Cite as: Rong JLT, Su H, Zhang RF, Zhang HR, Jia TT, Guo SH, Zhao J, Li X, Zhong X. Research progress on the regulation of signal pathways related to lung injury in sepsis by the active components of traditional Chinese medicine [J]. Chin J Clin Res, 2025, 38(8):1145-1149.

DOI: 10.13429/j.cnki.cjcr.2025.08.002

Research progress on the regulation of signal pathways related to lung injury in sepsis by the active components of traditional Chinese medicine

RONG Jilintai*, SU He, ZHANG Ruifen, ZHANG Hairong, JIA Tingting, GUO Sihan, ZHAO Jian, LI Xiao, ZHONG Xin

**Clinical College of Chinese Medicine, Inner Mongolia Medical University, Hohhot, Inner Mongolia 010000, China*

Corresponding author: ZHANG Ruifen, E-mail: 15849112400@163.com

Abstract: Sepsis is a systemic inflammatory response syndrome caused by infection, with resulting organ dysfunction being the key factor in mortality. The lung is one of the organs most frequently affected by sepsis. Recent studies have shown that active components of traditional Chinese medicine *medica* can exert anti-inflammatory, anti-oxidative stress, anti-pyroptosis, and anti-ferroptosis effects by regulating signaling pathways such as Toll-like receptor 4 (TLR4)/nuclear factor κB(NF-κB), mitogen-activated protein kinase (MAPK), NOD-like receptor family pyrin domain containing 3(NLRP3)/caspase-1, phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt), and nuclear factor E2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1), thereby alleviating sepsis-induced lung injury. This article reviews the mechanisms of these signaling pathways in sepsis-induced lung injury and the research progress on traditional Chinese medicine active components in regulating these pathways for the treatment of sepsis-induced lung injury. It is concluded that traditional Chinese medicine has advantages of multi-components, multi-targets, and overall regulation, showing significant therapeutic effects and promising research prospects. In the future, the scope of research on traditional Chinese medicine in regulating disease targets and mechanisms should be expanded to further explore its mechanisms and therapeutic potential, providing theoretical foundations and empirical references for the clinical diagnosis and treatment of critical illnesses.

Keywords: Chinese medicine; Active components of traditional Chinese medicine; Sepsis; Lung injury; Signaling pathways; Multiple organ dysfunction syndrome

Fund program: National Natural Science Foundation of China (82460926, 82460889); Central Leading Local Science and Technology Development Fund Project(2024SZY0962); Clinical Medical Research and New Clinical Technology Promotion Project of Inner Mongolia Autonomous Region Physician Association(YSXH2024KYF022) ; Scientific Research Project of the China Ethnic Medicine Association (2023MY073-46); Scientific Research Joint Fund Project of Public Hospitals in Inner Mongolia Autonomous Region (2023GLLH0119); Scientific Research Plan Project of Inner Mongolia Autonomous Region Traditional Chinese Medicine Hospital (2024Z-A012)

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. It is characterized by a high incidence and mortality rate and is one of the major causes of increased mortality and hospital costs in modern intensive care units (ICUs) [1]. The annual incidence of sepsis ranges from 276 to 678 per 100,000 people, with a total mortality rate of 22.5% to 26.7% [2]. Despite some progress in the diagnosis and treatment of sepsis, its incidence continues to rise year by year. Studies have shown that 40% to 60% of sepsis patients will develop acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) due to damage to alveolar epithelium or pulmonary endothelium, leading to the accumulation of inflammatory edema fluid in the alveolar space [3]. The main manifestations of this include respiratory distress, hypoxemia, and pulmonary edema. This not only exacerbates the systemic inflammatory response but also triggers multiple organ dysfunction syndrome (MODS), creating a vicious cycle and becoming an important cause of death in sepsis patients [4]. Currently, the clinical treatment of sepsis-related lung injury mainly includes infection control, fluid-restrictive resuscitation, lung-protective ventilation, glucocorticoid therapy, enteral nutritional support, and other treatments [5]. However, sepsis-induced lung injury is complex and life-threatening, involving various pathophysiological mechanisms, including inflammation, oxidative stress, cell apoptosis, and ferroptosis, with abnormal activation of multiple signaling pathways [6]. Understanding the mechanisms of sepsis-related lung injury and exploring effective and diverse therapeutic methods are of great significance for clinical diagnosis and

treatment. Chinese medicine, as a distinctive traditional medical system in China, has been widely recognized for its remarkable efficacy in treating critical and life-threatening conditions. This article summarizes recent research on the effective components of Traditional Chinese medicine in treating sepsis-induced lung injury through regulation of relevant signaling pathways (**Table 1** summarizes these mechanisms) and provides a reference for the treatment and research of sepsis-related lung injury and other critical conditions.

1 Toll-like Receptor 4 (TLR4)/Nuclear Factor Kappa B (NF-κB) Signaling Pathway

Sepsis is characterized by uncontrolled inflammatory responses, including a cytokine storm. Inflammatory cells accumulate and infiltrate lung tissue, leading to excessive production of reactive oxygen species (ROS) and free radicals, which activate strong oxidative stress and inflammatory responses, causing lung tissue damage. During sepsis, TLR4 recognizes pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), which activate downstream signaling pathways, resulting in the nuclear translocation of NF-κB and the massive release of inflammatory factors. These inflammatory factors further recruit immune cells, leading to damage of alveolar epithelial cells, increased vascular permeability, and subsequent lung injury [7]. In terms of treatment, inhibiting TLR4 signaling and NF-κB activation can alleviate inflammation and oxidative stress responses [8]. The TLR4/NF-κB signaling pathway plays a crucial role as a key regulator of the innate immune system in the pathological process of septic lung injury.

Xu *et al.* [9] found that baicalin (from *Radix Scutellariae*) can inhibit TLR4/NF-κB pathway activation, promote the transformation of regulatory T cells (Treg)/helper T cells 17 (Th17) balance towards Treg, reduce serum tumor necrosis factor α (TNF-α), interleukins (IL-6, IL-17), malondialdehyde (MDA) levels in lung tissue, and upregulate serum transforming growth factor-β (TGF-β) levels, thus alleviating lung tissue pathological injury in septic mice and repairing lung function. Huang *et al.* [10] found that *Ganoderma lucidum* polysaccharide can improve septic rat lung injury by inhibiting the TLR4/NF-κB signaling pathway, reducing TLR4, phosphorylated p65 (p-p65)/p65 protein expression in lung tissue, and the levels of related inflammatory factors in bronchoalveolar lavage fluid. Sun *et al.* [11] found that polydatin (from *Polygonum cuspidatum*) can alleviate thickening of the alveolar walls, edema, and inflammatory cell infiltration in septic ALI rats, protect lung function, and may be associated with the inhibition of the high mobility group box 1 (HMGB1)/TLR4/NF-κB signaling pathway activation. Kim *et al.* [12] found that procyanidin B2 can reduce the expression of TLR4/NF-κB in septic mice, increase the expression of phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB)/Akt, inhibit the Hippo signaling pathway and Rho GTPases (Rho)/Yes-associated protein (YAP) signaling pathway, significantly reduce the levels of inflammatory cytokines such as IL-1β, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-γ (IFN-γ), and TNF-α in serum, as well as IL-5 and IL-6 in lung tissue, controlling the cytokine storm caused by excessive immune system activation and protecting lung tissue. Zhu *et al.* [13] found that schizandrin B (from *Fructus Schisandrae Chinensis*) can directly bind to MyD88, regulate lipopolysaccharide-induced inflammatory factors in macrophages, inhibit key signaling mediators and pro-inflammatory factors such as transforming growth factor-β-activated kinase 1 (TAK1), mitogen-activated protein kinase (MAPK), and NF-κB. schizandrin B pretreatment of septic lung injury mice can reduce lung inflammatory cell infiltration and improve lung injury.

