Macrophage-driven pathogenesis in acute lung injury/acute respiratory disease syndrome: Harnessing natural products for therapeutic interventions (Review)

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Received May 15, 2024; Accepted September 27, 2024

DOI: 10.3892/mmr.2024.13381

Abstract. Acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) is a common respiratory disease characterized by hypoxemia and respiratory distress. It is associated with high morbidity and mortality. Due to the complex pathogenesis of ALI, the clinical management of patients with ALI/ARDS is challenging, resulting in numerous post-treatment sequelae and compromising the quality of life of patients. Macrophages, as a class of innate immune cells, play an important role in ALI/ARDS. In recent years, the functions and phenotypes of macrophages have been better understood due to the development of flow cytometry, immunofluorescence, single-cell sequencing and spatial genomics. However, no macrophage-targeted drugs for the treatment of ALI/ARDS currently exist in clinical practice. Natural products are important for drug development, and it has been shown that numerous natural compounds from herbal medicine can alleviate ALI/ARDS caused by various factors by modulating macrophage abnormalities. In the present review, the natural products from herbal medicine that can modulate macrophage abnormalities in ALI/ARDS to treat ALI/ARDS are introduced, and their mechanisms of action, discovered in the previous five years (2019-2024), are presented. This will provide novel ideas and directions for further research, to develop new drugs for the treatment of ALI/ARDS.

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Abbreviations: ALI, acute lung injury; ARDS, acute respiratory distress syndrome; AECs, alveolar epithelial cells; GM-CSF, granulocyte-macrophage colony-stimulating factor; MCP-1, monocyte chemoattractant protein 1; ROS, reactive oxygen species; COX-2, cyclooxygenase 2; BALF, bronchoalveolar lavage fluid; AM, alveolar macrophage

Key words: natural products, acute lung injury, acute respiratory distress syndrome, macrophages

Contents

1. Introduction

Acute lung injury (ALI) is a severe respiratory disease caused by uncontrolled acute inflammation of the lungs caused by various direct factors (such as severe lung infection, pulmonary embolism and lung injury) and indirect factors (such as sepsis, trauma and massive blood transfusions), resulting in impaired lung function. It can further develop into acute respiratory distress syndrome (ARDS) characterized by progressive respiratory distress and refractory hypoxemia (1). According to a study involving 459 intensive care units (ICUs) from 50 countries on 5 continents during 4 consecutive weeks in winter 2014, the prevalence of ARDS accounted for 10.4% of ICU admissions. This survey found that a total of 2,377 patients developed ARDS within the first 48 h of acute hypoxic respiratory failure, with 30.0% of patients presenting with mild ARDS, 46.6% of patients with moderate ARDS and 23.4% of patients with severe ARDS. The in-hospital mortality rate for ARDS was 34.9% in mild patients, 40.3% in moderate patients and 46.1% in patients with severe ARDS (2). Pathological features of ALI include diffuse alveolar damage and large

aggregates of neutrophils in lung tissue, which produce and secrete pro-inflammatory cytokines (3). This causes an uncontrolled inflammatory response, extensive apoptosis of lung epithelial cells, alveolar defects, impaired barrier function of capillary membranes and alveoli, and invasion of proteolytic edema fluid into the alveoli, which destroys surface cellular structures (4,5). However, the pathogenesis of ALI/ARDS is complex, and there is currently no effective, specific treatment in clinical practice. Therefore, innovative mechanisms and therapies are urgently needed to alter the onset and outcome of ALI/ARDS.

Numerous immune cells, such as neutrophils, lung macrophages, alveolar epithelial cells (AECs) and T cells, are involved in the development of ALI/ARDS, which involves the interaction between lung structures and a complex immune cell microenvironment that is essential for ALI/ARDS (6). Macrophages are the main cell type in innate immunity (7). They are widely distributed in the lung microenvironment, have a wide range of plasticity and respond to different stimuli to convert phenotypes (8). Therefore, lung macrophages, as the main effector cells in the lungs and play different roles at different stages of ALI/ARDS (9). Macrophages exacerbate ALI/ARDS by promoting the polarization of pro-inflammatory macrophages and the release of their products, decreasing the release of anti-inflammatory macrophages and their products, and inducing macrophage pyroptosis (10,11). In addition, by decreasing the phagocytosis of macrophages, increasing apoptosis can also promote ALI/ARDS (11). A relevant article has summarized existing and new drugs that have been tested or are currently being clinically tested for the treatment of ALI and ARDS, and different data may support the selective use of neuromuscular blocking agents, corticosteroids and neutrophil elastase inhibitors for the treatment of ARDS (12). However, these are not yet universally available (12). Data from patients with coronavirus disease (COVID) associated ALI /ARDS support using IL-6 monoclonal antibodies, corticosteroids and Janus kinase (JAK) inhibitors to treat this condition (12). Relatively few drugs that target macrophages are available for the treatment of ALI/ARDS (13). IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF) are important cytokines involved in the activation of monocytes and the induction of their differentiation into macrophages (14). In clinical practice, lung inflammation in patients with COVID-19 can be reduced using GM-CSF inhibitors (such as sargramostim and mavrilimumab), which directly target GM-CSF and block its interaction with macrophage surface receptors (15). However, this is only a preventive strategy and has no therapeutic effect on ARDS (16). Homeostatic effects of GM-CSF in the lungs and the blockade of GM-CSF in patients with COVID-19 have the potential risk of impairing alveolar macrophage function and impeding pathogen clearance (17). In previous years, preclinical studies have found that the use of natural compounds isolated from herbal medicine can effectively improve ALI/ARDS by regulating macrophage polarization and pyroptosis (18-20). Furthermore, several natural products also function by regulating phagocytosis and autophagy (21-23). In the present review, the natural products that have been shown to regulate macrophage abnormalities in ALI/ARDS within the past five years and their mechanisms of action are introduced. These products may undergo clinical trials and become potential drugs that treat ALI/ARDS by targeting macrophages, providing new ideas and further research directions for the development of ALI/ARDS therapeutic drugs.

2. Natural products that modulate macrophage polarization

Macrophages are heterogeneous and highly plastic immune cells that recognize pathogen-associated molecular patterns and trigger innate immune responses to activate host defenses and play a regulatory role in inflammatory responses (24). Under different stimuli, macrophages can polarize into two different subtypes, specifically the M1 macrophages (possessing pro-inflammatory characteristics) and the M2 macrophages (possessing properties that counter inflammation) (25). An imbalance in the polarization of the macrophages leads to an inflammatory response (26). Studies have found that balancing M1/M2 macrophages is beneficial to eliminate the inflammatory storm that occurs in ALI/ARDS, which enhances recovery (27-29). The natural products that may be used for the treatment of ALI/ARDS, which modulate macrophage polarization, are summarized in Table I and Fig. 1.

M1 macrophage polarization. Macrophage polarization plays an important role in the development of ALI/ARDS (10). In the early stages of ALI, pro-inflammatory (M1) macrophages predominate (27). Macrophages are usually polarized into the M1 subtype by Th1-related cytokines, such as IFN-γ and TNF-α, as well as through lipopolysaccharide (LPS) stimulation (30). These macrophages produce higher levels of TNF-α, IL-1, IL-6, IL-12, chemokine CC motif chemokine ligand 8, IL-23, monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 2, reactive oxygen species (ROS) and cyclooxygenase 2 (31). In addition, they strongly express CD16 and CD32 (28,31), thereby promoting lung inflammation. Functionally, this macrophage population is primarily involved in pro-inflammatory processes, chemotaxis, free radical formation, matrix degradation, antimicrobial activities and antitumor activities (32). When an inflammatory response occurs in the lungs, peripheral monocytes are recruited into the lung and undergo differentiation into pro-inflammatory macrophages, which modulate the inflammatory response (33). An analysis of bronchoalveolar lavage fluid (BALF) from patients with mild or severe COVID-19 showed that high levels of MCP-1/CCL2 recruit monocytes from the blood into the lungs, which differentiate into pro-inflammatory macrophages (34). Monocytic phagocytes account for 80% of the total cell count of BALF (34). In addition, the exosomal miR-30d-5p of neutrophils promotes M1 polarization in macrophages and initiates macrophage pyroptosis in sepsis-related ALI (35). Induced mitochondrial fusion can target the IκK/IκB/NF-κB pathway in RAW264.7 cells and inhibit M1 macrophage phenotypic switching in LPS-induced ALI (36).

Certain natural products have been found to attenuate ALI/ARDS by inhibiting the polarization of M1 macrophages (28). 5-Methoxyflavone activates nuclear factor erythroid 2-related factor 2 (Nrf2) signaling, which reduces the activation of signal transducer and activator of transcription (STAT)1 signaling, and blocks the LPS/IFN-γ-induced M1 polarization and M2 repolarization with an M1 phenotype

Table I. Natural products that modulate macrophage polarization.

