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Advances in research into the mechanisms of Chinese Materia Medica against acute lung injury

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ABSTRACT

Acute lung injury (ALI) is a common and serious disease. Numerous treatment options are available but they do not improve quality of life or reduce mortality for ALI patients. Here, we review the treatments for ALI to provide basic data for ALI drug therapy research and development. Chinese Materia Medica (CMM) has long been the traditional clinical approach in China for the treatment of ALI and it has proven efficacy. The continued study of CMM has disclosed new potential therapeutic ingredients for ALI. However, few reviews summarize the currently available CMM-based anti-ALI drugs. Therefore, the systematic analysis of research progress in anti-ALI CMM is of great academic and clinical value. The aim of the present review is to describe CMM-based research progress in ALI treatment. Data were compiled by electronic retrieval (CNKI, SciFinder, PubMeds, Google Scholar, Web of Science) and from articles, patents and ethnopharmacological literature in university libraries were systematically studied. This review introduces progress in research on the etiology and mechanisms of ALI, the anti-ALI theory and modes of action in traditional Chinese medicine (TCM), anti-ALI active constituents of CMM, research progress in experimental methods of CMM anti-ALI, the anti-ALI molecular mechanisms of CMM, the anti-ALI efficacy of CMM formulae, and the potential toxicity of CMM and the antidotes for it. Scholars have investigated the anti-ALI molecular mechanism of CMM from various direction and have made substantial progress. This research explored the above aspects, enriched the anti-ALI theory of CMM and established the clinical significance and developmental prospects of ALI treatment by CMM. Because of the high frequency of drugs such as glucocorticoids or antibiotics, Western medicine lacks the advantages of CMM in terms of overall anti-ALI efficacy. In the future, the development of CMM-based anti-ALI therapies will become a major trend in the field of ALI drug development. Successful clinical safety and efficacy validations will promote and encourage the use of CMM. It provides fundamental theoretical support for the discovery and use of CMM resources through the comprehensive analysis of various anti-ALI CMM report databases.

Abbreviations: ALI, acute lung injury; AMPK, adenosine monophosphate-activated protein kinase; APAF1, apoptotic protease-activating factor-1; Apo-3L, apolipoprotein 3-ligand; ARDS, acute respiratory distress syndrome; AT I, alveolar epithelial; ATP, adenosine triphosphate; BALF, bronchoalveolar lavage fluid; CLP, cecal ligation and puncture; CMM, Chinese Materia Medica; COX-2, cyclooxygenase-2; DAD, diffuse alveolar damage; DISC, the death-inducing signaling complex; ENaC, the epithelial sodium channel; ERK, extracellular regulated protein kinases; Fas-L, fas-ligand; GSH-Px, glutathione peroxidase; HIF-1α, the hypoxia inducible factor 1α; HMGB1, high mobility group box 1 protein; HO-1, heme oxygenase.1; IL-1, interleukin-1; IL-6, interleukin-6; iNOS, inducible NO synthase; IκB, inhibitor of NF-κB; JNK, C-JunN-terminal kinase; LPS, lipopolysaccharides; LT-α, lymphotoxin-alpha; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; NF-κB, nuclear factor-κB; NO, nitric oxide; NSAIDs, non-steroidal anti-inflammatory drugs; PMN, polymorphonuclear neutrophils; PPAR, peroxisome proliferators-activated receptors; ROS, reactive oxygen species; SOD, superoxide dismutase; TCM, traditional Chinese medicine; TLR, toll-like receptor; TNF-α, tumor necrosis factor-α; NLRP3, NACHT, LRR and PYD domains-containing protein 3; PI3K, phosphatidylinositol 3-kinases; mTOR, mammalian target of rapamycin

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1. Introduction

Acute lung injury (ALI) is caused by various pathogenic factors inside and outside the lungs. It is characterized by acute, progressive respiratory distress and persistent hypoxemia. Acute respiratory distress syndrome (ARDS) is a serious progression of this disorder and is a common clinical manifestation. Its mortality rate is as high as 40 % [1,2]. The pathophysiological and clinical factors inducing this disease have been investigated since the work of Ashbaugh et al. [3]. They first reported ARDS in 1967 but its pathogenesis has not been fully elucidated [4]. ALI is treated mainly by reducing inflammation and inhibiting respiratory failure. Anti-inflammatory drugs such as corticosteroids, aspirin, salbutamol, and ketoconazole are commonly used in clinical practice. Respiratory support is administered with ventilators to improve hypoxemia [5]. Under the effects of various pathogenic factors the activation of any links (mechanism) may lead to the occurrence of ALI/ARDS. Despite numerous treatment options for this condition, patient quality of life and mortality have not been substantially improved [6]. In recent years, several reports have been published on the prevention and treatment of ALI with Chinese Materia Medica (CMM). CMM and CMM formulae are widely used in China to treat various diseases and they have good curative effects. Therefore, CMM is a viable research prospect for the prevention and treatment of acute lung injury [7,8]. The aim of this review was to address progress in the application of CMM for the treatment of ALI. Five different research areas were addressed: current theoretical research status of CMM on ALI; active anti-ALI constituents in CMM; anti-ALI efficacy of CMM in an ALI model; anti-ALI mode of action of CMM; and anti-ALI efficacies of CMM formulae. This review lays the foundation for the development of CMM-based anti-ALI drugs. It also provides essential theoretical support for the further development and utilization of CMM resources *via* a comprehensive analysis of CMM-based anti-ALI efficacy studies.

2. Research progress on the mechanisms of ALI

2.1. Relevant pathological features

2.1.1. Pathogenesis

ALI is characterized by pulmonary edema resulting from alveolar-capillary barrier destruction and inflammation caused by leukocyte recruitment. The main cause of ALI is an imbalance in the inflammatory response [9]. Common causes of ALI/ARDS include severe pulmonary sepsis, trauma, multiple transfusions, acute pancreatitis, inhalation injury, and certain types of drug toxicity. Diffuse alveolar damage (DAD) is the main pathological feature of clinical ALI. The characteristic histology of this process develops early in infiltration or injury. It then undergoes proliferation or other histological transformation and finally enters the healing or regression stage [10]. The proliferative phase is characterized by interstitial edema and mild inflammatory thickening of the alveolar septa. This phase presents with alveolar epithelial cell (AT I) necrosis, endothelial cell injury, alveolar loss, and basement membrane alterations. Loss of alveolar integrity causes fibrin-rich fluids to leak into the alveolar cavity. Proinflammatory cells are recruited to this area [11]. Neutrophils attach to the injured capillary endothelium, pass through the interstitium, and enter the alveolar cavity filled with protein-rich edematous fluid. In the alveolar cavity, alveolar macrophages secrete cytokines such as interleukin-1 (IL-1), IL-6, IL-8, IL-10, and tumor necrosis factor (TNF)-α. These locally activate neutrophils and induce chemotaxis in them [12]. Proinflammatory factors are produced by alveolar and pulmonary vascular endothelial cells and other inflammatory mediators and damage the epithelia themselves. Destruction of the alveolar epithelial cells increases barrier permeability and decreases alveolar fluid clearance. Injury to vascular endothelial cells causes fluid and macromolecules to enter the interstitial space and induces pulmonary edema [13]. During ALI, polymorphonuclear neutrophils (PMN) release large amounts of reactive oxygen species (ROS) that oxidize unsaturated fatty acids in the cell membranes, reduce membrane fluidity, and increase membrane permeability. Moreover, ROS are released into the lung tissue, injure the alveolar and pulmonary vascular endothelial cells, disrupt the gas and blood barrier, and aggravate pulmonary edema [14].

The inflammatory response of ALI is divided into three stages: (i) Macrophages in the alveoli respond to inflammatory stimuli and produce proinflammatory factors such as TNF-α, IL-1, and IL-8. Macrophages, platelets, and vascular endothelial cells produce cytokines, chemokines, selective cytokines, and other inflammatory transmitters. Chemotactic neutrophils adhere, roll, deform, and swim out. (iii) Capillary wall permeability significantly changes. Alveolar endothelial cells are destroyed. Red blood corpuscles and large amounts of proteins enter the alveoli. The alveolar surface loses its surfactant and forms a transparent membrane in the lung. Numerous cells collapse in the alveoli, pulmonary fibrocytes proliferate in the interstitium, and fibrinolysis occurs [15].

Damage to the alveolar epithelium plays important roles in ALI development and recovery. The healthy alveolar epithelium consists of two types of cells. Type I flat cells comprise 90 % of the alveolar surface area and are injury-prone. Type II solid cells constitute the remaining 10 % of the alveolar surface area and are not easily damaged. The latter produce surfactant, transport ions, and differentiate and proliferate type I cells in response to trauma [16].

2.1.2. Mechanism of regression

ALI regresses as follows: (i) Alveolar epithelium is regenerated by alveolar type II cell proliferation and differentiation. Type I cells proliferate, cover the exposed basement membrane, differentiate, restore the normal alveolar structure, and increase the liquid transport capacity of the alveolar epithelium [17]. Alveolar edema is eliminated by the active transport of sodium and/or chloride ions from the distal alveolar space to the interstitium. Alveolar edema fluid is resorbed *via* the sodium/chloride pump across the membranes of type II cells. Sodium is absorbed through the basolateral membrane of the epithelial sodium channel (ENaC) and sodium pump (Na^+/K^+-ATPase)-type cells. The associated chloride transport mechanisms have not yet been elucidated [18]. (iii) Passive water transport is accomplished mainly by aquaporins on type I cells. In clinical studies, alveolar fluid clearance occurred early and was usually evident within the first few hours after intubation and mechanical ventilation were initiated. Removal of alveolar fluid and enhanced oxygenation were associated with improved survival [19,20]. ALI is also attenuated by removing soluble and insoluble proteins from the alveolar space. The transparent membrane provides a framework for the growth of fibrous tissue. Removal of insoluble proteins helps prevent pulmonary fibrosis. Soluble protein is removed mainly by passive diffusion between alveolar epithelial cells. Insoluble protein is removed by the endocytosis and exocytosis of alveolar epithelial cells and macrophages [21]. (v) The mechanisms by which inflammatory cell infiltration and fibrosis are eliminated are unclear. Apoptosis may be the primary mechanism for neutrophil clearance from inflammatory sites and damaged lungs [22]. The roles of proapoptotic and antiapoptotic mechanisms in alveolar epithelium and pulmonary endothelium damage and repair are important areas of future research.

