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Biomarkers, signaling pathways, and programmed cell death in acute lung injury and its treatment with Traditional Chinese Medicine: a narrative review

Y. AN[1], H. ZHANG[2], R. WANG[2], Y.-F. SHEN[3], J.-L. ZHAO[3], Y.-S. ZOU[2], G.-Z. WANG[4]

[1]Affiliated Geriatric Hospital of Wuhan University of Science and Technology, Wuhan, P.R. China
[2]Hubei Provincial Hospital of Traditional Chinese Medicine, Wuhan, P.R. China
[3]Hubei University of Chinese Medicine, Wuhan, P.R. China
[4]The Second Hospital of Dalian Medical University, Dalian, P.R. China

Y. An, H. Zhang, and R. Wang contributed equally to this work

Abstract. – Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are common life-threatening, high-mortality lung diseases associated with acute and severe inflammation of the lungs. However, research on diagnostic markers and signaling pathways associated with ALI/ARDS is lacking, and no specific drug therapy is available for ALI/ARDS. Therefore, in this study, biomarkers and signaling pathways associated with ALI/ARDS were summarized to provide a reference for future clinical and research work. A review of Traditional Chinese Medicine for the treatment or prevention of ALI/ARDS is also presented to provide a reference for further development of Traditional Chinese Medicine. In summary, this review will help raise awareness of ALI/ARDS and provide insight into the future exploitation of Traditional Chinese Medicine.

Key Words:
Acute lung injury, Acute respiratory distress syndrome, Biomarkers and signaling pathways, Traditional Chinese Medicine.

Abbreviations

Acute lung injury, ALI; Acute respiratory distress syndrome, ARDS; intensive care unit, ICU; Traditional Chinese Medicine, TCM; Lipopolysaccharide, LPS; bronchoalveolar lavage fluid, BALF; Interleukin–1beta, IL-1β; Interleukin–6, IL-6; Interleukin–18, IL-18; Mitogen-activated protein kinase, MAPK); Extracellular signal-regulated kinase, ERK; Jun N-terminal kinase, JNK; Toll-like receptor 4, TLR4; Myeloid differentiation protein 88, Myd88; Nuclear factor-kB, NF-kB; JAK/STAT3, Janus Kinase/ signal transducer and activator of transcription; NOD-like receptor thermal protein domain associated protein 3, NLRP3; Sirtuin 3, SIRT3; Manganese superoxide dismutase, MnSOD; Activated protein kinase, AMPK; Nuclear factor erythroid-2 related factor 2, Nrf2; Kelchlike ECH-associated protein 1, Keap1; Glutathione peroxidase 4, GPX4; Glutathione, GSH; PI3K/Akt/mTOR, phosphatidylinositol-3-kinase/protein kinase B/ mammalian target of rapamycin; Xuebijing, XBJ; Xiyanping injection, XYP; malondialdehyde, MDA; Superoxide dismutase, SOD.

Introduction

As a respiratory disease with a high mortality rate, acute lung injury (ALI) is characterized by acute hypoxic respiratory failure, increased alveolar permeability, and severe alveolar oedema[1,2]. Meanwhile, as ALI progresses, it can lead to acute respiratory distress syndrome (ARDS) and eventually cause death in patients[3]. Recent statistics[4] have shown that ALI has a high incidence (200,000 cases per year in the US) and a high overall mortality rate. Even if these patients recover after positive treatments, they are still burdened by functional limitations related to muscle weakness, endocrine disorders, and psychological trauma[5,6]. Currently, several studies[6] have confirmed that mechanical ventilation is an effective means of reducing mortality from ALI. However, effective drug treatment for ALI to significantly reduce mortality and improve patients' quality of life is still lacking[7]. Thus, exploring effective pharmacological therapies is of great clinical importance. Traditional Chinese Medicine (TCM) has played an important role in the treatment of pulmonary diseases for thousands of years. In China, TCM treatments have achieved remarkable results in combatting COVID-19,

Corresponding Authors: Jingling Zhao, MD; e-mail: ayin6666@163.com;
Yinshui Zou, MD; e-mail: jianze1969@sina.com;
Guangzhi Wang, MD; e-mail: wanggz@dmu.edu.cn

relieving clinical symptoms, and reducing the rate of severe illness and mortality[8]. Therefore, treating ALI with TCM has also attracted our interest. Meanwhile, numerous active ingredients isolated from Chinese herbal medicine have been shown to have significant efficacy against ALI1. For example, flavonoid components of herbs with anti-inflammatory and antioxidant activity render them useful candidates for pulmonary injury prevention[9]. Anthraquinone compounds have a variety of pharmacological effects, such as antifibrotic, antibacterial, and anti-inflammatory effects, which allow them to play a critical role in the treatment of ALI[10]. Similarly, TCM prescriptions also have potential therapeutic effects. Fusu decoction exerts its therapeutic effect in lipopolysaccharide (LPS)-induced ALI model rats potentially by suppressing HPA1 expression and attenuating cell injury[11]. However, a comprehensive review of TCM for ALI is currently unavailable. In this paper, we intend to summarize the pathogenesis of ALI and the pharmacological mechanisms of TCM treatments, which may increase researchers' understanding of the pathogenesis of ALI and provide a reference for natural drug development.

Search Methods Strategy

A literature search was conducted by the authors, using two online databases (PubMed, Web of Science). Keywords used in the search included "Acute lung injury", "ALI", "Biomarkers", "signaling pathways", "programmed cell death", "Traditional Chinese Medicine", and "treatment". Inclusion criteria consisted of biomarkers, signaling pathways, and programmed cell death in acute lung injury and its treatment with Traditional Chinese Medicine. Moreover, some articles were excluded, if they were not in the English language, if the biomarkers, signaling pathways, and programmed death were not correlated with acute lung injury, and/or if TCM treatment of acute lung injury is irrelevant. We set the search time as nearly 10 years, that is, 2013-2023.

All the abstracts were screened, and all the studies examining Biomarkers, signaling pathways, and programmed cell death in acute lung injury and its treatment with Traditional Chinese Medicine as an outcome were considered to meet the inclusion criteria. Then, the full articles were retrieved. All the eligible abstracts and articles were assessed for inclusion in this narrative review. Contact was made with the authors of the pieces when further information was required. Using a standardized approach, four reviewers (H. Zhang, Y.-F. Shen, Y.-S. Zou, and J.-L Zhao) independently assessed the extracted data, including titles, abstracts, references, and full-text articles. Each data set was reviewed by another reviewer (G.-Z. Wang), and any disagreements were solved by discussion. Y. An finalized the manuscript.

Biomarkers, Signaling Pathways, and Programmed Cell Death Involved in Acute Lung Injury

Biomarkers for ALI

The basic pathophysiological change in ALI is noncardiogenic pulmonary edema due to increased endothelial permeability of the alveolar epithelium and pulmonary capillaries[12]. In brief, dysfunction of the alveolar endothelial-epithelial barrier is thought to play a vital role in the development of ALI[13]. Hence, in addition to the blood, numerous biomarkers are mainly detected in bronchoalveolar lavage fluid (BALF)[13].

Clinicoradiologic diagnosis is currently the main diagnostic method for ALI and ARDS. Due to the hindrance of clinical detection tools, laboratory and diagnostic tests for ALI and ARDS still lack characteristic biomarkers[12]. However, some promising biomarkers can help diagnose ALI and ARDS. As a result of immunological recognition of the pathogen responsible for inducing a proinflammatory immune response, ALI in response to severe pulmonary microbial infections can occur[14]. In this process, many inflammatory factors can serve as natural predictors of ALI disease severity.

Tumor necrosis factor-α (TNF-α) is an inflammatory cytokine produced by macrophages/monocytes during acute inflammation[15]. Clinical evidence has shown that ARDS patients have elevated levels of TNF-α in peripheral blood[16]. However, the specific mechanisms have not been fully elucidated. TNF-α is an activator of neutrophils[17]. In ALI/ARDS patients, neutrophil-forming clusters can block capillaries and small arteries, leading to redistribution and obstruction of the pulmonary microcirculation[18], which is most likely to occur induced by TNF-α. In addition, macrophages also play critical roles in ALI/ARDS. Macrophages can typically be classified into two types: classically activated (M1) macrophages and alternatively activated (M2) macrophages[19]. During ALI progression, alveolar

epithelial cells and proinflammatory macrophages crosstalk with each other and accelerate the induction of lung injury[20]. During this process, macrophages can secrete exosomes and endosomes, which carry TNF-α that can induce the inflammatory effects of the lung[20]. Collectively, TNF-α may serve as a potential biomarker for the prognosis and diagnosis of ALI/ARDS.

Interleukins are classified into several subtypes, and most can influence the progression or remission of ALI[21]. Many studies[22,23] have confirmed that overproduction of interleukin-1beta (IL-1β), interleukin-6 (IL-6), and interleukin-18 (IL-18) accelerates the development of ALI/ARDS. Among these interleukins, IL-6 induces a severe inflammatory response, which also reacts with thrombin to promote clotting, leading to pulmonary capillary obstruction and further triggering ARDS[24]. IL-1β is an inflammation-related cytokine that is secreted mainly by macrophages and epithelial cells and exerts lung fibrosis effects via downstream cytokines[25]. However, one of the outcomes of ARDS is lung fibrosis[26]. Thus, IL-1β is partly predictive of the severity and prognosis of ALI/ARDS.

