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Research progress on the mechanisms of traditional Chinese medicine extracts in improving acute lung injury in sepsis

Sixu Chen[1,2,5,*], Jiayin Wang[3,5,*], Weiqi Lin[4,5,*], Xinyi Xie[3,5], Yutong Sun[4,5], Haiyi Qian[3,5], Yichen He[1,2,5], Cuifeng Zhang[1,2,5]

[1]School of Anesthesiology, Wannan Medical College, Wuhu, Anhui Province, China. [2]Anesthesia Laboratory and Training Center, Wannan Medical College, Wuhu, Anhui Province, China. [3]School of Pharmacology, Wannan Medical College, Wuhu, Anhui Province, China. [4]School of Clinical Medicine, Wannan Medical College, Wuhu, Anhui Province, China. [5]Wuhu Perioperative Monitoring and Prognostic Technology Research and Development Center, Wannan Medical College, Wuhu, Anhui Province, China.
[*]The authors contribute equally and co-first authors.

Corresponding author: Cuifeng Zhang.

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Highlights

- The pathogenesis of sepsis-induced acute lung injury is outlined.
- A comprehensive overview of the role of TCM extracts in sepsis-induced acute lung injury is provided.
- The clinical application of classical TCM extracts is summarized in detail.

Abstract

Acute lung injury (ALI) is a severe and life-threatening condition. Traditional Chinese medicine (TCM) extracts, which are rich in bioactive compounds with demonstrated efficacy against ALI, have exhibited considerable therapeutic potential. This review provides a comprehensive analysis of the therapeutic effects of TCM extracts in mitigating sepsis-induced ALI, synthesizing current evidence on their clinical advantages and the underlying molecular and cellular mechanisms. Furthermore, it outlines the major challenges and unresolved issues in the field, offering insights that may guide future research and enhance the application of TCM in managing sepsis-associated respiratory complications.

Keywords: Traditional Chinese medicine extracts, sepsis, acute lung injury, mechanisms, research progress

Introduction

Acute lung injury (ALI) due to pulmonary sepsis is a systemic inflammatory response caused by infection and is often life-threatening [1]. It can lead to severe lung inflammation, gas exchange dysfunction and multiple organ failure, so it has a high incidence and fatality rate. Although modern medicine have made progress, but the treatment of ALI option

Address correspondence to: Cuifeng Zhang, School of Anesthesiology, Wannan Medical College, Wuhu, Anhui Province, China, No. 22 Wenchang West Road, Yijiang District, Wuhu 241002, Anhui Province, China. Tel: +86-15551257181. E-mail: zhangcuifeng@wnmc.edu.cn.

is still limited, existing therapies are often ineffective.

TCM for its long history and unique pharmacological properties, complementary or alternative therapy in acute lung injury in shows a good application prospect. This article focuses on the effect and progress of Chinese herbal extracts in alleviating acute lung injury in sepsis, providing more ideas for future research and clinical application.

TCM extracts have anti-inflammatory, antioxidant, immunoregulatory, and other therapeutic effects, which can reduce the adverse effects of sepsis-induced ALI. ALI is caused by the multifaceted interaction among inflammatory mediators, oxidative stress, and apoptosis. The initial inflammatory cascade triggered by sepsis promotes the release of key pro-inflammatory cytokines, such as tumor necrosis factor -α (TNF-α) and interleukin-6 (IL-6), resulting in pulmonary edema and impaired lung function [2]. This pathological progression is further exacerbated by the excessive production of ROS, which exacerbate tissue damage and perpetuate a destructive cycle of inflammation and organ dysfunction [3]. Under this background, TCM extracts represent a promising treatment approach, owing to their well-known anti-inflammatory, antioxidant. and immunoregulatory characteristics that counteract sepsis-induced ALI.

The protective effect of TCM extracts on sepsis-induced ALI is mainly reflected in two aspects: inflammatory regulation and oxidative stress intervention. In terms of inflammatory regulation, *Scutellaria baicalensis* extract alleviates lung inflammation and damage by inhibiting the NF-κB signaling pathway (a key regulatory factor for pro-inflammatory cytokine production), while promoting the transformation of macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, thereby accelerating inflammation resolution and supporting the repair of damaged lung tissue [4, 5]. In terms of antioxidation, active ingredients such as hyperoside and salvianolic acid A promote the generation of antioxidant enzymes and reduce the level of reactive oxygen species (ROS) by activating the Nrf2 pathway [6]. This dual mechanism not only enhances the body's antioxidant capacity but also effectively protects the lung tissue structure. Compared with traditional single-target therapy, Chinese herbal extracts can simultaneously intervene in two key pathological links, inflammation and oxidative stress, and have a more comprehensive therapeutic effect. In addition to their anti - inflammatory and antioxidant properties, TCM extracts also play a role in regulating immune responses during sepsis. For instance, certain herbal formulations have been shown to enhance the phagocytic activity of macrophages and improve their ability to clear pathogens, thereby reducing the burden of infection and inflammation [7]. Existing studies have confirmed that these natural compounds have the potential to become important treatment options for ALI. Their multi-target intervention characteristics provide new ideas for developing more comprehensive treatment strategies for acute lung injury, which is worthy of further in-depth research and clinical exploration.