2.2. Relevant signaling pathway and receptor layer

When lung injury occurs, numerous inflammatory factors are transcribed. This process is regulated mainly by nuclear factor-κB (NF-κB) family transcription factors. The most common NF-κB is a heterodimer composed of p65 and p50. In the cytoplasm of resting cells, NF-κB-forms an inactive complex with inhibitor of NF-κB (IκB). When the cells are stimulated by extracellular signals, IκB is phosphorylated, and free NF-κB is rapidly transferred to the nucleus. There, it induces the transcription of genes encoding the proinflammatory factors IL-6 and TNF-α

which exacerbate ALI [23]. Mitogen-activated protein kinase (MAPK) induction participates in ALI occurrence and development. MAPK comprises the subfamilies extracellular regulated protein kinases (ERK), c-Jun N-terminal kinase (JNK), and p38 which regulate cytokine release and signal transduction in ALI. JNK and p38 control the production of proinflammatory factors such as IL-6 and TNF-α. The p38 modulates LPS-induced NF-κB activation by inhibiting polymorphonuclear neutrophils (PMN) migration. This mechanism aggravates ALI [24]. ALI occurrence and development are also influenced by the hypoxia-inducible factor (HIF)-1α, transforming growth factor (TGF)-β1/SMAD, Akt, adenosine monophosphate-activated protein kinase (AMPK), and cAMP/ protein kinase A (PKA) pathways.

Toll-like receptors (TLRs) are proteins involved in nonspecific immunity. TLR2 and TLR4 recognize lipopolysaccharides (LPS) and play important roles in their pathophysiology. When LPS invade the lungs, they bind to TLR2 or TLR4, activate the NF-κB pathway, and trigger inflammation [25]. Activated peroxisome proliferators-activated receptor (PPAR)-γ has anti-inflammatory and immunomodulatory effects. Increasing PPAR-γ content may inhibit NF-κB activation and improve the inflammatory response in ALI [26]. ALI is closely related to the inflammatory response, and endogenous adenosine inhibits it. Adenosine is released at the inflammatory site. Adenosine A_{2A} receptor, a member of the G protein-coupled receptor superfamily, is upregulated in immune cells. Its activation reduces the inflammatory response in ALI patients by regulating immune cell function [27].

2.3. Pathways leading to apoptosis in ALI/ARDS

Apoptosis participates in ALI/ARDS pathogenesis. It is initiated by two alternative convergent pathways. The exogenous pathway is mediated by cell surface death receptors while the endogenous pathway is mediated by mitochondria [28]. The former involves cell surface death receptors belonging to the tumor necrosis factor receptor (TNF-R) family. The ligands of the TNF-R family belong to the TNF family and include TNF-α, fas-ligand (Fas-L), lymphotoxin-alpha (LT-α), apolipoprotein 3-ligand (Apo-3L), and TNF-related apoptosis-inducing ligand [29]. Binding of a death ligand to a death receptor activates the latter by homotrimerization. The death receptors then recruit adaptor proteins. The binding protein then interacts with the apoptosis-initiating enzyme procaspase-8. The latter is recruited in the death-inducing signaling complex (DISC) and converted into active caspase-8 by autoproteolytic cleavage. The endogenous pathway is triggered by mitochondrial membrane stimulation. The mitochondria then release cytochrome c and other apoptogenic factors from their intramembranous spaces. Cytochrome c recruits the caspase adaptor molecule known as apoptotic protease-activating factor-1 (APAF1) and the apoptosis initiator enzyme procaspase-9. Cytochrome c, APAF1, procaspase-9, and adenosine triphosphate (ATP) form a holoenzyme complex called an apoptosome. Procaspase-9 is converted into active caspase-9 by autoproteolytic cleavage [30]. Both systems are highly upregulated in the acute phase of lung injury in septic ARDS patients. Thus, they may contribute to lung epithelial and endothelial cell death.

3. ALI and anti-ALI theory in traditional Chinese medicine (TCM)

The common pathological features of ALI are lung volume and compliance reduction and imbalance of the ventilation/blood flow ratio. The main clinical manifestations of ALI are shortness of breath, dyspnea, dizziness, high fever, stool stem node, crimson tongue, rapid and slippery pulse, and so on. ALI is classified as a “dyspnea syndrome,” “chest knot,” “sudden dyspnea,” or “dyspnea and dyspnea” in TCM. According to Western medicine, the most common causes of ALI/ARDS are severe pulmonary infection, sepsis, trauma, multiple blood transfusions, acute pancreatitis, inhalation of toxic gases, and so on. However, traditional Chinese medicine maintains that although ALI has multiple causes, they can be categorized as external sensation and internal injury. The external sensation may occur by sexual invasion while internal injury is mediated by diet, sentiment, fatigue, or prolonged illness. “Lung is the master of Qi.” Thus, the occurrence and development of ARDS are closely related to pathophysiological function and changes of the lung. “Lung and large intestine are interiorly-exteriorly related,” “Kidney is the root of Qi,” and other theories suggest that pathological changes to the viscera outside the lungs may contribute to the development of ALI/ARDS. From the patient's own constitution, multifaceted diagnosis in order to find the optimal treatment program, which is features and advantages of TCM treatment of ALI.

3.1. Pathogenic wind impairs lung and loss of lung xuanjiang

Loss of lung xuanjiang may cause respiratory abnormalities, such as cough and asthma symptoms. The lung does not govern Qi. Therefore, Qi activity is affected and renders the whole-body visceral function abnormal. TCM holds that Loss of lung xuanjiang is the pathogenic basis of ALI [31]. After the invasion of exogenous evil and the struggle between healthy and energy-evil, the circulation of Qi and blood accumulates heat in the lung and has pathological effects such as phlegm production, fluid retention, stasis, and others. Phlegm, blood stasis, and pathogenic heat interact in the lung and may aggravate dysfunction and parenchymal damage there. Various pathological factors may cause and influence each other, thereby collaborating in ALI/ARDS development and outcome. In this process, the main pathogenic factors are exogenous. Loss of lung xuanjiang by decanting is the pathogenic basis of this disease. Phlegm heat and heat and blood stasis are important pathological factors. As the disease progresses, lung Qi and Yin injury are gradually exacerbated.

The numerous antibiotics and liquid infusions administered for ALI therapy are Yin and cold according to TCM. Therefore, they cannot effectively control the disease and increase Qi and Yang consumption. In severe cases, the lung is not the master Qi and the whole body is out of balance. The Zang-fu function declines and imbalance between Yin and Yang occurs.

3.2. Phlegm-fire stasis and intermingling

As the lung has lost control of visceral activities, the waterways are no longer governed, the implantation of Qi, blood, and body fluid is obstructed, and sputum, heat, blood stasis, closure, and other pathological changes occur. Certain scholars discussed ALI pathogenesis in TCM from the perspective of the relationships among Qi, blood, water, and lung. They believe that ALI is the result of pulmonary Qi, blood, and water dysfunction [32]. Accumulation and activation of pulmonary macrophages and neutrophils indicate that heat toxin is obstructing the lung. Capillary and interstitial blood stasis in the lung occur when the gas and fluid are burned by heat toxin. Blood stasis causes water stagnation. Interstitial blood stasis provokes edema and alveolar clear membrane formation. Blood stasis and water pathogenic factors block Qi and cause lung Qi to be unfavorable for lung loss and descent. Therefore, the alveoli collapse and atelectasis and compensatory emphysema occur.

3.3. Lung stasis and intestinal blockade

In the late 1970s, a study of the theory of the lung and large intestine in TCM revealed that enterogenous endotoxemia is the main factor contributing to acute respiratory failure. It was proposed that ALI pathogenesis comprises the following: external evil affects the lung, evil heat is introduced into the yangming, the colon is hot and dry because of intestinal stagnation, the Qi obstructs the colon, the upper reverse causes asthma, the middle obstruction causes fullness, the heat forces blood stasis, the stasis and heat intermingle, the obstructed area is in the lung, the tunneling and regulating channels of the lung are blocked, and the water stops in the body [32].

ALI/ARDS is induced by lung loss, Qi stagnation, phlegm turbidity, water dampness, blood stasis and dreg, chronic lung Qi deficiency, chronic kidney disease, insufficient kidney essence, and inability of ingestion and Qi. These manifestations eventually develop into a dangerous dyspnea syndrome. The TCM theory holds that ALI treatment must start by adjusting the overall function of the Qi, blood, and water, promptly reducing or eliminating lung damage caused by various pathological factors, and restoring the dynamic balance of the internal environment of the body. In this way, malignant disease development may be reversed or prevented.

4. Research on the constituents of CMM with activity against ALI

The active ingredients in CMM play important and indispensable roles in preventing and treating ALI [33]. Several drugs have substituted for adrenocorticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) as their active ingredients have anti-inflammatory properties. The constituents of CMM are structurally diverse and have extensive pharmacological effects. However, they are not ordinarily used to synthesize anti-inflammatory drugs. Anti-ALI flavonoids, terpenoids, saponins, and other components, as well as certain Chinese herbal extracts may have therapeutic efficacy against ALI (Table 1). The classification of anti-ALI CMM active ingredients reported in the literature between 2014 and 2019 were analyzed in order to determine research trends in this field during that time (Fig. 1).

Flavonoids have numerous biological properties and definite anti-inflammatory effects [34]. In CMM, they are administered in the form of natural plant extracts. For example, the main active ingredients in *Scutellaria baicalensis* Georgi (黄芩) are flavonoid aglycogens (baicalein, wogonin, and oroxylin A) and glycosides. They have great potential therapeutic efficacy against ALI caused by influenza A virus. The total extract has superior therapeutic efficacy to baicalein alone [35]. Other flavonoids are listed in Table 1. In the treatment of ALI, they inhibit proinflammatory cytokines and/or mitigate oxidative stress.

Terpenoids are anti-ALI compounds that have been extensively studied in recent years. Certain terpenes have been administered for centuries as anti-inflammatory, antibacterial, and antitumor agents. Research on the anti-inflammatory potential of terpenoids has increased in recent decades. They are major sources of anti-ALI drugs in pharmacology [36]. For example, oridonin (Ori) is an active diterpene isolated from the traditional Chinese medicine *Rabdosia rubescens* (Hemsl.) Hara (冬凌草). It is anti-inflammatory, antitumor, antioxidant, and neuroregulatory. Experimental investigation showed that Ori significantly improves LPS-induced localized pulmonary pathology and downregulates the proinflammatory cytokines IL-1β, IL-6, and TNF-α in the serum. Other terpenoids with anti-ALI effects are listed in Table 1.

Saponins are also important anti-ALI components. Their anti-inflammatory activity has attracted much attention in recent years. Several studies showed that saponins isolated from TCM or natural medicine inhibit the release of proinflammatory factors and downregulate related proteins and other substances [37]. For example, ginsenosides (Rb1, Rg1, Rg3), the active ingredients in *Panax ginseng* C. A. Mey (人参), have good therapeutic efficacy against LPS-induced ALI. Ginsenoside Rg1 inhibits the apoptotic factor caspase 3 and NF-κB, reduces apoptosis and inflammation, and participates in ALI treatment. Other ginsenosides and saponins are listed in Table 1.

Polysaccharides are widely used in biomedicine as they have good therapeutic efficacy and low toxicity [38,39]. The importance of plant polysaccharides in anti-ALI has increased in recent years. For example, polysaccharides from *Houttuynia cordata* Thunb (鱼腥草) (CHCP) significantly attenuated pulmonary injury in a “two-hit” ALI model. They reduced pulmonary edema and protein exudation in bronchoalveolar lavage fluid (BALF). They also mitigated the deposition of complement activation products in the lung and improved oxidant-antioxidant imbalance. Inhibition of the inappropriate activation of the complement system by CHCP may play an important role in the treatment of inflammatory diseases.