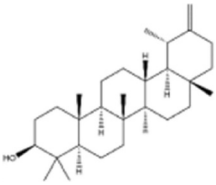
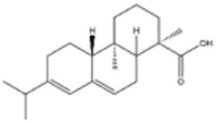
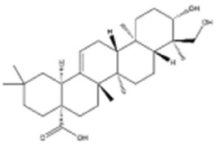
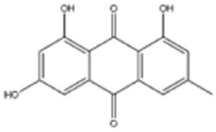
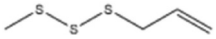
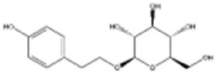
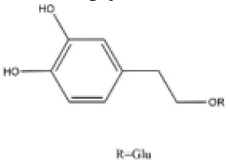
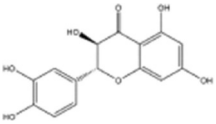
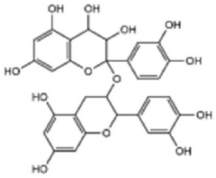
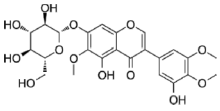
Product name and structure	Type of natural product structure	*In vitro* (effective dose)/ *in vivo* model (effective concentration)	Related molecular mechanisms	Macrophage-related indicators
Taraxasterol 	Flavonoids	LPS-induced murine ALI	Inhibits TNF-α, IL-6 and MCP1	Inhibits M1 macrophages
Abietic acid 	Terpenoids	CLP induces ALI in mice (40 mg/kg)/ RAW264.7 cells (20, 40 and 80 μM)	Inhibits NF-κB pathway	Inhibits M1 macrophages
Hederagenin 	Flavonoids	CLP induces ALI in rats (12.5, 25 and 50 mg/kg)/THP-1-derived macrophages	NF-κB/NLRP3 signaling pathway	Inhibits M1 macrophages
Emodin 	Quinones	SAP-ALI rat model (10 mg/kg)	PPARγ/NF-κB and NLRP3/ Caspase 1/ GSDMD pathway	Inhibits M1 macrophages
Allyl methyl trisulfide 	Thioether	LPS induces ALI in mice (25, 50 and 100 mg/kg)/RAW264.7 cells (50 μM)	NF-κB and MAPK pathways	Inhibits M1 macrophages
Salidroside 	Glycosides	LPS-induced ALI in rats (100 mg/kg).	TLR4/NF-κB and JNK/c-Jun signaling pathways	Inhibits M1 macrophages (AMs)
3,4-dihydroxyphenyletyl-alcohol glycoside 	Polyphenolic	LPS induces ALI in mice (20 mg/kg)/ MH-S (50 μM).	NF-κB, STAT3, and MAPKs signaling	Inhibits M1 macrophages
Dihydroquercetin 	Flavonoids	LPS induces ALI in mice.	Inhibits IRF4/ miR-132-3p/ F-box and FBXW7	Promotes M2 macrophages
Grape seed proanthocyanidin 	Phenols	LPS induces ALI in mice.	Inhibits Trem2/ PI3K/Akt	Macrophage polarization from M1 to M2
Iridin 	Flavonoids	LPS induces ALI in mice (20, 40 and 80 mg/kg)/LPS induces RAW264.7 cells (12.5, 25 and 50 μM).	PKM2-mediated JAK/STAT and NF-κB pathways	Macrophage polarization from M1 to M2

Table I. Continued.

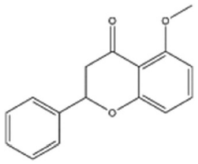
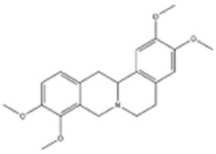
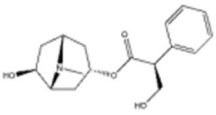
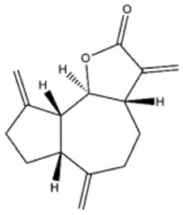
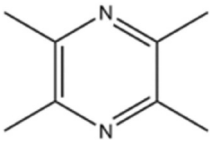
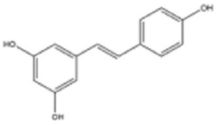
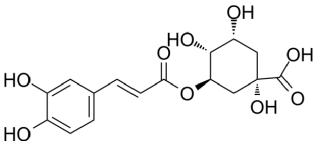
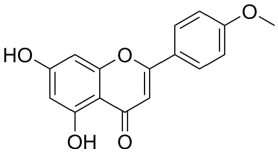
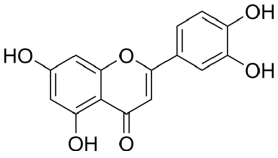
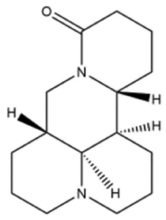
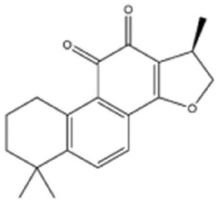
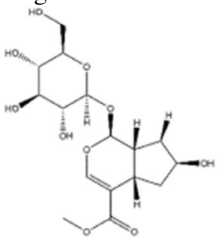
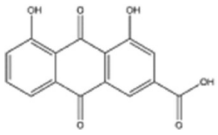
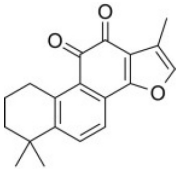
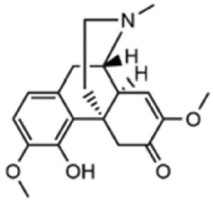
Product name and structure	Type of natural product structure	*In vitro* (effective dose)/ *in vivo* model (effective concentration)	Related molecular mechanisms	Macrophage-related indicators
5-Methoxyflavone 	Flavonoids	LPS/IFN-γ induces RAW264.7 cells (10, 20 and 30 μM).	Nrf2 signaling STAT1 signaling	Macrophage polarization from M1 to M2
Tetrahydropalmatine 	Alkaloids	IR-induced rat ALI	TLR4/NF-κB/ NLRP3 signaling pathway	Macrophage polarization from M1 to M2
Anisodamine 	Alkaloids	LPS induces ALI in mice (1 mg/kg)/ BMDM.	G9a-mediated IRF4 silencing	Promotes M2 macrophages
Dehydrocostus lactone 	Terpenoids	LPS induces ALI in rats (2.5 or 5 mg/kg)/ RAW264.7 cells (0.1, 3, 1 and 10 μM)	C/EBP-δ/ GSDMD/GSDME axis and p38 MAPK/Akt/ NF-κB signaling/ GSDME axis pathway	Macrophage polarization from M1 to M2
Ligustrazine 	Alkyl pyrazines	LPS induces ALI in mice (20, 40 and 80 mg/kg)/RAW264.7 cells (12.5, 25 and 50 μM).	Inhibits the TLR4/TRAF/ NF-κB/NLRP3/ caspase-1 and TLR4/caspase-8/ caspase-3	Macrophage polarization from M1 to M2
Resveratrol 	Polyphenols	LPS induces ALI in mice (30 mg/kg).	Promotes STAT3, inhibits SOCS3	Promotes M2 macrophages and CD45 Siglec F subtype macrophages
Chlorogenic acid 	Polyphenols	Klebsiella pneumoniae-induced pneumonia in mice	Activates SIRT1 to inhibit HMGB1	Promotes M2 macrophages
Acacetin 	Polyphenols	LPS induces ALI in mice/RAW264.7 cells	Inhibits TRAF6/ NF-κB/COX2 axis	Inhibits M1 macrophages, promotes M2 macrophages
Luteolin 	Flavonoids	CLP induces ALI in mice (0.2 mg/kg)/LPS induces RAW264.7.	IL-10	Promotes M2 macrophages and inhibits M1 macrophages

Table I. Continued.

Product name and structure	Type of natural product structure	*In vitro* (effective dose)/ *in vivo* model (effective concentration)	Related molecular mechanisms	Macrophage-related indicators
Matrine 	Alkaloids	LPS induces ALI in mice/RAW264.7 cells	SIRT1 and NF-κB p65 /p53	Inhibits M1 macrophages, promotes M2 macrophages
Cryptotanshinone 	Terpenoids	LPS induces ALI in rats (15, 30 and 60 mg/kg)/ RAW264.7 cells (2.5, 5 and 10 μM)	AMPK pathway	Promotes M2 macrophages inhibits M1 macrophages
Loganin 	Terpenoids	CLP induces ALI in mice/LPS induces RAW264.7 cells	ERK and NF-κB pathway	Promotes M2 macrophages inhibits M1 macrophages
Rhein 	Quinones	LPS induces ALI in mice (50 and 100 mg/kg)/RAW264.7 cells (10, 20 and 40 μM)	NFATc1/Trem2 axis and Sirtuin 1	Promotes M2 macrophages inhibits M1 macrophages
Tanshinone IIA 	Quinones	LPS-induced mouse ALI model (10 mg/kg)/ murine macrophages (100 ng/ml)	NF-κB and HIF pathway	Promotes M2 macrophage inhibits M1 macrophage
Sinomenine 	Alkaloid	LPS stimulates bone marrow-derived macrophages (1 mM)	Promotes PPARβ/δ, α7nAChR/ERK/ Egr-1 feedback pathway	Promotes M2 macrophages, inhibits M1 macrophages

LPS, lipopolysaccharide; PPARβ/δ, peroxisome proliferator-activated receptor β/δ; α7nAChR, nicotinic acetylcholine receptor; ERK, extracellular regulated protein kinase; Egr-1, early growth response 1; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; ALI, acute lung injury; CLP, cecal ligation and puncture; NLRP3, nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing protein 3; GSDMD, Gasdermin D; MAPK, mitogen-activated protein kinase; TLR4, Toll-like receptor 4; JNK, c-Jun N-terminal kinase; c-Jun, Jun proto-oncogene; IRF4, Interferon regulatory factor 4; FBXW7, WD-40 domain protein 7; Trem2, Recombinant triggering receptor expressed on myeloid cells 2; PI3K, phosphatidylinositol 3-kinase; Akt, RAC-α serine/threonine-protein kinase; PKM2, pyruvate kinase isozyme type M2; JAK, Janus kinase; STAT, signal transducing activator of transcription; Nrf2, nuclear factor erythroid 2-related factor 2; G9a, euchromatic histone-lysine N-methyltransferase 2; SOCS3, suppressors of cytokine signaling 3; IL-10, interleukin-10; SIRT1, Sirtuin 1; AMPK, adenosine 5'-monophosphate (AMP)-activated protein kinase; C/EBP-δ, CCAAT/enhancer binding protein-δ; GSDMD, Gasdermin D; GSDME, Gasdermin E; NFATc1, nuclear factor of activated T-cells, cytoplasmic 1; Caspase 1, cysteine-requiring aspartate protease 1; PPAR γ, peroxisome proliferator-activated receptor γ; AM, alveolar macrophages; BMDM, bone marrow-derived macrophages; ALI, acute lung injury.