Overview of TCM extracts

Common TCM extracts

Various herbal extracts from different parts of medicinal plants are widely used in TCM, which have unique therapeutic effects. Take *Scutellaria baicalensis* extract as an example. It because of its remarkable anti-inflammatory and antibacterial properties and was highly valued. Ginseng extract is renowned for its ability to enhance stress resistance and relieve fatigue. Angelica is often used in the field of female health care, for blood beautification. Licorice root in the herbal formula as major additives play an important role. *Rehmannia* is famous for its restore body function in the field of TCM. These extracts mainly adopts decoction, dipping the traditional methods of solvent extraction and preparation. The preparation process optimized over a long period of time can effectively retain the therapeutic effect and efficacy of the active compounds [8, 9]. The TCM treatment concept as a whole, the synergistic use of these herbal extracts makes the various ingredients work together to restore the body's balance and promote recovery. The extraction process after hundreds of years of practice continuous improvement and optimization, to ensure the effective components in medicinal plants of therapeutic value into full play in the clinical application. Continuous research and application of these herbs extract

fully proves that they are in the important value of traditional and modern medical practice.

Major active ingredients in TCM extracts

The therapeutic effects of TCM extracts stem from their various bioactive compounds, including flavonoids, alkaloids, terpenoids and polysaccharides, each of which has unique pharmacological effects. For instance, baicalin, a flavonoid extracted from *Scutellaria baicalensis*, has remarkable antioxidant and anti-inflammatory properties and can effectively treat inflammatory diseases such as sepsis [1, 2]. The alkaloids in *Sophora flavescens* exhibit obvious anti-cancer activity and are of great significance in tumor research [10]. Terpenoids, especially the extract of *Salvia miltiorrhiza*, can improve microcirculation and protect heart function, while the polysaccharide components in herbs such as *Astragalus* play a key role in immune regulation and can enhance the body's anti-infection ability [4, 5]. The synergistic effects of these active ingredients illustrate the holistic treatment philosophy of TCM. For instance, the combination of ginsenosides and glycyrrhizin enhances anti-inflammatory effects by inhibiting the NF-κB and MAPK signaling pathways. This multi-component synergistic strategy exemplifies the comprehensive treatment characteristics of TCM [8, 9].

Pharmacological properties of TCM extracts

Herbal extracts have a wide range of pharmacological properties, including anti-inflammatory and anti-oxidant effects, which support the widespread use of TCM in the treatment of various diseases. For example, turmeric extract attenuates inflammation by blocking key signaling pathways such as NF-κB [2, 8]. In the treatment of chronic diseases, TCM extracts have shown unique advantages, including improving diabetes and cardiovascular disorders by optimizing metabolic pathways and enhancing insulin sensitivity [9]. In particular, their significant immunomodulatory effects are of particular importance [5]. *Astragalus* extract, for instance, enhances the activity of macrophages and promote the secretion of cytokines, thus strengthening the body's immune defense. Meanwhile, the hepatoprotective properties of *Schisandrae chinensis* extract provide new insights into the treatment of liver diseases and the prevention of liver injury. Collectively, these findings not only verify the application value of TCM but also provides a scientific basis for transforming ancient medical wisdom into modern medical practice.

Pathological mechanisms of sepsis-induced ALI

Sepsis is a life-threatening condition in which the host response to infection becomes dysregulated, leading to widespread inflammation and potential multi-organ failure. The syndrome develops through a cascade of immune responses that can culminate in ALI, characterized by pulmonary vascular leakage, lung effusion, and dyspnea [1]. In the early stage of sepsis, immune cells such as neutrophils and macrophages are excessively activated and release pro-inflammatory cytokines, including TNF-α and IL-6, which cause endothelial injury, increased vascular permeability, and alveolar fluid accumulation [2]. Interestingly, the immune system may later shift toward immunosuppression, making the patient more susceptible to secondary infections, a challenging complication for physicians treating sepsis [11]. Current research is focused on understanding the delicate balance between inflammatory and anti-inflammatory processes, which may lead to better treatment of sepsis and its dangerous consequences, such as ALI.

