Mechanisms and Research Progress of Traditional Chinese Medicine Regulating NF-κB in the Treatment of Acute Lung Injury/Acute Respiratory Distress Syndrome

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Abstract

Acute lung injury (ALI) has multiple causes and can easily progress to acute respiratory distress syndrome (ARDS) if not properly treated. Nuclear factor κB (NF-κB) is a key pathway in the treatment of ALI/ARDS. By exploring the relevance of NF-κB and the pathogenesis of this disease, it was found that this disease was mainly associated with inflammation, dysfunction of the endothelial barrier, oxidative stress, impaired clearance of alveolar fluid, and coagulation disorders. Traditional Chinese medicine (TCM) has the characteristics of multitargeting, multipathway effects, and high safety, which can directly or indirectly affect the treatment of ALI/ARDS. This article summarizes the mechanism and treatment strategies of TCM in recent years through intervention in the NF-κB-related signaling pathways for treating ALI/ARDS. It provides an overview from the perspectives of Chinese herbal monomers, TCM couplet medicines, TCM injections, Chinese herbal compounds, and Chinese herbal preparations, offering insights into the prevention and treatment of ALI/ARDS with TCM.

Keywords
- acute lung injury
- acute respiratory distress syndrome
- traditional Chinese medicine
- NF-κB

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) refer to acute, progressive hypoxic respiratory failure caused by exudative pulmonary edema triggered by various internal and external factors other than cardiac origin. Common causes of pulmonary ALI include pneumonia, inhalation of smoke or toxic gases, and lung contusions, whereas non-pulmonary factors include sepsis, septicemia, and acute pancreatitis. ALI/ARDS can be divided into three stages: the early exudative phase characterized by significant damage to the alveolar–epithelial barrier, the proliferative phase marked by intensified inflammatory reactions and protein-rich fluid leakage into the alveolar space disrupting fluid balance, and the fibrotic phase involving differentiation of alveolar epithelial cells, regeneration of the alveolar–epithelial barrier, and clearance of edema fluid and/or proliferation of fibroblasts.[1] On one hand, ALI and ARDS share homogeneous pathophysiological changes characterized by reduced pulmonary compliance, increased intrapulmonary shunting, and ventilation/perfusion mismatch, with severe ALI defined as ARDS.[2] On the other hand, ALI diagnosis is clear but ARDS has a complex etiology. It shares symptoms such as respiratory distress and hypoxemia with severe pneumonia and pulmonary embolism, which requires differential diagnosis based on clinical criteria, with significant interobserver variability. Scholars have proposed the detection of biomarkers like programmed death ligand 1 and quantitative analysis of exhaled metabolites as emerging adjunct diagnostic methods.[3,4] At present. Western medicine

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treatment for ALI/ARDS mainly focuses on the treatment of the primary disease, respiratory support, and drug therapy. Overall, there is a lack of specific drugs and methods, which cannot achieve ideal treatment effects. ALI/ARDS mostly belong to the categories of "dyspnea syndrome" and "collapse syndrome" in traditional Chinese medicine (TCM). In recent years, with the exploration of TCM in the treatment of ALI/ARDS, the enormous advantages of TCM in treating ALI/ARDS have been demonstrated.

Research has shown that ALI/ARDS accounts for more than 10% of all admissions to intensive care units, and the quality of life for survivors of the acute phase of ALI significantly declines.[5] ALI/ARDS can occur secondary to other diseases and can also cause complications. Clinical treatments often include anti-inflammatory drugs, antioxidants, lung alveolar surfactants, anticoagulants, fibrinolytic agents, and neuromuscular blockers.[6] Currently, the signaling pathways involved in treating this disease mainly include nuclear factor-κB (NF-κB), Janus kinase/signal transducer and activator of transcription, mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), transforming growth factor-β/SMAD proteins (Smad) pathways, endoplasmic reticulum stress-mediated pathways, and reactive oxygen species (ROS)-mediated pathways.[7] Therefore, understanding the role and mechanism of NF-κB-related signaling pathways in ALI/ARDS can improve diagnostic capabilities for this disease.

Overview of Nuclear Factor-κB Signaling Pathway

NF-κB exists in the cytoplasm in an inactive state without transcriptional activity under resting conditions, where it forms a trimeric complex with the inhibitor of NF-κB (IκB) proteins located in the cytosol. Upon activation by upstream signals such as inflammation and immune responses, the inhibitor of κB kinase (IKK) catalyzes the phosphorylation of IκB proteins, leading to the dissociation of NF-κB from IκB. NF-κB then translocates into the nucleus where it binds to specific deoxyribonucleic acid (DNA) sequences to induce transcription and expression of inflammatory genes. The NF-κB pathway generates various cytokines such as tumor necrosis factor-α (TNF-α) and chemokines like interleukin (IL)-8 (IL-8), activating immune cells in peripheral tissues to initiate inflammatory responses. Additionally, NF-κB activation polarizes alveolar macrophages (Ams) into an M1 phenotype, and the production of large amounts of proinflammatory cytokines can promote inflammation. Inflammation triggers adhesion molecules to cross the alveolar–capillary barrier, causing sustained inflammatory damage in the alveolar space.

Role of Nuclear Factor-κB in Acute Respiratory Distress Syndrome Mechanism

Inflammatory Response

Inflammation is a critical pathophysiological change in ARDS.[8] Its mechanism involves polymorphonuclear leukocyte aggregation, adhesion, protease release, oxygen radicals damaging the alveolar membrane, and production of procoagulants leading to microthrombosis. Inflammatory mediators cause pulmonary vasoconstriction, bronchospasm, and increased permeability.

