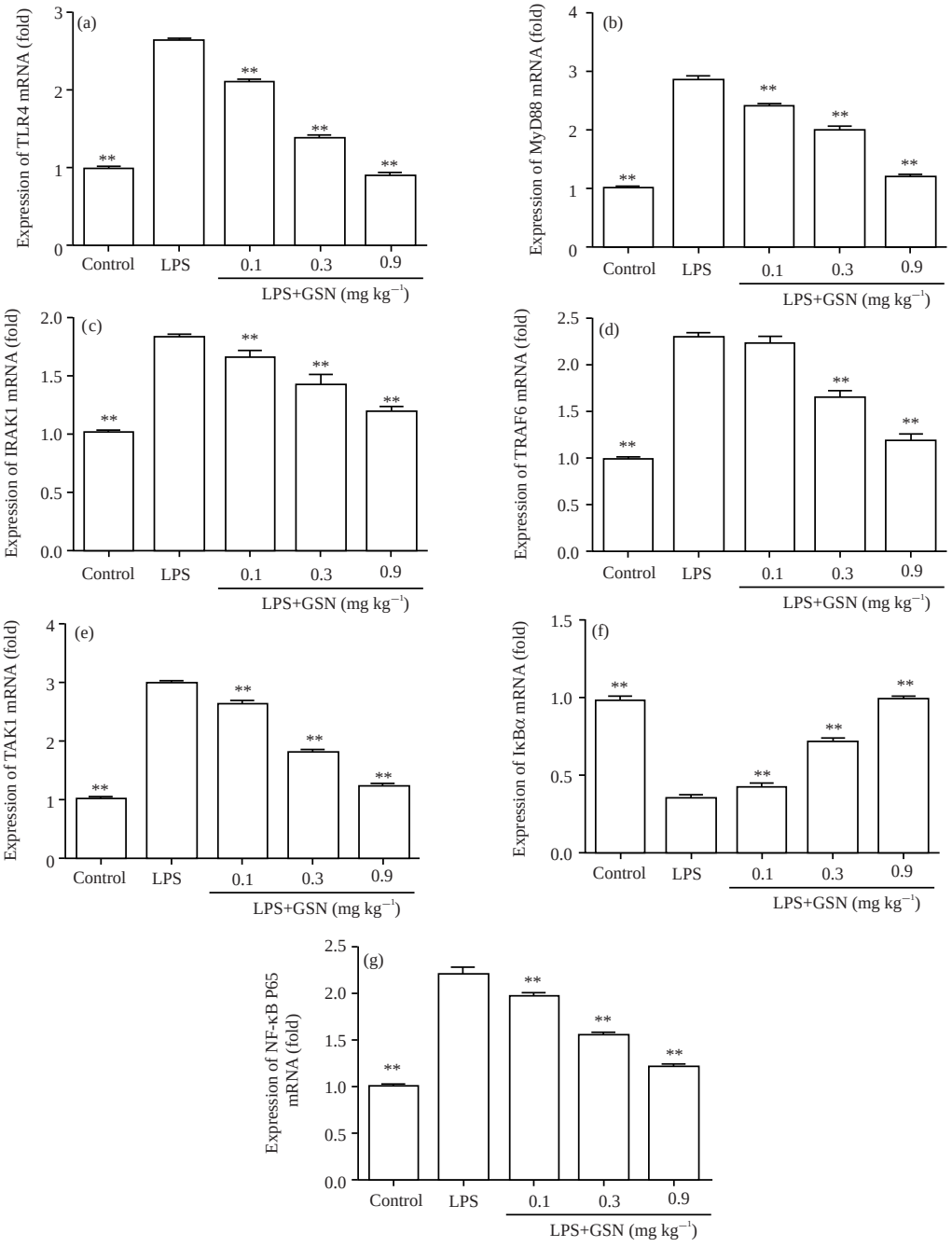

Fig. 6(a-g): Effect of GSN on gene expression of (a) TLR4, (b) MyD88, (c) IRAK1, (d) TRAF6, (e) TAK1, (f) IκBα and (g) NF-κB p65 in lung tissue

**p<0.01 vs. LPS group

Compared with the control group, the expression of IκBα in lung tissue of LPS-induced ALI rats decreased significantly ($p<0.01$) in Fig. 5f, while the intervention of GSN (0.3 and 0.9 mg kg^{-1}) could significantly increase the expression of IκBα ($p<0.01$). NF-κB p65 was not expressed in the control group but it was significantly expressed in each group of LPS induced ALI rats ($p<0.01$) in Fig. 5g.