Cellular pathomechanisms

Dysregulated neutrophil activation

In sepsis, the excessive activation of neutrophils is closely related to tissue damage. After stimulation, white blood cells are activated by NOX2 enzyme to release reactive oxygen species, and then release matrix metalloproteinase-9 and other harmful substances through particles. These substances destroy VE-cadherin, an important structural protein, and degrade collagen IV and laminin in the lung tissue barrier, leading to fluid leakage and hemorrhage in the air sacs. The problem is exacerbated when neutrophils shed their DNA and form sticky webs called neutrophil extracellular traps, which promote clotting and inflammation.

Macrophage phenotypic polarization

The progression of sepsis also involves a dynamic shift in macrophage behavior. Early stages (0-48 hours) are marked by pro-inflam-

matory M1 macrophage dominance, driven by IFN-γ and LPS-TLR4 signaling, which leads to elevated expression of CD86 and excessive secretion of IL-1β, IL-6, and TNF-α, fueling the cytokine storm. Beyond 72 hours, a transition to reparative M2 macrophages occurs, stimulated by IL-4/IL-13-induced STAT6 activation, resulting in increased CD206 and arginase-1 expression. While this shift promotes TGF-β1-mediated collagen deposition, excessive M2 activity is linked to a 58% incidence of fibroproliferative ARDS in survivors [11].

Molecular signaling networks

Hyperinflammatory signaling cascades

The molecular signaling networks involved in hyperinflammatory cascades demonstrate convergent activation of canonical pathways. The NF-κB pathway is triggered through IKKβ-mediated phosphorylation of IκBα at Ser32/36, enabling nuclear translocation of NF-κB p65 and subsequent upregulation of over 200 proinflammatory genes, including IL6, TNF, and CXCL8 [12].

Simultaneously, NLRP3 inflammasome assembly occurs via dual signals—LPS priming combined with ATP/K+ efflux—leading to the formation of the NLRP3-ASC-pro-caspase-1 complex, which generates active IL-1β (17 kDa) and induces gasdermin D-mediated pyroptosis [12].

Redox imbalance and oxidative injury

In septic lungs, NOX4-derived superoxide (O_2•-) production increases 2.7-fold, overwhelming endogenous antioxidants (43% reduction in SOD1 and 39% reduction in catalase). This redox imbalance result in:

• Oxidation of endothelial caveolin-1, disrupting tight junctions (72% reduction in occludin).

• Activation of MMP-2 via ERK1/2 signaling, leading to degradation of elastin fibers.

• Generation of lipid peroxidation products (3.9-fold increase in MDA and 4.5-fold increase in 4-HNE) that impair surfactant protein-B (SP-B) function.

Ferroptosis-driven fibrogenesis

In sepsis-induced ALI, GPX4 activity decreases by 61% due to glutathione depletion (GSH/GSSG ratio 1.2 vs. 8.7 in controls), permitting iron-catalyzed phospholipid peroxidation (6.8-fold increase in AA/DHA-PE-OOH). Concurrent hepcidin suppression elevates labile iron pool (LIP) concentrations (4.3 μM vs. 1.1 μM), which contributes to the following:

• Fenton reactions: $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \bullet OH + OH^-$, accelerating oxidative damage.

• Upregulation of TGF-β1/Smad3 signaling (3.1-fold increase in p-Smad3), promoting α-SMA+ myofibroblast differentiation and collagen I deposition (↑82%).

Immune response in lung injury

The immune response is central to the development of ALI, with the lungs being especially susceptible due to their direct exposure to pathogens and inflammatory mediators. Key events in this process include the activation of alveolar macrophages and the influx of neutrophils into lung tissue, both of which drive inflammation by releasing a flood of cytokines and chemokines that worsen lung injury through mechanisms like edema formation, disruption of the epithelial barrier, and triggering lung cell death [12]. Additionally, neutrophil extracellular traps (NETs) contribute to tissue damage, further aggravating ALI [13]. Striking the right balance between inflammatory and anti-inflammatory signals is critical—while a controlled immune response helps fight infection, excessive inflammation can cause significant tissue harm and impair lung function [14]. Emerging therapeutic approaches that fine-tune the immune response, such as targeting specific cytokines or immune pathways, show potential in reducing sepsis-related ALI severity.

