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A review on Angelica sinensis alleviates acute lung tissue injury through TLR-4/MyD88 signal pathway

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Highlights

- This review describes the main components of Angelica sinensis and their efficacy.
- Current status and basic mechanisms of the classical inflammatory signal pathways in lipopolysaccharide-in -duced acute lung injury (ALI) are discussed.
- Angelica sinensis contributes to the anti-inflammation in lipopolysaccharide-induced ALI and is expected to ex pand the application of traditional Chinese medicine in the treatment of ALI.

Abstract

Angelica sinensis (AS), commonly known as Danggui and hailed as a premier medicinal herb, holds a prominent place in traditional Chinese medicine due to its potent healing properties. It is widely used to boost blood and vital energy, promote blood flow, relieve blood stasis, regulate menstruation, and alleviate pain. With advances in medical technology, modern interest in Chinese medicine has surged, spurring more in-depth research into its pharmacological mechanisms. This review introduces the principal components of AS and its therapeutic efficacy, while also summarizing current research on fundamental mechanisms involving key inflammatory signal pathways, notably nuclear factor κB and mitogen-activated protein kinase. Z-Ligustilide, AS's primary bioactive compound, exhibits a range of pharmacological effects, including anti-inflammatory, anticancer, neuroprotective, anti-apoptotic, organ-protective, antioxidant, and analgesic properties. In addition to discuss the advancements in the treatment of acute lung injury (ALI), this review provides a detailed exploration of the main components of AS and its mechanisms for mitigating ALI induced by lipopolysaccharides, with the aim of providing a theoretical basis and inspiration for the development of drugs in Chinese medicine, with AS as a representative example. This manuscript offers a novel therapeutic method for clinical management of ALI, thereby presenting additional alternatives for pharmacological intervention.

Keywords: Angelica sinensis, ligustilide, anti-inflammation, acute lung injury, lipopolysaccharide, nuclear factor κB, mitogen-activated protein kinase, toll-like receptor 4, myeloid differentiation primary response 88

Introduction

Acute lung injury (ALI) is a common clinical complication of sepsis with high mortality rate. It is characterized by the sudden onset of respiratory insufficiency or failure, primarily triggered by non-cardiogenic factors such as severe infections, shock, trauma, and burns. At present, there are still no effective and specific therapeutic methods in treatment. Further research is required to explore specific and effective targeted inhibitors to interrupt lung injury based on different types of pathogens. Angelica sinensis (AS), known as the 'king of medicines' in traditional Chinese medicine, is a perennial herbaceous plant with its highest quality cultivation in southeastern Gansu, particularly Minxian County. The roots of AS are highly valued for

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their medicinal properties, including nourishing qi and blood, enhancing blood circulation, supporting cardiovascular health, regulating menstruation, relieving pain, moisturizing dryness, promoting gastrointestinal motility, and providing anticancer, anti-aging, hepatoprotective, neuroprotective, and immune-boosting benefits [1, 2]. Typically, the dried root of AS, harvested in late autumn, is used for medicinal purpose. This root is slightly cylindrical, with sections known as the 'head' (upper root), 'body' (primary root), and 'tail' (smaller branch roots). Its chemical composition includes volatile oils, polysaccharides, organic acids, and amino acids [2].

AS extract has demonstrated significant analgesic and anti-inflammatory effects, increasing the pain threshold in mice exposed to thermal stimuli and inhibiting the torsion response induced by acetic acid and other chemical irritants [3]. Ligustilide is a naturally occurring phthalide derivative and an active ingredient of AS, exhibits a wide range of pharmacological activities, including anti-atherosclerotic, neuroprotective, anti-cardiac hypertrophic, anti-inflammatory, and analgesic effects [4].