Severe pneumonia releases inflammatory mediators, and NF-κB regulates the expression of various inflammatory mediator genes while being activated by inflammatory mediators. Cytokines such as TNF-α and IL-1β, activate NF-κB through classical pathways. Activated NF-κB amplifies inflammation by increasing the transcription of genes encoding IL-6, IL-8, TNF-α, and IL-1β in host Ams, ultimately leading to ALI.[9] Inflammatory factors in ALI disrupt intercellular tight junctions and adhesion connections, increase cellular permeability, cause pulmonary edema, and trigger ARDS.[10] Numerous studies confirm that intervening in the NF-κB signaling pathway to inhibit the expression of inflammatory factors can alleviate the inflammatory response. Therefore, NF-κB is a versatile nuclear transcription factor that exacerbates the inflammatory response in ARDS when dysregulated. Conversely, modulating NF-κB and its related signaling pathways to inhibit its transcription and expression can mitigate the severity of the inflammatory storm and improve ARDS severity.[7]

Endothelial Barrier Dysfunction

Endothelial barrier dysfunction is another important pathophysiological change in ARDS.[8] Damaged vascular endothelium caused by factors such as immune response dysregulation and disruption of intercellular connections can activate platelets. This activation is accompanied by increased procoagulant substances, and activation of kinins, complement, and fibrinolytic systems, further promoting disseminated intravascular coagulation. This process increases the permeability of the alveolar–capillary membrane, leading to inflammatory edema and exacerbating ARDS.

NF-κB is an important signaling pathway that reduces endothelial cell permeability and barrier damage. Patients with uncontrolled or allergic reactions often develop septicopyemia and systemic inflammatory response syndrome (SIRS) after trimeresurus snakebite, with ARDS representing the pulmonary manifestation of SIRS. Treatment with Sheshang capsules, a representative agent for fire-purging and detoxification therapy, significantly reduces the expression of vascular endothelial cell IKK, NF-κB-inducing kinase, and NF-κB p65 (Rel-A) proteins.[11]

Oxidative Stress

Oxidative stress results from an imbalance between oxidation and antioxidation. In response to inflammatory stimuli, various lung cells produce ROS. ROS-induced oxidative stress plays a crucial role in lung injury and the progression of ARDS.

TNF-α induces ROS production and promotes neutrophil "oxidative burst," while ROS can also increase the level of TNF-α. TNF-α activates NF-κB-mediated transcription and expression of inflammatory mediators, forming a cyclic loop. ROS produced by neutrophils disrupt the endothelial barrier, allowing large

numbers of inflammatory cells to migrate through the endothelial barrier, thereby exacerbating inflammation.[12]

Therefore, under conditions of oxidative stress, NF-κB can exert a protective effect through antioxidation. Studies have shown that NF-κB has many antioxidant targets, such as superoxide dismutase (SOD).[12] Oxidative stress and inflammatory responses interact in ARDS, leading to intensified cellular damage and inflammation.

Impaired Alveolar Fluid Clearance

Impaired alveolar fluid clearance (AFC) is a significant cause of pulmonary edema in ARDS patients. Basal AFC is determined by ion and fluid transport across alveolar epithelium, where the epithelial Na^+ channel (EnaC) plays a critical role in sodium ion active transport.

Normally, pulmonary edema is resolved through the reabsorption of edema fluid by the alveolar–epithelial barrier. However, in most ARDS patients, epithelial barrier function is compromised due to inflammation, resulting in early impairment of AFC and persistent alveolar edema. Failure to clear alveolar edema significantly increases mortality in ARDS.[7] Zhai et al demonstrated that natural ferulic acid (FA) regulates ENaC via the IKKβ/NF-κB pathway. FA reduces phosphorylation of IKKβ/NF-κB, and eliminates the lipopolysaccharide (LPS)-inhibited ENaC expression, which is closely associated with NF-κB p65 regulation.[13] Therefore, NF-κB plays a crucial role in improving AFC.

Coagulation Dysfunction

ALI induces microthrombosis, degradation of fibrinogen products, and release of vasoactive substances, which further aggravate damage to the alveolar–capillary membrane. This results in increased permeability, manifested as gas diffusion impairment, intrapulmonary shunting, and dead space-like ventilation, ultimately leading to ventilation/perfusion mismatch and hypoxemia, and in severe cases, respiratory failure.[14]

Inflammatory factors released by NF-κB activation can cause local tissue factor (TF) exposure and upregulate plasminogen activator inhibitor-1 (PAI-1) and activated protein C (APC) expression. Therefore, NF-κB expression can regulate pulmonary tissue coagulation/fibrinolysis function.[15] For example, Richard et al found in a TNF-α-mediated mouse lung injury model that inhibiting NF-κB activation regulates APC expression, thus achieving antithrombotic and anticoagulant effects to mitigate lung injury.[16]

TCM Treatments for Acute Lung Injury/Acute Respiratory Distress Syndrome via Nuclear Factor-κB Signaling Pathway Intervention

Chinese Herbal Monomers

Alkaloid Compounds

Palmatine is a type of botanical medicine composed of palmatine chloride, which possesses antibacterial, anti-inflammatory, heat-clearing, and detoxifying effects and is mainly used for various inflammatory and infectious diseases.[17] Pretreatment of palmatine significantly inhibits IL-1β expression and secretion in bronchoalveolar lavage fluid (BALF) of LPS-induced ALI mice, and markedly reduces inducible nitric oxide synthase (iNOS) protein level. Further mechanistic studies revealed that palmatine and coptisine interact with AKT via hydrogen bonding, which can significantly inhibit AKT/NF-κB signaling pathway activation and effectively alleviate ALI.[18,19] By inhibiting NF-κB and NLRP3 protein (NOD-, LRR-, and pyrin domain-containing protein 3, NLRP3) transcription and protein expression levels, ligustrazine reduces the contents of inflammatory factors such as IL-2, IL-6, and TNF-α, improves lung injury in severely burned rats with ALI and increases their survival rate.[20] Peimine and peiminine derived from Zhebeimu (Bulbus Fritillariae Thunbergii). It was found that the combined use of the two and forsythin A was superior to that of forsythin A alone, and could significantly inhibit the upregulation of Toll-like receptor (TLR) 4 (TLR4)/MAPK/NF-κB signaling pathway-related proteins and activation of IL-17, and also improved the thickening of the bronchoalveolar wall.[21] Protostemonine (PSN) has an anti-inflammatory effect, which can reduce neutrophil infiltration and tissue permeability in ALI mice induced by methicillin-resistant *Staphylococcus aureus*. Simultaneously, PSN plays an anti-inflammatory role by reducing the production of nitric oxide (NO) in medullary macrophages induced by inflammation.[22]