2 MAPK-Related Signaling Pathways

In sepsis, pathogens or toxins can activate the MAPK signaling pathway through multiple pattern recognition receptors, participating in the onset and development of the disease *via* inflammatory responses, oxidative stress, and apoptosis. c-Jun N-terminal kinase (JNK), p38 MAPK, and extracellular signal-regulated kinase (ERK) are three important branches of this pathway [14]. In septic lung injury, activation of JNK and p38 MAPK can induce excessive expression of pro-inflammatory cytokines such as TNF-α and IL-1β, further exacerbating the inflammatory cascade, leading to the infiltration of inflammatory cells in the lung tissue, and disrupting the barrier function of pulmonary endothelial cells and alveolar epithelial cells. Over-activation of JNK can promote apoptosis of lung cells by phosphorylating downstream pro-apoptotic proteins, resulting in a decrease in the number of parenchymal cells and causing lung dysfunction. Activation of p38 MAPK can enhance reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity, increasing ROS production, which affects the redox balance in the lungs. The oxidative stress response further exacerbates lung tissue damage, leading to pulmonary edema and congestion, which affects the normal structure and function of the lungs. ERK can act bidirectionally in septic lung injury; moderate activation may contribute to cell survival and repair, while excessive activation may indirectly aggravate lung injury through pro-inflammatory responses.

Liu *et al.* [15] found that paeoniflorin (from *Radix Paeoniae Rubra* or *Radix Paeoniae Alba*) combined with luteolin could reduce the production of ROS, NO, TNF-α, IL-6, and IL-1β in RAW264.7 cells stimulated by lipopolysaccharides, decrease the levels of inflammatory factors and oxidative stress, and downregulate the expression of MAPK and NF-κB pathway proteins, thereby alleviating septic ALI. Gao *et al.* [16] reported that crocin (from *Croci stigma*) significantly inhibited the p38MAPK/NF-κB pathway, reducing pro-inflammatory cytokines IL-1β, TNF-α, IL-6, and IL-10 levels, and exerts anti-apoptotic effects through the Bcl-2/ BCL2-associated X (Bax) signaling pathway, protecting liver, kidney, and lung damage, and improving survival in septic mice.

Zhang *et al.* [17] discovered that loganin (from *Strychni semen*) inhibits the ERK/NF-κB pathway in septic lung injury mice, effectively suppressing the release of M1 macrophage-related pro-inflammatory factors and NLRP3 inflammasomes, while promoting the activation of M2 anti-inflammatory cytokines, alleviating lung structural damage and inflammatory cell infiltration, and improving the survival rate of mice. Wang *et al.* [18] found that pseudoephedrine and emodin combined therapy for septic ALI significantly inhibited NF-κB and MAPK phosphorylation, reduced serum levels of inflammatory cytokines IL-1β, TNF-α, IL-6, inducible nitric oxide synthase (iNOS), and increased the levels of anti-inflammatory cytokines IL-10 and Arg-1, promoting M2 polarization and inhibiting M1 polarization through the vasoactive intestinal peptide (VIP)/cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) signaling pathway, improving lung tissue damage.

3 NOD-like Receptor Family Pyrin Domain Containing protein (NLRP)3/Caspase-1 Signaling Pathway

During sepsis, PAMPs and DAMPs activate the NLRP3 inflammasome, recruiting pro-caspase-1 to form a functional complex. Activated caspase-1 cleaves pro-IL-1β and pro-IL-18 into their mature forms, IL-1β and IL-18, which are then released extracellularly, triggering a strong inflammatory response [19]. Meanwhile, caspase-1 cleaves gasdermin D (GSDMD) protein, leading to pyroptosis and further release of inflammatory factors and cellular contents, exacerbating lung tissue damage [20]. Additionally, the NLRP3/caspase-1 pathway promotes neutrophil infiltration, increases vascular permeability, and induces apoptosis of alveolar epithelial cells, worsening pulmonary edema and disruption of the alveolar barrier [21]. ROS, K^+ efflux, and lysosomal rupture are key signals in NLRP3 activation. Inhibiting the NLRP3/caspase-1 pathway may alleviate septic lung injury, providing a potential therapeutic target.

Xie *et al.* [22] found that syringin could alleviate lung tissue pathological damage and structural impairment in septic rats by downregulating the NLRP3/caspase-1 signaling pathway, reducing serum IL-6 and IL-17 levels, inhibiting inflammation and pyroptosis, and mitigating lung injury in septic rats. Sun *et al.* [23] discovered that asperuloside could downregulate the NLRP3/caspase-1/GSDMD pathway activity, reducing serum IL-6, IL-8, and IL-1β levels, as well as the expression of NLRP3, caspase-1, and GSDMD proteins in lung tissue, thereby alleviating inflammatory damage and pyroptosis in lung tissue cells, and improving lung function in rats.

4 PI3K/Akt Signaling Pathway

The PI3K/Akt signaling pathway plays a complex role in septic pulmonary injury, primarily influencing the disease progression by regulating inflammation, apoptosis, oxidative stress, and endothelial barrier function. In the early stages of sepsis, activation of the PI3K/Akt pathway has a protective effect: it reduces the release of pro-inflammatory factors (such as TNF-α and IL-6) by inhibiting NF-κB activation, thereby alleviating the inflammatory response. Meanwhile, Akt inhibits the apoptosis of alveolar epithelial and endothelial cells by phosphorylating pro-apoptotic proteins (such as BAD) and upregulating anti-apoptotic proteins (such as Bcl-2), maintaining lung tissue integrity [24]. In addition, the PI3K/Akt pathway promotes the expression of antioxidant genes like heme oxygenase-1 (HO-1) and superoxide dismutase (SOD) by activating the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, mitigating oxidative stress damage to lung tissue. Regarding endothelial barrier protection, the PI3K/Akt pathway enhances endothelial barrier function by regulating the cytoskeleton and tight junction proteins, reducing pulmonary edema and vascular leakage. However, in the later stages of sepsis or with excessive activation of the PI3K/Akt pathway, it may worsen lung injury by inhibiting autophagy or promoting immune suppression [25]. Therefore, intervention strategies targeting the PI3K/Akt pathway (such as Akt activators or mTOR modulators) could provide new directions for treating septic pulmonary injury.

Qin *et al.* [26] found that andrographolide can promote autophagy in alveolar macrophages through the RAGE/PI3K/Akt/mTOR pathway, inhibit the activation of the NLRP3 inflammasome, release of pro-inflammatory factors, and pyroptosis, playing an anti-inflammatory and lung-protective role. The RAGE pathway may be the direct target for andrographolide in regulating autophagic response. Xie *et al.* [27] explored the protective mechanism of *Wenqingyin* against septic pulmonary injury, and found that *Wenqingyin* regulates the RAGE and PI3K/Akt pathways to reduce the levels of TNF-α, IL-6, and IL-1β in lipopolysaccharide-induced RAW264.7 macrophages, inhibiting pro-inflammatory cytokines and the infiltration of macrophages and neutrophils, alleviating sepsis-induced lung injury. Baicalin, coptisine, and paeoniflorin may be the effective components of *Wenqingyin* that inhibit RAGE.

5 Nrf2/HO-1 Signaling Pathway

When sepsis happened, a large number of inflammatory factors are released, and oxidative stress levels increase, causing lung tissue damage. Under normal conditions, Nrf2 binds with Kelch-like ECH-associated protein 1 (Keap1) and is in an inactive state. However, in a septic environment, oxidative stress products and other stimuli cause Nrf2 to dissociate from Keap1, and the free Nrf2 enters the nucleus, binds to the antioxidant response element (ARE), and initiates the transcription of downstream genes, including HO-1 [28]. HO-1 catalyzes the breakdown of heme to produce CO, biliverdin, and iron ions. CO has anti-inflammatory and vasodilatory effects, while biliverdin and its reduced product bilirubin are potent antioxidants that neutralize free radicals, alleviating

oxidative stress damage to lung tissue [29]. At the same time, HO-1 also regulates inflammatory cytokines, inhibiting excessive activation of inflammation, thereby mitigating lung injury caused by sepsis and playing a significant role in maintaining the normal structure and function of lung tissue.