Major components and biological activities of AS

Angelica sinensis polysaccharide (ASP)

Recent studies have demonstrated that polysaccharides from Chinese herbs possess significant anti-tumor effects [5]. ASP, one of the principal bioactive constituents of AS. Typically obtained through aqueous alcohol extraction. ASP mainly consists of monosaccharides, such as glucose, galactose, and xylose, as well as acidic polysaccharides, including D-xylose and D-galactose. Research has revealed its immunomodulatory activity and diverse analgesic properties, such as the alleviation of uterine spasms induced by caprylyl estriol and histamine in mice [6]. Zhang's study demonstrated that ASP could reduce astrocyte apoptosis in the midbrain of mice with Parkinson's disease by inhibiting the Bax/Bcl2/Caspase-3 apoptotic signal pathway [7]. Furthermore, ASP shows therapeutic potential for osteoarthritis by inhibiting the nuclear factor κB (NF-κB) signal pathway [8]. Zhou's research found that an overdose of AS can significantly improve peripheral nerve injury in rats with diabetic neuropathy, potentially through blocking the toll-like receptor 4 (TLR-4)/myeloid differentiation primary response 88 (MyD88)/NF-κB inflammatory signal pathway [9].

AS volatile oil

The organic compounds of AS, such as its essential oil, are typically extracted using organic solvents or distillation. Due to its muscular irritability and limited stability, AS volatile oil is generally applied as a clathrate to enhance its stability in practice [10]. Z-Ligustilide, a key active component in AS volatile oil, exhibits diverse biological activities, including tumor inhibition, neuroprotection, anti-Alzheimer's effects, suppression of cardiac hypertrophy, anti-atherosclerosis, anti-inflammation, analgesic effects, cardiovascular system support, immunity enhancement, and cognitive function improvement [11]. AS volatile oil has shown significant inhibitory effects in animal models via mouse hot plate and writhing tests [3]. Additionally, Z-Ligustilide has demonstrated promising results in reducing pain responses induced by acetic acid and thermal stimuli in mice, as well as mitigating persistent pain caused by administration of complete Freund's adjuvant [4, 12].

Organic acids of AS

The primary organic acids in AS, shellacenoic acid and hesperidinic acid, have been shown to exhibit strong bacteriostatic effects against Pseudomonas aeruginosa, a pathogen predominantly affecting the respiratory system [13]. Furthermore, optimized organic acids can inhibit the expression of protein Jun NH2-terminal kinase (p-JNK) in lung tissues to various extents, underscoring their potent anti-inflammatory properties. In a rat model of lipopolysaccharides (LPS)-induced inflammatory pain, AS organic acids reduced blood levels of tumour necrosis factor alpha (TNF-α) and nitric oxide when combined with kaurenoic acid and pimaric acid in a 4:5 ratio [14]. Additionally, AS organic acids have been demonstrated to significantly alleviate inflammation in mice exposed to formalin [14].

Amino acids of AS

Amino acids, the fundamental units of proteins, are commonly present in various Chinese herbs. AS contains over 10 kinds of amino acids, with arginine, γ-aminobutyric acid and glutamic acid being the most abundant. Among different AS samples with different drying methods, total amino acids reached as high as 61.79 mg/g on average, while essential amino acids were 3.37 mg/g on average, confirming the high nutritional value of AS [15]. Wei et al. suggested that this variation may be attributed to the internal structural composition of the

medicinal material and the specific soil environment of each part [16]. Additionally, Liu et al. identified distinctive differences in amino acid content across various medicinal parts of AS [17]. For AS from different geographical origins, glutamic acid and methionine stand out as the amino acids with the most pronounced variation [18].

Other components

AS is rich in trace elements, including flavonoids, vitamins, Mn^{2+}, and other essential components vital for the body's metabolic processes [18]. **Table 1** summarizes the main bioactive components of AS and their chemical formulas.

Research on LPS-induced ALI

The etiology and pathogenesis of ALI

ALI is a common and serious complication in patients with sepsis, primarily triggered by trauma, infection, and shock, and is clinically characterized by progressive hypoxemia and dyspnea. If left untreated, ALI can progress to acute respiratory distress syndrome. Key factors in the development of ALI include apoptosis, lung fibrosis, oxidative stress, and inflammatory responses [19]. In the early phase of ALI, stimuli such as LPS prompt alveolar macrophages to produce and release numerous inflammatory factors, including IL-1, TNF-α, and NF-κB. This buildup of activated inflammatory cells and cytokines initiates an inflammatory cascade that damages lung epithelial cells, leading to the accumulation of protein-rich fluid, pulmonary edema, lymphocytic infiltration, and ultimately, lung fibrosis. Early intervention to suppress inflammatory responses and protect vascular endothelium is thus critical in ALI treatment, particularly through the inhibition of inflammatory responses and the TLR-4-mediated inflammatory signal pathway [20].