Polyphenols in CMM and fruits are reputed for their antioxidant properties and have been investigated and exploited for their anti-inflammatory and other medicinal properties [40]. Paeonol (Pae), the active ingredient in *Paeonia suffruticosa* Andr (牡丹皮), upregulated nuclear HMGB1 and downregulated p65 and cytoplasmic HMGB1 in lung cells in LPS-induced ALI rats. These findings corroborated those reported for *in vitro* experiments. Thus, Pae is a potential treatment for ALI as it represses the HMGB1-NF-κB-p65 signaling pathway. Alkaloids, volatile oils, also contribute to anti-ALI formulae. For example, protostemonine, an alkaloid extracted from *Stemona sessilifolia* (Miq.) Miq. (百部), suppresses MAPK and AKT phosphorylation and downregulates proinflammatory mediators. *Trans*-anethole, the aetherolea extract of *Foeniculum vulgare* Mill (茴香) reduced the number of inflammatory cells and IL-17 mRNA expression. It also promoted IL-10 mRNA expression in isolated lung tissue and Treg cells but inhibited it in splenic Th17 cells. Therefore, ALI may be treated by immunoregulation. The phenylpropanoids fraxin, the active ingredient in *Fraxinus rhynchophylla* Hance (秦皮), helps offset LPS-induced lung injury by inhibiting the NF-κB and NLRP3 signaling pathways. Other constituents of TCM anti-ALI are listed in Table 1.

The anti-ALI substances in CMM are structurally and functionally diverse and do not have equal efficacy against this condition. There is a close relationship between the mode of action of CMM and its active ingredients. As the composition of CMM continues to be elucidated, other active ingredients in it will be developed into anti-ALI drugs.

5. Progress in experimental methods for anti-ALI CMM application

Most animal models of ALI are based on the clinical manifestations of human ALI/ARDS. These include sepsis, multiple blood transfusions, multiple trauma, aspiration of gastric contents, and reperfusion of ischemic tissue [41]. CMM anti-ALI-related animal models reported in the literature between 2014 and 2019 were analyzed in order to determine research trends in this field during that time (Fig. 2).

According to Table 2, most recent animal models of CMM anti-ALI involved intratracheal LPS injection. LPS is an important regulator of Gram-negative bacterial sepsis. Systemic LPS administration simulates the consequences of this condition [42]. Intratracheal LPS injection directly induces neutrophilic inflammation in the lungs and upregulates inflammatory factors. As this method is simple and highly reproducible, it has become a mainstay for ALI model induction. However, it also has limitations. It provokes relatively mild changes in alveolar capillary permeability and does not perfectly replicate the symptoms of human ALI/ARDS.

Table 2 shows an unprecedented recent use of PM2.5 for ALI modeling. Airborne particulate matter (PM) < 2.5 μm in diameter (PM2.5) is a heterogeneous mixture of various substances generated by different sources. PM2.5 is an ongoing public health risk. Epidemiological studies have linked PM2.5 to pulmonary and cardiovascular disease [43]. The emergence of these models and methods indicates that air pollution may significantly influence the incidence of ALI. Therefore, the effects of air pollution and their attenuation are trending in current research.

Cecal ligation and puncture (CLP) is another classic ALI modeling method. Sepsis may arise from intraperitoneal infection [44]. CLP is widely used to induce a peritonitis model. The cecum is ligated 3–5× with a needle. The number of ligations varies with the number of perforations and needle size [45]. The changes in alveolar vascular permeability caused by CLP more nearly resemble those seen in ALI than those induced with LPS. However, the cycle of the CLP model was longer than that of LPS. Moreover, unlike LPS, CLP involved surgery and the risks and precautions associated with it.

Live bacteria, hemorrhagic shock and resuscitation, hyperoxia, bleomycin and other modeling methods may simulate the other causative factors of human ALI. However, these are not necessarily

Table 1
Anti-ALI active ingredients of CMM.

Classifications	Components	CMM	Pinyin	Refs.
Flavonoids	Naringin	Dry immature fruits of *Citrus aurantium* L. or Dry immature fruits of *Citrus sinensis* Osbeck	Zhi Qiao (枳壳)、Zhi Shi (枳实)	[69,70]
	Hesperidin	Dry immature fruits of *Citrus aurantium* L. or Dry immature fruits of *Citrus sinensis* Osbeck	Zhi Qiao (枳壳)、Zhi Shi (枳实)	[71]
	Baicalin	Dry roots of *Scutellaria baicalensis* Georgi	Huang Qin(黄芩)	[72,73]
	Wogonin	Dry roots of *Scutellaria baicalensis* Georgi	Huang Qin(黄芩)	[74]
	Amygdalin	Dry ripe seeds of *Prunus armeniaca* L. var. ansu Maxim.	Ku Xing Ren (苦杏仁)	[75]
	Acanthopanax senticosus	Dry roots and rhizomes of *Acanthopanax seuticosus* (Rupr.et Maxim.) Harms	Ci Wu Jia (刺五加)	[76]
	Ugonin M	The root and rhizome of *Helminthostachys zeylanica* L. Hook.	Wu Gong Cao (蜈蚣草)	[77]
	Smiglaside A	The root and rhizome of *Smilax riparia*	Niu Wei Cai (牛尾菜)	[78]
	Puerarin	Dry roots of *Pueraria lobata* (Willd.) Ohwi	Ge Gen (葛根)	[79]
	Nobiletin	Dry ripe peel of *Citrus reticulata* Blanco	Chen Pi (陈皮)	[80]
Terpenoids	Asatone	Dry roots and rhizomes of *Asarum heterotropoides* Fr. Schmidt var. *mandshuricum* (Maxim.) Kitag.	Xi Xin(细辛)	[81]
	Acanthoic acid	Dry roots and rhizomes of *Acanthopanax seuticosus* (Rupr.et Maxim.) Harms	Ci Wu Jia (刺五加)	[82]
	Jolkinolide B	Dry roots of *Euphorbia ebracteolata* Hayata or *Euphorbia fischeriana* Steud.。	Lang Du (狼毒)	[83]
	Taraxasterol	Whole herbs of *Taraxacum mongolicum* Hand. -Mazz. or *Taraxacum borealisinense* Kitam.	Pu Gong Ying (蒲公英)	[84]
	Triptolide	Dried roots, leaves and flowers of *Tripterygium wilfordii* Hook F	Lei Gong Teng(雷公藤)	[85,86]
	2α-Hydroxyl-3β-angeloylcinnamolide (HAC)	*Polygonum jucundum* Lindex. *(Polygonaceae)*	Yu Yue Liao (愉悦蓼)	[87]
	Asperuloside	Herbs of *Hedyotis diffusa* Willd.	Bai Hua She She Cao (白花蛇舌草)	[88]
	Glycyrrhizin	Dry roots and rhizomes of *Glycyrrhiza uralensis* Fisch	Gan Cao (甘草)	[89]
	Oridonin	The dry overground part of *Rabdosia rubescens* (Hemsl.) Hara	Dong Ling Cao (冬凌草)	[90]
Saponins	Platycodin D	Dry roots of *Platycodon gradiflorum* (Jacq.) A. DC	Jie Geng(桔梗)	[91,92];
	Asiaticoside	Whole herbs of *Centella asiatica* (L.) Urb.	Ji Xue Cao (积雪草)	[93]
	Tenuigenin	Dry roots of *Polygala tenuifolia* Willd.	Yuan Zhi(远志)	[94]
	Ginsenoside Rb1	Dry roots and rhizomes of *Panax ginseng* C. A. Mey.	Ren Shen (人参)	[95]
	Ginsenoside Rg1			[96]
	Ginsenoside Rg3			[97,98]
	Euphorbia factor L2	The air-dried seeds of *Euphorbia lathyris* L.	Qian Jin Zi (千金子)	[99]
Phenylpropanoids	Fraxin	Dried barks of *Cortex Fraxini*	Qin Pi (秦皮)	[100]
	Arctigenin	Dry ripe fruits of *Arctium lappa* L.	Niu Bang Zi(牛蒡子)	[101]
	Eugenol	Dried buds of *Eugenia caryophyllata* Thunb.	Ding Xiang (丁香)	[102]
	Chicoric acid	Chicory and the echinacea (purple coneflower) plant (*Echinacea purpurea*).	Zi Zhui Ju (紫锥菊)	[103]
Polyphenols	Paeonol	Dry Bark of *Paeonia suffruticosa* Andr.	Mu Dan Pi(牡丹皮)	[104,105]
	Bakuchiol	The seeds of *Psoralea Corylifolia* L	Bu Gu Zhi (补骨脂)	[106]
	Resveratrol	Dry roots and rhizomes of *Polygonum cuspidatum* Sieb. et Zucc.	Hu Zhang (虎杖)	[107]
Polysaccharides	Crude *Arnebiaeuchroma* polysaccharides	The root of *Arnebiaeuchroma* (Royle) Johnst (Ruanzicao)	Zi Cao (紫草)	[108]
	Houttuynia cordata polysaccharides	The dried whole plant of *Houttuynia cordata* Thunb.	Yu Xing Cao (鱼腥草)	[109,110]
	Lycium barbarum polysaccharide	The berry of *Lycium barbarum*	Gou Qi (枸杞)	[111]
	Bletilla striata polysaccharide	The rhizome of *Bletilla striata (Thunb.)* Reichb. f.	Bai Ji (白及)	[112]
Alkaloids	Protostemonine	Dry roots of *Stemona sessilifolia* (Miq.)	Bai Bu (百部)	[113]
	The total alkaloids of D. crepidatum	Roots of *Dendrobium nobile* Lindl.	Shi Hu (石斛)	[114]
	Berberine	The rhizome of *Coptis chinensis*	Huang Lian (黄连)	[115]
Volatile oils	Trans-anethole	The dry ripe fruit *Foeniculum vulgare* Mill	Hui Xiang (茴香)	[116]
Others	The aqueous extract of velvet antler	Velvet Antler (*Cervus elaphus*)	Lu Rong (鹿茸)	[117]
	The water extract of S. baicalensis (WSB)	The roots of *Scutellaria baicalensis* Georgi	Huang Qin (黄芩)	[118]
	Hydrostatin-SN1	A bioactive peptide extracted from the Hydrophis cyanocinctus venom gland T7 phage display library	She Du (蛇毒)	[119]
	The water extract of *Rhodiola rosea*	Dry roots and rhizomes of *Rhadiola crenulata* (Hr. f. et Thoms.) H. Ohba	Hong Jing Tian (红景天)	[120]
	Trollius altaicus extract powder	The flower of *Trollius altaicus*	Altai Jin Lian Hua (阿尔泰金莲花)	[121]
	Vitex *agnus-castus*	The total methanolic extract of the aerial parts of V. *agnus-castus*	Sui Hua Du Jing (穗花牡荆)	[122]

pertinent in TCM.