Terpenoids

Macrophages mainly derive from monocytes, and their phagocytic function can eliminate abnormal cells and regulate the body's immunity. Apoptosis of macrophages induced by ALI can upregulate the level of inflammatory responses and further exacerbate immune dysregulation, and potentially progress to ARDS. ALI/ARDS can polarize AMs toward the M1 phenotype, and promote secretion of proinflammatory cytokines and chemokines such as IL-6, IL-12, and TNF-α. Therefore, treatment with hederagenin reduces the number of M1 macrophages in the lung tissues of septic rats, which can inhibit the release of inflammatory factors, thereby improving the rats' survival rate and alleviating pulmonary inflammatory responses and pathological damage.[23] 23-O-acetylshengmanol-3-O-α-L-arabinoside (DA) is a triterpenoid compound found in the roots and stems of Shengma (Cimicifugae Rhizoma), which improves lung immune system disorders in ALI mice by regulating abnormal apoptosis of lung cells. Additionally, research by Chen found that DA also reduces lung inflammation damage, lung function impairment, and pulmonary edema by downregulating IκBα/NF-κB expression.[24] Loganin is a major active ingredient in Shanzhuyu (Corni Fructus), which can regulate macrophage polarization via the NF-κB pathway and inhibit NLRP3 inflammasome activation to alleviate ALI caused by sepsis.[25] Research has found that Euphorbia factor L2 can significantly inhibit the levels of inflammatory factors such as IL-1β, IL-6, TNF-α, and IL-8, and this effect is mediated by inhibiting the activation of NF-κB signaling.[26] Triptolide can significantly reduce the levels of white blood cells, pulmonary edema, and myeloperoxidase (MPO) activity in

ALI mice.[27] Tumor necrosis factor receptor- associated factor 6 (TRAF6) is a ubiquitin ligase that, when ubiquitinated, recruits Transforming growth factor β-activated kinase 1 (TAK1) through adaptor protein TAB, thereby activating NF-κB and MAPK to induce the release of inflammatory cytokines and chemokines. Effective parts of Andrographis diterpene lactone inhibit the interaction between TRAF6 and TAK1 to achieve deubiquitination and dephosphorylation purposes.[28] Limonene, abundant in kumquat peel essential oil, has antioxidative and antifibrotic functions. Different doses of limonene can reduce phosphorylation levels of p38, p65, and IκBα, thereby blocking the p38 MAPK/NF-κB signaling pathway and exerting anti-inflammatory effects.[29]

TLRs are transmembrane proteins that mediate recognition and responses to external pathogens. There are two signal transduction pathways of activated TLRs: myeloid differentiation primary response protein 88 (MyD88)-dependent signal transduction pathway and MyD88-independent signal transduction pathway. TLR4 can mediate both signaling pathways, and targeting TLR4 is a therapeutic approach for treating ALI.[30]

Bilobalide (BB) can regulate T Helper 1 Cell/ T Helper 2 Cell balance and improve lung tissue damage in septic ALI rats by inhibiting TLR4/NF-κB signaling pathway activation.[31] High doses of Chinese herbal monomers can achieve effects similar to glucocorticoids, and BB and splatycodin D can also achieve effects similar to glucocorticoids.[32] Researchers have found that ingredients in Chaihu (Bupleuri Radix), such as saikosaponins A, b1, b2, and D (SSA, SSb1, SSb2, SSD). The contents of SSb1 and SSb2 increased significantly after vinegar treatment, which can reduce lung edema in ALI mice. Both have anti-inflammatory effects through TLR4/NF-κB, with SSb2 showing superior lung protective effect at the same dose compared with other drugs.[33]

Flavonoid Compounds

Baicalin is the flavonoid compound found in the highest concentration in Huangqin (Scutellariae Radix), primarily existing in the form of a magnesium salt. The Mg^{2+} in baicalin magnesium salt (BA-Mg) promotes the generation of intracellular cyclic adenosine monophosphate to control the activity of sodium channels on alveolar epithelial cells, thereby alleviating pulmonary edema. Additionally, the antagonism of Mg^{2+} to Ca^{2+} can block its inflow into effector cells and aggravate lung injury. Studies indicate a close correlation between oxidative stress and the occurrence and development of ALI. Lipid peroxidation damages endothelial cells and alveolar epithelial cells. ROS stimulate increased activity of iNOS in blood, leading to excessive NO production, pulmonary vasodilation, and ultimately pulmonary edema. Excessive ROS also damages cellular DNA, causing DNA mutations and breakage, mitochondrial dysfunction, destroyed mitochondrial structure leading to insufficient cell energy supply, apoptosis, and necrosis. BA-Mg demonstrates superior antioxidant efficacy compared with equimolar doses of the baicalin group and magnesium sulfate group.[34,35]

Silymarin, extracted from the Compositae plant, *Silybum marianum*, possesses antioxidant, toxin-removing, and protein synthesis-promoting properties. It protects lung function in ALI rats by inhibiting oxidative stress and inflammatory reactions through modulation of the TLR4/NF-κB pathway.[36] Trifolium flavone improves lung function in elderly ALI mice through the MAPK/NF-κB pathway.[37] Ampelopsin, a major flavonoid in vine tea, enhances lung function by increasing lung volume, ventilation, and elasticity.[38] Nobiletin is extracted from Chenpi (Citri Reticulatae Pericarpium), which, at a dose of 50 mg/kg, downregulates MAPK/NF-κB expression in ALI mice, significantly inhibits NF-κB p65, p38 MAPK, extracellular regulated protein kinases (ERKs), and c-Jun N-terminal kinase phosphorylation.[39] Dihydroquercetin can reduce LPS-induced inflammation and cell apoptosis via the miR-132-3p/Forkhead Box O3 (FOXO3)/NF-κB pathway.[40]

Halofuginone can significantly inhibit the secretion of inflammatory factors (IL-1β, IL-6, IL-18) and reduce the peripheral blood $CD14^{+}$ cell count in ALI rats to regulate immune imbalance.[41] Zhong et al[42] found that isorhamnetin from sea buckthorn berry extract combined with Ressatovi significantly improved arterial oxygen partial pressure (PaO_2), decreased arterial partial pressure of carbon dioxide ($PaCO_2$), and markedly reduced lung injury in ALI rats induced by high-concentration oxygen therapy.