LPS, a key component of Gram-negative bacterial membranes, is frequently used to model ALI due to its potent inflammatory effect. ALI models can be created via intra-airway instillation or intraperitoneal injection of LPS in mice, with experimental evidence suggesting that intra-airway delivery of LPS provides higher efficacy in modeling ALI [21].

Inflammation signal pathways of LPS-induced ALI

TLR-4/MyD88

LPS initiates an inflammatory response primarily by interacting with TLRs in mammals. The TLR family consists of 13 distinct members, each specific to certain ligands; among these, TLR-4 is specialized for recognizing LPS. The Myeloid differentiation factor 88 (MyD88) protein plays a pivotal role as a linking molecule in the TLR-4/MyD88/NF-κB inflammatory pathway. TLRs operate through two signal pathways: the MyD88-dependent pathway and the MyD88-independent pathway [22]. Initially, the MyD88 molecule binds to the TLR, subsequently associating with interleukin receptor-associated kinase, which activates inhibitor of nuclear factor kappa-B kinase (IKK). This activation leads to the degradation of the NF-κB inhibitory protein, enabling NF-κB to enter the nucleus and promote the transcription of inflammatory genes.

NF-κB

The NF-κB molecule is a dimer composed of NF-κB1 (p50) and RelA (p65). When bound to IκB, NF-κB remains inactive. In the presence of inflammatory factors, signaling molecules bind to receptors on the plasma membrane, initiating a signaling cascade that activates IKK. As a kinase for IκB, IKK induces the phosphorylation of IκB, leading to its degradation and allowing NF-κB to dissociate and activate. The active NF-κB then translocates to the nucleus, where it promotes the transcription of downstream genes and facilitates cytokine release, thereby initiating a cascade of inflammatory responses [23].

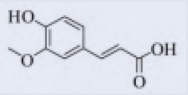
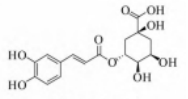
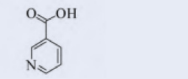
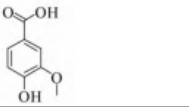
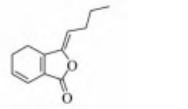
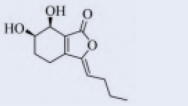
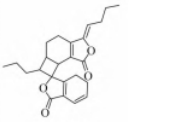
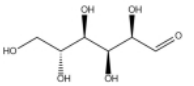
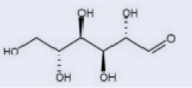
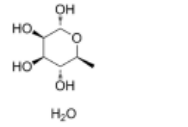
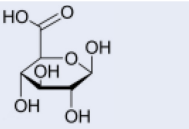
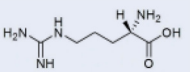
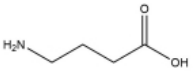
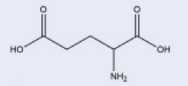
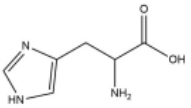
TLR-4/MyD88/NF-κB inflammation pathways

The NF-κB signal pathway is involved in inflammatory responses, oxidative stress, and apoptosis, regulates coagulation and fibrinolysis in lung tissue, and plays a crucial role in the onset and progression of ALI [24]. A study by Wang et al. demonstrated that fecal microbiota transplantation could alleviate LPS-induced ALI in rats via the TLR-4/NF-κB signal pathway. In the lung tissue of the fecal transplant group, levels of TLR-4 and NF-κB p65 were reduced, indicating that inhibiting the immune-inflammatory response can significantly aid in lung tissue recovery [25]. Additionally, TAK242 was shown to improve blood oxygen saturation in acute respiratory distress syndrome mice by inhibiting TLR-4 and NF-κB expression in lung tissues and reducing serum levels of inflammatory factors, including IL-6 and IL-18 [26].