An *in vitro* ALI model used RAW264.7 macrophages. While cell-level verification was comparatively simple, it did not effectively mimic the multicellular interactions that occur in ALI. Therefore, various *in vivo* and *in vitro* ALI models should be applied simultaneously to evaluate the efficacy and pharmacological mechanism of CMM and develop different ALI prevention and treatment approaches.

The use of animal disease models is vital to our understanding of ALI pathophysiology and the development of new strategies for treating it. Nevertheless, no animal model can fully replicate human diseases. The establishment of standardized criteria for defining lung injury in animals will facilitate model selection for specific protocols and improve the value of the data they generate. The following section introduces the experimental CMM-based anti-ALI models designed in recent years (Table 2).

6. Anti-ALI molecular mechanisms of CMM

Molecular biology technology is extensively used in pharmacological research. Thus, investigations into TCM-based anti-ALI are no longer restricted to "whole organ cell." They can now be explored at the level of "molecules and genes." In this way, the molecular mechanisms

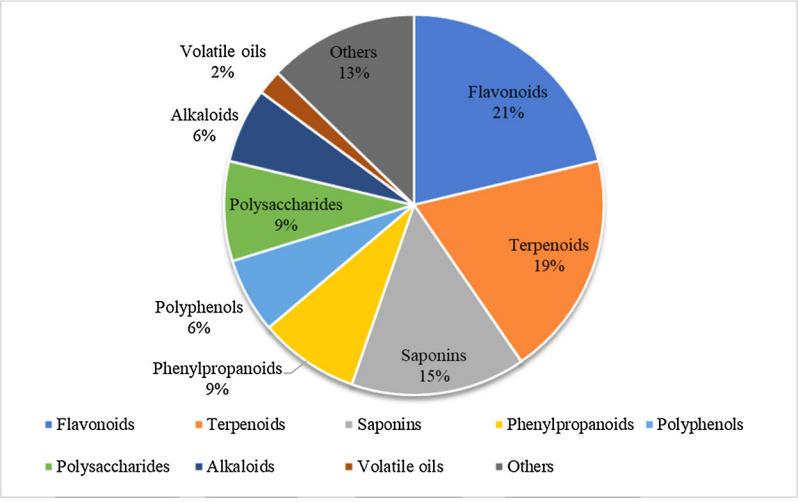

Fig. 1. The classification of anti-ALI CMM active ingredients between 2014 and 2019 (n = 47).

of CMM may be elucidated. As previously stated, the development of ALI is influenced by multiple signaling pathways such as MAPK, NF-κB, PI3K/Akt, and others [46]. The active ingredients in CMM have various molecular mechanisms that influence signaling pathways, inhibit the release of proinflammatory cytokines, reduce oxidative stress, increase resistance to apoptosis, and so on. In this way, they prevent and treat ALI. Here, we review recent progress in research on the molecular mechanisms of the anti-ALI effect of CMM (Table 3). Most current studies on CMM-based anti-ALI have profoundly examined its molecular mechanisms. It was determined that TCM has anti-ALI efficacy because it inhibits the release of proinflammatory factors and reduces oxidative stress.

6.1. Inhibition of the release of proinflammatory cytokines by CMM

LPS-induced ALI is associated with increased pulmonary inflammation. Increased levels of proinflammatory cytokines such as TNF-α, IL-6, and IL-1β have been detected in patients with lung injury [47,48]. In the LPS-induced ALI model in mice, TNF-α, IL-6, and IL-1β were significantly upregulated. Studies have shown that the inhibition of these cytokines could attenuate ALI [49]. Resveratrol is a polyphenol found in *Reynoutria japonica* Houtt (虎杖). It markedly downregulated TLR4, myd88, and NF-κB and lowered the concentrations of proinflammatory cytokines including IL-6 and COX-2. Therefore, the protective effect of resveratrol against LPS-induced ALI may be partially explained by its inhibition of the myd88-dependent TLR4 signaling pathway. Asatone is an active ingredient in the Chinese herb *Asarum sieboldii* Miq (细辛). It dramatically reduced the levels of TNF-α and IL-6 in the lung and liver but not the kidney of mice. Whereas LPS repressed antioxidant enzymes and NF-κB in bronchoalveolar lavage fluid, asatone upregulated these enzymes and induced NF-κB there. Thus, asatone may prevent ALI *via* the major anti-inflammatory NF-κB and mitogen-activated protein kinase MAPK pathways. These findings suggest that asatone could be used to treat ALI.

6.2. Reduction of oxidative stress

Acute inflammatory processes may be associated with neutrophil-derived active oxygen species and free radicals such as hydrogen peroxide, superoxide dismutase (SOD), nitric oxide (NO), and cytokines. The expression of iNOS may be an important mediator of inflammation [50]. SOD is a natural antioxidant enzyme in the body. It eliminates free radicals and protects against injury caused by them. SOD reduces lipid peroxidation and malondialdehyde (MDA) levels and maintains biological membrane integrity and function [51]. Glutathione peroxidase (GSH-Px) is ubiquitous in the body and an indicator of antiperoxidative capacity [52]. SOD, GSH-Px, catalase, and HO-1 are inducible enzymes that protect against oxidative stress. HO-1 is an antioxidant protein that

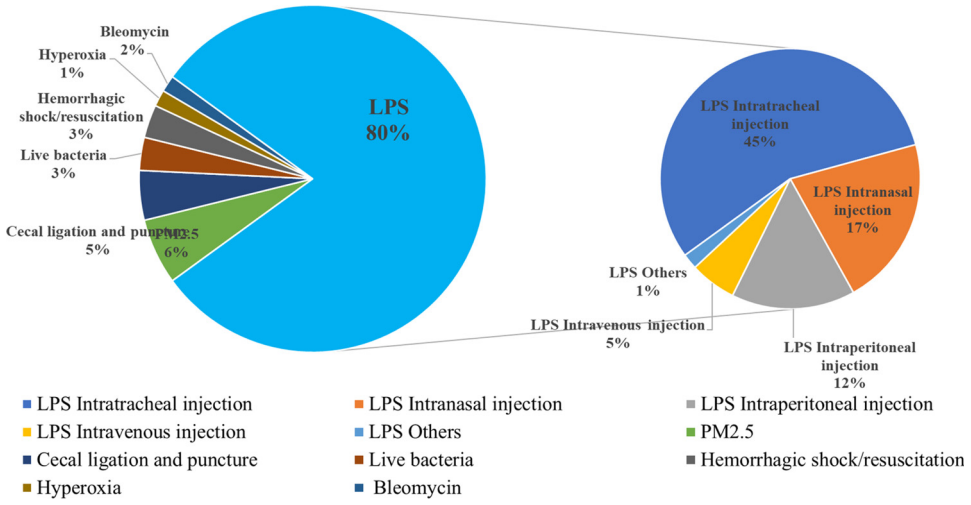

Fig. 2. CMM anti-ALI-related animal models reported in the literature between 2014 and 2019 (n = 65).

Table 2
Basic pharmacological data of anti-ALI effect of CMM mentioned in the text.

CMM	Type of extract	Anti-ALI experiments	Animal or cell	*N*	Dose range	Model	Positive controls	Negative controls	Duration	Refs.
A bioactive peptide extracted from the Hydrophis cyanocinctus venom gland T7 phage display library (蛇毒)	Hydrostatin-SN1	Intratracheal injection of LPS (2 mg/kg)	Male C57BL/6 mice	8	200, 400, 600, and 800 μg/kg	*In vivo*		Saline	24h	[119]
		LPS (1 μg/mL)	RAW264.7 cells		1,5 and 10μM	*In vitro*			6h	
Acanthopanax seuticosus (Rupr.et Maxim.) Harms (刺五加) (Roots and rhizomes)	Acanthopanax senticosus	Intratracheal injection of LPS (5 mg/kg)	Male C57BL/6 mice	12	20 mg/kg	*In vivo*		·	6h	[76]
	Acanthoic acid	Intranasal injection of LPS (200 mg/L)	Male BALB/c mice	12	15,30 and 60 mg/kg	*In vivo*	DXM	PBS	1h + 7h	[82]
		LPS (1 mg/L)	MH-S cells		25,50 and 100 μg/mL	*In vitro*			24h	
Arctium lappa L. (Ripe fruits) (牛蒡子)	Arctigenin	Intratracheal injection of LPS (5 mg/kg)	Male Sprague–Dawley rats	8	30 and 100 mg/kg	*In vivo*			1h + 6h	[101]
Arnebiaeuchroma (Royle) Johnst (Ruanzicao) (紫草) (Roots)	crude *Arnebiaeuchroma* polysaccharides	Ischemia-reperfusion (IR) injury and LPS (1.5 mg/kg) injection to induce ALI model.	Male Sprague Dawley rats	8	40, 80, and 120 mg/kg	*In vivo*	Hydro prednisone	Saline	4h	[108]
Asari Radix et Rhizoma (细辛) (Roots and rhizomes)	Asatone	Intratracheal injection of LPS (5 mg/kg)	Male mice	12	10,20 and 40 mg/kg	*In vivo*	DXM	Saline	6h	[81]
Bletilla striata (Thunb.) Reichb. f (白及) (Roots and rhizomes)	*Bletilla striata* polysaccharide	Intratracheal injection of MP2.5 (40 μl/n)	Male ICR mice		5, 20 and 40 mg/mL	*In vivo*		Saline	7d + 3d	[112]
Centella asiatica (L.) (积雪草)(Whole herbs)	Asiaticoside	Intranasal injection of LPS (200 mg/L)	Male BALB/c mice	6	15, 30, and 45 mg/kg	*In vivo*			1h + 6h	[93]
		LPS (4 mg/L)	RAW264.7 cells		10, 20, and 40 mg/L	*In vitro*			24h	
Citrus aurantium L. (枳壳)(Immature fruits)	Naringenin	Intravenous injection of LPS (5 mg/kg)	Male Sprague–Dawley rats	6-10	50, 100 mg/kg	*In vivo*		Saline	4d	[69,70]
	Hesperidin	Intranasal injection of LPS (0.5 mg/kg)	Male BALB/c mice	6-10	500 mg/kg	*In vivo*		PBS	10d + 24h	[71]
		LPS (1 μg/ml)	Peritoneal cavity macrophages		30 μg/ml	*In vitro*				
Citrus reticulata Blanco (陈皮) (Peel)	Nobiletin	Intranasal injection of LPS (30 mg/kg)	Male Kunming mice	12	5, 10, and 20 mg/kg	*In vivo*	DXM	CMC-Na	1h + 6h	[80]
		LPS (10 μg/mL)	A549 cells		10^{-4},10^{-3},10^{-2} mg/mL	*In vitro*			4 h + 12 h	
Coptis chinensis (黄连) (Rhizomes)	Berberine	Intraperitoneal injection of LPS (20 mg/ kg)	Male C57BL/6 mice	8	50, 100, and 200 mg/kg			Saline	Pre : 7d + 6 h Post : 6d + 3d	[115]
		LPS (1 μg/mL)	Human umbilical vein endothelial cells (HUVECs)		1.25, 2.5, and 5 μM	*In vitro*			Pre : 1h + 6 h Post : 6h + 18h	
Cortex Fraxini (秦皮) (Barks)	Fraxin	Intraperitoneal injection of LPS (30 mg/kg)	Kunming male mice	10	10, 20, and 40 mg/kg	*In vivo*	DXM	PBS	7d + 6h	[100]
Dendrobium nobile Lindl. (石斛) (Roots)	The total alkaloids of *D. crepidatum*	Intratracheal injection of LPS (5 mg/kg)	Male C57BL/6 mice	10	100 and 200 mg/kg	*In vivo*	prednisone		24h	[114]
Echinacea purpurea (紫锥菊) (Flowers)	Chicoric acid	Intranasal injection of LPS (0.5 mg/kg)	Male BALB/c mice	5	10, 20 or 40 mg/kg	*In vivo*	DXM	Saline	1h + 12h	[103]
Eugenia caryophyllata Thunb. (丁香) (Buds)	Eugenol	Intratracheal injection of LPS (400 mg/L)	Female BALB/c mice	10	5 or 10 mg/kg	*In vivo*	DXM	Saline	15min + 6h	[102]
Euphorbia ebracteolata Hayata (狼毒) (Roots)	Jolkinolide B	Intranasal injection of LPS (5 mg/kg)	Male C57BL/6 wild type mice	4-6	2 and 10 mg/kg	*In vivo*	DXM		1h + 24h	[83]
Euphorbia lathyris (千金子)(Seeds)	Euphorbia factor L2	Intratracheal injection of LPS (1 mg/mL)	Male C57BL/6 mice	12	10, 20 and 40 mg/kg	*In vivo*	–	PBS	24h	[99]
		LPS (1 mg/mL)	RAW264.7 cells		1, 5, 10 and 25 μM	*In vivo*		PBS	24h	
Foeniculum vulgare Mill. (茴香) (Ripes)	Trans-anethole	Intratracheal injection of LPS (24 mg/kg)	Male C57BL/6 mice	10	36.4, 72.8 or 145.6 mg/kg	*In vivo*	DXM	Saline	3d + 7d	[116]
Glycyrrhiza uralensis Fisch. (甘草) (Roots)	Glycyrrhizin	Intraperitoneal injection of viable S. *aureus* (10^7 CFU/0.2 mL PBS)	Female C57BL/6 mice	5	25 mg/kg	*In vivo*		PBS	7d	[89]