Generally, diffuse alveolar injury is the main pathological manifestation of ALI[27], and massive accumulation of inflammatory cells in the alveoli and interstitium is one of the pivotal pathological features[28]. Therefore, detecting these cells in BALF, which visually reflects lung injury severity, is critically important. In clinical practice, lymphocytes (B lymphocytes and T lymphocytes) and protein levels in BALF are significant indicators of the extent of alveolar lesions[29]. Notably, patients with ALI/ARDS have increased pulmonary vascular permeability due to endothelial barrier disruption caused by an excessive inflammatory response, which ultimately leads to protein and lymphocyte influx into the alveoli[30]. These findings also demonstrate that protein levels in BALF and lymphocyte assays have a strong potential to serve as biomarkers for the diagnosis of ALI/ARDS.

ALI Signaling Pathways

A number of signaling pathways play critical roles in the pathogenesis of ALI. The mitogen-activated protein kinase (MAPK) signaling pathway is a highly conserved regulator of eukaryotic cell function and is involved in several biological processes, such as the cell cycle, apoptosis, differentiation, protein biosynthesis, and tumorigenesis[31]. The MAPK signaling pathway consists of three subfamilies: P38, extracellular signal-regulated kinase (ERK), and c-Jun N-terminal kinase (JNK)[32]. The current view suggests that activation of either of these three subfamilies can accelerate ALI progression[33]. In animal models of ALI, activation of the MAPK signaling pathway is often induced by the binding of lipopolysaccharide (LPS) and Toll-like receptor 4 (TLR4) upstream; this signaling activates downstream myeloid differentiation protein 88 (Myd88) and triggers a downstream activation cascade involving the MAPK signaling pathway and IL-1β[34]. TLR4/NF-kappaB (NF-κB) signaling is another signaling pathway that has strong relevance to ALI. TLR4 is an important pattern recognition receptor that can recognize pathogenic bacteria that translocate into the circulation. This process initiates phosphorylation activation of the NF-κB pathway through MyD88 and upregulates the expression of various inflammatory factors, including TNF-α, IL-1β, and IL-635. Once NF-κB is activated by phosphorylation, it induces the production of several inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, which may play a synergistic role in the inflammatory response and lung tissue damage[36]. In addition, LPS stimulation triggers signaling pathways that ultimately lead to nuclear translocation of the NF-κB p65 component, which contains the primary transcriptional regulatory domain responsible for activating NF-κB-responsive genes[37]. Ultimately, the TLR4-related signaling pathway results in ALI progression (Figure 1). The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway may be a potential target for intervention in ALI. Generally, the JAK/STAT pathway transduces signals from activated receptors or intracellular kinases into the nucleus, thereby regulating the transcription of genes involving cytokines, adhesion molecules, and inflammatory mediators[38]. JAK2 is activated through phosphorylation, which subsequently leads to phosphorylation and dimerization of STAT3[39]. Currently, inhibition of the JAK/STAT3 pathway has been reported to improve ALI[40]. As a transcription factor, STAT3 plays a key role in inflammation and in the pathogenesis of ALI by regulating the expression of various cytokines and immune regulatory genes (IL-1β, IL-6, TNF-α, iNOS, CCL2, and MHC class II)[41]. In addition, activation of NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammatory vesicles may be associated with the JAK/STAT3 pathway[42]. NLRP3 has a critical role in ALI induced by the JAK/STAT3 signaling pathway. High phosphorylated STAT3 expression

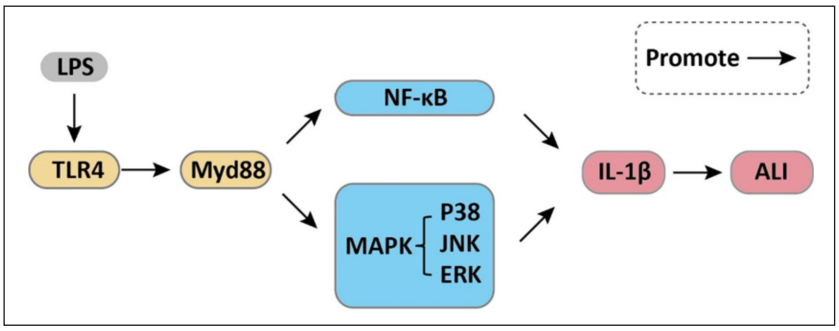

Figure 1. TLR4-related signalling pathway. LPS activates TLR4 and its downstream effector Myd88, which further activates the NF-κB and MAPK signalling pathways, leading to increased IL-1β secretion, which in turn induces the development of ALI.

can activate ac-H3 and AC-H4 levels on the NLRP3 promoter, resulting in NLRP3 activation[43]. Then, the assembled NLRP3 inflammasome activates the protease caspase-1 to induce pyroptosis and contributes to several types of cell death, including apoptosis, necroptosis, and ferroptosis, which are associated with the pathogenesis of various inflammatory diseases[44]. Notably, apoptosis, a topical component of emerging programmed cell death, can accelerate ALI progression[17]. Activated caspase-3 (downstream of NLRP3) is an attractive molecule in apoptosis, and caspase-3 activation causes an ALI cascade[45] (Figure 2). Sirtuin 3 (SIRT3), a mitochondrial member of the sirtuin family of NAD-dependent deacetylases, has been well-recognized for its antioxidant properties[46]. In a retrospective study, SIRT3 may be employed as a promising biomarker in the early diagnosis of lung cancer[47]. In addition, SIRT3 is essential for the inhibition of pulmonary fibrosis[48]. In mouse models of LPS-induced ALI, macrophage reprogramming and mitochondrial superoxide formation by SIRT3 are critical mediators of the heightened inflammation and severity of lung injury[49]. The underlying protective mechanism of SIRT3 in ALI may consist of the following aspects: SIRT3 overexpression increases the protein level and enzyme activity of manganese superoxide dismutase (MnSOD) and inhibits oxidative stress in the lungs of ALI mice[50]. Additionally, AMP-activated protein kinase (AMPK) is a signaling modulator of SIRT3 in mitochondrial biosynthesis and homeostasis[51]. Furthermore, AMPK affects the downstream nuclear factor erythroid-2 related Factor 2 (Nrf2). Upon ALI, Nrf2 dissociates from Kelchlike ECH-associated protein 1 (Keap1), translocates to the nucleus, and binds to antioxidant response elements (ARs) in the promoter region

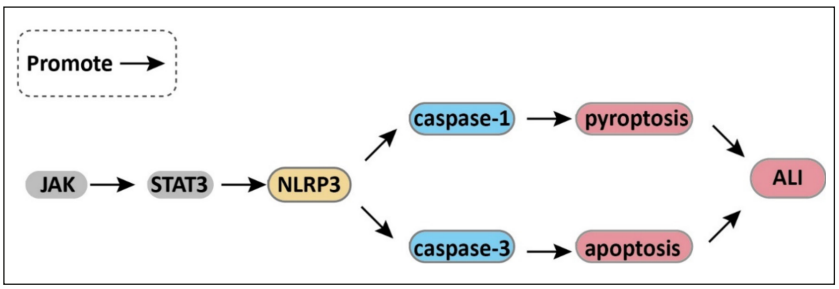

Figure 2. JAK/STAT3-related signalling pathway. Activation of the JAK/STAT3 signalling pathway induces NLRP3 activation and apoptosis via caspase-1 or scorch death *via* caspase-3, which ultimately leads to ALI.

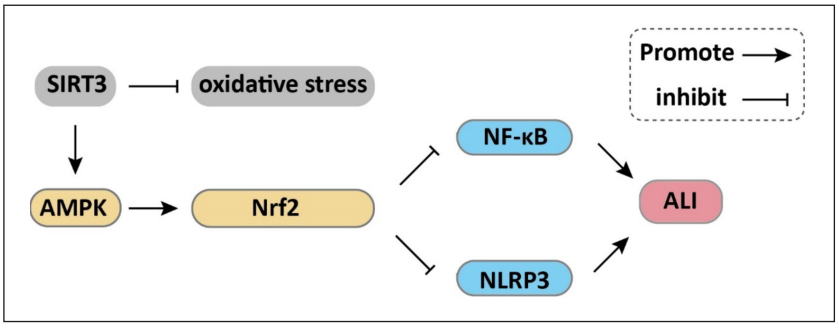

Figure 3. SIRT3-related signalling pathway. As an inhibitor of oxidative stress, SIRT3 promotes AMPK-induced activation of Nrf2 and inhibits the inflammation-associated NF-κB pathway and NLRP3 pathway, further alleviating ALI.

of cytoprotective genes[52]. Ultimately, the above protective effect inhibited NLRP3 and NF-κB activation and thus protected against LPS-induced lung injury in ALI mice[52] (Figure 3).