Glycoside Compounds

Cordycepin is an active component isolated from Dongchong Xiacao (Cordyceps). Li et al[43] demonstrated that intervening in ALI rats can improve rat capillary dilation, reduce red blood cell leakage, and decrease pulmonary tissue fluid secretion. It can also increase PaO_2 level, decrease $PaCO_2$ level, and exhibit dose dependency. Experimental results indicate that *Allium macrostemon* saponin can inhibit IκBα degradation, suppress inflammation, and reduce the expression of vascular cell adhesion molecule-1, thereby decreasing monocyte adhesion to endothelial cells to prevent and treat ALI.[44]

Research has confirmed that one of the clinical markers of ALI/ARDS is the deposition of fibrin in the alveoli. This is because the inflammatory storm caused by ALI damages pulmonary capillary endothelial cells, and activates the body's coagulation and fibrinolytic system, thus leading to early hypercoagulability, microcirculatory disorders, tissue ischemia, and hypoxia. Therefore, adjusting coagulation function has become one of the important clinical treatments for reducing fibrin deposition in the alveolar cavity.[45] *Panax notoginseng* saponins are the most effective components in Sanqi (Notoginseng Radix et Rhizoma). Besides significantly reducing NF-κB expression in ALI mice, they can improve coagulation function and resist non-microvascular thrombosis, thus contributing to their mechanism of treating ALI.[46]

Xu[47] found that high doses of ginsenosides Ro and Rb3 can block the binding of LPS to RAW 264.7 macrophages at the TLR4 cell membrane receptor level, improve pulmonary interstitial congestion and hemorrhage, reduce inflammatory cell infiltration, without affecting liver function. In the inflammatory response of ALI, the Rho A/ROCK pathway mainly regulates the activation of filamentous actin and globular actin and the stability of adhesive junctions, playing

an important role in protecting the reconstruction and permeability of the alveolar epithelium–pulmonary microvascular endothelial cytoskeleton. Astragaloside, by inhibiting the expression of the Rho A/ROCK/NF-κB signaling pathway, protects cellular structural function, decreases the contents of inflammatory factors induced by PM2.5 in ALI rats, and reduces edema fluid and protein leakage.[48] By inhibiting TLR4-NF-κB activation, salidroside delays the pathological process of lung injury in ALI rats poisoned by paraquat, thus reducing the severity of lung injury.[49] This study used high-dose polyphyllin VII to intervene in severe acute pancreatitis-induced ALI and reduce proinflammatory cytokine secretion while addressing pancreatic and pulmonary tissue damage.[50]

Phenylpropanoids

Cnidiadin can effectively alleviate ALI caused by hemorrhagic shock, which is associated with inhibition of the NF-κB signaling pathway-mediated inflammatory response.[51]

The PI3K/AKT signaling pathway is one of the important pathways involved in ALI/ARDS. Activation of the PI3K/AKT pathway leads to activation of downstream NF-κB signaling and increased production of inflammatory cytokines. Arctiin, a major component of Niubangzi (Arctii Fructus), belongs to lignan compounds. A high dose of arctiin can inhibit IκBα and NF-κB phosphorylation levels through PI3-K/AKT, and reduce lung inflammation.[52] However, research has shown that activation of PI3K/AKT can inhibit downstream NF-κB and NLRP3 inflammasome to alleviate lung inflammation in LPS-induced ALI models. Whether this pathway plays a positive or negative role in regulating inflammation in ARDS needs further clarification.[7]

Aesculetin is found in various natural plants (such as *Datura stramonium* and *Rehmannia*) and possesses anti-inflammatory properties. Pretreatment with aesculetin inhibits the expression of AKT/ERK/NF-κB, Retinoic acid receptor-related orphan receptor gamma-t (RORγt)/IL-17 pathways, which significantly reduce histopathological changes and inflammatory cell infiltration (such as TNF-α, IL-1β, IL-6) in lung tissue.[53]

Organic Compounds

Eupalinolide B (EB) exhibits anti-inflammatory and antiviral effects and can be used in the treatment of ALI. EB binds to the Cys174 site of TAK1, inhibits the activation of the target protein TAK1 and the activation of TAK1-mediated NF-κ-B/MAPKs pathway, thereby alleviating ALI.[54] Codonopsis polysaccharides not only reduce the levels of neutrophils and lymphocytes in the BALF of ALI mice, alleviate the infiltration of inflammatory cells into lung tissue and the proliferation of alveolar epithelial cells to varying degrees, but also improve lung function in ALI mice.[55] Chicoric acid has the effects of clearing heat and resolving toxicity, promoting diuresis, and reducing swelling. It can alleviate lung damage and pulmonary edema in ALI mice induced by sepsis by acting on key proteins MyD88 and P65 levels in the TLR9, Interferon regulatory factor 7 (IRF7), and NF-κB signaling pathways while reducing damage to normal lung epithelial cells and oxidative stress in LPS-induced patients.[56] Trans-cinnamaldehyde is a major component of cinnamon essential oil, which significantly improves lung function in ALI mice and can induce a shift of lung tissue M1 macrophages to the M2 phenotype, thereby reducing lung cell apoptosis.[57] Chinese yam glycoprotein is one of the components of Chinese yam polysaccharides. It has anti-inflammatory and immune-regulating functions, which are possibly associated with the regulation of TLR4/NF-κB/NLRP3 expression.[58]

Other Compounds

Ginger exhibits various medicinal forms with diverse functions. 6-shogaol, the main active ingredient in dried ginger, belongs to the phenolic compound category and shows therapeutic effects on cardiovascular, gastrointestinal, hepatic, and biliary diseases. Research has found that 6-shogaol inhibits NF-κB-related expression to reduce alveolar capillary permeability in the lung and alleviate neutrophil infiltration and pulmonary edema, thus exerting anti-inflammatory and antioxidant effects in a dose-dependent manner.[59] Gingerol is the primary active substance in ginger. Li et al[60] observed that gingerol not only downregulates TF and PAI-1 protein expression levels in the lung tissue but also improves the hypercoagulable state.