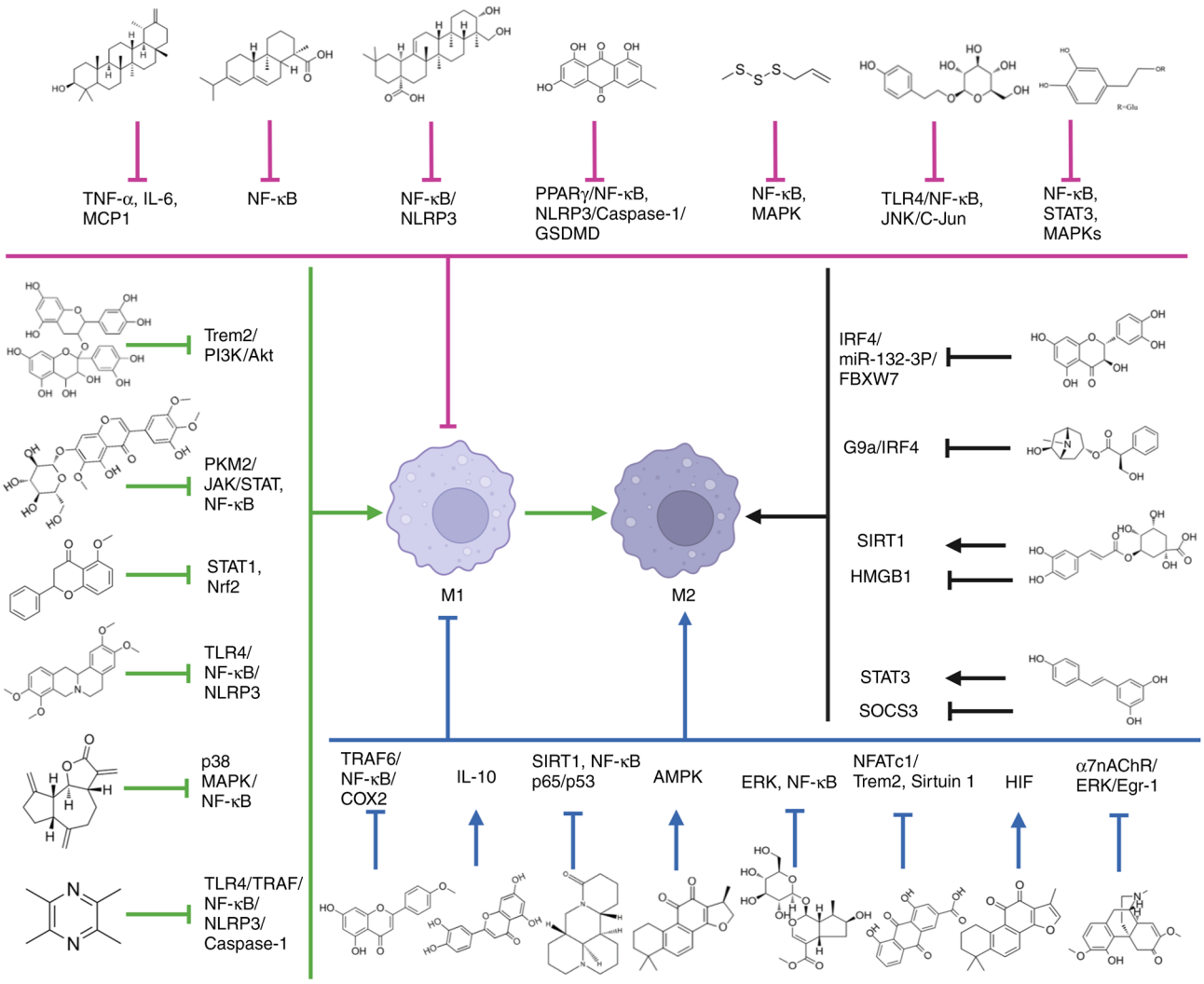


Figure 1. Molecules of natural products interfering with macrophage polarization. Created using BioRender.com. ↑ indicates promotion and ⊥ indicates inhibition. PPARγ, peroxisome proliferator-activated receptor γ; Nrf2, nuclear factor erythroid 2-related factor 2; α7nAChR, α7 nicotinic acetylcholine receptor; Erg-1, early growth response 1; NLRP3, pyrin domain-containing protein 3; Trem2, triggering receptor expressed on myeloid cells; GSDMD, gasdermin D; TLR4, Toll-like receptor 4; STAT3, signal transducer and activator of transcription 3; IRF4, interferon regulatory factor 4; FBXW7, F-box and WD repeat domain containing 7; HIF, hypoxia-inducible factor; SOCS3, suppressor of cytokine signaling 3; G9a, euchromatic histone-lysine N-methyltransferase 2; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; ERK, extracellular regulated protein kinases; Egr-1, early growth response 1; JNK, c-Jun N-terminal kinase; PKM2, pyruvate kinase M2; AMPK, adenosine 5'-monophosphate-activated protein kinase; NFACT1, nuclear factor of activated T cells 1; STRT1, silent information regulator 1.

in RAW264.7 cells; this protects RAW264.7 cells stimulated by LPS (37). Taraxasterol protects LPS-induced ALI in rats by decreasing the polarization of M1 macrophages and decreasing the levels of inflammatory cytokines (38). Abietic acid improves survival and attenuates sepsis-induced lung injury in mice; both *in vitro* and *in vivo* studies have suggested that abietic acid inhibits inflammation and M1 macrophage polarization, and activates the NF-κB pathway (39). This may be the mechanism through which abietic acid attenuates sepsis-induced lung injury (39). Hederagenin exerts anti-inflammatory effects in ALI by inhibiting the NF-κB signaling pathway *in vivo* and *in vitro*, thereby inhibiting M1 macrophage polarization (40). Salidroside can reduce the expression of the inflammatory cytokines, high-mobility group box 1 (HMGB1) and keratin 14, and has a significant therapeutic effect on the ALI/ARDS rat model (41). In addition, it is involved in the regulation of LPS-induced alveolar macrophage (AM) inflammatory activation by AECs (42). A further study found that salidroside attenuated lung inflammation by inhibiting M1 polarization of JNK/c-Jun-attenuated AMs (43). In LPS-induced ALI/ARDS, Rhein significantly attenuated tissue inflammatory responses and promoted macrophage M2 polarization shift (44). *In vitro*, Rhein (4,5-dihydroxy-anthraquinone-2-carboxylic acid) reduced intracellular ROS levels and activated P65, thereby attenuating M1 polarization in macrophages (44). Mechanistically, Rhein exerted its protective effect against LPS-induced ALI/ARDS by targeting the nuclear factor of activated T cells 1 (NFATc1)/triggering receptor expressed on myeloid cells 2 (Trem2) axis, which was significantly attenuated in both Trem2 and NFATc1 blockade assays (44). Rhein intervenes in the metabolic reprogramming of macrophages in inflammatory states via Sirtuin 1 (SIRT1), inhibits macrophage activation into pro-inflammatory M1 macrophages, and attenuates LPS damage to mouse lungs and RAW264.7

cells (45). Emodin (anthraquinone compound) demonstrates its therapeutic effects on severe acute pancreatitis (SAP)-ALI by modulating the nucleotide binding oligomerization domain containing-leucine-rich repeat and pyrin domain-containing protein 3 (NLRP3)/caspase 1/gasdermin D (GSDMD) signaling pathway (46). Emodin reduces the production of deleterious pancreatic exosomes under SAP conditions and alters the levels of these pathological exosomes, thereby inhibiting M1 polarization in AMs and cytokine release in the lungs by modulating the peroxisome proliferator-activated receptor γ (PPARγ)/NF-κB pathway (47). *In vitro* experiments have confirmed that allyl methyl trisulfide inhibits the NF-κB and MAPK pathways, reduces the expression of cyclooxygenase-2 (COX-2) and inducible NO synthase proteins, inhibits M1 polarization in macrophages, and reduces the inflammatory response in LPS-induced ALI (48). 3,4-dihydroxyphenylethyl alcohol glycoside inhibits the activation of NF-κB, STAT3 and p38 MAPK signaling pathways, reduces the polarization of M1 macrophages, and ameliorates CLP-induced inflammation in mice ALI and LPS-induced MH-S cells (49).

M2 macrophage polarization. In the pathological process of advanced pneumonia, the causative factor is eliminated and M1 macrophages are transformed into M2 macrophages, which are activated by Th2 cytokines (such as IL-4 and IL-13) as well as anti-inflammatory cytokines (such as IL-10) and TGF-β (28,50,51). Activated M2 macrophages express low IL-12 and high IL-1 receptor antagonists, chemokine CCL18 and arginase 1 (Arg-1), and are present in inflammatory zone 1 (31). M2 macrophages promote the repair of lung damage by releasing anti-inflammatory cytokines, inhibiting the production of pro-inflammatory mediators, and removing apoptotic neutrophils from the site of inflammation (52). By promoting the activation of M2 macrophages, inflammation can be eliminated, and ALI recovery can be favored (53-55).