mitogen-activated protein kinase (MAPK)/AP-1

Inflammatory factors recognize receptors

Table 1. Table of the main active ingredients of AS and its chemical structure formulas

Compound name	Chemical structure	CAS number
Organic acids		
Ferulic acid		1135-24-6
Chlorogenic acid		327-97-9
Nicotinic acid		59-67-6
Vanillic acid		121-34-6
volatile oil		
Z-Ligustilide		81944-09-4
Senkyunolide H		114586-51-5
Angelicid		92935-94-9
Polysaccharide		
Glucose		14431-43-7
Mannose		69-65-8
rhamnose monohydrate		10030-85-0
Glucuronic acid		6556-12-3
Amino acids		
L-Arginine		74-79-3
γ-aminobutyric acid (GABA)		56-12-2
L-Glutamic acid		56-86-0
L-Histidine		71-00-1

on the plasma membrane, initiating signal transmission into the cell. Through a series of cascade reactions, downstream MAPK protein kinases (MEKK) are activated, which, in turn, activate downstream MAPK kinases. This process ultimately activates p38 MAPK, extracellular signal-regulated kinase (ERK), and c-JNK, conveying signals to the nucleus to regulate gene expression. Another downstream pathway of TLR signaling involves the transcription factor AP-1 (activator protein 1), which regulates the expression of inflammatory factors [27]. Composed of c-Fos and c-Jun, AP-1 primarily mediates inflammation via the MAPK pathway. Key regulators of AP-1 transcription include p38 MAPK, JNK, and ERK, with the JNK/p38 MAPK pathway chiefly responsible for cytokine production and inflammatory responses, while the ERK pathway is primarily involved in cell proliferation, differentiation, apoptosis, and various pathological processes [28].

TLR-4/MAPK/AP-1 inflammation pathways

The MAPK inflammatory signal pathway is prevalent in lung tissue cells. Studies have shown that suppressing the p38 MAPK pathway can significantly reduce lung injury in ALI mice, likely by controlling cell apoptosis and regulating inflammation [29]. Additionally, MAPK is involved in respiratory bursts by modulating neutrophil activity [30]. Research has demonstrated that phosphorylated p38 MAPK promotes the production and release of inflammatory factors and induces overexpression of adhesion proteins, such as COX-2, thereby enhancing transcription factor activity.

In Gan's study, using an LPS-induced ALI mouse model, increased mRNA expression of p-p38 MAPK, c-fos, and c-jun were observed in the experimental group [28]. This suggests that activation of the p38 MAPK/AP-1 signal pathway may play a role in the early inflammatory response in ALI.

Therapeutic effects of AS on LPS-induced ALI

AS affects the inflammatory factors

Growing evidence indicates that inflammatory factors play significant roles in the development of LPS-induced ALI, making modulation of this pathway a promising strategy for treatment. Studies have shown that ferulic acid, an organic acid derived from AS, can effectively alleviate lung tissue edema and reduce inflammatory cells in the alveolar septum in mice with LPS-induced ALI by inhibiting the release of inflammatory mediators. Compared to the LPS model group, serum levels of TNF-α, IL-6, and IL-1β were significantly decreased in the ferulic acid treatment group [30].

In Zhu's study, ligustilide, a component of AS volatile oil, significantly reduced pulmonary interstitial inflammatory cell infiltration, interstitial pulmonary edema, and alveolar wall thickening, thus mitigating alveolar damage. Additionally, it decreased the total cell count, neutrophil ratio, total protein, as well as TNF-α and IL-1β levels in bronchoalveolar lavage fluid. Its therapeutic effect may be associated with the reduction of key pro-inflammatory cytokines in lung tissue, such as TNF-α and IL-1β [31].