(*continued on next page*)

Table 2 (*continued*)

CMM	Type of extract	Anti-ALI experiments	Animal or cell	*N*	Dose range	Model	Positive controls	Negative controls	Duration	Refs.
Hedyotis diffusa (白花蛇舌草) (Herbs)	Asperuloside	Intratracheal injection of LPS (200 mg/L)	Male BALB/c mice	6	20, 40, and 80 mg/kg	*In vivo*		PBS	1h + 6h	[88]
		LPS (4 mg/L)	RAW264.7 cells		20, 40, and 80 mg/L	*In vitro*			1h + 12h	
Helminthostachys zeylanica(L.)Hook. (蜈蚣草) (Roots and rhizomes)	Ugonin M	Intratracheal injection of LPS (5 mg/kg)	Male ICR mice	12	0.625, 1.25, and 2.5 mg/kg	*In vivo*	DXM	Saline	1h + 6h	[77]
Houttuynia cordata Thunb. (鱼腥草) (The dried whole plant)	*Houttuynia cordata* polysaccharides	Intratracheal injection of LPS (3 mg/kg)	Male BALB/c mice	8	40, 80, and 160 mg/kg	*In vivo*	DXM		24h	[109]
		Hemorrhagic shock/ resuscitation and LPS instillation to induce ALI	Male Sprague–Dawley (SD) rats	6	25, 50 and 100 mg/kg.	*In vivo*	Prednisone		4h	[110]
Lycium barbarum (枸杞) (Berry)	*Lycium barbarum* polysaccharides	Hyperoxia-induced ALI	C57BL/6 wild-type (WT) mice		100 mg/kg	*In vivo*			7d + 72h	[111]
Paeonia suffruticosa Andr. (牡丹皮) (Barks)	Paeonol	Right carotid artery injection of LPS (15 mg/kg)	Male Sprague Dawley rats	12	0.073, 0.146 and 0.219 mg/kg	*In vivo*	DXM	Saline	24h	[104]
		Intratracheal injection of LPS (8 mg/kg)	Male Sprague Dawley rats	6	25 and 50 mg/kg.	*In vivo*	DXM	Saline	8h	[105]
Panax ginseng C. A. Mey. (人参) (roots and rhizomes)	Ginsenoside Rb1	Infusing with LPS (5 mg/kg/h) *via* the left jugular vein for 90min	Male Wistar rats	10	5 mg/kg	*In vivo*		Saline	90min + 4d	[95]
		LPS (100 ng/ml)	Human umbilical vein endothelial cells (HUVECs)		100 μM	*In vitro*			90min	
	Ginsenoside Rg1	Intratracheal injection of LPS (400 mg/L)	Male BALB/c mice	6	40 mg/kg or 200 mg/kg	*In vivo*		PBS	1h + 6h	[96]
	Ginsenoside Rg3	Intranasal injection of LPS (200 mg/L)	Male C57Bl/6 wild type (WT) mice	15	30, 20, and 10 mg/kg.	*In vivo*	DXM	PBS	1h + 12h	[97,98]
		LPS (2 μg/ml)	RAW264.7 cells	–	25, 50, and 100 μg/mL	*In vitro*	DXM	–	12h	
		Intratracheal injection of LPS (200 mg/L)	Male BALB /c mice	6	10, 20, and 30 mg/kg	*In vivo*	GRg3	Saline	2d + 24h	
Platycodon gradiflorum (桔梗) (roots)	Platycodin D	Intratracheal injection of LPS (400 mg/L)	Female BALB/c mice	10	50 mg/kg, 100 mg/kg	*In vivo*	DXM	Saline	15min + 6h	[91,92];
		Intratracheal injection of bleomycin (BLE)(5 mg/kg)	Female BALB/c mice	10	50 mg/kg, 100 mg/kg	*In vivo*	DXM	Saline	15min + 6h	
		LPS (0.5 mg/ml)	MLE-12 cells		5, 10 and 20 μM	*In vitro*			4h + 6h	
Polygala tenuifolia Willd (远志) (roots)	Tenuigenin	CLP-induce ALI model	Adult male Sprague-Dawley rats	10	15,30 and 60 mg/kg	*In vivo*			6d	[94]
Polygonum cuspidatum Sieb. et Zucc. (虎杖) (Roots and rhizomes)	Resveratrol	Intratracheal injection of LPS (2.5 mg/kg)	Adult BALB/c mice	8	5 or 25 mg/kg	*In vivo*	DXM	Saline	3d + 24h	[107]
Polygonum jucundum Lindex. (愉悦蓼) (Whole herbs)	2α-Hydroxyl-3β-angeloylcinnamolide (HAC)	Intratracheal injection of LPS (5 mg/kg)	Male ICR mice	10	100 mg/kg	*In vivo*	DXM	Saline	24h	[87]
		LPS (1 μg/mL)	RAW264.7 cells		1,10 and 100 μmol/L	*In vitro*			24h	
Prunus armeniaca L. var. *ansu* Maxim. (苦杏仁) (Seeds)	Amygdalin	Intratracheal injection of LPS	Male BALB/c mice	12	0.5,1 and 2 mg/kg	*In vivo*			7h	[75]
Psoralea corylifolia L (补骨脂) (Seeds)	Bakuchiol	CLP-induce ALI model	Male C57BL/6 mice	6	15, 30, 60 mg/ kg	*In vivo*	–	Saline	6h	[106]
Pueraria lobata (Willd.) Ohwi (葛根) (Roots and rhizomes)	Puerarin	Intratracheal injection of LPS (200 mg/L)	The BALB/c mice	6	25, 50, 100 mg/ kg	*In vivo*			1h + 12h	[79]
		LPS	RAW264.7 cells		10, 20, and 40 μM	*In vitro*			1h + 24h	
			A549 cells		10, 20, and 40 μM	*In vitro*			1h + 24h	
Rabdosia rubescens (Hemsl.) Hara. (冬凌草) (Overground part)	Oridonin	Intranasal injection of LPS (2 mg/kg)	BALB/c mice	15	10, 20, and 40 mg/kg	*In vivo*		Saline	24h + 24h	[90]
		LPS (1 μg/mL)	RAW264.7 cells		5, 15, and 30 μg/mL	*In vitro*			1h + 3h	
Rhadiola crenulata (Hr. f. et Thoms.) H. Ohba (红景天) (The water extract)	*Trollius altaicus* extract powder	Intratracheal injection of PM2.5 (11.25 mg/N)	Male Wistar rats	10	0.0865 g/mL	*In vivo*			27d	[120]

(*continued on next page*)

Table 2 (*continued*)