A previous study has confirmed that dihydroquercetin alleviates LPS-induced ALI inflammation and apoptosis (56). Dihydroquercetin promotes macrophage M2 polarization through the interferon regulatory factor 4 (IRF4)/miR-132-3p/F-box and WD repeat domain containing 7 axis, inhibits a rise in inflammatory cytokine levels and attenuates LPS-induced lung injury (57). Anisodamine treatment was also found to attenuate LPS-induced lung injury and pulmonary edema by reversing LPS-induced changes in M1 and M2 polarization through the inhibition of G9a-mediated IRF4 silencing in an ALI mouse model (58). *In vivo* studies have confirmed that resveratrol can reduce the severity of ALI in animal models, while reducing the production of pro-inflammatory cytokines and increasing anti-inflammatory cytokines (59). Resveratrol is a specific SIRT1 activator, and SIRT1 knockout reduces the anti-inflammatory effects of resveratrol (60). In addition, resveratrol may inhibit inflammation by inducing macrophage pyroptosis and apoptosis (61). Resveratrol significantly regulates macrophage activation and polarization by modulating STAT3/suppressor of cytokine signaling 3 (SOCS3) signaling, and it enhances the polarization of anti-inflammatory M2 and CD45+Siglec-F(-) subtype macrophages, thereby inhibiting mouse ALI (62). A study has shown that the activation of SIRT1 by chlorogenic acid can inhibit the acetylation and nuclear translocation of HMGB1, thereby promoting M2 polarization in AMs and alleviating Kp-induced pneumonia (63). Acacetin can reduce LPS damage to RAW 264.7 cells (64) and has been found to significantly improve the survival of ALI mice. It alleviates lung damage by reducing M1 macrophages and promoting the polarization of M2 macrophages on the tumor necrosis factor receptor-associated factor 6/NF-κB/COX-2 axis, thereby inhibiting the production of TNF-α, IL-1β and IL-6 (65). Grape seed proanthocyanidin promotes LPS-induced polarization from M1 to M2a in primary mouse lung macrophages by inhibiting the triggering receptor expressed on myeloid cells 2/PI3K/Akt pathway (66). Tetrahydropalmatine induces the polarization of M1 macrophages to M2 and suppresses inflammation by inhibiting Toll-like receptor 4 (TLR4)/NF-κB/NLRP3 signaling, thereby attenuating ischemia-reperfusion-induced lung injury in rats (67). Dehydrocostus lactone can promote the polarization of M1 macrophages to the M2 phenotype by inhibiting p38 MAPK/NF-κB signaling and activating the AMPK/Nrf2 pathway (68). Ligustrazine can treat ALI/ARDS by inhibiting the TLR4/TRAF/NF-κB/NLRP3/caspase-1 and TLR4/caspase-8/caspase-3 signaling pathways in macrophages, promoting macrophage polarization from M1 to M2 in macrophages, and reducing the pyroptosis of macrophages (54).

In addition, some natural products reduce ALI by decreasing M1 macrophages and increasing M2 macrophages. Luteolin has a protective effect on cecal ligation puncture (CLP)-induced mouse ALI models and LPS-induced cell models by decreasing cytokines and IL-17A, increasing IL-10 levels, reducing M1 macrophage content, and increasing M2 macrophage number (69). Matrine restored sepsis-induced SIRT1 downregulation, and the deacetylation of the NF-κB p65 subunit and p53, thereby inactivating the NF-κB pathway and inhibiting the p53-induced pro-apoptotic pathway in septic lungs (70). It inhibited infiltration by M1 macrophages but increased infiltration by M2 macrophages, thus decreasing the M1 to M2 macrophage ratio in septic lungs (70). Cryptotanshinone inhibited the accumulation of M1 macrophages and increased the accumulation of M2 macrophages in lung tissue (71). A previous study has also suggested that cryptotanshinone regulates the reprogramming of macrophage metabolism by activating AMPK (72). Loganin blocks the ERK and NF-κB pathways to inhibit M1 macrophages, induce M2 activation and inhibit NLRP3 inflammasome-mediated caspase-1 activation by decreasing IL-1β secretion in sepsis-induced ALI (72). Tanshinone IIA has significant anti-inflammatory effects in LPS-stimulated RAW264.7 cell models. It exerts these effects by inhibiting the NLRP3 inflammasome and reducing oxidative stress (73). *In vitro* assays have also confirmed that tanshinone IIA inhibits the activation of NF-κB and hypoxia-inducible factor pathways, thereby increasing the relative amount of the M2 isoform and decreasing the relative amount of the M1 isoform (73). Iridin reduces glycolysis in LPS-activated macrophages by inhibiting pyruvate kinase M2 (PKM2)-mediated JAK/STAT and NF-κB pathways, reprogramming macrophages from the M1 polarized phenotype to the M2 phenotype and inhibiting the production of pro-inflammatory cytokines (74). Sinomenine reduces TNF-α and IL-6 in LPS-induced bone marrow-derived macrophages (BMDMs) by activating peroxisome proliferator activated receptor β/δ in macrophages (75). In addition,

sinomenine inhibits macrophage migration by downregulating Src/FAK/P130Cas activation (76) and inhibits LPS-induced macrophage inflammatory responses by acting on the α7 nicotinic acetylcholine receptor (α7nAChR) (77). A further study found that sinomenine downregulates abnormally high levels of α7nAChR through the α7nAChR/ERK/early growth response 1 feedback pathway, attenuates the M1 phenotype and promotes the M2 phenotype in LPS-stimulated macrophages (78).

In conclusion, in terms of the mechanism of natural products on cell polarization, natural products mainly inhibit the polarization of pro-inflammatory M1 macrophages and promote the transition from M1 to M2 by inhibiting NF-κB, NLRP3, Caspase-1, GSDMD and other signaling pathways, and promoting Nrf2 and AMPK signaling pathways. In addition, it promotes the polarization of anti-inflammatory M2 macrophages by inhibiting STAT1 and SOCS3, and promoting the STAT3 and HIF signaling pathways. In terms of the effects of different types of natural products on macrophage polarization, flavonoids, alkaloids, terpenoids and quinones affect macrophage polarization by inhibiting NF-κB and NLRP3, and activating major signaling pathways such as AMPK.

3. Natural products that regulate macrophage pyroptosis

Pyroptosis is mediated by programmed cell necrosis by gasdermin (79). It is characterized by the swelling and rupture of cells and the release of pro-inflammatory contents (80). Bacteria, viruses, toxins and drugs (such as chemotherapy drugs paclitaxel and cisplatin, and Anakinra) can cause pyroptosis, which helps to maintain the stability of the internal environment and combat external risk factors (81). There is growing evidence of pyroptosis in different types of lung cells during the development of ALI (81). AMs can respond to external stimuli through pyroptosis *in vivo*. *In vivo* studies have found that phenylalanine promotes AM pyroptosis by activating recombinant calcium sensing receptor and initiating the NLRP3 pathway, thereby exacerbating LPS-induced ALI in mice (82). LPS-induced ALI in mice was improved by inhibiting macrophage pyroptosis (83,84). Concurrently, it was found that in LPS-induced ALI in mice, the neutrophil extracellular traps (NETs) formed during neutrophil NETosis may cause macrophage pyroptosis and lead to the deterioration of ALI, while promoting DNA degradation in the NETs (85). In addition, silencing the AIM2 gene may prevent AM pyroptosis (85). 4-Hydroxynonenal, a lipid peroxidation product, has a protective effect on ALI by inhibiting the NLRP3 inflammasome, thereby preventing the activation of caspase-1 and reducing the release of inflammatory cytokines and macrophage pyroptosis (86). The natural products that treat ALI/ARDS by modulating macrophage pyroptosis are summarized in Table II and Fig. 2.

Tangeretin attenuates acute lung injury in sepsis mice by modulating the PLK1/AMPK/DRP1 signaling axis by inhibiting ROS-mediated NLRP3 inflammasome activation and reducing pyroptosis of macrophages (87). Matrine inhibits NLRP3 inflammasome activation by modulating the protein tyrosine phosphatase non-receptor type 2/JNK/sterol regulatory element-binding protein 2 pathway, reduces macrophage pyroptosis and decreases the CLP-induced invasion of ALI- and LPS-stimulated macrophages in mice (88). Inhibition of STAT3 phosphorylation by colchicine inhibits the acetylation of the NLRP3 promoter by the STAT3/E1A binding protein p300 (EP300) complex, reducing pyroptosis and apoptosis in mouse alveolar macrophages, thereby attenuating sepsis-induced ALI (89). Verbenalin attenuates acute lung inflammation induced by pseudomonas aeruginosa by acting on the G protein-coupled receptor 18 receptor (90). Further studies found that verbenalin inhibits macrophage focal death and alleviates sepsis and IgG immune complex-induced ALI by inhibiting the C/enhancer binding protein δ (EBP-δ)/GSDMD/GSDME axis (91). Quercetin inhibits the nuclear accumulation of PKM2, upregulates SIRT1, inhibits the activation of NLRP3 inflammasomes and reduces the release of pyroptosis-related cytokines (IL-1β, IL-18 and HMGB1) in macrophages (92). Tiliroside targets the AMPK pathway, ameliorates mitochondrial damage, attenuates NLRP3 inflammasome activation, reduces pyroptosis in macrophages and ameliorates LPS-induced ALI in mice (93). Tabersonine is a natural NLRP3 inhibitor that inhibits inflammasome activation in macrophages and attenuates NLRP3-driven ALI in mice (94). Britannin specifically inhibits the NLRP3 inflammasome activation step in BMDMs and binds directly to the NLRP3 NACHT domain at Arg-335 and Gly271 (95). In addition, it inhibits NLRP3 activation in an ATPase-independent manner, inhibits the cleavage of caspase-1 and the secretion of mature IL-1β, and inhibits NLRP3-mediated pyroptosis in mouse and human macrophages (95). Taraxasterol inhibits NLRP3 inflammatory vesicle activation and pyroptosis in macrophages by modulating the mTOR signaling pathway, and is protective against LPS-induced BMDMs in mice (96). (+)-Syringaresinol activates PPARγ, thereby inhibiting the expression of NF-κB and C/EBP and reducing the inflammatory response (97). By targeting the NLRP3/GSDMD/caspase-1 axis, it suppressed macrophage pyroptosis and effectively alleviated IgG-IC-induced ALI (98). Alantolactone inhibits the activation and assembly of NLRP3 inflammasomes, LPS-ATP-induced IL-1β secretion and caspase-1 activation in macrophages by binding directly to the NACHT domain of NLRP; it also reduces macrophage pyroptosis (99). α-linolenic acid can alleviate NET-induced AM pyroptosis and ALI/ARDS by mediating pyrin inflammasome activation (100).