Tang *et al.* [30] found that ferulic acid could inhibit ferroptosis in alveolar epithelial cells of septic ALI mice by activating the Nrf2/HO-1 pathway, reducing the levels of glutathione peroxidase 4 (GPX4) in lipopolysaccharide-induced MLE-12 cells, and downregulating the expression of tight junction proteins such as ZO-1, occludin, and claudin-1, improving alveolar epithelial dysfunction and alleviating sepsis-induced ALI. Feng *et al.* [31] found that cynaroside could inhibit lipopolysaccharide-induced macrophage polarization to the M1 phenotype and promote anti-inflammatory M2 polarization, upregulating Nrf2 and its downstream HO-1 in damaged organs, reducing IL-1β and TNF-α levels in serum, suggesting that cynaroside can modulate the Nrf2/HO-1 pathway to improve the systemic inflammatory response in septic mice and significantly reduce pathological damage in the heart, lungs, and kidneys of mice. Lai *et al.* [32] found that uridine activates the Nrf2 signaling pathway, upregulating the expression of ferroptosis biomarkers such as solute carrier family 7 member 11 (SLC7A11), GPX4, and HO-1, and inhibiting the expression of the lipid synthesis gene acyl-CoA synthetase long-chain family member 4 (ACSL4), indicating that uridine can inhibit macrophage ferroptosis, reduce inflammation, decrease tissue iron levels and lipid peroxidation, and improve lung injury in septic mice. Bajgai *et al.* [33] found that naringin, a widely found ingredient in Traditional Chinese medicine, can regulate many signaling pathways such as MAPK/Nrf2/HO-1, by downregulating pro-inflammatory M1 macrophage polarization while enhancing anti-inflammatory M2 polarization, counteracting endogenous mediators, reducing the production of inflammatory cytokines, exerting anti-inflammatory, anti-apoptotic, and antioxidant effects, and preventing sepsis-induced lung injury.

6 Conclusion

Sepsis-induced lung injury is a localized manifestation of systemic inflammatory response in the lungs and is one of the most common complications of sepsis. Its pathogenesis is complex, involving inflammation, oxidative stress, cell pyroptosis, autophagy, ferroptosis, and other factors. As the inflammatory response in sepsis spreads, the lungs, as an organ with high blood flow and rich microcirculation, become the main target for attack by inflammatory factors and immune cells. Inflammatory factors directly damage alveolar epithelial cells and vascular endothelial cells, compromising the integrity of the alveolar-capillary barrier, leading to increased vascular permeability. Plasma proteins and fluids infiltrate into the alveolar interstitium and alveolar lumen, forming pulmonary edema and severely affecting gas exchange function. Cell apoptosis, pyroptosis, and ferroptosis play important roles in the terminal stage of lung injury. Apoptosis of alveolar epithelial and endothelial cells leads to alveolar structural damage and barrier function loss, while pyroptosis activates inflammasomes, releasing large amounts of inflammatory factors, aggravating the inflammatory response. Ferroptosis, through lipid peroxidation and iron metabolism disorder, further damages the cell membrane structure and function.

This article summarizes the signaling pathways that play a major regulatory role in septic pulmonary injury based on recent studies and explores the mechanisms through which active ingredients from Traditional Chinese medicine regulate these pathways to treat septic pulmonary injury, aiming to provide reference for the mechanistic study and clinical treatment of septic pulmonary injury. By reviewing various studies, it is evident that among the active ingredients of Traditional Chinese medicine involved in this article, flavonoids, polyphenols, phenylpropanoids, and cyclic ether terpenoids are most common, primarily exerting anti-inflammatory, antioxidant stress, and inhibiting cell pyroptosis and autophagy. The signaling pathways involved in each mechanism are not isolated but are intertwined and interact with each other, forming a complex network of pathways that jointly regulate the disease progression of septic pulmonary injury.

Chinese medicine demonstrates a unique role in regulating septic pulmonary injury-related signaling pathways and therapeutic targets, but its specific molecular mechanisms still need further exploration. For example, how active ingredients from Traditional Chinese medicine interact with target proteins, how they influence the expression and activity of downstream signaling molecules, and how different signaling pathways interact to regulate disease progression. Given the numerous signaling pathways related to septic pulmonary injury, this article does not cover them all comprehensively. Future research could further expand the exploration of Traditional Chinese medicine in regulating these pathways and therapeutic targets, conducting studies on the regulation mechanisms of different types of herbal monomers and their active ingredients on key signaling pathways, systematically constructing a multi-dimensional research system of " Traditional Chinese medicine-target proteins-signaling pathways-biological effects," deeply elucidating the molecular mechanisms of Traditional Chinese medicine in regulating septic pulmonary injury, and identifying significantly effective herbal ingredients. Additionally, the optimization of Chinese medicine prescriptions and the in-depth exploration of the multi-component, multi-target, and multi-pathway characteristics of Chinese medicine formulas in the treatment of septic pulmonary injury should be carried out to tap into their therapeutic potential and advantages, providing new drug options and treatment strategies for clinical treatment of septic pulmonary injury.

Conflict of Interest None

Tab.1 Summary of the mechanism of active components of Traditional Chinese medicine regulating signal pathways related to sepsis-induced lung injury

Classification	Effective components of Traditional Chinese medicine	Signal pathway	Mechanism of action	References
Flavonoids	baicalin	TLR4/NF-κB, PI3K/Akt	Promote the transformation from Treg/Th17 balance towards Treg, reduce TNF-α, IL-6, IL-17, and MDA, and upregulate TGF-β	[9,27]
	naringin	MAPK/Nrf2/HO-1	Downregulate the pro-inflammatory M1 polarization of macrophages while enhancing the anti-inflammatory M2 polarization	[33]
	luteolin	MAPK, NF-κB	Reduce the levels of reactive oxygen species, nitric oxide, TNF-α, IL-6, and IL-1β	[15]
Polyphenols	polydatin	HMGB1/TLR4/NF-κB	Downregulation of HMGB1, TLR4, and NF-κB p65 mRNA and protein expression	[11]
	rocyanidin B2	TLR4/NF-κB, PI3K/Akt, Hippo, Rho/YAP	Reduce the levels of inflammatory cytokines, including serum IL-1β, GM-CSF, IFN-γ, and TNF-α	[12]
Phenylpropanoids	syringin	NLRP3/caspase-1	Reduce serum levels of IL-6, IL-8, and IL1β to inhibit cell pyroptosis	[22]
	ferulic acid	Nrf2/HO-1	Reduce the level of GPX4 in MLE-12 cells induced by lipopolysaccharide, and downregulate the expression of tight junction proteins ZO-1, occludin, and claudin-1	[30]
Iridoid Glycosides	loganin	ERK-NF-κB	Inhibit the release of M1 macrophage-related pro-inflammatory factors and NLRP3 inflammasome, and induce the activation of M2 anti-inflammatory cytokines	[17]
	asperuloside	NLRP3/caspase-1/GSDMD	Reduce serum levels of IL-6, IL-8, and IL1β	[23]
Monoterpenoid Glycosides	paeoniflorin	MAPK, NF-κB, PI3K/Akt	Reduce the levels of reactive oxygen species, nitric oxide, TNF-α, IL-6, and IL-1β	[15,27]
Diterpenoids	andrographolide	RAGE/PI3K/Akt/mTOR	Inhibit the activation of NLRP3 inflammasome, the release of pro-inflammatory factors, and pyroptosis, and promote autophagy of alveolar macrophages	[26]
Polysaccharides	*Ganoderma lucidum* polysaccharide	TLR4/NF-κB	Reduce the expression of TLR4 and p-p65/p65 proteins in lung tissue of septic rats	[10]
Lignans	schizandrin B	TLR4/NF-κB	Directly binds to MyD88, inhibiting TAK1, MAPKs, and NF-κB	[13]
Carotenoids	crocin	p38MAPK/NF-κB, Bcl-2/Bax	Reduce the levels of pro-inflammatory cytokines IL-1β, TNF-α, IL-6, and IL-10	[16]
Alkaloids	pseudoephedrine	MAPK, NF-κB, VIP/cAMP/PKA	Promote M2 polarization, inhibit M1 polarization, and reduce the levels of IL-1β, TNF-α, IL-6, and iNOS in serum	[18]
Anthraquinones	emodin	MAPK, NF-κB, VIP/cAMP/PKA	Promote M2 polarization, inhibit M1 polarization, and reduce the levels of IL-1β, TNF-α, IL-6, and iNOS in serum	[18]
Cyanogenides	cynaroside	Nrf2/HO-1	Inhibit macrophage polarization towards the M1 phenotype, promote anti-inflammatory M2 polarization, and reduce the levels of IL-1β and TNF-α in serum	[31]
Nucleosides	uridine	Nrf2/HO-1	Upregulate the expression of SLC7A11, GPX4, and HO-1, and inhibit the expression of ACSL4	[32]

References

[1] Liu D, Huang SY, Sun JH, et al. Sepsis-induced immunosuppression: mechanisms, diagnosis and current treatment options[J]. Mil Med Res, 2022, 9(1): 56.