Tanshinone IIA sodium sulfonate, derived from Danshen (Salviae Miltiorrhizae Radix et Rhizoma), belongs to the fat-soluble non-quinone pigment compounds. It exhibits a dose-dependent repair effect on firearm-induced ALI guinea pig lung injuries.[61] The combined use of resveratrol and curcumin significantly inhibits inflammation and apoptosis in septic ALI, with better results than using either alone.[62] High doses of pine cone of *Pinus yunnanensis* and extract of wartwort can reduce LPS-induced ALI in rats; the former inhibits the TLR4/NF-κB signaling pathway to lower levels of inflammatory and oxidative factors, while the latter achieves anti-inflammatory effects through the MAPK/NF-κB pathway.[63,64]

MBAP-5 is a novel flavonol polysaccharide extracted from *Tamarix chinensis*. Its oral administration can inhibit TLR4/NF-κB to reduce pulmonary edema, viral replication, and inflammatory responses in influenza A virus-induced ALI.[65] Research indicates that the ethanolic extract of atractylodis rhizoma (EEAR) is rich in four main components: atractylol, atractylenolide I, atractylenolide II, and atractylenolide III. After treatment with EEAR, it improved lung barrier function and inhibited oxidative stress by regulating nuclear factor-erythroid 2-related factor-2 and its downstream targets heme oxygenase-1 (HO-1) and NADPH quinone acceptor oxidoreductase 1 (NQO-1).[66] See ►**Table 1**.

TCM Couplet Medicines

Jingjie (Schizonepetae Herba) and Fangfeng (Saposhnikovia Radix) are both pungent-warm herbs that dispel exterior pathogenic factors. Their combination exhibits antipyretic, antalgic, anti-inflammatory, antiviral, antiallergic, and hemostatic effects. RAO extracted the effective anti-inflammatory parts of Jingjie and Fangfeng (Jing-Fang n-butanol extraction, JFNE) for the study of their effects on AIL. In vivo experiments confirmed that JFNE suppresses the release of

Table 1 Research models and action mechanisms of Chinese herbal monomers in treating acute lung injury/acute respiratory distress syndrome through nuclear factor-κB-related signaling pathways

Medicines	Models	Action mechanisms	References
Palmatine	ALI mice	AKT/NF-κB ↓, reducing inflammatory responses	18
Coptisine	ALI mice	PI3K/AKT/NF-κB ↓, reducing inflammatory responses	19
Ligustrazine	ALI rats	NF-κB/NLRP3 ↓, reducing inflammatory responses	20
Peimine, Peiminine	ALI mice	TLR4/MAPK/NF-κB ↓, reducing inflammatory responses	21
Stemonine	ALI mice	MAPK/NF-κB ↓, reducing inflammatory responses	22
Hederagenin	ALI rats	NF-κB/NLRP3 ↓, M1 macrophages ↓, reducing inflammatory responses, resisting oxidization stress	23
3-O-acetylshengmanol-3-O-α-L-arabinoside	ALI mice, RAW 264.7 macrophages	IκBα/NF-κB ↓, NLRP3 ↓, reducing inflammation	24
Loganin	ALI mice	NF-κB/NLRP3 ↓, reducing inflammatory responses	25
Euphorbia factor L2	RAW 264.7 macrophages, ALI mice	NF-κB ↓, reducing inflammatory responses	26
Triptolide	ALI mice	TLR4/NF-κB ↓, reducing inflammatory responses	27
Andrographolide	ALI mice, RAW 264.7 macrophages	TAK1/NF-κB ↓, inhibiting inflammatory responses	28
Limonene	ALI mice	MAPK/NF-κB ↓, reducing inflammatory responses	29
Bilobalide	ALI rats	TLR4/NF-κB ↓, reducing inflammatory responses	31
Platycodin D	ALI rats	NF-κB ↓, resisting oxidization stress	32
Saikosaponins A, b1, b2, and D	ALI mice	TLR4/NF-κB ↓, reducing inflammatory responses	33
Baicalin magnesium salt	ALI mice	TLR4/MyD88/NF-κB ↓, reducing inflammation, resisting oxidization stress	34
Silymarin	ALI rats	TLR4/NF-κB ↓, resisting oxidization stress, reducing inflammatory responses	36
Trifolium flavone	ALI mice	MAPK/NF-κB ↓, reducing inflammatory responses	37
Dihydromyricetin	ALI mice	TLR4/MyD88/NF-κB ↓, reducing inflammatory responses	38
Nobiletin	ALI mice	MAPK/NF-κB ↓, reducing inflammatory responses	39
Dihydroquercetin	TC-1 cell	miR-132-3p/FOXO3/NF-κB ↓, reducing inflammatory responses	40
Halofuginone	ALI rats	CD14/NF-κB ↓, reducing inflammatory responses	41
Isorhamnetin	ALI rats	TLR4/NF-κB ↓, reducing inflammatory responses	42
Cordycepin	ALI rats	TLR4/NF-κB ↓, reducing inflammatory responses	43
Allium macrostemon saponin	ALI mice, human umbilical vein endothelial cell (HUVEC) cell	NF-κB/VCAM-1 ↓, inhibiting inflammatory factors	44
Panax notoginseng saponin	ALI mice	NF-κB ↓, resisting coagulation, inhibiting inflammatory responses	46
Gginsenoside Ro, Rb3	ALI mice, RAW 264.7 macrophages	TLR4/NF-κB/MAPK ↓, reducing inflammatory responses	47
Astragaloside	ALI rats	Rho A/ROCK/NF-κB ↓, reducing inflammatory responses	48
Salidroside	ALI rats	TLR4/NF-κB ↓, reducing inflammatory responses	49
Polyphyllin VII	severe acute pancreatitis-associated acute lung injury (SAP-ALI) rats	NF-κB ↓, reducing inflammatory responses	50
Forsythin A	ALI mice		21

Table 1 (*Continued*)