In conclusion, both flavonoids and terpenoids (except Verbenalin) inhibit macrophage autophagy through NLRP3 inflammasomes associated with cellular pyroptosis, and play a role in the treatment of ALI/ARDS.

4. Natural products that regulate macrophage phagocytosis

Macrophages are widely recognized as one of the main phagocytes that eliminate apoptotic cells (101). The exposed phosphatidylserine on the surface of apoptotic cells can be recognized and cleared by macrophages, which are subsequently activated to exert anti-inflammatory and immune responses (102,103). However, the HMGB1 protein binds to the receptor for advanced glycation end-products and αVβ3 on macrophages, and inhibits endocytosis (104). A study has shown that in patients with sepsis-associated ARDS, endocytosis by AMs is impaired, leading to the accumulation of apoptotic neutrophils, which can lead to long-term

Table II. Natural products that modulate macrophage pyroptosis.

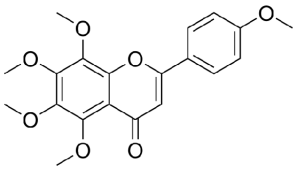
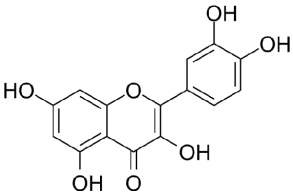
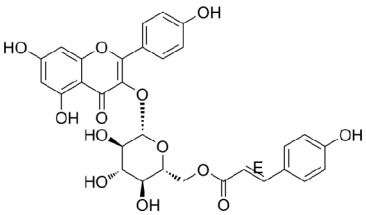
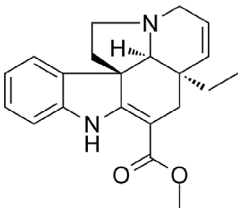
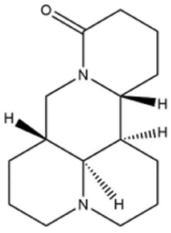
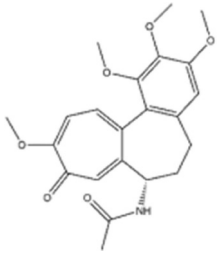
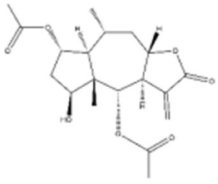
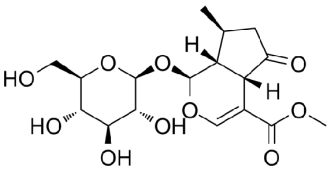
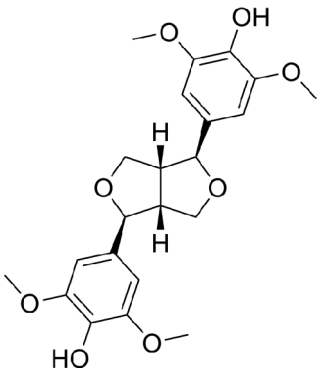
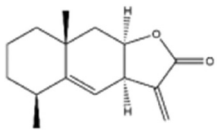
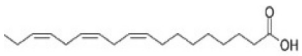
Product structure	Type of natural product structure	*In vitro* (effective dose)/ *in vivo* model (effective concentration)	Related molecular mechanisms	Macrophage-related indicators
Tangeretin 	Flavonoids	LPS induces ALI in mice	Inhibits PLK1/ AMPK/DRP1/ ROS/NLRP3 inflammasome signaling axis	Inhibits macrophage pyroptosis
Quercetin 	Flavonoids	LPS induces ALI in mice (50 mg/kg)/LPS induces murine J774 A.1 macrophages (40 μM)	Inhibits PKM2 and NLRP3 inflammasome, promotes SIRT1	Inhibits macrophage pyroptosis
Tiliroside 	Flavonoids	LPS induces ALI in mice (50, 100 mg/kg)/LPS induces THP-1 (3, 10 and 30 mM).	Promotes AMPK, inhibits NLRP3 inflammation	Inhibits macrophage pyroptosis
Tabersonine 	Alkaloids	LPS-induced BMDM	NLRP3 inflammasome	Inhibits macrophage pyroptosis
Matrine 	Alkaloids	LPS induces ALI in mice/ RAW264.7 cells	PTPN2/JNK/ SREBP2 /NLRP3 inflammasome pathways	Inhibits macrophages pyroptosis
Colchicine 	Alkaloids	Sepsis-induced ALI in mice	STAT3/EP300	Inhibits macrophage pyroptosis and apoptosis
Britannin 	Terpenoids	LPS induces ALI in mice (20 mg/kg)	Inhibits NLRP3 inflammasome	Inhibits macrophage pyroptosis

Table II. Continued.

Product structure	Type of natural product structure	*In vitro* (effective dose)/ *in vivo* model (effective concentration)	Related molecular mechanisms	Macrophage-related indicators
Verbenalin 	Terpenoids	IgG-IC/CLP-induced ALI in mice (50 mg/kg)/LPS and IgG stimulated MH-S cells	C/EBP-δ/GSDMD/ GSDME axis	Inhibits macrophage pyroptosis
(+)-Syringaresinol 	Lignans	IgG-IC/CLP-induced ALI in mice, CLP-induced ALI in mice/LPS induces RAW264.7 cells	NLRP3/GSDMD/ caspase-1 axis	Inhibits macrophage pyroptosis, inhibits M1 macrophages
Alantolactone 	Sesquiterpene lactones	LPS + ATP-induced BMDM	NLRP3-NEK7 interaction	Inhibits macrophage pyroptosis
α-linolenic acid 	Unsaturated fatty acid	LPS induces ALI in mice (1,800 mg/kg).	Pyrin inflammasome activation	Inhibits macrophage pyroptosis (AMS)

LPS, lipopolysaccharide; CLP, cecal ligation and puncture; PLK1, polo-like kinase 1; AMPK, adenosine 5'-monophosphate (AMP)-activated protein kinase; DRP1, dynamin-related protein 1; ROS, reactive oxygen species; NLRP3, nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing 3; PKM2, pyruvate kinase isozyme type M2; SIRT1, Sirtuin 1; mTOR, mammalian target of rapamycin; LRP3, low density lipoprotein receptor-related protein 3; PTPN2, protein tyrosine phosphatase non-receptor type 2; JNK, c-Jun N-terminal kinase; SREBP2, sterol regulatory element-binding protein 2; STAT3, signal transducing activator of transcription 3; C/EBP-δ, CCAAT/enhancer binding protein δ ; GSDMD, Gasdermin D; GSDME, Gasdermin E; Caspase 1, cysteine-requiring aspartate protease 1; NEK7, never in mitosis A-related kinase 7; ALI, acute lung injury; AM, alveolar macrophages; BMDM, bone marrow-derived macrophages.

inflammation (105). Therefore, increasing endocytosis by macrophages can improve ALI/ARDS. Glucocorticoids upregulate endocytosis by macrophages through the type 1 isozyme of 3β-hydroxysteroid dehydrogenase (HSD-1), and HSD-1 deletion leads to impaired endocytosis by AMs, resulting in their inability to eliminate apoptotic neutrophils in model animals (106). AMs in the regression phase of ALI increased pinocytosis by upregulating integrin αv through vascular endothelial growth factor (VEGF)-C/VEGFR-3 signaling, thereby digesting the majority of exogenous apoptotic neutrophils and improving LPS-induced ALI (107). In addition, phagocytosis of apoptotic neutrophils by AMs is eliminated by reducing the expression of Gas6 following STAT6 (108). Macrophages have anti-inflammatory effects after engulfing human umbilical cord mesenchymal stem cell-derived apoptotic bodies (ABs). This is achieved by ABs expressing programmed death-ligand 1, which binds to PD1 on macrophages, affecting metabolic programming in macrophages and promoting their transition to an anti-inflammatory state (109). A Rab43 knockout study showed that the HMGB1 protein inhibits the phagocytosis of apoptotic cells by macrophages through inhibiting the transport of Rab43-controlled CD91 (a key receptor for macrophage pinocytosis) to the cell surface, which aggravates ALI/ARDS (110). Phagocytosis by macrophages is an important way to eliminate apoptotic neutrophils. This can reduce the release of harmful substances such as NETs, MPO and cytokines by neutrophils following, apoptosis and can effectively alleviate ALI/ARDS (111). The natural products that treat ALI/ARDS by regulating macrophage phagocytosis are summarized in Table III. An *in vivo*