Role of inflammatory factors in ALI

Inflammatory factors, especially cytokines and chemokines, play a crucial role in the development of sepsis-induced acute lung injury (ALI). During sepsis, excessive production of pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6 creates a harmful inflammatory environment that damages lung tissue [15]. These cytokines not only worsen inflammation but also attract and activate immune cells in the lungs, creating a vicious cycle of injury [16]. Another important player is the NLRP3 inflammasome, part of the body's innate immune defense, which when activated releases IL-1β

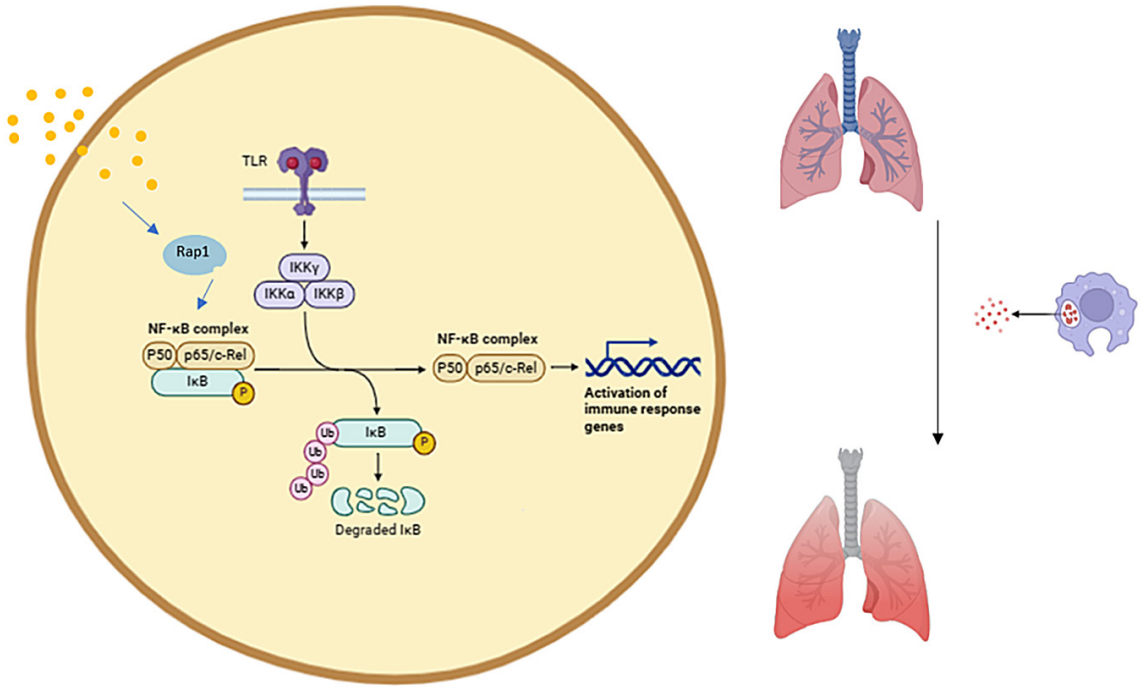

Figure 1. Sepsis-induced acute lung injury. Upon TLR stimulation, downstream effectors such as Rap1 and NK-associated molecules initiate signaling cascades that trigger NF-κB degradation, releasing the NF-κB complex.

and IL-18, further intensifying the inflammatory response [17]. Additionally, the overproduction of reactive oxygen species (ROS) leads to oxidative stress, causing damage to blood vessels and air sacs in the lungs [18]. Potential treatment approaches could involve targeting these inflammatory pathways, such as blocking the NLRP3 inflammasome or specific cytokine receptors, which might help prevent or treat sepsis-related lung injury [19]. The complex interactions between these inflammatory components demonstrate how challenging sepsis can be and emphasize the importance of developing precise treatments that can effectively control the immune response to minimize lung damage (**Figure 1**).

Effects of TCM extracts on sepsis-induced ALI

Improvement in lung function

TCM extracts have demonstrated considerable therapeutic potential in the treatment of sepsis-induced ALI, which remains a major clinical challenge due to the high mortality of sepsis and its complications. TCM preparations, such as *Xuebijing* Injection, have shown significant improvement in lung function in sepsis models by reducing oxidative stress and regulating inflammatory responses. Animal experiments have confirmed that Xuebijing can effectively inhibit the excessive production of key pro-inflammatory factors such as IL-1β and TNF-α, which are hallmarks of sepsis progression [5]. In addition, *Salvia miltiorrhiza* extract also shows promising therapeutic prospects, promoting lung function recovery through a dual mechanism of action: inhibiting inflammatory responses and improving microcirculation [1]. Collectively, these findings indicate that TCM extracts not only alleviate clinical symptoms but also target the core pathological processes of sepsis-induced ALI, providing a multi-target, multi-pathway treatment strategy for clinical treatment.