Different Types of Programmed Cell Death Involved in ALI

Apoptosis, a form of programmed cell death, is an autonomously ordered cell death controlled by genes. Under pathological conditions, dysregulated apoptotic pathways have been shown to damage alveolar epithelial cells and endothelial cells[53]. Therefore, apoptosis may be closely related to the severity of ALI, which has been confirmed in several studies. For example, extensive apoptosis of pulmonary alveolar type II epithelial cells has been shown to be responsible for impaired epithelial barrier function and remodeling of certain mesenchymal cells in ALI[53]. In addition, uncontrolled activation of the apoptosis pathway results in inflammation and destruction of lung tissues, ultimately inducing lung cell death by apoptosis[54], which also suggests that apoptosis has a major role in the mechanisms of ALI development. In particular, the mitochondrial pathway is very important in regulating apoptosis in the pathogenesis of ALI. After receiving stimulation to produce large amounts of ROS and/or inflammation in ALI, a complex of Bax and Bcl-2 proteins (key proteins for apoptosis) enters the mitochondria, increasing the permeability of the mitochondrial membrane and leading to a decrease in membrane potential (a hallmark event in the early stages of apoptosis)[55]. Additionally, the transcription factor p53, another proapoptotic regulator, is a trigger for DNA repair mechanisms and cell cycle arrest. The mechanism of action lies in the fact that p53 targets a promoter region that controls the expression of several pro-apoptotic Bax proteins[2]. Then, the above pathways lead to the activation of critical proteins that initiate apoptosis (cleaved-caspase-9 and cleaved-caspase-3), causing the generation of apoptotic bodies and leading to apoptosis of lung epithelial cells[56] (Figure 4). Ferroptosis is thought to be a novel form of regulated cell death characterized by lipid peroxidation, which is strongly dependent on the accumulation of iron and ROS[57]. Recent studies have confirmed that Nrf2 inhibits ferroptosis and protects against ALI by regulating SLC7A11 and HO-1[58]. Nrf2 is a transcription factor that coordinates basal and stress-induced activation of several cellular protection genes, such as free radicals, lipid peroxidation, and reactive oxygen species (ROS), byproducts of physiological and pathological cellular processes occurring in mitochondria, peroxisomes, and endoplasmic reticulum[59]. In particular, lipid peroxidation is the key initiator of the ferroptosis cascade reaction[60]. A previous study also demonstrated that upregulation of Nrf2 expression conferred resistance to ferroptosis damage by inhibiting lipid peroxidation in ALI models[58]. Therefore, we suggest that Nrf2 is a protective gene against ferroptosis damage in ALI models. Glutathione peroxidase 4 (GPX4), which is also an established transcriptional target of Nrf2, is a reducer of lipid peroxide against ferroptosis[61]. Glutathione (GSH), a simple tripeptide consisting of glutamate, cysteine, and glycine, is one of the most important components of cellular antioxidant defense. Typically, GSH is used by GPX4 to reduce lipid peroxides to an alcoholic form, which can act as an anti-ferroptosis agent[62]. One study found that GSH and GPX4 were significantly reduced in LPS-induced ALI models, suggesting that they may be protective regulators against ferroptosis in ALI mice[63]. SLC7A11 also plays an essential role in ferroptosis as a downstream target of Nrf2. Specifically, Nrf2 binds to antioxidant response elements in gene promoters and governs the transcription of genes involved in antioxidant defense and redox maintenance, including SLC7A11[64]. Inhibition of SLC7A11 indirectly inactivates GPX4 and increases toxic lipid peroxidation by reducing cystine

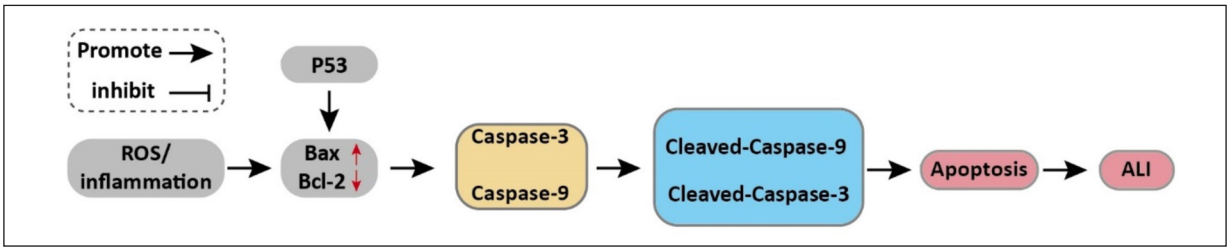

Figure 4. Apoptosis-related signalling pathway. ROS, inflammation, and/or P53 cause elevated Bax and reduced Bcl-2, thereby inducing apoptosis in ALI. Then, the above pathways lead to the activation of critical proteins that initiate apoptosis (cleaved caspase-9 and cleaved caspase-3), eventually causing apoptosis and exacerbating ALI progression.

input and limiting GSH synthesis, resulting in ferroptosis progression and ALI[65]. Furthermore, p53 is also one of the major ferroptosis regulators in the nucleus, which may improve ALI induced by intestinal ischemia/reperfusion. The detailed mechanism may be associated with inhibition of cysteine uptake through p53-mediated downregulation of SLC7A11, thereby reducing GPX activity and GSH synthesis[66] (Figure 5).

Autophagy is a self-degrading process that removes misfolded or aggregated proteins, clears damaged organelles (such as mitochondria, endoplasmic reticulum, and peroxisomes), and eliminates intracellular pathogens[67]. Numerous autophagy factors play vital roles in the pathological process of ALI. Activation of the PI3K/Akt/mTOR (phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin) signaling pathway inhibits autophagy in bronchial epithelial cells during ALI, which in turn relieves pulmonary fibrosis and lung inflammation[68]. As a serine/threonine kinase, mTOR has a tight inverse coupling between its activation and autophagy induction: activation of mTOR inhibits autophagy through the phosphorylation of multiple autophagy-related proteins, which promote autophagy initiation and autophagosome nucleation[69]. As a result, the expression of autophagy biomarkers (LC3, Beclin1, p62) is upregulated due to the activation of autophagy[70]. In addition, the cytoplasmic clearance function of autophagy has an anti-inflammatory effect in any cell capable of activating autonomous inflammation, which is one of the main mechanisms underlying the protective effect of autophagy against ALI[67,71]. Nevertheless, several studies[72] have suggested that autophagy may serve both protective and damaging functions in the progression of ALI. A previous study[72] showed that the expression of inflammatory cytokines, histological injuries, and the expression level of NLRP3 inflammatory vesicle-associated protein were markedly reduced in a mouse model of ALI by enhancing autophagy with rapamycin. However, autophagy may also have a detrimental role in ALI pathogenesis under certain circumstances. For instance, activation of the NLRP3 inflammasome and subsequent release of IL-1β and IL-18 could be initiated by increased LC3 expression in lung macrophages[73], which may be related to the stage and level of autophagy and the disease evolution of ALI. This study[74] elucidate the "double-edged" role of autophagy in the pathogenesis of ALI, and researchers have summarized the following: 1) when autophagy is decreased from its basal level, autophagy is protective; 2) when autophagy is deleterious, it is generally upregulated by stimulation; and 3) the endosomal/exosomal pathways may be associated with the deleterious function of autophagy in airway epithelial injury. Pyroptosis, also known as inflammatory necrosis, is a form of programmed cell death that occurs when cells swell until their membranes rupture,

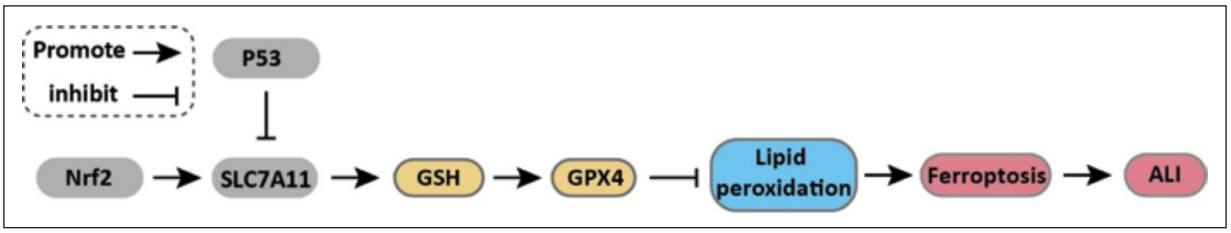

Figure 5. Ferroptosis-related signalling pathway. Nrf2 can promote downstream transcription of SLC7A11. SLC7A11 further promotes GSH synthesis, increases GPX4 activity, and inhibits lipid peroxidation. Finally, ferroptosis and ALI can be alleviated.