CMM	Type of extract	Anti-ALI experiments	Animal or cell	*N*	Dose range	Model	Positive controls	Negative controls	Duration	Refs.
Scutellaria baicalensis Georgi (黄芩) (Roots)	Baicalin	Intratracheal injection of LPS (3 mg/kg)	Male BALB/c mice(120) male C57BL/6 mice lacking the CX3CL1 gene(70)wild-type (WT) mice	24	50,100 and 200 mg/kg	*In vivo*			7d + 48h	[73]
		Intratracheal injection of LPS (5 mg/kg)	Male Sprague-Dawley (SD) rats	6	20 mg/kg	*In vivo*		PBS	1h + 6h	[72]
	The water extract of S. baicalensis (WSB)	Intratracheal injection of LPS (5 mg/kg)	ICR mice	9	31.25, 62.5, and 125 mg/kg	*In vivo*	DXM	Saline	5d + 6h	[118]
		LPS(100 ng/mL)	RAW264.7 cells		0, 31.25, 62.5, and 125 μg/mL	*In vitro*	DXM		24h	
	Wogonin	Intratracheal injection of LPS (2 g/L)	Male ICR mice	8	0, 0.03, 0.28 or 2.84 mg/kg	*In vivo*	DXM	Saline	30min + 6h	[74]
Smilax riparia (牛尾菜) (Roots and rhizomes)	Smiglaside A	Intraperitoneal injection of LPS (10 mg /kg)	Male C57BL/6 mice	40	3 and 10 mg/kg	*In vivo*		Saline	3d + 6h	[78]
		100 ng/mL LPS	RAW264.7 cells		10 μM	*In vitro*			2h + 24h	
Stemona sessilifolia Miq (百部) (Roots)	Protostemonine	Intratracheal injection of LPS (5 mg/kg)	Male C57BL/6 mice	5	10 mg/kg	*In vivo*			24h	[113]
		LPS (0.1 μg/mL)	RAW264.7 cells		1, 3, 10, 30 and 100 μmol/L	*In vitro*			24h	
		LPS (0.1 μg/mL)	BMDM cells		1, 3, 10, 30 and 100 μmol/L	*In vitro*			48h	
Taraxacum mongolicum Hand. -Mazz. (蒲公英) (Whole herbs)	Taraxasterol	Intranasal injection of LPS (200 mg/L)	Male BALB/c mice	12	2.5, 5, and 10 mg/kg	*In vivo*	DXM	PBS	1h + 7d	[84]
Tripterygium wilfordii Hook F (雷公藤) (Roots, leaves and flowers)	Triptolide	Intranasal injection of LPS (200 mg/L)	Male BALB/c mice	4–6	5, 10, and 15 μg/kg	*In vivo*	DXM	PBS	1h + 7h	[85,86]
		Intratracheal injection of LPS (1 mg/kg).	Male BALB/c mice	> 10	1, 10 and 50 μg/kg	*In vivo*		DMSO	30min + 12h	
Trollius altaicus (阿拉泰金莲花) (Extract powder)	The extract powder of *Trollius altaicus*	Intratracheal injection of PM2.5 (14 mg/kg)	Sprague Dawley rats	10	125, 250 and 500 mg/kg	*In vivo*	DXM		30d + 3h	[121]
V. *agnus-castus* (穗花牡荆) (The aerial parts)	Vitex *agnus-castus*	Intraperitoneal injection of LPS (10 mg/ kg)	Male BALB/c mice	6	50 and 100 mg/kg	*In vivo*			5d + 24h	[122]
Velvet Antler (鹿茸) (*Cervus elaphus*)	The aqueous extract of Velvet Antler	Intratracheal injection of LPS (5 mg/kg)	Male ICR mice	6	123,250 and 500 mg/kg	*In vivo*	DXM	Saline	5d + 6h	[117]

Table 3
CMM anti-ALI effects on molecular mechanisms.

Classifications	Components	CMM	Pinyin	Related pharmacological indicators											Related Molecular Mechanisms	Refs.
				MPO	TNF-α	IL-6	IL-1β	COX-2	NO	iNOS	SOD	MDA	GPx	Others		
Flavonoids	Naringin	Dry immature fruits of *Citrus aurantium* L. or Dry immature fruits of *Citrus sinensis* Osbeck	Zhi Qiao (枳壳)、Zhi Shi (枳实)	↓		↓			↓			↓		Caspase-3↓ H_2O↓	Inhibition of the PI3K/AKT signaling pathways and apoptosis	[69,70]
	Hesperidin	Dry immature fruits of *Citrus aurantium* L. or Dry immature fruits of *Citrus sinensis* Osbeck	Zhi Qiao (枳壳)、Zhi Shi (枳实)	↓	↓	↓								MCP-1↓	Reducing the release of HMGB1 *via* suppressing the infiltration of macrophages and production of MCP-1	[71]
	Baicalin	Dry roots of *Scutellaria baicalensis* Georgi	Huang Qin (黄芩)	↓	↓	↓	↓	↓						TGF-β↓ IL-18↓	Inhibition of the NF-κB and up-regulation of the Nrf2/HO-1 signaling pathway	[72,73]
	Wogonin	Dry roots of *Scutellaria baicalensis* Georgi	Huang Qin (黄芩)	↓		↓								ICAM-1↓ VCAM-1↓ MIP-2↓	Inhibition of Akt phosphorylation and RhoA activation	[74]
	Amygdalin	Dry ripe seeds of *Prunus armeniaca* L. var. ansu Maxim.	Ku Xing Ren (苦杏仁)	↓	↓	↓	↓								Inhibition of NF-κB and NLRP3 signaling pathways	[75]
	Acanthopanax senticosus	Dry roots and rhizomes of *Acanthopanax seuticosus* (Rupr.et Maxim.) Harms	Ci Wu Jia (刺五加)		↓	↓									Inhibition of NF-κB signaling pathways	[76]
	Ugonin M	The root and rhizome of *Helminthostachys zeylanica* L. Hook.	Wu Gong Cao (蜈蚣草)	↓	↓	↓	↓	↓	↓	↓	↑	↑		CAT↑ HO-1↑	Inhibition of the NF-κB, MAPK signaling pathways and the protein expression level of TLR4	[77]
	Smiglaside A	The root and rhizome of *Smilax riparia*	Niu Wei Cai (牛尾菜)		↓	↓	↓							AMPK↑ PPARγ↑	Promoting macrophage polarization *via* stimulating the AMPK-PPARγ signaling pathway.	[78]
	Puerarin	Dry roots of *Pueraria lobata* (Willd.)Ohwi	Ge Gen (葛根)	↓	↓	↓	↓							IL-8↓	Inhibiting NF-κB activation and activating LXRα	[79]
	Nobiletin	Dry ripe peel of *Citrus reticulata* Blanco	Chen Pi (陈皮)	↓	↓	↓			↓	↓					Inhibition of the NF-κB signaling pathways	[80]
Terpenoids	Asatone	Dry roots and rhizomes of *Asarum heterotropoides* Fr. Schmidt var. *mandshuricum* (Maxim.) Kitag.	Xi Xin(细辛)	↓	↓	↓	↓	↓	↓	↓	↑		↑	CAT↑	Inhibition of the NF-κB and MAPK signaling pathways	[81]
	Acanthoic acid	Dry roots and rhizomes of *Acanthopanax seuticosus* (Rupr.et Maxim.) Harms	Ci Wu Jia (刺五加)	↓	↓	↓	↓							LXRα↑	Reducing Expressions of inflammatory cytokines *via* activating LXRα	[82]
	Jolkinolide B	Dry roots of *Euphorbia ebracteolata* Hayata or *Euphorbia fischeriana* Steud.。	Lang Du (狼毒)	↓	↓	↓	↓								Inhibition of the NF-κB and MAPK signaling pathways	[83]
	Taraxasterol	Whole herbs of *Taraxacum mongolicum* Hand. -Mazz. or *Taraxacum borealisinense* Kitam.	Pu Gong YING (蒲公英)	↓	↓	↓	↓	↓	↓					PEG2↓	Inhibition of the NF-κB and MAPK signaling pathways	[84]
	Triptolide	Dried roots, leaves and flowers of *Tripterygium wilfordii* Hook F	Lei Gong Teng (雷公藤)	↓	↓	↓	↓							PPARγ↑	Inhibition of TLR4 activity and increasing the content of PPARγ	[85,86]
	2α-Hydroxyl-3β-angeloylcinnamolide	*Polygonum jucundum* Lindex. *(Polygonaceae)*	Yu Yue Liao (愉悦蓼)		↓				↓	↓					Downregulating TLR4 mediated MAPK-iNOS pathways	[87]
	Asperuloside	Herbs of *Hedyotis diffusa* Willd.	Bai Hua She She Cao (白花蛇舌草)	↓	↓	↓	↓								Inhibition of the NF-κB and MAPK signaling pathways	[88]
	Glycyrrhizin	Dry roots and rhizomes of *Glycyrrhiza uralensis* Fisch	Gan Cao (甘草)		↓	↓	↓							IL-8↓ HMGB1↓	Inhibition of the NF-κB and MAPK signaling pathways	[89]
	Oridonin	The dry overground part of *Rabdosia rubescens* (Hemsl.) Hara	Dong Ling Cao (冬凌草)		↓	↓	↓								Inhibition of the TLR4/MyD88/NF-κB activation.	[90]

(*continued on next page*)

Table 3 (*continued*)

Classifications	Components	CMM	Pinyin	Related pharmacological indicators											Related Molecular Mechanisms	Refs.
				MPO	TNF-α	IL-6	IL-1β	COX-2	NO	iNOS	SOD	MDA	GPx	Others		
Saponins	Platycodin D	Dry roots of *Platycodon gradiflorum* (Jacq.) A. DC	Jie Geng (桔梗)	↓	↓	↓					↑			Caspase-3↓ Bax↓ Bcl-2↓	Inhibition of lung epithelial cell apoptosis and NF-κB signaling pathway	[91,92];
	Asiaticoside	Whole herbs of *Centella asiatica* (L.) Urb.	Ji Xue Cao (积雪草)	↓	↓	↓									Inhibition of the NF-κB signaling pathway	[93]
	Tenuigenin	Dry roots of *Polygala tenuifolia* Willd.	Yuan Zhi (远志)	↓	↓	↓	↓	↓							Inhibition of the NF-κB and MAPK signaling pathways	[94]
	Ginsenoside Rb1	Dry roots and rhizomes of *Panax ginseng* C. A. Mey.	Ren Shen (人参)		↓	↓									Inhibition of Cav-1 and VE-Cadherin phosphorylation, and ZO-1 degradation, NF-κB p65 nuclear translocation, and Src kinase activation.	[95]
	Ginsenoside Rg1				↓	↓	↓							Caspase-3↓	Suppressing NF-κB and caspase-3 activation.	[96]
	Ginsenoside Rg3			↓	↓	↓	↓							IL-10↑ TGF-β↓	Activation of the PI3K/AKT/mTOR signaling pathway	[97,98]
	Euphorbia factor L2	The air-dried seeds of *Euphorbia lathyris* L.	Qian Jin Zi (千金子)	↓	↓	↓	↓							IL-8↓	Inhibition of the NF-κB signaling pathway	[99]
Phenylpropanoids	Fraxin	Dried barks of *Cortex Fraxini*	Qin Pi (秦皮)	↓	↓	↓	↓				↑	↓	↑		Inhibition of the NF-κB and NLRP3 signaling pathways	[100]
	Arctigenin	Dry ripe fruits of *Arctium lappa* L.	Niu Bang Zi (牛蒡子)	↓	↓	↓	↓							AMPK↑	Excitation of the AMPK and inhibition of the NF-κB signaling pathways	[101]
	Eugenol	Dried buds of *Eugenia caryophyllata* Thunb.	Ding Xiang (丁香)	↓	↓	↓					↑		↑	CAT↑ GST↑	Inhibition of the inflammation and oxidant stress.	[102]
	Chicoric acid	Chicory and the echinacea (purple coneflower) plant (*Echinacea purpurea*).	Zi Zhui Ju (紫锥菊)	↓	↓	↓	↓				↑	↓	↑	Nrf2↑ HO-1↑	Inhibition of MAPK and NLRP3 inflammasome and the activation of the Nrf2 and its downstream genes.	[103]
Polyphenols	Paeonol	Dry Bark of *Paeonia suffruticosa* Andr.	Mu Dan Pi (牡丹皮)		↓									HMGB1↓	Reducing the content of HMGB1	[104,105]
	Bakuchiol	The seeds of *Psoralea Corylifolia* L	Bu Gu Zhi (补骨脂)	↓	↓	↓	↓				↑	↓		8-OHdG↓ 3-NT↓	Suppressing inflammation, oxidative stress, and endothelial barrier disruption.	[106]
	Resveratrol	Dry roots and rhizomes of *Polygonum cuspidatum* Sieb. et Zucc.	Hu Zhang (虎杖)			↓		↓							Inhibition of the TLR4-mediated MyD88/MAPK signaling pathway	[107]
Alkaloids	Protostemonine	Dry roots of *Stemona sessilifolia* (Miq.)	Bai Bu (百部)	↓	↓	↓	↓		↓	↓					Inhibition of the MAPK and AKT signaling pathway	[113]
	the total alkaloids of D. crepidatum	Roots of *Dendrobium nobile* Lindl.	Shi Hu (石斛)	↓					↓	↓					Downregulating the TLR4-mediated MyD88/MAPK signaling pathway	[114]
	Berberine	The rhizome of *Coptis chinensis*	Huang Lian (黄连)		↓	↓	↓					↓		ROS↓	Alleviating endothelial glycocalyx degradation	[115]
Polysaccharides	Crude *Arnebiaeuchroma* polysaccharides	The root of *Arnebiaeuchroma* (Royle) Johnst (Ruanzicao)	Zi Cao (紫草)	↓							↑	↓			Inhibition of the inappropriate activation of complement system.	[108]
	Houttuynia cordata polysaccharides	The dried whole plant of *Houttuynia cordata* Thunb.	Yu Xing Cao (鱼腥草)		↓	↓	↓		↓					IL-10↑	Alleviating inflammatory injury by inhibiting the inappropriate activation of complement system.	[109,110]
	Lycium barbarum polysaccharide	The berry of *Lycium barbarum*	Gou Qi (枸杞)			↓	↓					↓	↑	HO-1↑	Reduction oxidative stress *via* Nrf2-dependent manner.	[111]
	Bletilla striata polysaccharide	The rhizome of *Bletilla striata (Thunb.)* Reichb. f.	Bai Ji (白及)		↓	↓								IFN - γ↓ MCP-1↓ IL-10↑ IL-12↑	Reducing expressions of inflammatory cytokines	[112]
Volatile oils	Trans-anethole	The dry ripe fruit *Foeniculum vulgare* Mill	Hui Xiang (茴香)											IL-17↓ IL-10↑	Regulation of Th17/Treg function	[116]