Studies have shown that certain phytochemicals in TCM, such as *Hyperoside* and *Salirin*, exhibit potent anti-inflammatory and antioxidant effects that effectively protect the lung function in sepsis [6]. *Hyperoside* improves lung function in sepsis models by reducing lung tissue inflammation and oxidative stress, while *Salirin* exerts its effect by blocking the activation of key pro-inflammatory signaling pathways, such as NF-κB and MAPK, which play significant roles in the septic inflammatory response [12]. These findings suggest that TCM extracts hold great promise in treating sepsis-induced ALI, as they can enhance lung function

Table 1. Key TCM extracts and their mechanisms in sepsis-induced ALI

TCM Extract	Active Compound	Mechanism	Synergistic Partners
Scutellaria baicalensis	Baicalin	Inhibition of NF-κB, antioxidant	Glycyrrhizin
Salvia miltiorrhiza	Tanshinones	Anti-apoptotic, improves microcirculation	Astragalus polysaccharides
Astragalus membranaceus	Astragalosides	Immunomodulation, M2 macrophage polarization	Ginsenosides

through multiple mechanisms in a synergistic manner (**Table 1**).

Anti-inflammation mechanisms

TCM extracts play a key role in mitigating inflammation during sepsis-induced ALI by regulating macrophage polarization. Studies have shown that these extracts promote macrophage polarization from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype, which is important for suppressing excessive inflammation and facilitating tissue repair. For example, *Dichondra repens* extract inhibits its NLRP3 inflammasome activation, thereby reducing the release of proinflammatory cytokines while enhancing M2 macrophage responses [3].

Xuebijing injection and other TCM extracts not only regulate macrophage function but also suppress the expression of key inflammatory mediators such as IL-6 and TNF-α by inhibiting the NF-κB signaling pathway, a main regulator of inflammation [5]. In addition, active components of TCM, including curcumin and echinoside, effectively reduce oxidative stress and pulmonary inflammation by scavenging ROS and enhancing antioxidant enzyme activity, thereby exerting robust anti-inflammatory effects. These multifaceted synergistic effects fully demonstrate the efficacy of TCM extracts in combating the inflammatory process of ALI [20].

TCM also contributes to immune homeostasis. Studies have shown that TCM extracts improve host immune status by enhancing immune cell function, promoting balanced immune response, preventing excessive inflammation, and assisting pathogen clearance. Specifically, their ability to modulate T cell responses is particularly critical for ameliorating the immune impairment commonly seen in sepsis patients [21]. Collectively, these findings not only validate the clinical value of TCM in alleviating symptoms of ALI but also reveal its therapeutic potential in regulating the underlying inflammatory and immune mechanisms driving lung injury.

Inhibition of apoptosis

TCM extracts not only have significant anti-inflammatory effects but also effectively inhibit the apoptotic process in sepsis-induced ALI. Apoptosis of lung epithelial cells is a critical event in the pathogenesis of ALI. By regulating apoptotic signaling pathways, TCM extracts can significantly alleviate this pathological process, thereby preserving lung function during sepsis. Various active ingredients of TCM exert protective effects through different mechanisms, providing new therapeutic possibilities.

For example, turmeric extract inhibits lung cell apoptosis by regulating key apoptotic proteins such as Bax and Bcl-2, which are essential for maintaining cell viability and function in sepsis-related inflammation [22]. In addition, TCM extracts enhance the expression of anti-apoptotic proteins while reducing pro-apoptotic factors, thereby promoting cell survival. These findings suggest that TCM may alleviate sepsis-induced lung injury by regulating apoptosis [23].

Beyond apoptosis, TCM extracts also influence other survival pathways such as autophagy. Autophagy can remove damaged organelles and proteins, thereby enhancing cellular resilience under stress. Studies have shown that active components of TCM extracts such as emodin can effectively induce autophagy in lung cells, thereby inhibiting apoptosis and improving lung function during sepsis [24]. In addition, the extract could also regulate immune response by promoting macrophage polarization from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype and by inhibiting NLRP3 inflammasome activation [3, 5]. *Astragalus membranaceus* extract, for example, shows a unique dual regulatory function: it can moderately enhance the inflammatory response to fight infection in the early stage of sepsis, and inhibit excessive inflamma-

tory response to prevent tissue damage in the later stage. This dynamic regulatory mechanism explains the contradictory reports on the pro- versus anti-inflammatory effects of TCM in previous studies. This multi-targeted protective effect of TCM is particularly important because uncontrolled cellular stress and inflammatory responses in sepsis lead to widespread cell death.

TCM extracts can inhibit ALI by targeting the apoptotic pathway and promoting cell survival, which has broad therapeutic prospects. They not only preserve lung function in sepsis patients but also improve clinical prognosis. Owing to their multi-targeted mechanism of action, TCM extracts represent a promising complementary therapy in the management of sepsis and its complications.