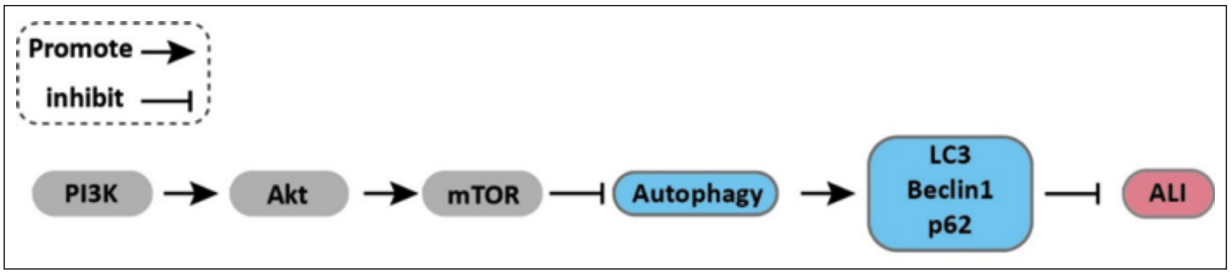

Figure 6. Autophagy-related signalling pathway. PI3K/AKT/mTOR negatively regulates autophagy signature proteins (LC3, Beclin1, p62), which can alleviate ALI progression.

leading to the release of cellular contents and the activation of an intense inflammatory response[75] (Figure 6). Pyroptosis is an important natural immune response in the body and plays an important role in the fight against infection. Pyroptosis is caspase 1 dependent, and its activation induces cell swelling, perforates the plasma membrane and leads to potassium efflux, resulting in the extracellular release of proinflammatory substances[76]. Endothelial cell pyroptosis has a facilitative role in LPS-induced lung tissue injury in ALI mice[77], and LPS induces NLRP3 inflammasome-mediated cell scorching by promoting ROS production[78]. In addition, the adaptor protein Apoptosis-Associated Speck-Like Protein Containing CARD plays a critical role in connecting pyrin domains connecting inflammasomes (such as NLRP3) to caspase-1[79]. NLRP3 is oligomerized and exhibits clustered pyrin domains (PYDs) interacting with ASCs. The ASC-containing caspase recruitment domain (CARD) then interacts with the CARD of pro-caspase-1, thereby activating caspase-1[80]. Furthermore, caspase-1 converts precursors of the proinflammatory cytokines IL-1β and IL-18 into their active forms (mature IL-1β and IL-18)[81]. Considering the enormous damaging role of inflammation in ALI, apoptosis inhibition and maturation of IL-1β and IL-18 may be important targets in the treatment of ALI[21] (Figure 7).

Treatment of ALI with Traditional Chinese Medicine

The understanding of ALI/ARDS has improved considerably over the past decades. However, mortality remains high due to the limited efficacy of therapeutic approaches. Lung-protective mechanical ventilation is currently the most effective nonpharmacological intervention, but it is only "temporary" and cannot be maintained in the long term[3]. In addition, some corticosteroid drugs also play a certain therapeutic role. However, the ensuing side effects cannot be ignored[82]. Thus, we focus on Traditional Chinese Medicine, which may have fewer side effects and effective therapeutic roles.

Traditional Chinese Medicine, as a kind of natural product resource, plays an irreplaceable role in adjuvant therapy for ALI. The invention of Chinese herbal injection (CHI) is a critical innovation in the modernization of Traditional Chinese Medicine, and its utilization during ALI/ARDS therapy has been widely accepted in China[83]. For example, Xuebijing (XBJ) injection is effective in controlling the inflammatory response (to reduce the serum levels of IL-6, IL-8, and TNF-α) and thus is widely used for ALI/ARDS and COVID-19 in China[84,85]. Its effects may be attributed to the multi-component composition of XBJ (safflower, peony, Ligusticum chuanxiong, Salvia miltiorrhiz, and Angelica), which operates through a "multicomponent, multitarget, multi-pathway" approach[32]. Specifically, XBJ mainly relies on its anti-inflammatory, anticoagulant, immunomodulatory, endothelial protective, and antioxidant effects in ALI/ARDS therapy[32]. The other representative CHI is the Xiyanping injection (XYP). Andrographolide sulfonate, the active ingredient of XYP, is the water-soluble form of andrographolide, which has anti-inflammatory properties[86]. The efficacy of XYP in infectious pulmonary diseases has been confirmed by several clinical studies86-88, including COVID-19, pneumonia, and acute bronchi-

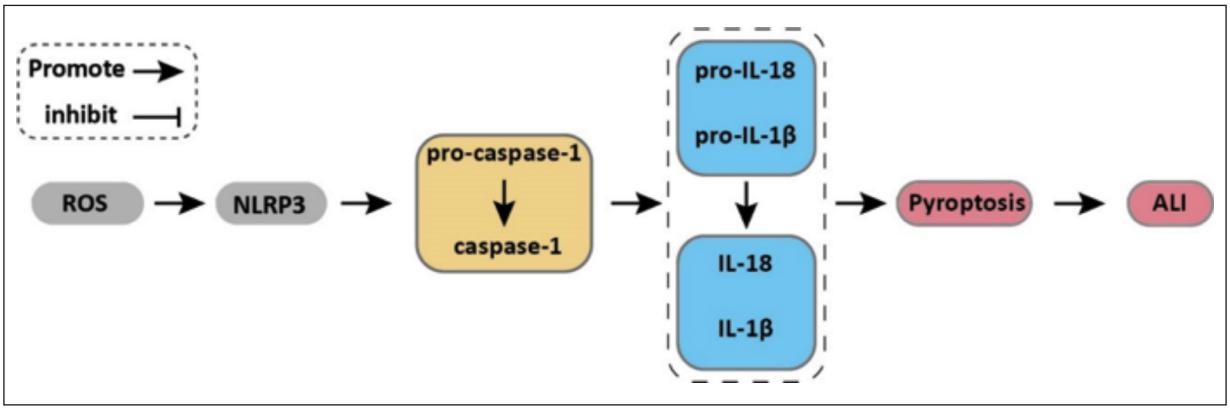

Figure 7. Pyroptosis-related signalling pathway. Reactive oxygen species lead to activation of NLRP3, which converts caspase-1 precursors to mature caspase-1, which in turn converts IL-18 and IL-1β precursors to mature forms, resulting in cell death and ALI.

tis. However, in addition to the efficacy of CHI, the development of adverse effects should not be ignored. In China, of the 31,913 patients monitored on XBJ, 234 experienced adverse reactions, including skin pruritus, erythra, chest tightness, fever, and labored breathing[89]. Based on the results of a prospective, post-marketing, large-scale, hospital-based centralized surveillance study[90] that collected a total of 30,759 patients who adopted XYP, 23 patients experienced XYP-related adverse reactions. The most significant adverse reactions to XYP are allergic reactions, including rash, itching, and even anaphylaxis[90]. Therefore, monitoring for occasional adverse reactions and using CHI appropriately and based on its efficacy are important. Many studies[91] of herbal ingredients in the treatment of ALI have confirmed the beneficial effects of single herbs. Rhubarb is one of these representative medicines. Traditional Chinese Medicine (TCM) theory suggests that rhubarb has pharmacological effects of supporting defecation, relieving heat, and promoting blood circulation[92]. These effects are attributed to multiple natural active ingredients from rhubarb, including rhein, emodin, aloe emodin, physcion, and chrysophanol, for their antibacterial, antifibrotic, and anti-inflammatory efficacy[93]. To date, these main components of rhubarb have been shown to have beneficial therapeutic effects against ALI. For example, rhein inhibits human respiratory syncytial virus-induced lung inflammatory injury by inhibiting NLRP3 inflammatory vesicle activation through the NF-κB pathway in mice[94]. Emodin attenuates silica-induced lung injury by inhibiting inflammation, apoptosis, and epithelial-mesenchymal transition[95]. *Scutellaria baicalensis* ameliorates LPS-induced ALI by inhibiting inflammation *in vitro* and *in vivo*[96]. Due to the complex composition of *Scutellaria baicalensis*, the ingredients that play a role in healing can vary. *Scutellaria baicalensis* is used as a medicine in the root, the most dominant component of which is the flavonoid group[97]. The total flavonoid extract of *Scutellaria baicalensis* has huge potential in the treatment of ALI *via* its antiviral, anti-inflammatory, and anti-complement properties[97]. Furthermore, the most important of these flavonoid components is baicalin. Baicalin inhibits numerous inflammation-related signaling pathways owing to its strong anti-inflammatory effect. For instance, baicalein has been shown to inhibit NF-κB-mediated inflammatory responses and upregulate the Nrf2/HO-1 pathway for the treatment of LPS-induced ALI in rats98. Baicalin attenuates LPS-induced ALI in mice by inhibiting the TLR4/JNK/ERK/NF-κB pathway[99]. In addition, Bupleurum, another herb with beneficial anti-inflammatory effects, may be used as a potential treatment for ALI. In contrast, the therapeutic effect of the polysaccharide component of Bupleurum on ALI has been more frequently reported[100]. The main anti-inflammatory effect of Bupleurum polysaccharide is due to inhibition of the TLR4, MAPK, and NF-κB signalling pathways, which in turn suppress the secretion of proinflammatory factors[101]. In addition to the above anti-inflammatory herbs, tonic herbs also have potential therapeutic effects on ALI. Licorice has an influential position in various formulas for its tonic and harmonizing effects and presents various modalities in the treatment of ALI. Licorice reduced pulmonary oedema and fibrosis, reduced malondialdehyde (MDA) levels and increased superoxide dismutase (SOD) activity in paraquat-induced ALI mice while also protecting the morphological appearance of lung tissue and protecting or improving liver and kidney function in mice, thus increasing survival rates[102]. In addition, glycyrrhizic acid, a major component of licorice, can mitigate ALI progression through the regulation of autophagy by PI3K/AKT/mTOR[103]. Furthermore, a few reports are available on the efficacy of some herbs for ALI, including Citrus aurantium and amygdalin[104-106].