AS influences NF-κB inflammatory signal pathway

Decursinol angelate, an active ingredient of AS, is a promising candidate for ALI treatment. By inhibiting the AKT/NF-κB signal pathway in LPS-induced ALI, decursinol angelate alleviates cell damage and apoptosis, reduces oxidative stress, and mitigates inflammation [32]. Treatment with decursinol angelate decreases the expression of TNF-α, IL-1β, and IL-6, while inflammation is further suppressed by reducing the phosphorylation of p65, IκBα, and AKT, thereby preventing p65 from entering the nucleus.

In Zheng's experiments, ligustilide was shown to inhibit the stimulator of interferon genes (STING)/tank-binding kinase 1/NF-κB signal pathway, and reduce lung tissue damage in a mouse model of LPS-induced ALI [33]. STING activates NF-κB, with p65 as its central component. It has been demonstrated that ligustilide specifically inhibits NF-κB activity by reducing the expression of p65 and STING, effectively alleviating lung tissue inflammation and oxidative damage.

The combination of safflower and AS improved inflammatory infiltrates in the lungs and reduced alveolar wall thickening in an LPS-induced ALI mouse model [34]. The synergy of safflower with AS effectively regulates the phosphorylation of ERK1/2 and p38, which reduces IκB depolymerization and NF-κB p65/p50 activation, limiting the nuclear transport of NF-κB p65/p50 and exerting anti-inflammatory effects. This, in turn, mitigates immune cell apoptosis and helps prevent lung damage.

ALI can progress to pulmonary fibrosis. In a pulmonary fibrosis mouse model, ligustilide treatment significantly reduced the protein expression of TLR-4, MyD88, and NF-κB p-P65/P65.

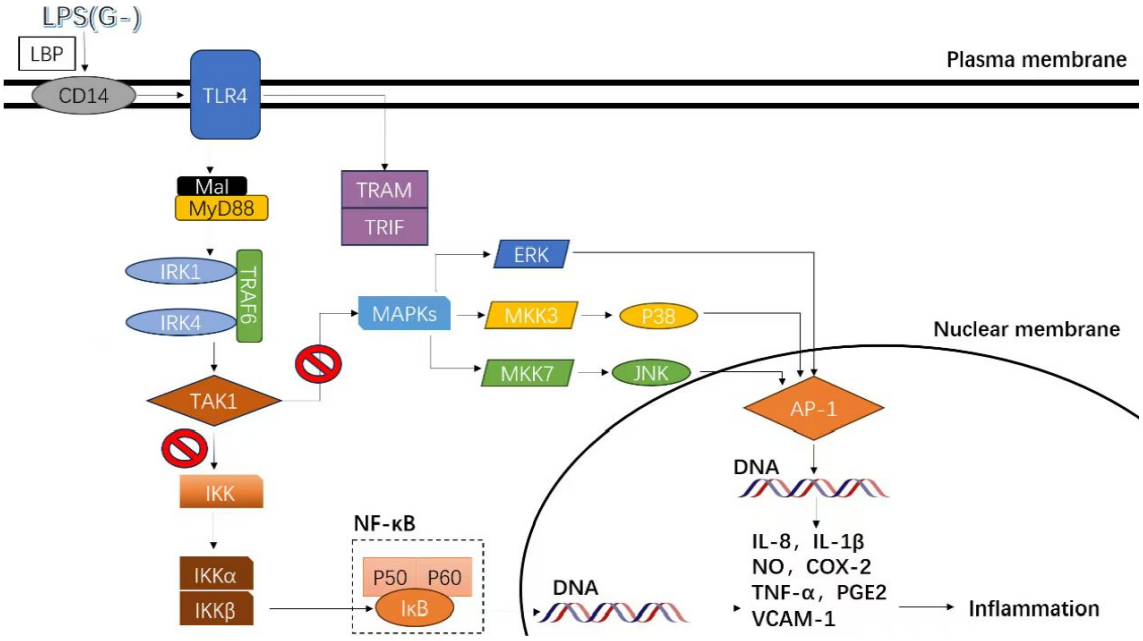


Figure 1. Diagram of the effects of Angelica sinensis on the signalling pathway

Additionally, ligustilide demonstrated inhibition of oxidative stress and apoptosis in mice with pulmonary fibrosis [35]. These results indicate that ligustilide improves pulmonary fibrosis by enhancing ventilation, reducing fibroblast proliferation, and decreasing oxidative stress and apoptosis via the TLR4/MyD88/NF-κB P65 signal pathway. **Figure 1** reveals that ligustilide reduces the production of inflammatory factors by affecting the TLR4/NF-κB pathway.