[2] Fleischmann-Struzek C, Rudd K. Challenges of assessing the burden of sepsis[J]. Med Klin Intensivmed Notfmed, 2023, 118(Suppl 2): 68-74.

[3] Zampieri FG, Bagshaw SM, Semler MW. Fluid therapy for critically ill adults with sepsis: a review[J]. JAMA, 2023, 329(22): 1967-1980.

[4] Sinha P, Meyer NJ, Calfee CS. Biological phenotyping in sepsis and acute respiratory distress syndrome[J]. Annu Rev Med, 2023, 74: 457-471.

[5] Bos LDJ, Ware LB. Acute respiratory distress syndrome: causes, pathophysiology, and phenotypes[J]. Lancet, 2022, 400(10358): 1145-1156.

[6] Zhang YY, Ning BT. Signaling pathways and intervention therapies in sepsis[J]. Sig Transduct Target Ther, 2021, 6: 407.

[7] Fitzgerald KA, Kagan JC. Toll-like receptors and the control of immunity[J]. Cell, 2020, 180(6): 1044-1066.

[8] Wang YB, Zhang ST, Li HY, et al. Small-molecule modulators of toll-like receptors[J]. Acc Chem Res, 2020, 53(5): 1046-1055.

[9] Xu LW, Wang HB, Wang Q, et al. Effects of Baicalin on TLR4/NF-κB pathway and Treg/Th17 balance in mice with sepsis-induced acute lung injury [J]. Chin J Immunol, 2022, 38(15): 1813-1818, 1823.**[In Chinese]**

[10] Huang H, Li FZ, Li Y, et al. Effect of *Ganoderma lucidum* polysaccharides on lung function and TLR4/NF-κB pathway in sepsis rats with acute lung injury [J]. Chinese Traditional and Herbal Drugs, 2021, 52(8): 2351-2356. **[In Chinese]**

[11] Sun P, Chen M Zhang XL, et al. The Protective Effect of Polydatin on Sepsis-induced Acute Lung Injury in Rats by Regulating HMGB1/TLR4/NF-κB Signaling Pathway [J]. Journal of Zhejiang Chinese Medical University, 2021, 45(7): 691-699. **[In Chinese]**

[12] Kim GO, Park DH, Bae JS. Procyanidin B2 attenuates sepsis-induced acute lung injury via regulating hippo/rho/PI3K/NF-κB signaling pathway[J]. Int J Mol Sci, 2023, 24(9): 7930.

[13] Zhu WW, Luo W, Han JB, et al. Schisandrin B protects against LPS-induced inflammatory lung injury by targeting MyD88[J]. Phytomedicine, 2023, 108: 154489.

[14] Park HB, Baek KH. E3 ligases and deubiquitinating enzymes regulating the MAPK signaling pathway in cancers[J]. Biochim Biophys Acta Rev Cancer, 2022, 1877(3): 188736.

[15] Liu Z, Gao JL, Ban YX, et al. Synergistic effect of paeoniflorin combined with luteolin in alleviating Lipopolysaccharides-induced acute lung injury[J]. J Ethnopharmacol, 2024, 327: 118022.

[16] Gao J, Zhao F, Yi SN, et al. Protective role of crocin against sepsis-induced injury in the liver, kidney and lungs via inhibition of p38 MAPK/NF-κB and Bax/Bcl-2 signalling pathways[J]. Pharm Biol, 2022, 60(1): 543-552.

[17] Zhang J, Wang CS, Wang HL, et al. Loganin alleviates sepsis-induced

acute lung injury by regulating macrophage polarization and inhibiting NLRP3 inflammasome activation[J]. Int Immunopharmacol, 2021, 95: 107529.
[18] Wang WB, Li JT, Hui Y, et al. Combination of pseudoephedrine and emodin ameliorates LPS-induced acute lung injury by regulating macrophage M1/M2 polarization through the VIP/cAMP/PKA pathway[J]. Chin Med, 2022, 17(1): 19.
[19] Coudereau R, Monneret G, Lukaszewicz AC, et al. Altered ex vivo NLRP3 inflammasome activation is associated with 28-day mortality in septic patients[J]. Viruses, 2023, 15(12): 2419.
[20] Du WJ, Ren N, Xu Y, et al. Programmed cell death 4 governs NLRP3-mediated pyroptosis in septic lung disorders[J]. Mol Biol Rep, 2024, 51(1): 77.
[21] Gleeson TA, Kaiser C, Lawrence CB, et al. The NLRP3 inflammasome is essential for IL-18 production in a murine model of macrophage activation syndrome[J]. Dis Model Mech, 2024, 17(7): dmm050762.
[22] Xie XF, Zhao ZQ, Fu MC. Effect of Syringin on cell pyroptosis in septic-induced lung injury rats by regulating NLRP3/Caspase-1 signal pathway [J]. Chinese Pharmaceutical Journal, 2023, 58(19): 1744-1751. **[In Chinese]**
[23] Sun LY, Liu ZR, Su YS, et al. Effect of asperuloside on pyroptosis of lung tissue in septic rats by regulating NLRP3/Caspase-1/GSDMD signaling pathway [J]. Tianjin Medical Journal, 2023, 51(6): 607-613. **[In Chinese]**
[24] Guo W, Hu ZS. SRPK1 promotes sepsis-induced acute lung injury via regulating PI3K/AKT/FOXO3 signaling[J]. Immunopharmacol Immunotoxicol, 2023, 45(2): 203-212.
[25] Wang X, Lin F, Guo L. TILRR aggravates sepsis-induced acute lung injury by suppressing the PI3K/Akt pathway[J]. Evid Based Complement Alternat Med, 2022, 2022: 7341504.
[26] Qin YP, Li WJ, Liu JL, et al. Andrographolide ameliorates sepsis-induced acute lung injury by promoting autophagy in alveolar macrophages via the RAGE/PI3K/AKT/mTOR pathway[J]. Int Immunopharmacol, 2024, 139: 112719.
[27] Xie LP, Zhang GY, Wu YT, et al. Protective effects of Wenqingyin on sepsis-induced acute lung injury through regulation of the receptor for advanced glycation end products pathway[J]. Phytomedicine, 2024, 129: 155654.
[28] He F, Ru XL, Wen T. NRF2, a transcription factor for stress response and beyond[J]. Int J Mol Sci, 2020, 21(13): 4777.
[29] Gunne S, Heinicke U, Parnham MJ, et al. Nrf2—a molecular target for sepsis patients in critical care[J]. Biomolecules, 2020, 10(12): 1688.
[30] Tang XM, Liu JQ, Yao S, et al. Ferulic acid alleviates alveolar epithelial barrier dysfunction in sepsis-induced acute lung injury by activating the Nrf2/HO-1 pathway and inhibiting ferroptosis[J]. Pharm Biol, 2022, 60(1): 2286-2294.
[31] Feng JF, Liu ZJ, Chen H, et al. Protective effect of cynaroside on sepsis-induced multiple organ injury through Nrf2/HO-1-dependent macrophage polarization[J]. Eur J Pharmacol, 2021, 911: 174522.
[32] Lai K, Song CK, Gao ML, et al. Uridine alleviates sepsis-induced acute lung injury by inhibiting ferroptosis of macrophage[J]. Int J Mol Sci, 2023, 24(6): 5093.
[33] Bajgai B, Suri M, Singh H, et al. Naringin: a flavanone with a multifaceted target against sepsis-associated organ injuries[J]. Phytomedicine, 2024, 130: 155707.