In Traditional Chinese Medicine, herbal formulas have been the primary therapy for thousands of years. The representative formulas are as follows: Xiao-Chai-Hu-Tang, a classical formula of the "Treatise on Febrile Diseases", has been widely used in China for thousands of years to remedy infectious diseases[107]. One study confirmed that Xiao Chai Hu Tang precisely inhibited activation of the NF-κB signaling pathway and, therefore, downstream inflammatory factors and chemokines in ALI mice[108]. Fusu agent, which is made from *Aconitum carmichaelii Debx, Carapax Testudinis, Fructus Amomi, Rhizome Zingiberis, Radix Glycyrrhizae Prepa, rata* and *Herba Ephedrae*, is widely applied in China for ALI therapy. Stabilization of mitochondrial membrane potential, activation of caspase-3-induced apoptosis, and reduction of ROS accumulation were the mechanisms by which the Fusu agent inhibited ALI. Meanwhile, Fusu agent treatment effectively inhibited the expression of heparanase 1 *in vitro* and *in vivo*, which played a vital role in endothelial cell injury[11]. Qing Ying Tang, a classic Chinese formula, is often used clinically to treat serious infectious diseases. Qing Ying Tang upregulates AQP-1 synthesis by suppressing the inflammatory response and reducing the secretion

of TNF-α, thereby reducing the extent of pulmonary edema and mitigating ALI progression[109]. In addition, several Chinese medicinal preparations, such as Liang Di San, Xia Bai San, Sheng Lung Healing Asthma Tang, and Wild Chrysanthemum Capsules, can alleviate ALI progression through anti-inflammatory effects[110-113]. However, based on both clinical and basic studies[113] confirming the efficacy of herbal formulas for ALI, we did not find strong evidence for the study of the pharmacological basis of these herbal formulas. The complex composition of herbs is a double-edged sword. On the one hand, this complex composition forms the basis of the medicinal effect, but it also hinders further intensification of herbal research. Even though methods such as liquid mass spectrometry (LC-MS) and gas chromatography (GC-MS) are available for analyses of herbal formula components, their high price and analytical errors have hindered the progress of herbal medicine research. As a unique form of therapy in Traditional Chinese Medicine, acupuncture is extremely useful in the treatment of acute diseases. Thousands of years ago, acupuncture was documented in "Zhenjiu jiayi jing" to treat lung diseases. Acupuncture targeting some specific points can provide good therapeutic effects. For example, stimulation of acupuncture points of ST-36 (Zusanli) and lung acupoints in a model of ALI was found to effectively reduce apoptosis, increase HO-1 expression, and alleviate the progression of lung injury[114]. In addition, the concept of treating untreated patients is the core idea of TCM, and the role of acupuncture in preventing ALI should not be overlooked. Acute lung injury was induced with LPS after pre-acupuncture of the ST-36 (Zusanli), and acupuncture was found to confer a good preventive effect, reducing the degree of lung injury, lung iNOS expression, and lung NO biosynthesis[115]. However, the lack of randomized, double-blind controlled studies and compelling clinical evidence remains an obstacle to acupuncture use for lung injury.

Conclusions

ALI/ARDS is a serious clinical syndrome with a very high mortality rate and a poor prognosis. In this review, we summarize the main biomarkers and signalling pathways of ALI to facilitate clinical research. Furthermore, we have summarized the efficacy of current TCM treatments for ALI. TCM has shown considerable potential benefits in the treatment of ALI/ARDS. However, RCT studies with a high level of medical evidence based on clinically good efficacy are lacking, which might restrict the clinical use of TCM for ALI. In addition, research on Chinese medicinal ingredients will also be on the agenda. These items will be the focus of future research. The development and application of TCM still require extensive effort, but we must start immediately.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics Approval

Not applicable.

Authors' Contributions

Rui Wang and Yi An contributed equally to this work. Jingling Zhao and Guangzhi Wang designed the study. Rui Wang and Guangzhi Wang were the major contributors in drafting and revising the manuscript. Yinshui Zou, Yinfeng Shen, and Hao Zhang finally revised the manuscript. All authors read and approved the final manuscript.

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ORCID ID

Yi An: 0009-0007-2080-9500
Hao Zhang: 0000-0002-9664-1309
Rui Wang: 0000-0002-4605-9644
Yinfeng Shen: 0000-0003-3892-1318
Jingling Zhao: 0000-0002-7845-9204
Yinshui Zou: 0009-0008-6957-3014
Guangzhi Wang: 0000-0002-8216-648X.

References

1) Agostini L, Martinon F, Burns K, McDermott MF, Hawkins PN, Tschopp J. Natural product derived phytochemicals in managing acute lung injury by multiple mechanisms. Pharmacol Res 2021; 163: 105224.
2) Bertheloot D, Latz E, Franklin BS. Necroptosis, pyroptosis and apoptosis: an intricate game of cell death. Cell Mol Immunol 2021; 18: 1106-1121.
3) Mokrá D. Acute lung injury - from pathophysiology to treatment. Physiol Res 2020; 69: S353-S366.
4) Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, Gattinoni L, van Haren F, Larsson A, McAuley DF, Ranieri M, Rubenfeld G, Thompson BT, Wrigge H, Slutsky AS, Pesenti A. Epidemiology, Patterns of Care, and Mortality for Patients with Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA 2016; 315: 788-800.
5) Petrucci N, De Feo C. Lung protective ventilation strategy for the acute respiratory distress syndrome. Cochrane Database Syst Rev 2013; 2013: Cd003844.
6) Lu J, Wang X, Chen M, Cheng L, Chen Q, Jiang H, Sun Z. An Open Lung Strategy in the Management of Acute Respiratory Distress Syndrome: A Systematic Review and Meta-Analysis. Shock 2017; 48: 43-53.
7) Fan E, Brodie D, Slutsky AS. Acute Respiratory Distress Syndrome: Advances in Diagnosis and Treatment. JAMA 2018; 319: 698-710.
8) Zhao Z, Li Y, Zhou L, Zhou X, Xie B, Zhang W, Sun J. Prevention and treatment of COVID-19 using Traditional Chinese Medicine: A review. Phytomedicine 2021; 85: 153308.
9) Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. J Nutr Sci 2016; 5: e47.
10) Dong X, Fu J, Yin X, Cao S, Li X, Lin L, Ni J. Emodin: A Review of its Pharmacology, Toxicity and Pharmacokinetics. Phytother Res 2016; 30: 1207-1218.
11) Gao P, Zhao Z, Zhang C, Wang C, Long K, Guo L, Li B. The therapeutic effects of traditional Chinese medicine Fusu agent in LPS-induced acute lung injury model rats. Drug Des Devel Ther 2018; 12: 3867-3878.
12) Butt Y, Kurdowska A, Allen TC. Acute Lung Injury: A Clinical and Molecular Review. Arch Pathol Lab Med 2016; 140: 345-350.
13) Mokra D, Kosutova P. Biomarkers in acute lung injury. Respir Physiol Neurobiol 2015; 209: 52-58.
14) Kumar V. Pulmonary Innate Immune Response Determines the Outcome of Inflammation During Pneumonia and Sepsis-Associated Acute Lung Injury. Front Immunol 2020; 11: 1722.
15) Idriss HT, Naismith JH. TNF alpha and the TNF receptor superfamily: structure-function relationship(s). Microsc Res Tech 2000; 50: 184-195.
16) Li T, Luo N, Du L, Liu J, Gong L, Zhou J. Early and marked up-regulation of TNF-α in acute respiratory distress syndrome after cardiopulmonary bypass. Front Med 2012; 6: 296-301.
17) Jiao Y, Zhang T, Zhang C, Ji H, Tong X, Xia R, Wang W, Ma Z, Shi X. Exosomal miR-30d-5p of neutrophils induces M1 macrophage polarization and primes macrophage pyroptosis in sepsis-related acute lung injury. Crit Care 2021; 25: 356.
18) Park I, Kim M, Choe K, Song E, Seo H, Hwang Y, Ahn J, Lee SH, Lee JH, Jo YH, Kim K, Koh GY, Kim P. Neutrophils disturb pulmonary microcirculation in sepsis-induced acute lung injury. Eur Respir J 2019; 53: 1800786.
19) Hu Q, Lyon CJ, Fletcher JK, Tang W, Wan M, Hu TY. Extracellular vesicle activities regulating macrophage- and tissue-mediated injury and repair responses. Acta Pharm Sin B 2021; 11: 1493-1512.
20) Li ZG, Scott MJ, Brzóska T, Sundd P, Li YH, Billiar TR, Wilson MA, Wang P, Fan J. Lung epithelial cell-derived IL-25 negatively regulates LPS-induced exosome release from macrophages. Mil Med Res 2018; 5: 24.
21) Peukert K, Fox M, Schulz S, Feuerborn C, Frede S, Putensen C, Wrigge H, Kümmerer BM, David S, Seeliger B, Welte T, Latz E. Inhibition of Caspase-1 with Tetracycline Ameliorates Acute Lung Injury. Am J Respir Crit Care Med 2021; 204: 53-63.
22) Rogers AJ, Guan J, Trtchounian A, Hunninghake GM, Kaimal R, Desai M, Kozikowski LA, DeSouza L, Mogan S, Liu KD, Matthay MA, Steingrub J, Wheeler A, Yoon JH, Nakahira K, Choi AM, Baron RM. Association of Elevated Plasma Interleukin-18 Level With Increased Mortality in a Clinical Trial of Statin Treatment for Acute Respiratory Distress Syndrome. Crit Care Med 2019; 47: 1089-1096.
23) Wang Y, Wang H, Zhang C, Zhang C, Yang H, Gao R, Tong Z. Lung fluid biomarkers for acute respiratory distress syndrome: a systematic review and meta-analysis. Crit Care 2019; 23: 43.
24) Liu B, Zhao H, Wang Y, Zhang H, Ma Y. Astragaloside IV Attenuates Lipopolysaccharides-Induced Pulmonary Epithelial Cell Injury through Inhibiting Autophagy. Pharmacology 2020; 105: 90-101.
25) Shimodaira T, Matsuda K, Uchibori T, Sugano M, Uehara T, Honda T. Upregulation of osteopontin expression via the interaction of macrophages and fibroblasts under IL-1b stimulation. Cytokine 2018; 110: 63-69.
26) Villar J, Zhang H, Slutsky AS. Lung Repair and Regeneration in ARDS: Role of PECAM1 and Wnt Signaling. Chest 2019; 155: 587-594.
27) Soni S, Wilson MR, O'Dea KP, Yoshida M, Katbeh U, Woods SJ, Takata M. Alveolar macrophage-derived microvesicles mediate acute lung injury. Thorax 2016; 71: 1020-1029.
28) Li Y, Huang J, Foley NM, Xu Y, Li YP, Pan J, Redmond HP, Wang JH, Wang J. B7H3 ameliorates LPS-induced acute lung injury via attenuation of neutrophil migration and infiltration. Sci Rep 2016; 6: 31284.