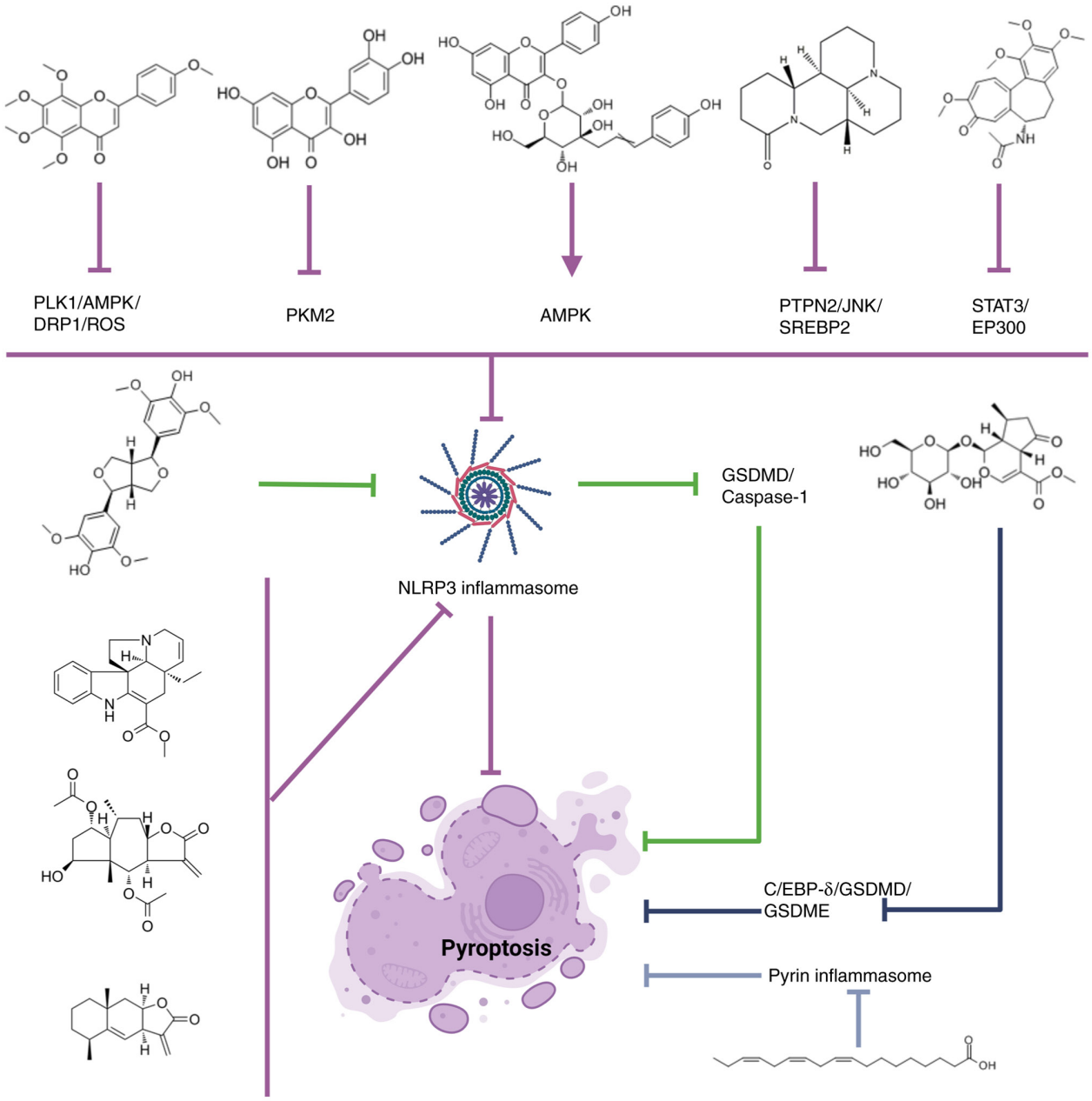


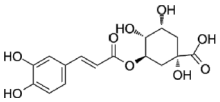
Figure 2. Molecular mechanisms through which natural products regulate macrophage pyroptosis. Created using BioRender.com. ↑ indicates promotion and ⊥ indicates inhibition. PKM2, pyruvate kinase M2; SIRT1, Sirtuin 1; PLK1, polo-like kinase 1; DRP1, dynamin-related protein 1; ROS, reactive oxygen species; EP300, E1A binding protein p300; NLRP3, pyrin domain-containing protein 3; GSDMD, gasdermin D; EBP-δ, enhancer binding protein δ; GSDME, Gasdermin E.

study has shown that chlorogenic acid significantly improves the lipopolysaccharide-induced inflammatory response and survival in CLP-induced ARDS mice by increasing phagocytosis by AMs (112). In addition, chlorogenic acid significantly upregulates the expression of GPR37 *in vivo* and *in vitro*. In addition, the protective effect of chlorogenic acid on ARDS was reversed after silencing GPR37 expression (112).

5. Natural products that regulate macrophage autophagy

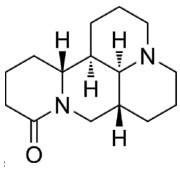
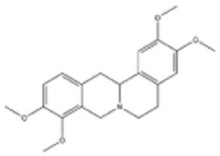
Autophagy is a highly conserved protein degradation process involved in the degradation of protein cell components, such as lipoproteins and misfolded proteins (113). Cellular autophagy includes macroautophagy, microautophagy and chaperone-mediated autophagy (114). In general, autophagy has two functions, one of which is an early adaptive mechanism of the tissue, specifically the removal of organelles or proteins to maintain intracellular homeostasis (115). As an important component of innate immunity, macrophages play an important role in regulating the inflammatory response and the balance of the immune system (116). Autophagy also has an impact on ALI/ARDS. Studies have found that autophagy can regulate macrophage phagocytosis, antigen presentation and polarization. Furthermore, macrophage autophagy has a negative and positive role in the progression of ALI/ARDS (117). On the one hand, macrophage autophagy reduces the release of inflammatory cytokines and removes cellular debris, thereby attenuating lung injury and providing a protective

Table III. Natural products that regulate macrophage phagocytosis.

Product structure	Type of natural product structure	*In vitro* (effective dose)/*in vivo* model (effective concentration)	Related molecular mechanisms	Macrophage-related indicators
Chlorogenic acid 	Organic acids	CLP-induced ALI in mice/LPS induces RAW264.7 cells (100, 200 and 400 μM).	Promotes G protein-coupled receptor 37	AM phagocytosis

LPS, lipopolysaccharide; CLP, cecal ligation and puncture; ALI, acute lung injury; AM, alveolar macrophages.

Table IV. Natural products that regulate macrophage autophagy.

Product structure	Type of natural product structure	*In vitro* (effective dose)/ *in vivo* model (effective concentration)	Related molecular mechanisms	Macrophage-related indicators
Sophoridine 	Alkaloids	LPS induces ALI in mice/RAW264.7 cells	Inhibits TLR4/ MyD88/NF-κB	Promotes macrophage autophagy
Tetrahydropalmatine 	Alkaloids	IR-induced rat ALI	Inhibits PI3K/ AKT/mTOR signaling pathway	Promotes macrophage autophagy

LPS, lipopolysaccharide; CLP, cecal ligation and puncture; ALI, acute lung injury; TLR4, Toll-like receptor 4; MyD88, myeloid differentiation primary response gene (88); NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; PI3K, phosphatidylinositol 3-kinase; Akt, RAC-α serine/threonine-protein kinase; mTOR, mammalian target of rapamycin; IR, ischemia-reperfusion.

effect (118). In a mouse model that lacked autophagy, excessive lung inflammation and injury occurred in the lungs of the mice, and treatment with an autophagy inducer activated the autophagy pathway in macrophages, resulting in a significant reduction in lung inflammation and injury (119). On the other hand, autophagy can exacerbate the damage and cause apoptosis, which can aggravate lung injury (117). Autoapoptosis, caused by increased autophagy of AMs, is one of the causes of LPS-induced lung injury in rats (120). The natural products that treat ALI/ARDS by regulating macrophage autophagy are summarized in Table IV. Sophoridine decreases the mRNA and protein expression of TLR4/myeloid differentiation primary response 88 (MyD88)/NF-κB and mTOR, enhances macrophage autophagy and reduces inflammation, thereby inhibiting LPS-induced ALI (121). Tetrahydropalmatine attenuates limb ischemia-reperfusion-induced ALI in rats by restoring autophagy mediated by the PI3K/AKT/mTOR pathway (122).

In conclusion, alkaloids play a role in the prevention and treatment of ALI/ARDS by inhibiting the TLR4/MyD88/NF-κB and PI3K/AKT/mTOR signaling pathways and increasing macrophage autophagy.

6. Discussion

Macrophages play an important role in ALI/ARDS, and the regulation of macrophages may be an important means of intervention in ALI/ARDS (123). The present review summarizes and classifies the natural products that may be used for the treatment of ALI/ARDS discovered within the previous five years. These agents act by regulating macrophage abnormalities. Their main molecular mechanisms of action are summarized in Figs. 1 and 2. These products include flavonoids, alkaloids, terpenoids and quinones. The majority of these products work by regulating the polarization of macrophages. Their mechanisms of action include reducing M1 pro-inflammatory phenotype macrophages and increasing M2 anti-inflammatory phenotype macrophages to achieve anti-inflammatory effects. Metabolic programming is another factor that influences macrophage polarization, and interfering with macrophage metabolism also affects ALI/ARDS. M1 and M2 macrophages require different sources of energy for proliferation and cytokine production, with M1 macrophages highly dependent on aerobic glycolysis for energy, while M2 macrophages rely on mitochondrial oxidative phosphorylation and fatty acid oxidation for energy (124). Therefore,

ALI can be prevented and treated by modulating metabolic programs to control macrophage polarization. Feng *et al* (125) found that M2-like immunophenotyping and metabolic reprogramming can be maintained by modulating high Ca^{2+} reactivity and long-term calcium signaling. Reprogramming glucose metabolism by activating the mTOR/HIF-1α/glycolytic pathway in macrophages activated by Trem-1 attenuates the inflammatory response in ALI (126,127). The inhibition of macrophage pyroptosis is also an important method for natural compounds to affect ALI/ARDS. In addition, some natural products also protect against alveolar damage by reducing macrophage autophagy and apoptosis, thereby protecting lung function and reducing pulmonary edema. Some natural products can alleviate ALI/ARDS by enhancing phagocytosis by macrophages.

In conclusion, different compounds may interfere with the development of ALI/ARDS by regulating polarization, pyroptosis, autophagy and phagocytosis of lung macrophages through the same or similar pathways or targets. Macrophage polarization often involves the NF-κB and AMPK pathways (Fig. 1), while pyroptosis mainly involves the NLRP3 inflammasome (Fig. 2). In addition, macrophage autophagy is associated with the TLR4/MyD88/NF-κB and PI3K/AKT/mTOR signaling pathways, whereas AM phagocytosis is associated with G-protein coupled receptor 37 enhancement (128). In addition, the main types of natural products that affect macrophage polarization are flavonoids, alkaloids, terpenoids and quinones, while the types of natural products that affect macrophage pyroptosis are flavonoids, alkaloids and terpenoids; at the same time, alkaloids can also increase macrophage autophagy. Notably, these natural products may all regulate both macrophage polarization and pyroptosis by affecting NF-κB, AMPK and NLRP3 inflammasomes. AMs are the first immune defenders against pathogens and foreign particles (129), accounting for ~95% of leukocytes in the lungs (130). AMs have a significant impact on the development of ALI after both infectious and non-infectious stimuli (10). Therefore, developing AM-specific drugs may be an important measure to target macrophages for the treatment of ALI/ARDS. However, most of the existing research results come from animal and cell experiments, and targeted therapy based on lung macrophages and macrophage-based treatment of ALI are still undergoing preclinical research. The clinical application of these findings remains a huge challenge.