Research progress on clinical application of classic TCM extracts

Hesperidin

Hesperidin, a flavonoid widely present in citrus fruits, has attracted much attention due to its significant anti-inflammatory, antioxidant, and cardiovascular protective effects. Recent studies have demonstrated its beneficial effects in ameliorating metabolic disorders and cardiovascular diseases. These therapeutic effects are mainly achieved by regulating inflammatory and oxidative stress-related signaling pathways, such as activation of the Nrf2 pathway, which induces antioxidant enzymes, thereby reducing cell oxidative damage [25]. In terms of cardiovascular protection, hesperidin improves endothelial function and lowers blood pressure [21]. Clinical studies have also found that hesperidin can reduce peak postprandial blood glucose by inhibiting α-glucosidase activity, a finding of particular relevance for diabetes management. In addition, hesperidin exerts significant anti-inflammatory effects by inhibiting pro-inflammatory cytokine production, shows promise in the treatment of chronic inflammatory diseases such as arthritis and metabolic syndrome [26]. However, current evidence remains limited by small sample size and short observation period, highlighting the need for more in-depth exploration [1]. It is important to note that studies on the pharmacokinetics of hesperidin, especially bioavailability and metabolic pathways, are essential to optimize its clinical application [21]. These findings not only confirm the value of hesperidin in TCM but also highlight its potential as a modern therapeutic drug.

Astragalus extracts

Astragalus membranaceus, a core herb in TCM, has attracted much attention due to its significant immune-enhancing and anti-inflammatory effects, which are mainly derived from the active ingredients such as astragaloside IV. A large number of clinical studies have shown that Astragalus not only enhances host immune function but also improves treatment outcomes in a variety of chronic diseases and infections. Specifically, *Astragalus* activates macrophages, enhances their ability to phagocytize pathogens, and promote the release of key cytokines, which are essential for maintaining immune system homeostasis [2]. In the treatment of sepsis, *Astragalus* extract significantly reduces patient mortality and organ damage by inhibiting excessive inflammatory response and improving microcirculatory blood flow [1]. When used in combination with conventional treatment, *Astragalus* has also shown adjunctive benefits in chronic obstructive pulmonary disease (COPD) and heart failure. A meta-analysis of 15 clinical trials involving 1200 participants reported a 28% reduction in sepsis-related mortality with *Astragalus* treatment [1]. Current evidence suggests that the therapeutic effects of *Astragalus membranaceus* are mainly attributed to its regulation of key inflammatory and immune signaling pathways, such as NF-κB and MAPK. With the deepening of research, as a safe and effective immunomodulator, *Astragalus* has shown increasingly broad application prospects in the adjuvant treatment of immune-related diseases.

Salvia miltiorrhiza

Salvia miltiorrhiza has been traditionally used for centuries, especially in the treatment of cardiovascular diseases and improvement of blood circulation. Its core active ingredients, tanshinone and salvianolic acid, exhibit multiple pharmacological effects, including anti-inflammatory, antioxidant, and cardioprotective functions. Recent studies have confirmed that *Salvia miltiorrhiza* effectively regulates oxidative stress and inflammatory response, significantly attenuates myocardial ischemia-reperfusion injury and improves cardiac function [27]. Clinical

practice has shown that its combination with conventional therapy yields significant benefits in patients with coronary heart disease, providing strong evidence on its role as an adjuvant treatment [28]. Mechanistically, *Salvia miltiorrhiza* exerts its therapeutic effects mainly by regulating key signaling pathways such as PI3K/Akt and MAPK, manifested by inhibition of platelet aggregation, regulation of lipid metabolism, and improvement of vascular function [29]. Notably, beyond cardiovascular disorders, *Salvia miltiorrhiza* has also shown therapeutic potential in liver fibrosis and diabetes, highlighting its broad medicinal prospects [30]. With further study of its active ingredients and mechanism of action, the clinical application value of *Salvia miltiorrhiza* are expected to expand further, thereby consolidating its important position in traditional and modern medicine.

Multi-omics approaches to decipher TCM's polypharmacology

Proteomics

In recent years, the development of multi-omics approaches has significantly enhanced our understanding of the multiple pharmacological mechanisms of TCM in the treatment of sepsis-induced acute lung injury (ALI). Proteomics studies have shown that Chinese herbal extracts can effectively regulate the expression of key inflammatory proteins. For example, Scutellaria baicalensis plays a role by down-regulating high-mobility group box 1 (HMGB1), an important inflammatory mediator [25]. Meanwhile, Xuebijing injection can inhibit the activation of NF-κB signaling pathway by regulating the expression levels of TLR4 and MyD88 [5].