29) Friedmann D, Unger S, Keller B, Rakhmanov M, Goldacker S, Zissel G, Frye BC, Schupp JC, Prasse A, Warnatz K. Bronchoalveolar Lavage Fluid Reflects a T(H)1-CD21(low) B-Cell Interaction in CVID-Related Interstitial Lung Disease. Front Immunol 2020; 11: 616832.

30) Jiang J, Huang K, Xu S, Garcia JGN, Wang C, Cai H. Targeting NOX4 alleviates sepsis-induced acute lung injury via attenuation of redox-sensitive activation of CaMKII/ERK1/2/MLCK and endothelial cell barrier dysfunction. Redox Biol 2020; 36: 101638.

31) Hepworth EMW, Hinton SD. Pseudophosphatases as Regulators of MAPK Signaling. I Int J Mol Sci 2021; 22: 12595.

32) Li C, Wang P, Li M, Zheng R, Chen S, Liu S, Feng Z, Yao Y, Shang H. The current evidence for the treatment of sepsis with Xuebijing injection: Bioactive constituents, findings of clinical studies and potential mechanisms. J Ethnopharmacol 2021; 265: 113301.

33) Nie Y, Wang Z, Chai G, Xiong Y, Li B, Zhang H, Xin R, Qian X, Tang Z, Wu J, Zhao P. Dehydrocostus Lactone Suppresses LPS-induced Acute Lung Injury and Macrophage Activation through NF-κB Signaling Pathway Mediated by p38 MAPK and Akt. Molecules 2019; 24: 1510.

34) Li Y, Zhang J, Liu H, Yuan J, Yin Y, Wang T, Cheng B, Sun S, Guo Z. Curcumin ameliorates glyoxylate-induced calcium oxalate deposition and renal injuries in mice. Phytomedicine 2019; 61: 152861.

35) Dolinay T, Kim YS, Howrylak J, Hunninghake GM, An CH, Fredenburgh L, Massaro AF, Rogers A, Gazourian L, Nakahira K, Haspel JA, Landazury R, Eppanapally S, Christie JD, Meyer NJ, Ware LB, Christiani DC, Ryter SW, Baron RM, Choi AM. Inflammasome-regulated cytokines are critical mediators of acute lung injury. Am J Respir Crit Care Med 2012; 185: 1225-1234.

36) Behjani ZZ, Ai J, Soleimani M, Atashi A, Taheri B, Ebrahimi-Barough S, Siavashi V, Shirian S, Hamidieh AA. Human unrestricted somatic stem cells ameliorate sepsis-related acute lung injury in mice. J Cell Physiol 2019; 234: 13942-13950.

37) Kawai T, Akira S. Signaling to NF-kappaB by Toll-like receptors. Trends Mol Med 2007; 13: 460-469.

38) Chen WD, Zhang JL, Wang XY, Hu ZW, Qian YB. The JAK2/STAT3 signaling pathway is required for inflammation and cell death induced by cerulein in AR42J cells. Eur Rev Med Pharmacol Sci 2019; 23: 1770-1777.

39) Owais K, Huang T, Mahmood F, Hubbard J, Saraf R, Bardia A, Khabbaz KR, Li Y, Bhasin M, Sabe AA, Sellke F, Matyal R. Cardiopulmonary Bypass Decreases Activation of the Signal Transducer and Activator of Transcription 3 (STAT3) Pathway in Diabetic Human Myocardium. Ann Thorac Surg 2015; 100: 1636-1645.

40) Qin MZ, Qin MB, Liang ZH, Tang GD. Effect of SOCS3 on lung injury in rats with severe acute pancreatitis through regulating JAK2/STAT3 signaling pathway. Eur Rev Med Pharmacol Sci 2019; 23: 10123-10131.

41) Zhao J, Yu H, Liu Y, Gibson SA, Yan Z, Xu X, Gaggar A, Li PK, Li C, Wei S, Benveniste EN, Qin H. Protective effect of suppressing STAT3 activity in LPS-induced acute lung injury. Am J Physiol Lung Cell Mol Physiol 2016; 311: L868-L880.

42) Zhu H, Jian Z, Zhong Y, Ye Y, Zhang Y, Hu X, Pu B, Gu L, Xiong X. Janus Kinase Inhibition Ameliorates Ischemic Stroke Injury and Neuroinflammation Through Reducing NLRP3 Inflammasome Activation via JAK2/STAT3 Pathway Inhibition. Front Immunol 2021; 12: 714943.

43) Liu CC, Huang ZX, Li X, Shen KF, Liu M, Ouyang HD, Zhang SB, Ruan YT, Zhang XL, Wu SL, Xin WJ, Ma C. Upregulation of NLRP3 via STAT3-dependent histone acetylation contributes to painful neuropathy induced by bortezomib. Exp Neurol 2018; 302: 104-111.

44) Komada T, Muruve DA. The role of inflammasomes in kidney disease. Nat Rev Nephrol 2019; 15: 501-520.

45) Li X, Li Y, Shen K, Li H, Bai J. The protective effect of ticagrelor on renal function in a mouse model of sepsis-induced acute kidney injury. Platelets 2019; 30: 199-205.

46) Singh CK, Chhabra G, Ndiaye MA, Garcia-Peterson LM, Mack NJ, Ahmad N. The Role of Sirtuins in Antioxidant and Redox Signaling. Antioxid Redox Signal 2018; 28: 643-661.

47) Tao F, Gu C, Li N, Ying Y, Feng Y, Ni D, Zhang Q, Xiao Q. SIRT3 acts as a novel biomarker for the diagnosis of lung cancer: A retrospective study. Medicine 2021; 100: e26580.

48) Cheresh P, Kim SJ, Jablonski R, Watanabe S, Lu Z, Chi M, Helmin KA, Gius D, Budinger GRS, Kamp DW. SIRT3 Overexpression Ameliorates Asbestos-Induced Pulmonary Fibrosis, mt-DNA Damage, and Lung Fibrogenic Monocyte Recruitment. Int J Mol Sci 2021; 22: 6856.

49) Kurundkar D, Kurundkar AR, Bone NB, Becker EJ Jr, Liu W, Chacko B, Darley-Usmar V, Zmijewski JW, Thannickal VJ. SIRT3 diminishes inflammation and mitigates endotoxin-induced acute lung injury. JCI Insight 2019; 4: e120722.

50) Tian YG, Zhang J. Protective effect of SIRT3 on acute lung injury by increasing manganese superoxide dismutase-mediated antioxidation. Mol Med Rep 2018; 17: 5557-5565.

51) Chen L, Li W, Qi D, Lu L, Zhang Z, Wang D. Honokiol protects pulmonary microvascular endothelial barrier against lipopolysaccharide-induced ARDS partially via the Sirt3/AMPK signaling axis. Life Sci 2018; 210: 86-95.

52) Liu Q, Lv H, Wen Z, Ci X, Peng L. Isoliquiritigenin Activates Nuclear Factor Erythroid-2 Related Factor 2 to Suppress the NOD-Like Receptor Protein 3 Inflammasome and Inhibits the NF-κB Pathway in Macrophages and in Acute Lung Injury. Front Immunol 2017; 8: 1518.