Submission received: 2025-04-28

·研究进展·

中药有效成分调控脓毒症肺损伤相关信号通路的研究进展

荣吉林太[1]， 苏和[2]， 张瑞芬[1]， 张海荣[2]， 贾婷婷[2]， 郭思含[1]， 赵建[2]， 李晓[2]， 钟鑫[2]

1. 内蒙古医科大学中医临床医学院，内蒙古 呼和浩特 010000；

2. 内蒙古自治区中医医院，内蒙古 呼和浩特 010000

摘要： 脓毒症是一种由感染引起的全身反应综合征，其导致的器官功能障碍是致命的关键，肺脏是脓毒症最易累及的器官。近年来研究表明，中药有效成分可通过调控Toll样受体4（TLR4）/核因子κB（NF-κB）、丝裂原活化蛋白激酶（MAPK）、NOD样受体家族含pyrin结构域蛋白3（NLRP3）/caspase-1、磷脂酰肌醇3-激酶（PI3K）/蛋白激酶B（Akt）、核因子E2相关因子2（Nf2）/血红素加氧酶-1（HO-1）等信号通路，发挥抗炎、抗氧化应激、抑制细胞焦亡和自噬、抑制铁死亡的作用，减轻脓毒症肺损伤。本文就以上信号通路在脓毒症肺损伤中的作用机制以及中药有效成分调控信号通路治疗脓毒症肺损伤的研究进展进行综述，认为中医药治疗脓毒症肺损伤具有多成分、多靶点、整体调节的优势，治疗效果显著，研究前景广阔。未来可扩大中医药调控疾病靶点和机制研究范围，深入探讨其作用机制和治疗潜力，为急危重症的临床诊疗提供理论依据和经验参考。

关键词： 中医药；中药有效成分；脓毒症；肺损伤；信号通路；多器官功能障碍综合征

中图分类号： R563 R631 **文献标识码：** A **文章编号：** 1674-8182(2025)08-1145-05

Research progress on the regulation of signal pathways related to lung injury in sepsis by the active components of traditional Chinese medicine

RONG Jilintai*, SU He, ZHANG Ruifen, ZHANG Hairong, JIA Tingting, GUO Sihan, ZHAO Jian, LI Xiao, ZHONG Xin

Clinical College of Chinese Medicine, Inner Mongolia Medical University, Hohhot, Inner Mongolia 010000, China

Corresponding author: ZHANG Ruifen, E-mail: 15849112400@163.com

Abstract: Sepsis is a systemic inflammatory response syndrome caused by infection, with resulting organ dysfunction being the key factor in mortality. The lung is one of the organs most frequently affected by sepsis. Recent studies have shown that active components of traditional Chinese medicine (TCM) can exert anti-inflammatory, anti-oxidative stress, anti-pyroptosis, and anti-ferroptosis effects by regulating signaling pathways such as Toll-like receptor 4 (TLR4)/nuclear factor κB (NF-κB), mitogen-activated protein kinase (MAPK), NOD-like receptor family pyrin domain containing 3 (NLRP3)/caspase-1, phosphatidylinositol 3-kinase/protein kinase B, and nuclear factor E2-related factor 2/heme oxygenase-1, thereby alleviating sepsis-induced lung injury. This article reviews the mechanisms of these signaling pathways in sepsis-induced lung injury and the research progress on TCM active components in regulating these pathways for the treatment of sepsis-induced lung injury. It is concluded that TCM has advantages of multi-components, multi-targets, and overall regulation, showing significant therapeutic effects and promising research prospects. In the future, the scope of research on TCM in regulating disease targets and mechanisms should be expanded to further explore its mechanisms and therapeutic potential, providing theoretical foundations and empirical references for the clinical diagnosis and treatment of critical illnesses.

Keywords: Traditional Chinese medicine; Active components of traditional Chinese medicine; Sepsis; Lung injury; Signaling pathways; Multiple organ dysfunction syndrome

DOI:10.13429/j.cnki.cjcr.2025.08.002

基金项目： 国家自然科学基金项目(82460926, 82460889)；中央引导地方科技发展资金项目(2024SZY0962)；中国民族医药学会科研项目(2023MY073-46)；内蒙古自治区公立医院科研联合基金科技项目(2023GLLH0119)；内蒙古自治区医师协会临床医学研究和临床新技术推广项目(YSXH2024KYF022)；内蒙古自治区中医医院科研计划项目(2024Z-A012)

通信作者： 张瑞芬，E-mail：15849112400@163.com

出版日期： 2025-08-20

QR code for English version

Fund program: National Natural Science Foundation of China (82460926, 82460889); Central Leading Local Science and Technology Development Fund Project (2024SZY0962); China Association of Ethnic Medicine Scientific Research Project (2023MY073-46); Inner Mongolia Autonomous Region Public Hospital Scientific Research Joint Fund Science and Technology Project (2023GLLH0119); Clinical Medical Research and New Clinical Technology Promotion Project of Inner Mongolia Autonomous Region Physician Association (YSXH2024KYF022); Inner Mongolia Autonomous Region Chinese Medicine Hospital Scientific Research Project (2024Z-A012)

脓毒症被定义为由机体对感染的反应失调引起的危及生命的器官功能障碍性疾病,具有高发病率和高死亡率的特点,是现代重症监护病房患者死亡和住院成本增加的重要原因之一[1]。脓毒症的年发病率为(276~678)/10万人,总死亡率为22.5%~26.7%[2]。尽管脓毒症的诊疗方面取得了一定进展,但其发病率仍呈逐年上升趋势。研究表明,40%~60%的脓毒症患者会因肺泡上皮或肺内皮损伤导致肺泡腔中的炎性水肿液体积聚,进而出现急性肺损伤(acute lung injury,ALI)或急性呼吸窘迫综合征(acute respiratory distress syndrome,ARDS)[3],主要表现为呼吸困难、低氧血症、肺水肿等,不仅会加重全身炎性反应,还会引发多器官功能障碍综合征(multiple organ dysfunction syndrome,MODS),形成恶性循环,成为脓毒症患者死亡的重要诱因[4]。目前,临床上对于脓毒症肺损伤的治疗主要包括控制感染、液体限制性复苏、肺保护性通气、糖皮质激素等药物治疗、肠内营养支持等[5]。但脓毒症肺损伤病情复杂、病势危重,涉及包括炎症反应、氧化应激、细胞凋亡、铁死亡在内的多种发病机制,涵盖多种信号通路的异常激活[6],阐明脓毒症肺损伤的机制并探寻有效且多样化的治疗方法对临床诊疗具有积极的意义。中医药作为我国独具特色的传统医学体系,在治疗急危重症方面的显著疗效已经被广泛认可。本文结合近年来的文献,对中药有效成分通过调控相关信号通路治疗脓毒症肺损伤(表1为其机制的总结)的研究进展进行概述,为脓毒症肺损伤和相关急危重症的治疗和研究提供参考。

1 Toll样受体4(TLR4)/核因子κB(NF-κB)信号通路

脓毒症时,炎性反应失控的特征是细胞因子风暴,肺组织内聚集并浸润大量的炎症细胞,活性氧、自由基过量产生,激活强烈的氧化应激和炎症反应,造成肺组织损伤。脓毒症时,TLR4通过识别病原体相关分子模式(pathogen-associated molecular patterns,PAMPs)和损伤相关分子模式(damage associated molecular patterns, DAMPs),激活下游信号传导,导致NF-κB的核转位和炎症因子的大量释放。这些炎症因子进一步募集免疫细胞,导致肺泡上皮细胞损伤,血管通透性增加,发生肺损伤[7]。在治疗方面,抑制TLR4信号传导和NF-κB的活化,可以减轻炎症和氧化应激反应[8]。TLR4/NF-κB信号通路作为先天免疫系统的关键调控者,在脓毒症肺损伤的病理过程中发挥着至关重要的作用。