Medicines	Models	Action mechanisms	References
		TLR4/MAPK/NF-κB ↓, reducing inflammatory responses	
Cnidiadin	ALI rats	NF-κB ↓, reducing inflammatory responses	51
Arctiin	RAW 264.7 macrophages	PI3K/AKT/NF-κB ↓, reducing inflammatory responses	52
Aesculetin	ALI mice	AKT/ERK/NF-κB ↓, RORγt/IL-17 ↓, reducing inflammatory responses	53
Eupalinolide B	ALI mice, RAW 264.7 cell	NF-κB ↓, reducing inflammatory responses	54
Codonopsis polysaccharide	ALI mice	MAPK/NF-κB ↓, reducing inflammatory responses	55
Chicoric acid	ALI mice, BEAS-2B cell	TLR9/NF-κB ↓, reducing inflammatory responses	56
Trans-cinnamaldehyde	ALI mice	TLR4/MyD88/NF-κB ↓, reducing inflammatory responses	57
Chinese yam glycoprotein	ALI mice	TLR4/NF-κB/NLRP3 ↓, reducing inflammatory responses	58
6-shogaol	ALI mice	NF-κB ↓, resisting oxidization stress, reducing inflammatory responses	59
Gingerol	ALI rats	NF-κB ↓, resisting coagulation, reducing inflammatory responses	60
Tanshinone IIA sodium sulfonate	ALI guinea pigs	NF-κB ↓, reducing inflammatory responses	61
Resveratrol, curcumin	ALI mice	NF-κB ↓, inhibiting inflammatory responses	62
Extract of pine cone of *Pinus yunnanensis*	ALI rats	TLR4/NF-κB ↓, resisting oxidization stress, reducing inflammatory responses	63
Alcohol extract of wartwort	ALI mice	MAPK/NF-κB ↓, reducing inflammatory responses	64
MBAP-5	ALI mice	TLR4/NF-κB ↓, reducing inflammatory responses	65
Atractylodes root nodule ethanol extract	ALI rats	TLR4/NF-κB ↓ , kelch-like ECH-associated protein 1 (Keap1)/Nrf2 ↓ , resisting oxidization stress, reducing inflammatory responses	66

Abbreviations: AKT, protein kinase B; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ERK, extracellular regulated protein kinase; IL-17, interleukin-17; IκB, inhibitor of NF-κB; MAPK, mitogen-activated protein kinase; MyD88, myeloid differentiation primary response protein 88; NF-κB, nuclear factor-κB, NLRP3; NOD-, LRR-, and pyrin domain-containing protein 3; Nrf2, nuclear factor-erythroid 2-related factor-2; PI3K, phosphoinositide 3-kinase; TLR, Toll-like receptor; VCAM-1, vascular cell adhesion molecule-1.

inflammatory factors IL-6, IL-1β, IFN-γ, and TNF-α, thus significantly inhibiting the transcription levels of target genes related to the NF-κB signaling pathways. Moreover, JFNE can downregulate the level of iNOS, control the excessive secretion of proinflammatory cytokines, and simultaneously resist tissue oxidative damage. In vitro experiments, the inhibitory effect of JFNE on the expression level of target protein related to NF-κB signaling pathway in RAW 264.7 cells and A549 cells was consistent with in vivo experiments. Cimifugin, hesperetin, luteolin, and 5-O-methylvisamminol glycoside are its main effective active substances with anti-inflammatory and antioxidant effects, and luteolin is particularly superior.[67]

The simultaneous treatment of the lung and intestine is highly effective in the treatment of ALI, represented by Mahuang Decoction and Dachengqi Decoction. Mahuang (Ephedrae Herba) and Dahuang (Rhei Radix et Rhizoma) are the main couplet medicines used in this method, which can significantly inhibit inflammation cell infitration in ALI rats, reduce activation of AMs and polarization of M1 macrophages, and improve pathological conditions such as interstitial edema and pulmonary tissue structure disorder.[68]

The Huangqi–Danshen couplet medicines have anti-inflammatory, anti-infection, and immune-regulating effects, and show remarkable therapeutic effects on sepsis, pulmonary fibrosis, liver damage, and diabetic nephropathy.[69] They can inhibit the TLR4/NF-κB signaling pathway to prevent lung injury in ALI rats and improve the extent of lung tissue damage, and pretreatment is particularly beneficial in reducing inflammatory damage.[70] See ►**Table 2**.

TCM Injections

Re Du Ning Injection is a TCM injection mainly composed of Qinghao (Artemisiae Annuae Herba), Jinyinhua (Lonicerae Japonicae Flos), and Zhizi (Gardeniae Fructus). It has the

Table 2 Research models and action mechanisms of Chinese couplet medicines treating acute lung injury/acute respiratory distress syndrome through nuclear factor-κB-related signaling pathways

Medicines	Models	Action mechanisms	References
Jingjie–Fangfeng	ALI mice, RAW 264.7 macrophages, A549 cell	NF-κB ↓, reducing inflammation, resisting oxidization	67
Mahuang–Dahuang	ALI rats	NF-κB ↓, M1 macrophages ↓, reducing inflammatory responses	68
Huangqi–Danshen	ALI rats	TLR4/NF-κB ↓, reducing inflammatory responses	70

Abbreviations: ALI, acute lung injury; ARDS, acute respiratory distress syndrome; Nf-κB, nuclear factor-κB; TLR, Toll-like receptor.

effects of clearing heat and resolving toxins, reducing swelling and stopping bleeding, protecting the liver and benefiting the gallbladder, relieving summer heat, and eliminating steaming heat. It is widely used in the treatment of pneumonia and upper respiratory tract infections.[71] Research shows that Re Du Ning Injection can reduce the level of inflammatory factors, alleviate the "inflammatory storm" of ALI/ARDS, which is associated with its ability to inhibit the activation of the TLR4/MyD88/NF-κB pathway and block the recruitment of neutrophils.[72] Chuan Ke Zhi Injection acts by inhibiting the TLR4/NF-κB/NLRP3 pathway to exert its anti-lung injury effect.[73]

Cylindromatosis (CYLD) is a negative regulator of NF-κB. Studies have found that CYLD plays a negative regulatory role in the process of ALI. Compound Danshen Injection can activate lung tissue CYLD and inhibit NF-κB signaling pathway activation to alleviate inflammation-induced ALI in rats.[74]

Tan Re Qing Injection is composed of Huangqin (Scutellariae Radix), bear gall powder, goat horn, Jinyinhua (Lonicerae Japonicae Flos), and Lianqiao (Forsythiae Fructus). It has the effects of clearing heat and removing toxins, dispersing the lung, and relieving the exterior, which can inhibit lung tissue NF-κB activation in septic ALI/ARDS rats and block the inflammatory cascade reaction.[75] Dazhu Hongjingtian Injection can also be used for septic ALI.[76] Jin Na Duo Injection is composed of the Yinxingye (Ginkgo Folium) extracts (ginaton), which has the effects of scavenging free radicals, resisting oxidant reactions, protecting vascular endothelium, and improving microcirculation. After treatment with ginaton, NF-κB expression decreases and TNF-α content reduces.[77] Within a certain range, moderate doses of Xuebijing Injection have the best protective effect on the lung tissue of firearm injury-induced ALI rabbits, but the protective effect of Xuebijing Injection weakens with doses exceeding the moderate level.[78] See ►**Table 3**.