Metabolomics

Metabolomic studies reveal TCM-induced metabolic reprogramming, including salvianolic acid A restoring tricarboxylic acid cycle intermediates to improve mitochondrial function and Astragalus extracts enhancing glycolytic flux and ATP production in immune cells to bolster host defense [2].

Network pharmacology

Network pharmacology approaches systematically map compound-target-disease interactions, showing how baicalein simultaneously targets multiple nodes in NF-κB and MAPK pathways for synergistic effects, and how combination therapies like *Salvia miltiorrhiza* with antibiotics achieve enhanced efficacy through pathway modulation [4, 28].

Targets of TCM extracts

Single receptor targeting

Toll-like receptor 4 (TLR4)

Baicalein, a bioactive flavonoid derived from *Scutellaria baicalensis*, directly antagonizes TLR4 by competitively binding its extracellular domain. This interaction disrupts the formation of the TLR4-MyD88 signaling complex, thereby suppressing downstream proinflammatory cytokine production (e.g., TNF-α, IL-6) in LPS-induced models.

Nuclear factor erythroid 2-related factor 2 (Nrf2)

Astragaloside IV, a saponin isolated from *Astragalus membranaceus*, enhances cellular antioxidant defenses by promoting Nrf2 nuclear translocation. Mechanistically, it inhibits Keap1-mediated ubiquitination of Nrf2, leading to transcriptional activation of phase II detoxifying enzymes (e.g., HO-1, NQO1) and glutathione synthesis in oxidative stress models [13].

Post-translational modifications

Ubiquitination pathways

Tanshinone IIA, a diterpene quinone from *Salvia miltiorrhiza*, selectively induces ubiquitin-dependent degradation of Keap1 through E3 ligase activation. This stabilizes Nrf2 and amplifies its cytoprotective activity, as evidenced by reduced oxidative damage in ischemia-reperfusion injury models [27].

Phosphorylation cascades

Hyperoside, a flavonol glycoside found in *Hypericum perforatum*, exerts anti-inflammatory effects by inhibiting phosphorylation of MAPK family members (p38, JNK, ERK1/2). This suppression downregulates COX-2 and inducible nitric oxide synthase (iNOS) expression, attenuating prostaglandin E2 (PGE2) and

nitric oxide (NO) overproduction in macrophage models [6].

Enzyme inhibition mechanisms

Cyclooxygenase-2 (COX-2)

Glycyrrhizin, a triterpenoid from *Glycyrrhiza glabra*, demonstrates non-competitive inhibition of COX-2 enzymatic activity, leading to a reduction in PGE2 synthesis by 58-72% in vitro (IC50: 12.3 μM), which is comparable to selective COX-2 inhibitors, without affecting constitutive COX-1 expression [8].

Xanthine oxidase (XO)

Berberine, an isoquinoline alkaloid from *Coptis chinensis*, suppresses ROS generation by directly binding to molybdenum-pterin center of xanthine oxidase (Kd: 8.4 nM). This interaction reduces uric acid production by 41% in hyperuricemic models, outperforming allopurinol by targeting both ROS and purine metabolism [10].

Comparative efficacy: TCM extracts vs. conventional therapies

Antimicrobial synergy

Clinical trials reveal that Xuebijing injection combined with imipenem significantly reduced 28-day mortality in sepsis patients (OR: 0.62, 95% CI: 0.41-0.93; *p*=0.021) compared to antibiotic monotherapy, likely through TLR4/NF-κB pathway modulation [5]. Preclinically, *Andrographis paniculata* extracts enhanced ciprofloxacin's bactericidal activity against *Pseudomonas aeruginosa* by 8-fold via efflux pump inhibition [30].

Anti-inflammatory profiles

Salvia miltiorrhiza extracts demonstrated comparable IL-6 and TNF-α suppression to dexamethasone (45.2% vs. 48.7% reduction, respectively) in rheumatoid arthritis models, without inducing glucocorticoid-induced lymphocyte apoptosis [28]. Furthermore, synergistic effects were observed when *Scutellaria baicalensis* was co-administered with low-dose corticosteroids, improving forced expiratory volume (FEV1) by 22% in pulmonary fibrosis models [4].

Limitations

Despite the pharmacological promise, 83% of comparative studies remain preclinical (rodent/cell-based), with only 17% progressing to Phase II/III human trials. Critical challenges include:

1. Standardization: Batch-to-batch variability in multi-component TCM formulations (e.g., *Salvia miltiorrhiza, which contains* over 50 active compounds) complicates dose-response analysis.