AS regulates MAPK inflammation pathways

Traditional Chinese medicine can enhance immune function in the lungs, reduce inflammatory damage to lung tissue, and alleviate ALI symptoms by modulating macrophage activity [36]. In a study by Won et al., Z-ligustilide demonstrated anti-inflammatory effects by regulating NF-κB and MAPK signal pathways in LPS-stimulated RAW264.7 macrophages [37]. Their results showed that Z-ligustilide inhibited the phosphorylation and subsequent degradation of IκBα (an NF-κB inhibitor), as well as p38 MAPK, ERK, and JNK, in a dose-dependent manner.

The Chuanxiong Rhizome and Paeoniae Radix Rubra herbal pair (CX-CS), a traditional Chinese medicine formula for treating ALI, includes AS as one of its components. Studies indicate that CX-CS effectively suppresses LPS-induced ALI by reducing the release of TNF-α, IL-1β, and IL-6. Additionally, CX-CS inhibits the expression of p38, ERK, IκBα, p65, caspase 3, and PARP, while upregulating AKT and the Bcl-2/Bax ratio [38]. This study confirms the synergistic effect of the CX-CS herbal pair in preventing ALI by mitigating inflammation, oxidative stress, and apoptosis through the MAPK/NF-κB and PI3K/AKT signal pathways.

Figure 1 reveals that ligustilide reduces the production of inflammatory factors by affecting the TLR4/MAPK pathway.

Conclusion

The traditional Chinese medicine AS has demonstrated significant medicinal value, particularly for its antibacterial, analgesic, and anti-inflammatory properties. While AS exhibits a broad spectrum of therapeutic effects, this review focuses specifically on its anti-inflammatory role in LPS-induced ALI.

The principal components of AS include ASP, volatile oils, organic acids, and amino acids. This review introduces these key active ingredients and provides a table summarizing their chemical structures to support further research.

Apoptosis, lung fibrosis, oxidative stress, and inflammatory responses are critical factors in the progression of ALI. Therefore, early suppression of the inflammatory response and protection of the vascular endothelium are crucial for effective ALI treatment.

Growing evidence suggests that AS and its extracts can mitigate ALI by inhibiting the NF-κB inflammatory signal pathway and reducing inflammatory cytokine release. Thus, modulating

this pathway presents a promising strategy for treating LPS-induced ALI. AS and its extracts are known to alleviate inflammation by directly suppressing immune cell activity and modulating various inflammatory mediators and signaling molecules. However, the specific role of AS in ALI remains underexplored and warrants further experimental investigation. Currently, no studies have directly demonstrated that AS exerts its pharmacological effects through particular inflammatory signal pathways, such as TLR-4/MyD88/NF-κB and TLR-4/MAPK/AT-1.

This review summarizes the impact of AS and its extracts on LPS-induced ALI, suggesting that AS may inhibit inflammatory factor release by blocking the TLR-4/MyD88/NF-κB and TLR-4/MAPK/AT-1 signal pathways. Inhibiting these pathways ultimately alleviates lung epithelial cell damage, and reduces protein-rich fluid accumulation, pulmonary edema, lymphocytic infiltration, and lung fibrosis.

In the context of integrating Chinese and Western medicine, numerous scientific methodologies are available to explore the efficacy and mechanisms of Chinese medicine. This integration offers a novel perspective on traditional Chinese medical culture and opens new avenues for natural therapeutics. It is anticipated that, in the near future, new anti-inflammatory drugs incorporating AS extracts will become available for clinical use, marking a continuation of Chinese medical traditions. With advancements in modern medical technology, Chinese medicine—exemplified by AS—continues to demonstrate remarkable vitality.

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