Effect of GSN on gene expressions of TLR receptor and its downstream signal pathway: The gene expressions of TLR receptor and its downstream signal pathway are shown in Fig. 6. Compared with the control group, LPS could up-regulate the gene expressions of TLR4, MyD88, IRAK1, TRAF6, TAK1 and NF-κB p65 ($p<0.01$) and down-regulate the gene expression of IκBα ($p<0.01$). After the treatment of GSN (0.1,

0.3 and 0.9 mg kg^{-1}), the gene expressions of TLR4, MyD88, IRAK1, TAK1 and NF-κB p65 in lung tissue were significantly down-regulated and there was a dose-response relationship between the down-regulation and drug content($p<0.01$) in Fig. 6(a-c), e and g. When the concentration of GSN was 0.3 and 0.9 mg kg^{-1}, the gene expression of TRAF6 could be down-regulated, which was statistically significant compared with the LPS group ($p<0.01$) Fig. 6d. The gene expression of IκBα was significantly up-regulated after the treatment of GSN ($p<0.01$) in Fig. 6f.

DISCUSSION

Acute Lung Injury (ALI) refers to acute progressive hypoxemia and respiratory distress caused by various pathogenic factors, which is a common type of respiratory failure. It is characterized by diffuse alveolar injury, with alveolar epithelial and capillary endothelial injury, high protein alveolar and interstitial oedema caused by increased permeability of alveolar membrane[1,25]. ALI has always been a difficult and hot spot in clinical critical care medicine. It is of great significance to find new drugs for the treatment of ALI.

Gelsolin (GSN) as an important component of cytoskeleton protein, is a widely existing multifunctional protein. Regulated by calcium ions, it can cut, block actin filaments or make them nucleate[26]. At the same time, it participates in cell movement, apoptosis and phagocytosis and plays an important role in regulating cell morphology and metabolism[27]. When the lung is injured, actin is released and the circulating gelsolin level decreases. The rapid depletion of GSN suggests that this actin scavenging protein may protect the lung injury and delay the occurrence of complications[28,29]. At the same time, GSN may be a marker of ALI development and prognosis and the supplementation of GSN can reduce lung injury.

The pro-inflammatory and anti-inflammatory factors are in balance in the normal body. During ALI, a variety of inflammatory factors are released into the blood, resulting in increased apoptosis and permeability of alveolar epithelial cells and then pulmonary oedema. TNF-α is an important pro-inflammatory factor, which is up-regulated in the development of ALI. TNF-α can induce the accumulation of inflammatory cells, stimulate the production of inflammatory mediators, cause oxidative stress and play multiple roles in diseases[30,31]. IL-6 is an inflammatory factor produced by macrophages and fibroblasts and activated by TNF-α. Its main function is to regulate the proliferation of B lymphocytes and secrete antibodies. At the same time, IL-6 can induce hepatocytes to produce acute reactive protein, which leads to a faster and more severe inflammatory reaction. It is one of the key factors to start the inflammatory reaction. The current study found GSN could reduce the content of inflammatory factors in BALF, serum and lung tissue of LPS-induced ALI rats, to inhibit the inflammatory reaction.

Studies have shown that oxidants in the lung can mediate the occurrence and development of ALI. When excessive tissue damage and inflammation worsen, there are a lot of antioxidants in the lung to maintain the redox state[32]. This study found the contents of MPO and MDA in lung tissue increased significantly, while the content of SOD decreased in LPS-induced ALI rats. After GSN treatment, the contents of MPO and MDA decreased significantly, while the value of SOD increased significantly. These results indicate that GSN can inhibit the production of MPO and MDA, keep SOD at a relatively high level, maintain redox state and inhibit the pathophysiological state of ALI caused by the production of oxidants.

TLR4 receptor plays an important role in the occurrence and development of LPS-induced ALI. After activation of TLR4, it can continue to activate its downstream myeloid differentiation factor (MyD88)/nuclear factor κB (NF-κB). In this way, a large number of inflammatory factors will be released, resulting in lung tissue damage[33]. MyD88 dependent signalling pathway can produce a large number of pro-inflammatory factors. The activation of the process is completed by the activation of the TIR domain and the combination of MyD88. MyD88 recruits downstream signal mediators such as IRAK-1, IRAK-4 and TRAF6 to form receptor complexes. These complexes further activate TAK1 and NF-κB phosphorylation and ultimately activate the transcription of inflammatory cytokines[34]. Studies suggest that the intervention of TLR4/MyD88/NF-κB pathway activation may be a potentially effective target to improve the treatment of LPS-induced ALI[19,35,36]. The results showed that gene and protein expression of TLR4, MyD88, TRAF6, IRAK1, TAK1 and NF-κB p65 in lung tissue of ALI rats were significantly down-regulated after different doses of GSN intervention, suggesting that GSN may improve LPS-induced ALI by inhibiting TLR4/MyD88/NF-κB pathway activation.

CONCLUSION

GSN can reduce lung injury in LPS-induced ALI rats and its mechanism may be related to the regulation of the TLR4/MyD88/NF-κB signalling pathway. The intervention effect of GSN on LPS-induced ALI provides a new idea for the clinical treatment of ALI.

SIGNIFICANCE STATEMENT

This study explored that gelsolin, closely related to apoptosis, coagulation, immunity, tumour and inflammation, attenuated LPS-induced acute lung injury in rats by modulating TLR4/MyD88/NF-κB signalling pathway. The results provide a new idea for the clinical treatment of acute lung injury.

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