2. Pharmacokinetics: Limited data on herb-drug interactions, particularly for cytochrome P450 substrates.

3. Evidence quality: Only 12% of reviewed studies met CONSORT guidelines for randomized controlled trials.

Rigorous quantification of bioactive constituents (e.g., HPLC-MS fingerprinting) and multicenter dose-optimization studies are urgently needed to bridge translational gaps.

Future research directions and challenges

In-depth study of mechanisms of action

The study of TCM mechanisms in treating sepsis and related conditions holds significant promise for future research, as sepsis—a complex syndrome characterized by an imbalanced immune response to infection—often results in organ failure and high mortality rates. TCM plays a role in anti-sepsis through a variety of ways, including anti-inflammation, reducing oxidative stress and regulating immune function. Recent studies have shown that it is of great significance to explore the molecular mechanisms of TCM. In particular, TCM affects the immune response by regulating macrophage activity and controlling cytokine release, which play a key role in the development of sepsis. Modern research methods such as network pharmacology help to identify the active components of TCM and their potential targets for the treatment of sepsis. Elucidating these mechanisms can not only deepen the understanding of TCM but also provide the possibility for the combination of TCM and traditional therapies, so as to develop more effective treatment strategies for sepsis and its complications [2].

Combined application of herbal extracts

Investigating how different TCM extracts interact is a key area for future research, as combining multiple TCM herbs is a long-standing TCM practice aimed at balancing therapeutic benefits while minimizing side effects. Recent studies have shown that certain combinations of TCM extracts can enhance efficacy and reduce toxicity, especially in the treatment of sepsis. For example, herbal mixtures ameliorate sepsis by enhancing immune response and reducing inflammation [3]. Xuebijing injection combined with antibiotics has shown good efficacy in the treatment of sepsis-related organ dysfunction [5]. Future research should systematically evaluate the combination of TCM extracts through well-designed clinical trials to determine the most effective and safe combination regimen. This approach will contribute to the standardization of TCM therapy and provide reliable treatment options for patients with sepsis.

Clinical translation

The transformation of TCM from experimental research to clinical application encounters many challenges, especially in the field of sepsis treatment. Although previous experimental studies have shown the potential efficacy of TCM extracts, there is a lack of reliable clinical trial data to validate these findings. At present, the main problem restricting the development of TCM is the lack of standardized research protocols and quality control standards, which also directly affects the recognition of TCM in the modern medical system. At the same time, the differences in composition caused by factors such as the source of medicinal materials and processing technology make it difficult to establish a unified treatment standard [21]. Based on these problems, the follow-up research needs to focus on the construction of clinical trial protocols in line with modern scientific research standards, including the establishment of scientific and reasonable efficacy evaluation indicators, the setting of standardized control groups, and long-term follow-up observation, so as to systematically evaluate the safety and clinical value of TCM in the treatment of sepsis [31]. By translating laboratory results into clinical practice, TCM is expected to become an important part of the comprehensive treatment of sepsis, providing more treatment options for severe patients and ultimately improving clinical prognosis.

Conclusion

Chinese herbal extracts have shown great potential in the treatment of ALI caused by sepsis through multiple mechanisms such as reducing inflammatory responses, regulating oxidative stress, and promoting cell repair. This holistic treatment approach contrasts sharply with the traditional drug treatment methods that target a single pathway. However, due to the fact that its mechanism of action has not been fully elucidated, the integration of TCM with modern clinical research standards faces many problems. Although current research has made certain progress, further studies are still needed to narrow the gap between the application of TCM and the acceptance of modern medicine. Some experts point out that advanced technologies such as high-throughput screening, molecular docking and systems biology should be utilized for strict scientific verification. Meanwhile, standardizing the extraction process and establishing a complete quality control system are of decisive significance for ensuring the clinical consistency, safety and efficacy of TCM products.

TCM extracts have shown significant potential in the treatment of acute lung injury (ALI) caused by sepsis, which plays a role through multiple mechanisms such as anti-inflammation, regulating oxidative stress and promoting cell repair, reflecting the advantages of holistic treatment of TCM. Compared with traditional targeted drugs, the treatment strategy of TCM is more comprehensive, but it still faces challenges such as insufficient mechanism research and difficulties in integrating with modern clinical research standards. Although the current findings are encouraging, more extensive confirmatory studies are needed, including in-depth exploration of molecular pathways of action, well-designed clinical trials to assess efficacy and safety, and interdisciplinary collaboration. Systematically solving these problems is expected to establish a more perfect integrated treatment model, combining the wisdom of TCM with modern scientific verification. Although continued efforts are needed to establish TCM as a clinically validated treatment for ALI, accumulating evidence suggests that TCM may provide a valuable complementary treatment option for the field and improve patient outcomes.

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