At present, numerous studies of macrophages are systematic, and there are no further studies on the role of different types of macrophages in ALI/ARDS. However, lung macrophages are products of different macrophages, which may differ in function. Secondly, it has been reported that M1 and M2 phenotype changes may be associated with changes in different subgroups of cells during ARDS, and simply focusing on the M1 and M2 phenotypes cannot describe the multidimensional, complex and dynamic changes in macrophages in detail (9). The majority of current studies investigated the effect of macrophage polarization on ALI through cell labeling using molecules that were specific to the surface of M1 and M2 cells. Therefore, in the future, it is necessary to further explore the heterogeneity of macrophages with the help of advanced technologies such as single-cell RNA sequencing, assay for transposase-accessible chromatin with high throughput sequencing and mass spectrometry. This will improve the understanding of the role of different macrophages in the pathogenesis of ALI/ARDS, clarify the molecular mechanism of natural products that target and regulate macrophages during the treatment of ALI/ARDS, and provide new ideas and further research directions for the development of new drugs for the treatment of ALI/ARDS.

Acknowledgements

Not applicable.

Funding

This work was financially supported by the Yunnan Fundamental Research Projects (grant nos. 202201AU070167 and 202301AT070258), and the Yunnan Key Laboratory of Formulated Granules (grant no. 202105AG070014).

Availability of data and materials

Not applicable.

Authors' contributions

JL and WM conceived and designed the study; ZT, YL and RZ collected and organized data; YX wrote, reviewed and edited the manuscript; GL conceptualized and supervised the study, and performed project administration and funding acquisition. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Zhu W, Zhang Y and Wang Y: Immunotherapy strategies and prospects for acute lung injury: Focus on immune cells and cytokines. Front Pharmacol 13: 1103309, 2022.
2. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, Gattinoni L, van Haren F, Larsson A, McAuley DF, *et al*: Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 315: 788-800, 2016.
3. Hsieh PC, Wu YK, Yang MC, Su WL, Kuo CY and Lan CC: Deciphering the role of damage-associated molecular patterns and inflammatory responses in acute lung injury. Life Sci 305: 120782, 2022.
4. Mokrá D: Acute lung injury-from pathophysiology to treatment. Physiol Res 69: S353-S366, 2020.
5. Mokra D, Mikolka P, Kosutova P and Mokry J: Corticosteroids in acute lung injury: The dilemma continues. Int J Mol Sci 20: 4765, 2019.
6. Wang F, Chen M, Ma J, Wang C, Wang J, Xia H, Zhang D and Yao S: Integrating bulk and single-cell sequencing reveals the phenotype-associated cell subpopulations in sepsis-induced acute lung injury. Front Immunol 13: 981784, 2022.

7. Lendeckel U, Venz S and Wolke C: Macrophages: Shapes and functions. ChemTexts 8: 12, 2022.
8. Johnston LK, Rims CR, Gill SE, McGuire JK and Manicone AM: Pulmonary macrophage subpopulations in the induction and resolution of acute lung injury. Am J Respir Cell Mol Biol 47: 417-426, 2012.
9. Dang W, Tao Y, Xu X, Zhao H, Zou L and Li Y: The role of lung macrophages in acute respiratory distress syndrome. Inflamm Res 71: 1417-1432, 2022.
10. Wang Z and Wang Z: The role of macrophages polarization in sepsis-induced acute lung injury. Front Immunol 14: 1209438, 2023.
11. Cheng P, Li S and Chen H: Macrophages in lung injury, repair, and fibrosis. Cells 10: 436, 2021.
12. Aribindi K, Lim M, Lakshminrusimha S and Albertson T: Investigational pharmacological agents for the treatment of ARDS. Expert Opin Investig Drugs 33: 243-277, 2024.
13. Vichare R and Janjic JM: Macrophage-targeted nanomedicines for ARDS/ALI: Promise and potential. Inflammation 45: 2124-2141, 2022.
14. Booz GW, Altara R, Eid AH, Wehbe Z, Fares S, Zaraket H, Habeichi NJ and Zouein FA: Macrophage responses associated with COVID-19: A pharmacological perspective. Eur J 887: 173547, 2020.
15. Panahi Y, Gorabi AM, Talaei S, Beiraghdar F, Akbarzadeh A, Tarhriz V and Mellatyar H: An overview on the treatments and prevention against COVID-19. Virol J 20: 23, 2023.
16. Matera MG, Rogliani P, Bianco A and Cazzola M: Pharmacological management of adult patients with acute respiratory distress syndrome. Expert Opin Pharmacother 21: 2169-2183, 2020.
17. Lang FM, Lee KMC, Teijaro JR, Becher B and Hamilton JA: GM-CSF-based treatments in COVID-19: Reconciling opposing therapeutic approaches. Nat Rev Immunol 20: 507-514, 2020.
18. Li S, Feng T, Zhang Y, Shi Q, Wang W, Ren J, Shen G, Gu H, Luo C and Li Y: Lianhua Qingwen protects LPS-induced acute lung injury by promoting M2 macrophage infiltration. J Ethnopharmacol 320: 117467, 2024.
19. Liang X and Liu JX: Role of macrophage polarization in pulmonary diseases and intervention of traditional Chinese medicines. Zhongguo Zhong Yao Za Zhi 49: 334-343, 2024 (In Chinese).
20. Dong J, Liu W, Liu W, Wen Y, Liu Q, Wang H, Xiang G, Liu Y and Hao H: Acute lung injury: A view from the perspective of necroptosis. Inflamm Res 73: 997-1018, 2024.
21. Qin Y, Li W, Liu J, Wang F, Zhou W, Xiao L, Zhou P, Wu F, Chen X, Xu S, *et al*: Andrographolide ameliorates sepsis-induced acute lung injury by promoting autophagy in alveolar macrophages via the RAGE/PI3K/AKT/mTOR pathway. Int Immunopharmacol 139: 112719, 2024.
22. Ma J, Wang J, Wang J, Zhou J, Jiang C, Chen W, Zhang X, Pan J, Zhu J and Chen M: Araloside A alleviates sepsis-induced acute lung injury via PHD2/HIF-1α in macrophages. Phytomedicine 135: 156089, 2024.
23. Wang WT, Zhang YY, Li ZR, Li JM, Deng HS, Li YY, Yang HY, Lau CC, Yao YJ, Pan HD, *et al*: Syringic acid attenuates acute lung injury by modulating macrophage polarization in LPS-induced mice. Phytomedicine 129: 155591, 2024.
24. Helou DG, Quach C, Hurrell BP, Li X, Li M, Akbari A, Shen S, Shafiei-Jahani P and Akbari O: LAIR-1 limits macrophage activation in acute inflammatory lung injury. Mucosal Immunol 16: 788-800, 2023.
25. Short KR, Kroeze EJBV, Fouchier RAM and Kuiken T: Pathogenesis of influenza-induced acute respiratory distress syndrome. Lancet Infect Dis 14: 57-69, 2014.
26. Luo M, Zhao F, Cheng H, Su M and Wang Y: Macrophage polarization: An important role in inflammatory diseases. Front Immunol 15: 1352946, 2024.
27. Liu C, Xiao K and Xie L: Advances in the regulation of macrophage polarization by mesenchymal stem cells and implications for ALI/ARDS treatment. Front Immunol 13: 928134, 2022.
28. Chen X, Tang J, Shuai W, Meng J, Feng J and Han Z: Macrophage polarization and its role in the pathogenesis of acute lung injury/acute respiratory distress syndrome. Inflamm Res 69: 883-895, 2020.
29. Wang L, Wang D, Zhang T, Ma Y, Tong X and Fan H: The role of immunometabolism in macrophage polarization and its impact on acute lung injury/acute respiratory distress syndrome. Front Immunol 14: 1117548, 2023.
30. Murray PJ, Allen JE, Biswas SK, Fisher EA, Gilroy DW, Goerdt S, Gordon S, Hamilton JA, Ivashkiv LB, Lawrence T, *et al*: Macrophage activation and polarization: Nomenclature and experimental guidelines. Immunity 41: 14-20, 2014.
31. Aggarwal NR, King LS and D'alessio FR: Diverse macrophage populations mediate acute lung inflammation and resolution. Am J Physiol Lung Cell Mol Physiol 306: L709-L725, 2014.
32. Fukui S, Iwamoto N, Takatani A, Igawa T, Shimizu T, Umeda M, Nishino A, Horai Y, Hirai Y, Koga T, *et al*: M1 and M2 monocytes in rheumatoid arthritis: A contribution of imbalance of M1/M2 monocytes to osteoclastogenesis. Front Immunol 8: 1958, 2017.
33. Shi C and Pamer EG: Monocyte recruitment during infection and inflammation. Nat Rev Immunol 11: 762-774, 2011.
34. Wang J, Li Q, Qiu Y and Lu H: COVID-19: Imbalanced cell-mediated immune response drives to immunopathology. Emerg Microbes Infect 11: 2393-2404, 2022.
35. Jiao Y, Zhang T, Zhang C, Ji H, Tong X, Xia R, Wang W, Ma Z and Shi X: Exosomal miR-30d-5p of neutrophils induces M1 macrophage polarization and primes macrophage pyroptosis in sepsis-related acute lung injury. Crit Care 25: 356, 2021.
36. Li Z, Pan H, Yang J, Chen D, Wang Y, Zhang H and Cheng Y: Xuanfei Baidu formula alleviates impaired mitochondrial dynamics and activated NLRP3 inflammasome by repressing NF-κB and MAPK pathways in LPS-induced ALI and inflammation models. Phytomedicine 108: 154545, 2023.
37. Liang P, Wang L, Yang S, Pan X, Li J, Zhang Y, Liang Y, Li J and Zhou B: 5-Methoxyflavone alleviates LPS-mediated lung injury by promoting Nrf2-mediated the suppression of NOX4/TLR4 axis in bronchial epithelial cells and M1 polarization in macrophages. J Inflamm (Lond) 19: 24, 2022.
38. Bu C, Wang R, Wang Y, Lu B, He S and Zhao X: Taraxasterol inhibits hyperactivation of macrophages to alleviate the sepsis-induced inflammatory response of ARDS rats. Cell Biochem Biophys 80: 763-770, 2022.
39. Fang H, Chen J, Luo J, Hu J, Wang D, Lv L and Zhang W: Abietic acid attenuates sepsis-induced lung injury by inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway to inhibit M1 macrophage polarization. Exp Anim 71: 481-490, 2022.
40. Wang L and Zhao M: Suppression of NOD-like receptor protein 3 inflammasome activation and macrophage M1 polarization by hederagenin contributes to attenuation of sepsis-induced acute lung injury in rats. Bioengineered 13: 7262-7276, 2022.
41. Zheng L, Su J, Zhang Z, Jiang L, Wei J, Xu X and Lv S: Salidroside regulates inflammatory pathway of alveolar macrophages by influencing the secretion of miRNA-146a exosomes by lung epithelial cells. Sci Rep 10: 20750, 2020.
42. Cai YC, Huang Q, Wei XL, Mei RH, Sa LN and Hu XL: Effects of salidroside on the secretion of inflammatory mediators induced by lipopolysaccharide in the co-culture of rat alveolar macrophages and type II alveolar epithelial cells. Sheng Li Xue Bao 71: 575-580, 2019 (In Chinese).
43. Feng H, Zhang D, Yin Y, Kang J and Zheng R: Salidroside ameliorated the pulmonary inflammation induced by cigarette smoke via mitigating M1 macrophage polarization by JNK/c-Jun. Phytother Res 37: 4251-4264, 2023.
44. Li X, Xiao C, Yuan J, Chen X, Li Q and Shen F: Rhein-attenuates LPS-induced acute lung injury via targeting NFATc1/Trem2 axis. Inflamm Res 72: 1237-1255, 2023.
45. Wang W, Wang Z, Yang X, Song W, Chen P, Gao Z, Wu J and Huang F: Rhein ameliorates septic lung injury and intervenes in macrophage metabolic reprogramming in the inflammatory state by sirtuin 1. Life Sci 310: 121115, 2022.
46. Wu X, Yao J, Hu Q, Kang H, Miao Y, Zhu L, Li C, Zhao X, Li J, Wan M and Tang W: Emodin ameliorates acute pancreatitis-associated lung injury through inhibiting the alveolar macrophages pyroptosis. Front Pharmacol 13: 873053, 2022.
47. Hu Q, Yao J, Wu X, Li J, Li G, Tang W, Liu J and Wan M: Emodin attenuates severe acute pancreatitis-associated acute lung injury by suppressing pancreatic exosome-mediated alveolar macrophage activation. Acta Pharm Sin B 12: 3986-4003, 2022.
48. Wang S, Liu J, Dong J, Fan Z, Wang F, Wu P, Li X, Kou R and Chen F: Allyl methyl trisulfide protected against LPS-induced acute lung injury in mice via inhibition of the NF-κB and MAPK pathways. Front Pharmacol 13: 919898, 2022.
49. Zhuo Y, Li D, Cui L, Li C, Zhang S, Zhang Q, Zhang L, Wang X and Yang L: Treatment with 3,4-dihydroxyphenylethyl alcohol glycoside ameliorates sepsis-induced ALI in mice by reducing inflammation and regulating M1 polarization. Biomed Pharmacother 116: 109012, 2019.
50. Mantovani A, Biswas SK, Galdiero MR, Sica A and Locati M: Macrophage plasticity and polarization in tissue repair and remodelling. J Pathol 229: 176-185, 2012.