53) Wu X, Kong Q, Zhan L, Qiu Z, Huang Q, Song X. TIPE2 ameliorates lipopolysaccharide-induced apoptosis and inflammation in acute lung injury. Inflamm Res 2019; 68: 981-992.

54) Ju M, Liu B, He H, Gu Z, Liu Y, Su Y, Zhu D, Cang J, Luo Z. MicroRNA-27a alleviates LPS-induced acute lung injury in mice via inhibiting inflammation and apoptosis through modulating TLR4/MyD88/NF-κB pathway. Cell Cycle 2018; 17: 2001-2018.

55) Zhang Q, Feng A, Zeng M, Zhang B, Shi J, Lv Y, Cao B, Zhao C, Wang M, Ding Y, Zheng X. Chrysosplenol D protects mice against LPS-induced acute lung injury by inhibiting oxidative stress, inflammation, and apoptosis via TLR4-MAPKs/NF-κB signaling pathways. Innate Immun 2021; 27: 514-524.

56) Xie W, Lu Q, Wang K, Lu J, Gu X, Zhu D, Liu F, Guo Z. miR-34b-5p inhibition attenuates lung inflammation and apoptosis in an LPS-induced acute lung injury mouse model by targeting progranulin. J Cell Physiol 2018; 233: 6615-6631.

57) Chen X, Li J, Kang R, Klionsky DJ, Tang D. Ferroptosis: machinery and regulation. Autophagy 2021; 17: 2054-2081.

58) Dong H, Qiang Z, Chai D, Peng J, Xia Y, Hu R, Jiang H. Nrf2 inhibits ferroptosis and protects against acute lung injury due to intestinal ischemia reperfusion via regulating SLC7A11 and HO-1. Aging (Albany NY) 2020; 12: 12943-12959.

59) 59)Tonelli C, Chio IIC, Tuveson DA. Transcriptional Regulation by Nrf2. Antioxid Redox Signal 2018; 29: 1727-1745.

60) Yin H, Xu L, Porter NA. Free radical lipid peroxidation: mechanisms and analysis. Chem Rev 2011; 111: 5944-5972.

61) Salazar M, Rojo AI, Velasco D, de Sagarra RM, Cuadrado A. Glycogen synthase kinase-3beta inhibits the xenobiotic and antioxidant cell response by direct phosphorylation and nuclear exclusion of the transcription factor Nrf2. J Biol Chem 2006; 281: 14841-14851.

62) Yang WS, SriRamaratnam R, Welsch ME, Shimada K, Skouta R, Viswanathan VS, Cheah JH, Clemons PA, Shamji AF, Clish CB, Brown LM, Girotti AW, Cornish VW, Schreiber SL, Stockwell BR. Regulation of ferroptotic cancer cell death by GPX4. Cell 2014; 156: 317-331.

63) Liu P, Feng Y, Li H, Chen X, Wang G, Xu S, Li Y, Zhao L. Ferrostatin-1 alleviates lipopolysaccharide-induced acute lung injury via inhibiting ferroptosis. Cell Mol Biol Lett 2020; 25: 10.

64) Koppula P, Zhuang L, Gan B. Cystine transporter SLC7A11/xCT in cancer: ferroptosis, nutrient dependency, and cancer therapy. Protein Cell 2021; 12: 599-620.

65) Lin W, Wang C, Liu G, Bi C, Wang X, Zhou Q, Jin H. SLC7A11/xCT in cancer: biological functions and therapeutic implications. Am J Cancer Res 2020; 10: 3106-3126.

66) Jiang L, Kon N, Li T, Wang SJ, Su T, Hibshoosh H, Baer R, Gu W. Ferroptosis as a p53-mediated activity during tumour suppression. Nature 2015; 520: 57-62.

67) Glick D, Barth S, Macleod KF. Autophagy: cellular and molecular mechanisms. J Pathol 2010; 221: 3-12.

68) Cong LH, Li T, Wang H, Wu YN, Wang SP, Zhao YY, Zhang GQ, Duan J. IL-17A-producing T cells exacerbate fine particulate matter-induced lung inflammation and fibrosis by inhibiting PI3K/Akt/mTOR-mediated autophagy. J Cell Mol Med 2020; 24: 8532-8544.

69) Kim YC, Guan KL. mTOR: a pharmacologic target for autophagy regulation. J Clin Invest 2015; 125: 25-32.

70) Xue JF, Shi ZM, Zou J, Li XL. Inhibition of PI3K/AKT/mTOR signaling pathway promotes autophagy of articular chondrocytes and attenuates inflammatory response in rats with osteoarthritis. Biomed Pharmacother 2017; 89: 1252-1261.

71) Zeng Z, Liang J, Wu L, Zhang H, Lv J, Chen N. Exercise-Induced Autophagy Suppresses Sarcopenia Through Akt/mTOR and Akt/FoxO3a Signal Pathways and AMPK-Mediated Mitochondrial Quality Control. Front Physiol 2020; 11: 583478.

72) Peng W, Peng F, Lou Y, Li Y, Zhao N, Shao Q, Chen J, Qian K, Zeng Z, Zhan Y, Jiang R, Liu F. Autophagy alleviates mitochondrial DAMP-induced acute lung injury by inhibiting NLRP3 inflammasome. Life Sci 2021; 265: 118833.a

73) Zhang Y, Liu G, Dull RO, Schwartz DE, Hu G. Autophagy in pulmonary macrophages mediates lung inflammatory injury via NLRP3 inflammasome activation during mechanical ventilation. Am J Physiol Lung Cell Mol Physiol 2014; 307: L173-L185.

74) Li ZY, Wu YF, Xu XC, Zhou JS, Wang Y, Shen HH, Chen ZH. Autophagy as a double-edged sword in pulmonary epithelial injury: a review and perspective. Am J Physiol Lung Cell Mol Physiol 2017; 313: L207- L217.

75) Yu P, Zhang X, Liu N, Tang L, Peng C, Chen X. Pyroptosis: mechanisms and diseases. Signal Transduct Target Ther 2021; 6: 128.

76) Cheng P, Li S, Chen H. Macrophages in Lung Injury, Repair, and Fibrosis. Cells 2021; 10: 436.

77) Cheng KT, Xiong S, Ye Z, Hong Z, Di A, Tsang KM, Gao X, An S, Mittal M, Vogel SM, Miao EA, Rehman J, Malik AB. Caspase-11-mediated endothelial pyroptosis underlies endotoxemia-induced lung injury. J Clin Invest 2017; 127: 4124-4135.

78) Qiu Z, He Y, Ming H, Lei S, Leng Y, Xia ZY. Lipopolysaccharide (LPS) Aggravates High Glucose- and Hypoxia/Reoxygenation-Induced Injury through Activating ROS-Dependent NLRP3 Inflammasome-Mediated Pyroptosis in H9C2 Cardiomyocytes. J Diabetes Res 2019; 2019: 8151836.

79) Agostini L, Martinon F, Burns K, McDermott MF, Hawkins PN, Tschopp J. NALP3 forms an IL-1beta-processing inflammasome with increased activity in Muckle-Wells autoinflammatory disorder. Immunity 2004; 20: 319-325.

80) Yang Y, Liu PY, Bao W, Chen SJ, Wu FS, Zhu PY. Hydrogen inhibits endometrial cancer growth via

a ROS/NLRP3/caspase-1/GSDMD-mediated pyroptotic pathway. BMC Cancer 2020; 20: 28.

81) Miao EA, Rajan JV, Aderem A. Caspase-1-induced pyroptotic cell death. Immunol Rev 2011; 243: 206-214

82) Mokra D, Mikolka P, Kosutova P, Mokry J. Corticosteroids in Acute Lung Injury: The Dilemma Continues. Int J Mol Sci 2019; 20: 4765.

83) Li Y, Zhang J. [Improvement and enhancement of traditional Chinese medicine injections]. Zhongguo Zhong Yao Za Zhi 2011; 36: 1905-1909.

84) Song Y, Yao C, Yao Y, Han H, Zhao X, Yu K, Liu L, Xu Y, Liu Z, Zhou Q, Wang Y, Ma Z, Zheng Y, Wu D, Tang Z, Zhang M, Pan S, Chai Y, Song Y, Zhang J, Pan L, Liu Y, Yu H, Yu X, Zhang H, Wang X, Du Z, Wan X, Tang Y, Tian Y, Zhu Y, Wang H, Yan X, Liu Z, Zhang B, Zhong N, Shang H, Bai C. XueBiJing Injection Versus Placebo for Critically Ill Patients With Severe Community-Acquired Pneumonia: A Randomized Controlled Trial. Crit Care Med 2019; 47: e735-e743.

85) Luo Z, Chen W, Xiang M, Wang H, Xiao W, Xu C, Li Y, Min J, Tu Q. The preventive effect of Xuebijing injection against cytokine storm for severe patients with COVID-19: A prospective randomized controlled trial. Eur J Integr Med 2021; 42: 101305.

86) Zhang XY, Lv L, Zhou YL, Xie LD, Xu Q, Zou XF, Ding Y, Tian J, Fan JL, Fan HW, Yang YX, Ye XQ. Efficacy and safety of Xiyanping injection in the treatment of COVID-19: A multicenter, prospective, open-label and randomized controlled trial. Phytother Res 2021; 35: 4401-4410.