徐玲文等[9]发现黄芩苷可以抑制TLR4/NF-κB通路激活,促使调节性T细胞(Treg)/辅助性T细胞17(Th17)平衡向Treg转化,降低血清肿瘤坏死因子α(tumor necrosis factor α,TNF-α)、白细胞介素(interleukin,IL-6、IL-17)、肺组织丙二醛(malondialdehyde,MDA)水平,上调血清转化生长因子β(transforming growth factor-β,TGF-β)水平,减轻脓毒症小鼠肺组织病理损伤,修复肺功能。黄晗等[10]发现灵芝多糖通过抑制TLR4/NF-κB信号通路,降低脓毒症大鼠肺组织中TLR4、磷酸化p65(phosphorylated p65,p-p65)/p65蛋白表达和肺泡灌洗液中相关炎性因子水平,改善脓毒症大鼠肺损伤。孙鹏等[11]发现虎杖苷能够减轻脓毒症ALI大鼠肺泡壁增厚、水肿及炎性细胞浸润,保护肺功能,可能与抑制高迁移率族蛋白B1(high mobility group box 1,HMGB1)/TLR4/NF-κB信号通路的活化相关。Kim等[12]发现,原花青素B2可以降低脓毒症小鼠TLR4/NF-κB的表达、增加磷脂酰肌醇3-激酶(phosphoinositide 3-kinase,PI3K)/蛋白激酶B(protein kinase B,PKB/Akt)的表达、抑制Hippo信号通路和Rho GTPases(Rho)/Yes-associated protein(YAP)信号通路,显著降低血清中IL-1β、粒细胞-巨噬细胞集落刺激因子(granulocyte-macrophage colony-stimulating factor,GM-CSF)、γ干扰素(IFN-γ)和TNF-α等炎性细胞因子水平,以及肺组织中IL-5、IL-6的水平,控制免疫系统过度激活导致的细胞因子风暴,保护肺组织。Zhu等[13]研究发现,五味子素B可通过直接结合MyD88,调节巨噬细胞中脂多糖诱导的炎症因子,抑制转化生长因子β激活激酶1(TAK1)、丝裂原活化蛋白激酶(MAPK)和NF-κB等关键信号介质和促炎因子,应用五味子素B预处理脓毒症肺损伤小鼠,可以减少肺部炎性细胞浸润,改善肺损伤情况。

2 MAPK相关信号通路

脓毒症时,病原微生物或毒素可通过多种模式识别受体激活MAPK信号通路,通过炎症反应、氧化应激和细胞凋亡参与疾病的发生和发展。c-Jun末端激酶(c-Jun N-terminal kinase, JNK)、p38 MAPK、细胞外信号调节激酶(extracellular signal-regulated kinase,ERK)是该通路中的三条重要分支[14]。在脓毒症肺损伤中,JNK和p38 MAPK的激活可诱导一系列促炎细胞因子如TNF-α、IL-1β的过度表达,进一步加剧炎症级联反应,导致肺组织内大量炎性细胞浸润,破坏肺血管内皮细胞和肺泡上皮细胞的屏障功能。过度激活的JNK可通过磷酸化下游促凋亡蛋白,促进肺细胞的凋亡进程,导致肺实质细胞数量减少,造成肺功能障碍。p38 MAPK的激活可增强烟酰胺腺嘌呤二核苷酸磷酸氧化酶(NADPH)活性,促使活性氧生成增加,影响肺内氧化还原平衡,氧化应激反应会进一步加重肺组织损伤,引发肺水肿和肺充血,影响肺的正常结构和功能。ERK可以双向作用于脓毒症肺损伤,其适度激活可能参与细

胞存活和修复，过度激活也会通过促炎反应间接加重肺损伤。

Liu等[15]研究发现，芍药苷联合木犀草素可降低脂多糖刺激RAW264.7细胞产生的的活性氧、一氧化氮、TNF-α、IL-6和IL-1β，降低炎症因子和氧化应激水平，下调MAPK和NF-κB信号通路蛋白的表达，减轻脓毒症ALI。Gao等[16]研究发现，藏红花素可显著抑制p38MAPK/NF-κB信号通路，降低促炎细胞因子IL-1β、TNF-α、IL-6和IL-10水平，并通过B细胞淋巴瘤/白血病-2(B-cell lymphoma 2，Bcl-2)/Bcl-2-相关x蛋白(Bax)信号通路发挥抗凋亡活性，保护肝、肾和肺损伤，提高脓毒症小鼠存活率。Zhang等[17]研究发现，马钱苷通过阻断脓毒症肺损伤小鼠ERK/NF-κB通路，有效抑制M1巨噬细胞相关促炎因子和NLRP3炎性小体的释放，并诱导M2型抗炎细胞因子的激活，减轻肺结构损伤和炎性细胞浸润，提高小鼠存活率。Wang等[18]研究发现，伪麻黄碱和大黄素联合治疗脓毒症ALI，可以显著抑制NF-κB、MAPK磷酸化，降低大鼠血清中炎性细胞因子IL-1β、TNF-α、IL-6、诱导型一氧化氮合酶(inducible nitric oxide synthase，iNOS)的含量，增加抗炎细胞因子IL-10、Arg-1的含量，通过血管活性肠肽(vasoactive intestinal peptide，VIP)/环磷酸腺苷(cyclic adenosine monophosphate，cAMP)/蛋白激酶A(protein kinase a，PKA)信号通路促进M2极化，抑制M1极化，改善肺组织结构损伤。

3 NOD样受体家族含pyrin结构域蛋白3(NLRP3)/半胱天冬酶-1(caspase-1)信号通路

脓毒症时，PAMPs和DAMPs激活NLRP3炎症小体，招募pro-caspase-1，形成功能性复合体。活化的caspase-1将pro-IL-1β和pro-IL-18切割为成熟的IL-1β和IL-18，释放到细胞外，引发强烈的炎症反应[19]。同时，caspase-1切割gasdermin D(GSDMD)蛋白，导致细胞焦亡，进一步释放炎症因子和细胞内容物，加重肺组织损伤[20]。此外，NLRP3/caspase-1通路通过促进中性粒细胞浸润、增加血管通透性和诱导肺泡上皮细胞凋亡，加剧肺水肿和肺泡屏障破坏[21]。活性氧、K^+外流和溶酶体破裂是NLRP3激活的关键信号。抑制NLRP3/caspase-1通路可减轻脓毒症肺损伤，为治疗提供了潜在靶点。

谢小芳等[22]研究发现，丁香苷通过下调NLRP3/caspase-1信号通路，减轻脓毒症大鼠的肺组织病理损伤和肺结构受损，降低血清IL-6、IL-17水平，抑制炎症和细胞焦亡，减轻脓毒症大鼠肺组织损伤。孙立燕等[23]研究发现，车叶草苷能通过下调NLRP3/caspase-1/GSDMD通路活性，降低血清IL-6、IL-8和IL-1β水平，降低肺组织NLRP3、caspase-1和GSDMD蛋白表达，减轻肺组织炎性损伤和肺组织细胞焦亡，改善大鼠肺功能。

4 PI3K/Akt信号通路

PI3K/Akt信号通路在脓毒症肺损伤中发挥复杂作用，主要通过调控炎症、细胞凋亡、氧化应激和内皮屏障功能影响疾病进程。在脓毒症早期，PI3K/Akt通路的激活具有保护作用：它通过抑制NF-κB的活化，减少促炎因子(如TNF-α、IL-6)的释放，从而减轻炎症反应；同时，Akt通过磷酸化促凋亡蛋白(如BAD)和上调抗凋亡蛋白(如Bcl-2)，抑制肺泡上皮细胞和内皮细胞的凋亡，维持肺组织完整性[24]。此外，PI3K/Akt通路通过激活核因子E2相关因子2(Nrf2)通路，促进抗氧化基因如血红素加氧酶-1(HO-1)、SOD的表达，减轻氧化应激对肺组织的损伤。在内皮屏障保护方面，PI3K/Akt通路通过调控细胞骨架和紧密连接蛋白，增强内皮屏障功能，减少肺水肿和血管渗漏。然而，在脓毒症晚期或PI3K/Akt通路过度激活时，可能通过抑制自噬或促进免疫抑制加重肺损伤[25]。因此，靶向PI3K/Akt通路的干预策略(如Akt激活剂或mTOR调节剂)可为脓毒症肺损伤的治疗提供新的方向。

Qin等[26]研究发现，穿心莲内酯可通过RAGE/PI3K/Akt/mTOR途径促进肺泡巨噬细胞自噬，抑制NLRP3炎性小体的激活和促炎因子的释放和焦亡，发挥抗炎和肺保护作用，RAGE通路可能是穿心莲内酯调节自噬反应的直接靶点。Xie等[27]探究温清饮对脓毒症肺损伤的保护机制，发现温清饮可以通过调节RAGE和PI3K/Akt通路，降低脂多糖诱导的RAW264.7巨噬细胞中的TNF-α、IL-6和IL-1β水平，抑制促炎细胞因子和巨噬细胞、中性粒细胞的浸润，减轻脓毒症诱导的肺损伤，其中黄芩苷、黄檀、芍药苷可能是温清饮抑制RAGE通路的有效成分。