(*continued on next page*)

Table 3 (*continued*)

Classifications	Components	CMM	Pinyin	Related pharmacological indicators										Related Molecular Mechanisms	Refs.
				MPO	TNF-α	IL-6	IL-1β	COX-2	NO	iNOS	SOD	MDA	GPx	Others	
Others	The aqueous extract of velvet antler	Velvet Antler (*Cervus elaphus*)	Lu Rong (鹿茸)	↓	↓	↓	↓	↓	↓	↓	↑		↑	IL-10↑ CAT↑ HO-1↑	Suppressing the NF- κB and MAPK activation and promoting AMPK/Nrf2 signaling pathways	[117]
	The water extract of S. baicalensis	The roots of *Scutellaria baicalensis* Georgi	Huang Qin (黄芩)	↓	↓	↓	↓	↓	↓	↓	↑		↑	CAT↑	Inhibition of the NF-κB and MAPK signaling pathways	[118]
	Hydrostatin-SN1	A bioactive peptide extracted from the Hydrophis cyanocinctus venom	She Du (蛇毒)	↓	↓	↓	↓								Inhibition of the ERK1/2 and NF-κB signaling pathways.	[119]
	The water extract of *Rhodiola rosea*	Dry roots and rhizomes of *Rhodiola crenulata* (Hr. f. et Thoms.) H. Ohba	Hong Jing Tian (红景天)								↑	↓		ACP↓ AKP↓ LDH↓	Reduction oxidative stress	[120]
	Trollius altaicus extract powder	The flower of *Trollius altaicus*	Altai Jin Lian Hua (阿尔泰金莲花)		↓	↓	↓				↑	↓	↑	LDH↓	Reduction oxidative stress and inhibition of the expressions of inflammatory cytokines	[121]
	Vitex *agnus-castus*	The total methanolic extract of the aerial parts of V. *agnus-castus*	Sui Hua Du Jing (穗花牡荆)								↑	↓	↑	LDH↓	Reduction oxidative stress	[122]

catabolizes heme. It ameliorates the symptoms of ALI by inhibiting NF-κB phosphorylation [53]. *Lycium barbarum* (枸杞) polysaccharide (LBP) mitigates the hyperoxia of ALI *via* Nrf2. HO-1 and GSH-Px upregulation was observed in mice treated with LBP. The AMPK pathway partially mediates LBP-induced Nrf2 activation. *Vitex agnus-castus* Linn (VAC, 穗花牡荆) is widely used in TCM as an anti-inflammatory agent. VAC counteracted LPS-induced oxidative stress by attenuating the lipid peroxidation marker MDA in the lung. It upregulated SOD and increased the concentration of reduced GSH in the lung tissue. Therefore, VAC protects against LPS-induced ALI *via* its antioxidant potential.

Anti-ALI activity in one CMM may be mediated by several molecular mechanisms. Several different components within a single CMM may have similar anti-ALI modes of action that interact with each other. Thus, the anti-ALI efficacy of CMM is highly complex. In general, CMM participates in both the prevention and treatment of ALI. Though its components and mechanisms have a definite anti-ALI effect, as they are very intricate, the clinical efficacy of CMM does not meet theoretical expectations. Therefore, we must enhance interdisciplinary communication to elucidate the entire CMM-based anti-ALI process. Further study on other anti-ALI approaches and effects are required to provide a new rationale for CMM administration in the management of ALI.

7. Progress in the anti-ALI effect of formulae

7.1. Anti-ALI effects of CMM formulae

CMM formulae are prescriptions comprising at least two different CMM. The prescription process and application methods were designed and established to treat certain diseases and syndromes. CMM formula is the main component of TCM prescription [54]. There is no record of ALI in TCM. However, based on the clinical manifestations of this disease, it is classified in TCM in the categories "febrile disease (温病)", "asthma (喘脱)". and "violent asthma (暴喘)" and is caused mainly by external pathogens such as liuyin, trauma, pathogenic toxin, and pathogenic gas generated by lung injury induced by pathogenic toxin. As CMM formula is a combination of various individual CMM, it has multiple therapeutic targets. Interactions among CMM may reduce net toxicity and increase final efficacy [55]. Relevant anti-ALI CMM formulae used in recent years are summarized in Table 4.

Based on the clinical manifestations and pathogenesis of ALI, TCM asserts that external evil causes lung injury, evil heat, phlegm, dampness, and Qi and blood deficiency. Modern pharmacological research showed that CMM-based treatments are administered with the intention of inhibiting inflammation, regulating immune function, improving microcirculation, regulating water channel proteins, and so on. The advantages of this approach include minimal side effects and multiple targets. The efficacy of a CMM formula is determined by its chemical composition. CMM formulae comprise a wide range of complex constituents as they are made up of several herbs rich in active ingredients. The compatibility of various TCM is determined by the interactions among their active ingredients. Novel compounds and their metabolites may be generated during drug extraction and preparation. They may be integrated into the formulation and produce comprehensive pharmacological effects. Most complex inflammatory diseases are the result of a disequilibrium of conditions caused by imbalances in genes or their products. Based on its intrinsic properties, the CMM formula has unique pharmacological effects not found in any single herb. Therefore, the CMM formula is very effective for the treatment of complex diseases. Reduning injection (RDN) is a proprietary TCM formulae extracted from *Artemisia annua* Linn(青蒿), *Gardenia jasminoides* Ellis(栀子), and *Lonicera japonica* Thunb (金银花). These components have potential antiviral and substantial anti-inflammatory and immunomodulatory activity. A partial least-squares discriminant analysis was run to identify differences in the metabolic profiles of rats. Fourteen putative biomarkers were identified in lung tissue. They were related mainly to phospholipid, sphingolipid, nucleotide, and energy metabolism. This

Table 4
Relevant anti-ALI CMM formulae used in recent years.

CMM formula	Object	Pharmacological Effects	Anti-ALI experiments	*N*	Dose range	Model	Positive controls	Negative controls	Duration	Refs
Sini decoction	ICR male mice	Equilibrating ACE-AngII-AT1R and ACE2-Ang-(1–7)-Mas axis.	Intratracheal injection with E. *coli* (5×10^8 CFU/40 μL PBS)	21	5 g/kg, 400 μL	*In vivo*		PBS	4h + 7d	[123]
Fusu agent	Male Wistar Rats	Suppressing HPA1 expression, and thus exerts prosurvival effect *via* maintaining MTP and attenuating cell injury.	Intraperitoneal injection of LPS (3 mg/kg)	8-16	2, 4 and 6 g/kg	*In vivo*			48h	[124]
	HUVECs		LPS (1 μg/mL)		1μg/mL	*In vitro*			6h	
Xuebijing Injection	C57B/L6 mice	Regulating purine, glutathione, arachidonic acid, and sphingolipid metabolisms	(CLP) Sepsis-Induced ALI Model	9	4 mL/kg	*In vivo*		Saline	72h	[125]
Reduning injection (RDN)	Male Sprague-Dawley rats	Regulating phospholipid, sphingolipid, nucleotide, energy, and other metabolic pathways.	Intravenous injection of LPS (7 mg/kg)	7	5 mL/kg	*In vivo*		Saline	6h	[126]
Astragalus membranaceus and *Salvia miltiorrhiza*	Male Sprague-Dawley rats	Regulating the TLR4/NF-κB signaling pathways	Intratracheal injection of LPS (5 mg/kg)	8	0.59 g/mL, 10 mL/kg	*In vivo*	DXM	PBS	6d + 6h	[127]
Lianqinjiedu decoction	Male Sprague–Dawley rats	Inhibiting protein expression of TLR4 and NF-κBp65 activation.	Intraperitoneal injection of LPS (5 mg/kg)	8	0.61, 1.22 and 2.44 g/kg	*In vivo*	Aspirin	Saline	7h	[128]
ShuFengJieDu Capsule	Male Sprague–Dawley rats	Potentially due to AKT1 regulation during ALI progression.	Intraperitoneal injection of LPS (10 mg/kg)	8	100 mg/kg	*In vivo*		Saline	5d	[129]
Qingfei Xiaoyan Wan	Kunming male mice	Regulated the PI3K/AKT and Ras/MAPK pathways to inhibit pathogenic bacterial infections effectively	Intratracheal PAK suspension (approximately 4×10^7 colony-forming units/lung)	10	2, 6 and 18 g/kg/d	*In vivo*	LEV		7d + 24h	[130]
YiQiFuMai lyophilized injection	C57 male mice	Regulating both TLR4-MyD88 and mTOR-autophagy pathways,	Intratracheal injection of PM2.5 (50 mg/kg)	6	0.33, 0.67 and 1.34 g/kg	*In vivo*	DEX		30min + 24h	[131]
Qingwen Baidu Decoction	SD male rats	Improving pathological features	Intratracheal injection of LPS (5 mg/kg)		9.5, 19 and 38 g/kg	*In vivo*	DEX	Saline	48h + 12h	[132]
Sangxingtang	Female BALB/c mice	Down-regulating the MAPK/NF-κB pathway	Intratracheal injection of LPS (200 mg/L)	10	3.5 and 7 g/kg	*In vivo*	DEX	Saline	15min + 6h	[133]
Jie-Geng-Tang	Male BALB/c mice	Regulating PI3K/Akt signal pathway inhibition of NF- κB	Intranasal injection of LPS (0.5 mg/kg)	6	0.45, 1.35 and 4.05 g/kg	*In vivo*	DEX	Saline	7d + 24h	[134]
Dachengqi decoction	SD male rats	Inhibits inflammatory cytokines production through TLR4/NF-κB signaling pathway	Intraperitoneal injection of LPS (10 mg/kg)	10	0.9 g/kg	*In vivo*		Saline	12h + 8h	[135]
	HULEC-5a cells		LPS (100 ng/mL)		100 μg/mL	*In vitro*			6h + 12h	