Chinese Herbal Compound Formulas and Their Preparations

Chinese herbal compound formulas and their preparations are an important therapeutic approach for downregulating NF-κB expression in ALI. Yantiao Formula, Qingfu Tongchang Granules, and dexamethasone have similar effects and can avoid the adverse effects of systemic glucocorticoid application.[79,80] Linggui Zhugan Decoction is a representative formula for warming yang and transforming water retention. Research has confirmed that after treatment with Linggui Zhugan Decoction, inflammatory cell and red blood cell exudation in lung tissues is significantly reduced, especially in the low-dose group.[81] Meanwhile, Jinyin Qingre Oral Liquid shows the most significant improvement in lung alveolar capillary permeability and lung tissue lesions in the high-dose group.[82] Extrapulmonary ARDS in patients primarily exhibits diffuse inflammatory exudation in the lung early on, followed by respiratory failure. According to TCM, the main pathogenesis involves a deficiency of primordial yang and diffuse invasion of yin pathogens. The Fusu Mixture (Resuscitation Compound) is composed of the Qianyang Bunus for treating edema and the Sini Decoction for treating collapse syndrome which jointly warms the kidney

Table 3 Research models and action mechanisms of TCM injections treating acute lung injury/acute respiratory distress syndrome through nuclear factor-κB-related signaling pathways

Medicines	Models	Action mechanisms	References
Re Du Ning Injection	ALI mice	TLR4/MyD88/NF-κB ↓, reducing inflammatory responses	72
Chuan Ke Zhi Injection	ALI mice	TLR4/NF-κB/NLRP3 ↓, reducing inflammatory responses	73
Compound Danshen Injection	ALI rats	CYLD/NF-κB ↓, reducing inflammatory responses	74
Tan Re Qing Injection	ALI rats	NF-κB ↓, reducing inflammatory responses	75
Dazhu Hongjingtian Injection	ALI mice	NF-κB ↓, reducing inflammatory responses	76
Jin Na Duo Injection	ALI rats	NF-κB ↓, reducing inflammatory responses	77
Xuebiqing Injection	ALI rabbits	NF-κB ↓, reducing inflammatory responses	78

Abbreviations: ALI, acute lung injury; CYLD, Cylindromatosis; MyD88, myeloid differentiation primary response protein 88; NF-κB, nuclear factor-κB; NLRP3, NOD-, LRR-, and pyrin domain-containing protein 3; TLR, Toll-like receptor.

and suppresses yang, and warms yang and dredges the meridians. The Fusu Mixture has a protective effect on human microvascular endothelial cells,[83] involving long noncoding RNA in regulating NF-κB to alleviate the inflammatory response and oxidative stress associated with sepsis-related ARDS.[84]

The TLR4-mediated NF-κB pathway is also a common therapeutic target for the treatment of ALI. Yiqi Kangfei Formula, derived from modified Xiangsha Liujunzi Decoction, Yupingfeng Powder, and Xiaoxianxiong Decoction, can inhibit the activation of the TLR4/MyD88/NF-κB signaling pathway to reduce the synthesis and release of inflammatory factors, thereby improving the capillary membrane permeability and pulmonary edema in ALI hamster.[85] The active ingredients in Shengjiang Powder (Ascending and Descending Powder) for the treatment of ALI are mainly phytosterols such as campesterol and cholesterol because the powder contains more phytosterols. Therefore, the efficacy of powder is superior to decoction.[86] Qingfei Litan Formula originates from *Traditional Chinese Medicine Diagnosis and Treatment Plan for Wind-Warm Disease with Lung Heat* issued by the National Administration of Traditional Chinese Medicine, with effects of relieving the fleshy exterior and clearing heat, eliminating restlessness and quenching thirst, so it can be used for lung heat syndrome. Experimental results confirm that Qingfei Litan Formula also acts on ALI rats.[87]

NLRP3 is the most common inflammasome in ALI mechanism research, whose activation induces the maturation of effector protein caspase-1 promotes the production of IL-1β and IL-18, and further accelerates cell apoptosis and ALI progression.[88] Therefore, inhibiting the TLR4/NF-κB/NLRP3 signaling pathway activation is an effective approach to improving ALI. Through this pathway, Yiqi Huayu Jiedu Formula can reduce downstream inflammatory factor content and cell apoptosis to alleviate lung alveolar and interstitial congestion and edema.[89] Additionally, Shiwei Qingwen Decoction (SWQD) also acts through this pathway. High-performance liquid chromatography and liquid chromatography mass spectrometry techniques have identified effective chemical components in SWQD derived mainly from Jinyinhua (Lonicerae Japonicae Flos), Fangfeng (Saposhnikovia Radix), and Huangqin (Scutellariae Radix). Among them, cimifugin in Fangfeng is the main chemical

Table 4 Research models and action mechanisms of Chinese herbal compounds and their preparations for treating acute lung injury/acute respiratory distress syndrome through nuclear factor-κB signaling pathways

Medicines	Models	Action mechanisms	References
Inflammation Regulation Formula	ALI rats	NF-κB ↓, reducing inflammatory responses	79
Qingfu Tongchang Granules	ALI rats	NF-κB ↓, reducing inflammatory responses	80
Linggui Zhugan Decoction	ALI mice	NF-κB ↓, reducing inflammatory responses	81
Jinyin Qingre Oral Liquid	ALI mice	NF-κB ↓, reducing inflammatory responses	82
Fusu Mixture	ALI rats, human pulmonary microvascular endothelial cell (HPMEC) cell	NF-κB ↓, reducing inflammatory responses	84
Yiqi Kangfei Formula	ALI hamsters	TLR4/MyD88/NF-κB ↓, reducing inflammatory responses	85
Ascending and Descending Powder	ALI mice	TLR4/NF-κB/MAPK ↓, reducing inflammation	86
Qingfei Litan Formula	ALI rats	TLR4/NF-κB ↓, reducing inflammatory responses	87
Yiqi Huayu Jiedu Formula	ALI rats	TLR4/NF-κB/NLRP3 ↓, reducing inflammatory responses	89
Shiwei Qingwen Decoction	ALI rats, THP-1 cell	TLR4/NF-κB/NLRP3 ↓, THP-1 cell ↓, reducing inflammatory responses	90
Maxing Shigan Decoction	ALI mice	MAPK/NF-κB ↓, reducing inflammation, resisting oxidization	91
Qingyi Decoction	ALI mice	MAPK/NF-κB/NLRP3 ↓, reducing inflammatory responses	92
Mahuang Shengma Decoction	ALI mice	RAGE/NF-κB ↓, reducing inflammatory responses	93
Qingwen Baidu Beverage	ALI rats	IKKα/NF-κB ↓, reducing inflammatory responses	94
Jinzhen Oral Liquid	ALI mice	PI3K/AKT/NF-κB ↓, reducing inflammatory responses	95
Qidong Huoxue Drink	ALI rats	Cav-1/NF-κB ↓, reducing inflammation	96