5 Nrf2/HO-1信号通路

脓毒症发生时，大量炎症因子释放，氧化应激水平增加，导致肺组织受损。正常情况下，Nrf2与Kelch样环氧氯丙烷相关蛋白1(Keap1)结合，处于失活状态。但在脓毒症环境中，氧化应激产物等刺激使Nrf2与Keap1解离，游离的Nrf2进入细胞核，与抗氧化反应元件(ARE)结合，启动下游基因转录，其中就包括HO-1[28]。HO-1可催化血红素分解，产生一氧化碳、胆绿素和铁离子。一氧化碳具有抗炎、舒张血管作用；胆绿素及其还原产物胆红素是强效抗氧化剂，能中和自由基，减轻氧化应激对肺组织的损伤[29]。同时，HO-1还能通过调节炎症细胞因子，抑制炎症反应过度激活，从而缓解脓毒症引发的肺损伤，对维持肺组织正常结构和功能意义重大。

Tang等[30]研究发现，阿魏酸可通过激活Nrf2/HO-1通路抑制脓毒症ALI小鼠肺泡上皮细胞的铁死亡，降低脂多糖诱导的MLE-12细胞中谷胱甘肽过氧化物酶4(GPX4)的水平，并下调胞质紧密黏连蛋白-1(ZO-1)、occludin和claudin-1紧密连接蛋白的表达，改善肺泡上皮功能障碍，缓解脓毒症诱导的ALI。Feng等[31]研究发现，氯那苷可以抑制脂多糖诱导的巨噬细胞极化为M1表型，并促进抗炎M2极化，上调损伤器官中Nrf2及其下游的HO-1，减轻血清中IL-1β和TNF-α水平，表明氯那苷可通过调控Nrf2/HO-1通路，改善脓毒症小鼠的系统性炎症反应，明显减轻小鼠心、肺、肾脏的病理损害。Lai等[32]研究发现，尿苷通过激活Nrf2信号通路，上调溶质载体家族7成员11(solute carrier family 7 member 11，SLC7A11)、GPX4和HO-1铁死亡生物标志物的表达，抑制脂质合成基因酰基辅酶A合成酶长链家族成员4(acyl-coa synthetase long-chain family member 4，ACSL4)的表达，表明尿苷可抑制巨噬细胞铁死亡，

表 1　中药有效成分调控脓毒症肺损伤相关信号通路机制总结

Tab.1　Summary of the mechanism of active components of traditional Chinese medicine regulating signal pathways related to sepsis-induced lung injury

分类	中药有效成分	信号通路	作用机制	参考文献
黄酮类	黄芩苷	TLR4/NF-κB、PI3K/Akt	促使Treg/Th17平衡向Treg转化，降低TNF-α、IL-6、IL-17、MDA，上调TGF-β	［9，27］
	柚皮苷	MAPK/Nrf2/HO-1	下调巨噬细胞促炎M1型相极化的同时提高抗炎M2型相极化	［33］
	木犀草素	MAPK、NF-κB	降低活性氧、一氧化氮、TNF-α、IL-6、IL-1β水平	［15］
多酚类	虎杖苷	HMGB1/TLR4/NF-κB	下调HMGB1、TLR4和NF-κB p65 m RNA和蛋白表达	［11］
	原花青素B2	TLR4/NF-κB、PI3K/Akt、Hippo、Rho/YAP	降低血清IL-1β、GM-CSF、IFN-γ、TNF-α炎性细胞因子水平	［12］
苯丙素类	丁香苷	NLRP3/caspase-1	降低血清IL-6、IL-8、IL1β水平，抑制细胞焦亡	［22］
	阿魏酸	Nrf2/HO-1	降低脂多糖诱导的MLE-12细胞中GPX4的水平，下调ZO-1、occludin、claudin-1紧密连接蛋白的表达	［30］
环烯醚萜苷类	马钱苷	ERK-NF-κB	抑制M1巨噬细胞相关促炎因子和NLRP3炎性小体的释放，诱导M2型抗炎细胞因子的激活	［17］
	车叶草苷	NLRP3/caspase-1/GSDMD	降低血清IL-6、IL-8、IL1β水平	［23］
单萜苷类	芍药苷	MAPK、NF-κB、PI3K/Akt	降低活性氧、一氧化氮、TNF-α、IL-6、IL-1β水平	［15，27］
二萜类	穿心莲内酯	RAGE/PI3K/Akt/mTOR	抑制NLRP3炎性小体的激活和促炎因子的释放和焦亡，促进肺泡巨噬细胞自噬	［26］
多糖类	灵芝多糖	TLR4/NF-κB	降低脓毒症大鼠肺组织中TLR4、p-p65/p65蛋白表达	［10］
木脂素类	五味子素B	TLR4/NF-κB	直接结合MyD88，抑制TAK1、MAPKs、NF-κB	［13］
类胡萝卜素类	藏红花素	p38MAPK/NF-κB、Bcl-2/Bax	降低促炎细胞因子IL-1β、TNF-α、IL-6、IL-10水平	［16］
生物碱类	伪麻黄碱	MAPK、NF-κB、VIP/cAMP/PKA	促进M2极化，抑制M1极化，降低血清中IL-1β、TNF-α、IL-6、iNOS水平	［18］
蒽醌类	大黄素	MAPK、NF-κB、VIP/cAMP/PKA	促进M2极化，抑制M1极化，降低血清中IL-1β、TNF-α、IL-6、iNOS水平	［18］
氰苷类	氰那苷	Nrf2/HO-1	抑制巨噬细胞极化为M1表型，促进抗炎M2极化，降低血清中IL-1β和TNF-α水平	［31］
核苷类	尿苷	Nrf2/HO-1	上调SLC7A11、GPX4、HO-1，抑制ACSL4表达	［32］

减轻炎症，降低组织铁水平和脂质过氧化，改善脓毒症小鼠肺损伤。Bajgai等[33]研究表明，中草药中广泛存在的成分柚皮苷可调节包括MAPK/Nrf2/HO-1在内的许多信号通路级联反应，通过下调巨噬细胞促炎M1型相极化的同时提高抗炎M2型相极化，对抗内源性介质、减少炎性细胞因子的产生，发挥抗炎、抗凋亡和抗氧化作用，防止脓毒症诱导的肺损伤。

6　结　语

脓毒症导致的肺损伤是全身性炎症反应在肺部的局部表现，其发病机制复杂，涉及炎症反应、氧化应激、细胞焦亡与自噬、铁死亡等多个方面。随着脓毒症炎症反应的扩散，肺作为高血流量和微循环丰富的器官，成为炎症因子和免疫细胞攻击的主要靶点，炎症因子直接损伤肺泡上皮细胞和血管内皮细胞，破坏肺泡-毛细血管屏障的完整性，导致血管通透性增加。血浆蛋白和液体渗入肺泡间隙和肺泡腔，形成肺水肿，严重影响气体交换功能。细胞凋亡、焦亡和铁死亡在肺损伤的终末阶段起到重要作用，肺泡上皮细胞和内皮细胞的凋亡导致肺泡结构破坏和屏障功能丧失，焦亡通过激活炎症小体，释放大量炎症因子，加剧炎症反应，铁死亡则通过脂质过氧化和铁代谢紊乱，进一步破坏细胞膜结构和功能。

本文总结了近年来在各项研究中，对脓毒症肺损伤发挥主要调控作用的信号通路，并探讨了中药有效成分通过调控这些信号通路治疗脓毒症肺损伤的机制，以期为脓毒症肺损伤的机制研究和临床治疗提供参考。通过回顾各项研究可以看出，在本文所涉及的中药有效成分中，以黄酮类、多酚类、苯丙素类和环烯醚萜苷类居多，主要发挥抗炎、抗氧化应激、抑制细胞焦亡和自噬的作用，各个机制所涉及的信号通路并非孤立，而是相互交织、相互影响，构成复杂的通路机制网络，共同调控脓毒症肺损伤的病情进展。

中医药在调控脓毒症肺损伤相关信号通路和治疗靶点方面展现出独特的作用，但其具体分子机制仍需进一步探索。例如，中药有效成分如何与靶点蛋白结合发挥作用，通过何种途径影响下游信号分子的表达和活性，以及不同信号通路之间如何发挥交互作用，进而调控疾病进程。脓毒症肺损伤相关信号通路众多，本文涵盖不够全面，未来研究可以进一步扩展中药在调控脓毒症肺损伤相关信号通路和治疗靶点方面的探索范围，开展不同种类中药单体及其有效成分对关键信号通路的调控机制研究，系统构建“中药成分-作用靶点-信号通路-生物学效应”的多维研究体系，深入阐明中医药调控脓毒症肺损伤的分子机制，并筛选出具有显著疗效的中药成分，优化中药组方配伍，同时深入探讨中药复方在脓毒症肺损伤治疗方面多成分、多靶点、多途径的特点，挖掘其治疗潜力，发挥其治疗优势，为脓毒症肺损伤的临床治疗提供新的药物选择和治疗策略。

利益冲突 无

参考文献

[1] Liu D, Huang SY, Sun JH, et al. Sepsis-induced immunosuppression: mechanisms, diagnosis and current treatment options[J]. Mil Med Res, 2022, 9(1): 56.