combined analytical method furnished complementary metabolomics information to be used in the exploration of the mode of action of RDN against ALI. Xuebijing injection (XBJ), a traditional Chinese herbal prescription, has been approved by the State Food and Drug Administration (SFDA) and is widely used in the clinical treatment of severe sepsis. The comprehensive changes in lung tissue and the therapeutic action of XBJ on ALI in a mouse model of sepsis were evaluated by metabolomics. The results suggested that the purine, glutathione, sphingomyelin, arachidonic acid, and phospholipid metabolic pathways may be therapeutic targets in the treatment of sepsis-induced ALI.

The preceding illustrations demonstrate that metabolomics plays an important role in the study of CMM formulae. Metabolomics analyzes entire living systems rather than isolated parts (cells, tissues, and organs). This approach harmonizes well with the systemic and integral methodology of TCM [56]. With the advent of network pharmacology, transcriptomics, and other methods, there are more options at our disposal to elucidate the multitarget and multifaceted approaches of CMM and traditional CMM formulae. Therefore, the strategic application and combination of these disciplines and technologies for the research and development and safety and efficacy testing of CMM are future objectives. With the deepening of research, it is believed that these methods will elucidate the complete molecular mechanism of anti-ALI CMM and accurately forecast antagonism, additivity, or synergy among the constituents in the CMM formula, thereby greatly improving the degree of verification at the human clinical trial level.

7.2. The combined application of CMM with western medicine in the clinic

There is currently no drug in modern medicine that can specifically improve the prognosis of ALI. Many scholars are actively conducting basic and clinical research to explore a satisfactory diagnosis and treatment method. TCM has a unique understanding of ALI, and its prevention and treatment have attracted increasing attention. With the emphasis on ALI, the clinical treatment of ALI has gradually shifted from Western medicine to the combination of CMM with western medicine, and has achieved satisfactory results. Ulinastatin is clinically used for the treatment of acute or chronic recurrent inflammation. It can also be used as a rescue aid for acute circulatory failure. It is a commonly used western medicine for the treatment of ALI. It has favorable anti-inflammatory, anti-enzyme and micro-circulation effects. However, occasionally patients will have more severe allergic reactions and other side effects; therefore, the clinical efficacy of ulinastatin alone is not satisfactory. [57]. Xuanbai Chengqi Decoction (XBCQ) is a CMM formula consisting of *Gypsum Fibrosum* (生石膏), *Armeniacae Amarum* Semen (苦杏仁), *Trichosanthes kirilowii* Maxim. (瓜蒌皮) and *Rheum palmatum* L. (大黄). According to the theory of TCM, XBCQ also plays a vital role clinically against ALI [58]. The combination of ulinastatin and XBCQ proves that the combination of traditional Chinese and Western medicine can help ALI patients to relieve symptoms such as shortness of breath and difficulty, reduce inflammation, improve respiratory mechanics and lung function, and the effect is remarkable. Table 5 lists the clinical cases of ALI in combination with traditional Chinese and Western medicine in recent years.

8. A solution for the potential toxicity of CMM

TCM has been used in China for thousands of years to treat numerous diseases. TCM is relatively inexpensive, widely available, and has a reliable therapeutic efficacy [59,60]. It is commonly thought that TCM is generally safe as they are derived from natural materials. However, this belief has been greatly challenged in recent years. The safety and toxicity of TCM has raised concerns in the international community. Consequently, there has been an increasing demand for information regarding the identification of the plant constituents, their preparation methods, and their potential to interact with other herbal medicines and conventional drugs [61,62]. TCM includes an intimate

Table 5
The combination application of CMM with Western medicine in clinic.

CMM(formula)	Western medicine	Cause	Case number	Relevant clinical indicators						Mortality	Related cytokines	Refs
				Respiratory rate	ICU days	Total length of stay in hospital	Incidence of ARDS	The duration of ventilatory support	Oxygenation index			
Shenmai Injection	Ulinastatin	Acute pancreatitis	20		↓	↓	↓	↓	↑		TNF-α ↓ IL-6 ↓ IL-1β ↓	[136]
Danhong Injection	Ulinastatin	Acute inflammation	36	↓	↓	↓	↓		↑	↓	TNF-α ↓ IL-6 ↓	[137]
Xuanbai Chengqi Decoction	Ulinastatin	–	45						↑		IL-6 ↓	[138]
Xuanbai Chengqi Decoction	Mechanical ventilation	–	28	↓						↓		[139]
Xuanbai Chengqi Decoction	Continuous venovenous hemofiltration	–	24		↓	↓	↓		↑			[140]
Danshen injection	Ulinastatin	Trauma	30	↓	↓	↓	↓		↑	↓	TNF-α↓ IL-6 ↓	[141]
Danshen injection	Troxerutin	Trauma	35	↓	↓	↓	↓		↑	↓	TNF-α↓ IL-6 ↓	[142]
Reduning	Cefoxitin	Pneumonia	30								TNF-α ↓ IL-6 ↓CPR↓	[143]
Rheum palmatum L. (大黄)	Anisodamine	Trauma	42	↓	↓	–	↓	↓				[144]
Tanreqing Injection	Dexamethasone	–	44		↓	↓	↓	↓	↑	↓		[145]
Shenfu injection	Edaravone	Trauma	43		↓	↓			↑		SOD↑ MDA↓ GSH↑ VEGF↓	[146]
Qingfei Qutan Decoction (home-made)	Ambroxol hydrochloride	–	46	↓					↑	↓	HIF-1α↓TNF-α↓ IL-6 ↓	[147]

and unique understanding of the safe application of toxic substances. In both modern and ancient TCM books, TCM toxicity classifications (highly toxic, moderately toxic, nontoxic), medication quality, processing agents, medication dosages, administration routes, safe and efficacious combinations, and individual differences among patients have all been considered in determining the safe application of CMM in clinical practice. This approach formed the basis for the TCM toxicity theory and is an effective means of controlling TCM toxicity [63]. As seen in the above tables, some toxic CMM provides significant effects in the treatment of ALI, but most are administered with processed products or active ingredients to ensure their safety and effectiveness. For example, *Armeniacae Amarum* Semen (苦杏仁), a CMM with a long history, has effects in relieving cough and relieving asthma, anti-inflammatory and analgesic, and relaxing bowel movements. Amygdalin is an effective component of bitter almond to stop coughs and asthma. It has a favorable effect on the treatment of lung diseases, such as ALI. However, an excess of hydrocyanic acid produced by the enzymatic hydrolysis of amygdalin can poison the body. When *Armeniacae Amarum* Semen is processed, its bitter almond enzyme is destroyed. The bitter almond glycoside slowly decomposes and releases a therapeutic level of hydrocyanic acid which contributes to the antitussive and antiasthmatic effects of this anti-ALI [64]. The investigation of anti-ALI TCM revealed that toxicity is an intrinsic property of some of its constituents. They will produce side effects when directly applied in clinical treatment. Physicians are highly concerned about TCM toxicity. To that end, they propose corresponding alexipharmic solutions.

TCM processing helps attenuate the side effects of toxic TCM. In anti-ALI CMM, the toxicity of the ingredient *Euphorbia lathyris* Linn. (千金子) may be reduced by frying, use of the raw herb, combination with cold or hot cream or wine, and steaming. Of these, the most effective at attenuating and concocting the CMM is steaming. However, the use of hot and cold cream may balance drug efficacy and toxicity. The method actually used is left to the discretion of the clinical pharmacist [65]. The toxicity of *Euphorbia jolkinii* Boiss (狼毒) may be mitigated through vinegar processing [66]. The side effects provoked by *Tripterygium Wilfordii* Hook. f (雷公藤) may be reduced by combining it with *Glycyrrhiza uralensis* Fisch, *Radix paeoniae* Alba and *Pteris multifada* poir. Vinegar processing will augment the anti-ALI efficacy of the mixture in clinical application [67]. Recent research showed that modern stir-fry, alkali, wine, low-temperature ultrafine comminution and other processing methods effectively reduce the toxicity of *Asarum sieboldii* Miq (细辛) and enhance its safety in clinical application [68].

The science-based understanding and utilization of toxic constituents are imperative for future development and progress in TCM especially as it undergoes global modernization. TCM toxicity may now be studied using both traditional TCM theory and methods of modern toxicology. New TCM technology may help identify the toxicity characteristics of TCM more scientifically and objectively. It was proposed that TCM should be administered to supplement conventional allopathic drug therapies. Numerous investigations and standard analytical methods have been conducted to identify optimal drug candidates, such as HPLC, GS-MS/MS, and other types of chromatography. These methods have been used to identify and determine the concentrations of toxicants in the CMM before and after attenuation, elucidate their modes of action, and minimize their toxicity without compromising their therapeutic efficacy.

9. Conclusion

Progress has been made in empirical research on the anti-ALI effect of CMM. However, most of it has focused on inflammatory cytokines, oxidative stress, and inflammatory cell infiltration in the lungs. There have been relatively few in-depth investigations into the pulmonary lesions associated with ALI. Clinical treatments have been developed by combining the theory of CMM properties with therapies based on CMM syndrome differentiation. Nevertheless, there have been no horizontal comparisons among various CMM in terms of their efficacy or mechanisms in treating the various causes of ALI. Future studies should explore the etiology and pathogenesis of ALI. Fundamental research on TCM-based prevention and treatment of ALI should be expanded. The modes of action of anti-ALI CMM must be examined at multiple levels. The pharmacodynamic material basis for anti-ALI should be clarified to provide a scientific foundation for ALI prevention and treatment using CMM.

Author contributions

ZS, BY, and XS designed the work. ZD, RZ, TX, YY, YW, and ZS collected and reviewed the references. ZD and YY wrote the first draft. WW, NX participated in the addition and modification of tables in the manuscript. ZS wrote and ZD reviewed the final version of the manuscript. All authors discussed and contributed to the manuscript.

Data availability

The data used to support the findings of this study are included within the article.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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