Abbreviations: ALI, acute lung injury; AKT, protein kinase B; ARDS, acute respiratory distress syndrome; IKKα, inhibitor of κB kinase α; MAPK, mitogen-activated protein kinase; MyD88, myeloid differentiation primary response protein 88; NF-κB, nuclear factor-κB; NLRP3, NOD-, LRR-, and pyrin domain-containing protein 3; PI3K, phosphoinositide 3-kinase; TLR, Toll-like receptor.

component of SWQD's medicinal serum. SWQD can upregulate the expression of Aquaporin (AQP) 1 (AQP1) and AQP5 to promote lung alveolar fluid transport and thus reduce pulmonary edema, and alleviate lung tissue pathological damage by inhibiting MPO and neutrophil elastase expression. In vitro experiments show that SWQD can suppress the level of NO secreted by human monocytic-leukemia cells (THP-1) macrophages by inhibiting the expression of iNOS.[90] Maxing Shigan Decoction can reduce inflammatory cytokine levels in ALI mice, increase SOD activity and glutathione content, reduce malondialdehyde level, enhance antioxidant capacity, and improve lung function and lung CT scan results.[91]

Qingyi Decoction promotes the recovery of ALI associated with severe acute pancreatitis while enhancing intestinal barrier function treatment. Its mechanism is related to targeted regulation along the gut–lung axis via the MAPK/NF-κB/NLRP3 pathway.[92] The primary compound in Mahuang Shengma Decoction mainly derives Mahuang (Ephedrae Herba), which has been found to inhibit the expression of key gene receptor for advanced glycation end products (RAGE) and downstream NF-κB p65 in the RAGE/NF-κB signaling pathway.[93] Qingwen Baidu Beverage has the effects of clearing heat and purging fire, and simultaneously clearing qi and blood, which is a classical prescription for the treatment of warm diseases and can significantly reduce the mortality rate of ALI rats.[94] Jinzhen Oral Liquid originates from the empirical formula Lingyang Qingfei Powder, with effects of clearing heat and removing toxins, resolving phlegm and stopping cough. It is clinically used for infantile acute bronchitis and pediatric pneumonia. And by inhibiting protein phosphorylation of the PI3K/AKT/NF-κB pathway, it can improve lung tissue interstitial edema and inflammatory reactions in LPS-induced ALI.[95] Qidong Huoxue Drink consists of Huzhang (Polygoni Cuspidati Rhizoma et Radix), Danggui (Angelicae Sinensis Radix), Huangqi (Astragali Radix) and Maidong (Ophiopogonis Radix). The whole formula exerts the effects of clearing heat and nourishing yin, tonifying qi and lifting yang, nourishing blood and dispelling blood stasis, and expelling pathogens while reinforcing healthy qi. Medium and high doses of Qidong Huoxue Drink can significantly reduce Cav-1 expression. Through pathways such as endothelial NO synthase and HO-1, it can regulate NF-κB activation, reduce the synthesis and secretion of proinflammatory cytokines, increase anti-inflammatory cytokine levels, and correct inflammatory imbalance.[96] See ►**Table 4**.

Conclusions

In summary, the NF-κB signaling pathway is widely utilized in the treatment of ALI/ARDS, serving as both a mediator of inflammation and an important potential treatment target. It has been found that the NF-κB signaling pathway interacts with various targets such as PI3K, AKT, NLRP3, TAK1, MAPK, and TLR4. By inhibiting the protein expression levels of related signaling pathways, it can reduce the generation of proinflammatory cells, exert anti-inflammatory, antioxidant, and antiapoptotic effects, and improve pathological damage, pulmonary edema severity, and lung function caused by ALI. Furthermore, the regulation of the NF-κB signaling pathway can improve coagulation status and microcirculation, and alleviate lung tissue bleeding.

The significant role of TCM in regulating NF-κB-related signaling pathways for treating ALI/ARDS is evident. Chinese herbal monomers, couplet medicines, injections, and compound formulas and their preparations can all be used for the treatment of this disease. In this paper, the effective chemical components and their sources for the treatment of ALI/ARDS in recent years were summarized and analyzed, to provide theoretical evidence for the diversified treatment of ALI/ARDS and facilitate the follow-up research.

There are still many shortcomings in the study of NF-κB-related signaling pathways in TCM treatment of ALI/ARDS: (1) Studies indicate the effectiveness of various Chinese herbal monomers in treating ALI/ARDS but they lack clinical data. Western medicine hospitals lack promotion data on Chinese patent medicines, Chinese herbal injections, or Chinese compound formulas. (2) ALI/ARDS patients often face challenges such as multiple medications and difficulty in compliance. Research is needed on dose conversion using small doses, different dosage forms, or alternative administration methods (such as external treatment methods like application of TCM transparent medicine and TCM fumigation), as well as further evaluation of the medicinal efficacy. Therefore, further research is needed to grasp the key points of applying these treatments for ALI/ARDS and fully leverage the advantages of TCM, thus providing new medication strategies for modern medical treatments of this disease.

CRediT Authorship Contribution

Wanzhao Zuo: conceptualization, data curation, and writing—original draft. **Fanian Tian**: visualization and formal analysis. **Jia Ke**: funding acquisition. **Cheng Jiang**: data curation. **Yi Yang**: funding acquisition and project administration. **Cong He**: supervision, funding acquisition, and writing—review and editing.

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Conflict of Interest

The authors declare no conflict of interest.

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