87) Li Q, Li ZY, Zhang J, Guo WN, Xu XM, Sun FX, Xu H. Xiyanping Plus Azithromycin Chemotherapy in Pediatric Patients with Mycoplasma pneumoniae Pneumonia: A Systematic Review and Meta-Analysis of Efficacy and Safety. Evid Based Complement Alternat Med 2019; 2019: 2346583.

88) Sun MH, Lyu J, Zhang YL, Wang ZF, Yang J, Xie YM. [Systematic evaluation and Meta-analysis on effectiveness and safety of Xiyanping Injection in treatment of acute bronchitis in children]. Zhongguo Zhong Yao Za Zhi 2019; 44: 4387-4396.

89) Zheng R, Wang H, Liu Z, Wang X, Li J, Lei X, Fan Y, Liu S, Feng Z, Shang, H. A real-world study on adverse drug reactions to Xuebijing injection: hospital intensive monitoring based on 93 hospitals (31,913 cases). Ann Transl Med 2019; 7: 117.

90) Chen S, Kwong JSW, Zheng R, Wang Y, Shang H. Normative Application of Xiyanping Injection: A Systematic Review of Adverse Case Reports. Evid Based Complement Alternat Med 2018; 2018: 4013912.

91) Tang T, Wang F, Liu J, Ye W, Zhao T, Li Z. Rhubarb Alleviates Acute Lung Injury by Modulating Gut Microbiota Dysbiosis in Mice. Curr Microbiol 2022; 79: 116.

92) Zhuang T, Gu X, Zhou N, Ding L, Yang L, Zhou M. Hepatoprotection and hepatotoxicity of Chinese herb Rhubarb (Dahuang): How to properly control the "General (Jiang Jun)" in Chinese medical herb. Biomed Pharmacother 2020; 127: 110224.

93) Cao YJ, Pu ZJ, Tang YP, Shen J, Chen YY, Kang A, Zhou GS, Duan JA. Advances in bio-active constituents, pharmacology, and clinical applications of rhubarb. Chin Med 2017; 12: 36.

94) Shen C, Zhang Z, Xie T, Ji J, Xu J, Lin L, Yan J, Kang A, Dai Q, Dong Y, Shan J, Wang S, Zhao X. Rhein Suppresses Lung Inflammatory Injury Induced by Human Respiratory Syncytial Virus Through Inhibiting NLRP3 Inflammasome Activation via NF-κB Pathway in Mice. Front Pharmacol 2020; 10: 1600.

95) Pang X, Shao L, Nie X, Yan H, Li C, Yeo AJ, Lavin MF, Xia Q, Shao H, Yu G, Jia Q, Peng C. Emodin attenuates silica-induced lung injury by inhibition of inflammation, apoptosis, and epithelial-mesenchymal transition. Int Immunopharmacol 2021; 91: 107277.

96) Tu Y, Gu L, Chen D, Wu W, Liu H, Hu H, Wan Y, Sun W. Rhein Inhibits Autophagy in Rat Renal Tubular Cells by Regulation of AMPK/mTOR Signaling. Sci Rep 2017; 7: 43790.

97) Zhi HJ, Zhu HY, Zhang YY, Lu Y, Li H, Chen DF. In vivo effect of quantified flavonoids-enriched extract of Scutellaria baicalensis root on acute lung injury induced by influenza A virus. Phytomedicine 2019; 57: 105-116.

98) Tsai CL, Lin YC, Wang HM, Chou TC. Baicalein, an active component of Scutellaria baicalensis, protects against lipopolysaccharide-induced acute lung injury in rats. J Ethnopharmacol. 2014; 153: 197-206.

99) Long Y, Xiang Y, Liu S, Zhang Y, Wan J, Yang Q, Cui M, Ci Z, Li N, Peng W. Baicalin Liposome Alleviates Lipopolysaccharide-Induced Acute Lung Injury in Mice via Inhibiting TLR4/JNK/ERK/NF-κB Pathway. Mediators Inflamm 2020; 2020: 8414062.

100) Tong H, Tian D, Li T, Wang B, Jiang G, Sun X. Inhibition of inflammatory injure by polysaccharides from Bupleurum chinense through antagonizing P-selectin. Carbohydr Polym 2014; 105: 20-25.

101) Wu J, Zhang YY, Guo L, Li H, Chen DF. Bupleurum polysaccharides attenuates lipopolysaccharide-induced inflammation via modulating Toll-like receptor 4 signaling. PLoS One 2013; 8: e78051.

102) Liu ZJ, Zhong J, Zhang M, Chen ZH, Wang JY, Chen HY, Wang XQ, Zhang B. The Alexipharmic Mechanisms of Five Licorice Ingredients Involved in CYP450 and Nrf2 Pathways in Paraquat-Induced Mice Acute Lung Injury. Oxid Med Cell Longev 2019; 2019: 7283104.

103) Qu L, Chen C, He W, Chen Y, Li Y, Wen Y, Zhou S, Jiang Y, Yang X, Zhang R, Shen L. Glycyrrhizic acid ameliorates LPS-induced acute lung injury by regulating autophagy through the PI3K/AKT/mTOR pathway. Am J Transl Res 2019; 11: 2042-2055.

104) Zhang A, Pan W, Lv J, Wu H. Protective Effect of Amygdalin on LPS-Induced Acute Lung Injury by Inhibiting NF-κB and NLRP3 Signaling Pathways. Inflammation 2017; 40: 745-751.

105) Guo S, Jiang K, Wu H, Yang C, Yang Y, Yang J, Zhao G, Deng G. Magnoflorine Ameliorates Lipopolysaccharide-Induced Acute Lung Injury via Suppressing NF-κB and MAPK Activation. Front Pharmacol 2018; 9: 982.

106) Li L, Chen J, Lin L, Pan G, Zhang S, Chen H, Zhang M, Xuan Y, Wang Y, You Z. Quzhou Fructus Aurantii Extract suppresses inflammation via regulation of MAPK, NF-κB, and AMPK signaling pathway. Sci Rep 2020; 10: 1593.

107) Oh YC, Cho WK, Jeong YH, Im GY, Lee KJ, Yang HJ, Ma JY. Anti-inflammatory effect of Sosihotang via inhibition of nuclear factor-κB and mitogen-activated protein kinases signaling pathways in lipopolysaccharide-stimulated RAW 264.7 macrophage cells. Food Chem Toxicol 2013; 53: 343-351.

108) Choi Y, Kim MH, Jung DH, Yang WM. Anti-Inflammatory Effects of Sosiho-Tang, a Traditional Herbal Formula, on Acute Lung Injury in LPS-Sensitized Mice and -Raw 264.7 Cells. Evid Based Complement Alternat Med 2021; 2021: 6641689.

109) Gao Z, Xu J, Sun D, Zhang R, Liang R, Wang L, Fan R. Traditional Chinese medicine, Qing Ying Tang, ameliorates the severity of acute lung injury induced by severe acute pancreatitis in rats via the upregulation of aquaporin-1. Exp Ther Med 2014; 8: 1819-1824.

110) Yeh CC, Lin CC, Wang SD, Chen YS, Su BH, Kao ST. Protective and anti-inflammatory effect of a traditional Chinese medicine, Xia-Bai-San, by modulating lung local cytokine in a murine model of acute lung injury. Int Immunopharmacol 2006; 6: 1506-1514.

111) Lin CH, Yeh CH, Lin LJ, Wang SD, Wang JS, Kao ST. Immunomodulatory effect of chinese herbal medicine formula sheng-fei-yu-chuan-tang in lipopolysaccharide-induced acute lung injury mice. Evid Based Complement Alternat Med 2013; 2013: 976342.

112) Li CW, Chen ZW, Wu XL, Ning ZX, Su ZQ, Li YC, Su ZR, Lai XP. A Standardized Traditional Chinese Medicine Preparation Named Yejuhua Capsule Ameliorates Lipopolysaccharide-Induced Acute Lung Injury in Mice via Downregulating Toll-Like Receptor 4/Nuclear Factor-κB. Evid Based Complement Alternat Med 2015; 2015: 264612.

113) Yang H, Lu Z, Huo C, Chen Y, Cao H, Xie P, Zhou H, Liu D, Liu J, Yu L. Liang-Ge-San. Liang-Ge-San, a Classic Traditional Chinese Medicine Formula, Attenuates Lipopolysaccharide-Induced Acute Lung Injury Through Up-Regulating miR-21. Front Pharmacol 2019; 10: 1332.

114) Yu JB, Dong SA, Luo XQ, Gong LR, Zhang Y, Wang M, Cao XS, Liu DQ. Role of HO-1 in protective effect of electro-acupuncture against endotoxin shock-induced acute lung injury in rabbits. Exp Biol Med (Maywood) 2013; 238: 705-712.

115) Huang CL, Huang CJ, Tsai PS, Yan LP, Xu HZ. Acupuncture stimulation of ST-36 (Zusanli) significantly mitigates acute lung injury in lipopolysaccharide-stimulated rats. Acta Anaesthesiol Scand 2006; 50: 722-730.