[2] Fleischmann-Struzek C, Rudd K. Challenges of assessing the burden of sepsis[J]. Med Klin Intensivmed Notfmed, 2023, 118(Suppl)2: 68-74.

[3] Zampieri FG, Bagshaw SM, Semler MW. Fluid therapy for critically ill adults with sepsis: a review[J]. JAMA, 2023, 329(22): 1967-1980.

[4] Sinha P, Meyer NJ, Calfee CS. Biological phenotyping in sepsis and acute respiratory distress syndrome[J]. Ann Rev Med, 2023, 74: 457-471.

[5] Bos LDJ, Ware LB. Acute respiratory distress syndrome: causes, pathophysiology, and phenotypes[J]. Lancet, 2022, 400(10358): 1145-1156.

[6] Zhang YY, Ning BT. Signaling pathways and intervention therapies in sepsis[J]. Sig Transduct Target Ther, 2021, 6: 407.

[7] Fitzgerald KA, Kagan JC. Toll-like receptors and the control of immunity[J]. Cell, 2020, 180(6): 1044-1066.

[8] Wang YB, Zhang ST, Li HY, et al. Small-molecule modulators of toll-like receptors[J]. Acc Chem Res, 2020, 53(5): 1046-1055.

[9] 徐玲文, 王华兵, 王倩, 等. 黄芩苷对脓毒症急性肺损伤小鼠TLR4/NF-κB通路及Treg/Th17平衡的影响[J]. 中国免疫学杂志, 2022, 38(15): 1813-1818, 1823.

[10] 黄晗, 李凤芝, 李杨, 等. 灵芝多糖对脓毒症急性肺损伤大鼠肺功能及TLR4/NF-κB通路的影响[J]. 中草药, 2021, 52(8): 2351-2356.

[11] 孙鹏, 陈敏, 张细六, 等. 虎杖苷通过调控HMGB1/TLR4/NF-κB信号通路对脓毒症急性肺损伤的保护作用[J]. 浙江中医药大学学报, 2021, 45(7): 691-699.

[12] Kim GO, Park DH, Bae JS. Procyanidin B2 attenuates sepsis-induced acute lung injury via regulating hippo/rho/PI3K/NF-κB signaling pathway[J]. Int J Mol Sci, 2023, 24(9): 7930.

[13] Zhu WW, Luo W, Han JB, et al. Schisandrin B protects against LPS-induced inflammatory lung injury by targeting MyD88[J]. Phytomedicine, 2023, 108: 154489.

[14] Park HB, Baek KH. E3 ligases and deubiquitinating enzymes regulating the MAPK signaling pathway in cancers[J]. Biochim Biophys Acta Rev Cancer, 2022, 1877(3): 188736.

[15] Liu Z, Gao JL, Ban YX, et al. Synergistic effect of paeoniflorin combined with luteolin in alleviating Lipopolysaccharides-induced acute lung injury[J]. J Ethnopharmacol, 2024, 327: 118022.

[16] Gao J, Zhao F, Yi SN, et al. Protective role of crocin against sepsis-induced injury in the liver, kidney and lungs via inhibition of p38 MAPK/NF-κB and Bax/Bcl-2 signalling pathways[J]. Pharm Biol, 2022, 60(1): 543-552.

[17] Zhang J, Wang CS, Wang HL, et al. Loganin alleviates sepsis-induced acute lung injury by regulating macrophage polarization and inhibiting NLRP3 inflammasome activation[J]. Int Immunopharmacol, 2021, 95: 107529.

[18] Wang WB, Li JT, Hui Y, et al. Combination of pseudoephedrine and emodin ameliorates LPS-induced acute lung injury by regulating macrophage M1/M2 polarization through the VIP/cAMP/PKA pathway[J]. Chin Med, 2022, 17(1): 19.

[19] Coudereau R, Monneret G, Lukaszewicz AC, et al. Altered *ex vivo* NLRP3 inflammasome activation is associated with 28-day mortality in septic patients[J]. Viruses, 2023, 15(12): 2419.

[20] Du WJ, Ren N, Xu Y, et al. Programmed cell death 4 governs NLRP3-mediated pyroptosis in septic lung disorders[J]. Mol Biol Rep, 2024, 51(1): 77.

[21] Gleeson TA, Kaiser C, Lawrence CB, et al. The NLRP3 inflammasome is essential for IL-18 production in a murine model of macrophage activation syndrome[J]. Dis Model Mech, 2024, 17(7): dmm050762.

[22] 谢小芳, 赵展庆, 符妹垂. 丁香苷调节NLRP3/Caspase-1信号通路对脓毒症肺损伤大鼠细胞焦亡的影响[J]. 中国药学杂志, 2023, 58(19): 1744-1751.

[23] 孙立燕, 刘泽茹, 苏永胜, 等. 车叶草苷调节NLRP3/Caspase-1/GSDMD信号通路对脓毒症大鼠肺组织细胞焦亡的影响[J]. 天津医药, 2023, 51(6): 607-613.

[24] Guo W, Hu ZS. SRPK1 promotes sepsis-induced acute lung injury via regulating PI3K/AKT/FOXO3 signaling[J]. Immunopharmacol Immunotoxicol, 2023, 45(2): 203-212.

[25] Wang X, Lin F, Guo L. TILRR aggravates sepsis-induced acute lung injury by suppressing the PI3K/Akt pathway[J]. Evid Based Complement Alternat Med, 2022, 2022: 7341504.

[26] Qin YP, Li WJ, Liu JL, et al. Andrographolide ameliorates sepsis-induced acute lung injury by promoting autophagy in alveolar macrophages via the RAGE/PI3K/AKT/mTOR pathway[J]. Int Immunopharmacol, 2024, 139: 112719.

[27] Xie LP, Zhang GY, Wu YT, et al. Protective effects of *Wenqingyin* on sepsis-induced acute lung injury through regulation of the receptor for advanced glycation end products pathway[J]. Phytomedicine, 2024, 129: 155654.

[28] He F, Ru XL, Wen T. NRF2, a transcription factor for stress response and beyond[J]. Int J Mol Sci, 2020, 21(13): 4777.

[29] Gunne S, Heinicke U, Parnham MJ, et al. Nrf2—a molecular target for sepsis patients in critical care[J]. Biomolecules, 2020, 10(12): 1688.

[30] Tang XM, Liu JQ, Yao S, et al. Ferulic acid alleviates alveolar epithelial barrier dysfunction in sepsis-induced acute lung injury by activating the Nrf2/HO-1 pathway and inhibiting ferroptosis[J]. Pharm Biol, 2022, 60(1): 2286-2294.

[31] Feng JF, Liu ZJ, Chen H, et al. Protective effect of cynaroside on sepsis-induced multiple organ injury through Nrf2/HO-1-dependent macrophage polarization[J]. Eur J Pharmacol, 2021, 911: 174522.

[32] Lai K, Song CK, Gao ML, et al. Uridine alleviates sepsis-induced acute lung injury by inhibiting ferroptosis of macrophage[J]. Int J Mol Sci, 2023, 24(6): 5093.

[33] Bajgai B, Suri M, Singh H, et al. Naringin: a flavanone with a multifaceted target against sepsis-associated organ injuries[J]. Phytomedicine, 2024, 130: 155707.

收稿日期:2025-04-28 **编辑**:王娜娜