51. Yadav S, Priya A, Borade DR and Agrawal-Rajput R: Macrophage subsets and their role: Co-relation with colony-stimulating factor-1 receptor and clinical relevance. Immunol Res 71: 130-152, 2022.
52. Shapouri-Moghaddam A, Mohammadian S, Vazini H, Taghadosi M, Esmaeili SA, Mardani F, Seifi B, Mohammadi A, Afshari JT and Sahebkar A: Macrophage plasticity, polarization, and function in health and disease. J Cell Physiol 233: 6425-6440, 2018.
53. Liang L, Xu W, Shen A, Fu X, Cen H, Wang S, Lin Z, Zhang L, Lin F and Zhang X: Inhibition of YAP1 activity ameliorates acute lung injury through promotion of M2 macrophage polarization. MedComm (2020) 4: e293, 2023.
54. Jiang R, Xu J, Zhang Y, Zhu X, Liu J and Tan Y: Ligustrazine alleviate acute lung injury through suppressing pyroptosis and apoptosis of alveolar macrophages. Front Pharmacol 12: 680512, 2021.
55. Zhou W, Hong J, Liu T, Li M, Jin H and Wang X: Polygonatum polysaccharide regulates macrophage polarization and improves LPS-Induced acute lung injury through TLR4-MAPK/NF-κB pathway. Can Respir J 2022: 1-11, 2022.
56. Liu JH, Cao L, Zhang CH, Li C, Zhang ZH and Wu Q: Dihydroquercetin attenuates lipopolysaccharide-induced acute lung injury through modulating FOXO3-mediated NF-κB signaling via miR-132-3p. Pulm Pharmacol Ther 64: 101934, 2020.
57. Li C, Liu J, Zhang C, Cao L, Zou F and Zhang Z: Dihydroquercetin (DHQ) ameliorates LPS-induced acute lung injury by regulating macrophage M2 polarization through IRF4/miR-132-3p/FBXW7 axis. Pulm Pharmacol Ther 83: 102249, 2023.
58. Zhang Y, Song D, Peng Z, Wang R, Li K, Ren H, Sun X, Du N and Tang SC: Anisodamine enhances macrophage M2 polarization through suppressing G9a-mediated interferon regulatory factor 4 silencing to alleviate lipopolysaccharide-induced acute lung injury. J Pharmacol Exp Ther 381: 247-256, 2022.
59. Wang Y, Wang X, Zhang L and Zhang R: Alleviation of acute lung injury in rats with sepsis by resveratrol via the phosphatidylinositol 3-Kinase/Nuclear factor-erythroid 2 related factor 2/Heme oxygenase-1 (PI3K/Nrf2/HO-1) pathway. Med Sci Monit 24: 3604-3611, 2018.
60. Zhu X, Liu Q, Wang M, Liang M, Yang X, Xu X, Zou H and Qiu J: Activation of Sirt1 by resveratrol inhibits TNF-α induced inflammation in fibroblasts. PLoS One 6: e27081, 2011.
61. Misawa T, Saitoh T, Kozaki T, Park S, Takahama M and Akira S: Resveratrol inhibits the acetylated α-tubulin-mediated assembly of the NLRP3-inflammasome. Int Immunol 27: 425-434, 2015.
62. Hu L, Chen Z, Li L, Jiang Z and Zhu L: Resveratrol decreases $CD45^+CD206^-$ subtype macrophages in LPS-induced murine acute lung injury by SOCS3 signalling pathway. J Cell Mol Med 23: 8101-8113, 2019.
63. Li QR, Tan SR, Yang L, He W, Chen L, Shen FX, Wang Z and Wang HF: Mechanism of chlorogenic acid in alveolar macrophage polarization in Klebsiella pneumoniae-induced pneumonia. J Leukoc Biol 112: 9-21, 2022.
64. Pan MH, Lai CS, Wang YJ and Ho CT: Acacetin suppressed LPS-induced up-expression of iNOS and COX-2 in murine macrophages and TPA-induced tumor promotion in mice. Biochem Pharmacol 72: 1293-1303, 2006.
65. Chang B, Wang Z, Cheng H, Xu T, Chen J, Wu W, Li Y and Zhang Y: Acacetin protects against sepsis-induced acute lung injury by facilitating M2 macrophage polarization via TRAF6/NF-κB/COX2 axis. Innate Immun 30: 11-20, 2023.
66. Qiao X, Wang H, He Y, Song D, Altawil A, Wang Q and Yin Y: Grape seed proanthocyanidin ameliorates LPS-induced acute lung injury by modulating M2a macrophage polarization via the TREM2/PI3K/Akt pathway. Inflammation 46: 2147-2164, 2023.
67. Wen H, Lu D, Chen H, Zhu Y, Xie Q, Zhang Z and Wu Z: Tetrahydropalmatine induces the polarization of M1 macrophages to M2 to relieve limb ischemia-reperfusion-induced lung injury via inhibiting the TLR4/NF-κB/NLRP3 signaling pathway. Drug Dev Res 83: 1362-1372, 2022.
68. Wu YX, Jiang FJ, Liu G, Wang YY, Gao ZQ, Jin SH, Nie YJ, Chen D, Chen JL and Pang QF: Dehydrocostus lactone attenuates methicillin-resistant staphylococcus aureus-induced inflammation and acute lung injury via modulating macrophage polarization. Int J Mol Sci 22: 9754, 2021.
69. Xie K, Chai YS, Lin SH, Xu F and Wang CJ: Luteolin regulates the differentiation of regulatory T cells and activates IL-10-dependent macrophage polarization against acute lung injury. J Immunol Res 2021: 1-12, 2021.
70. Yang L, Zhang YM, Guo MN, Zhang H, Zhu XY, Xu C and Liu YJ: Matrine attenuates lung injury by modulating macrophage polarization and suppressing apoptosis. J Surg Res 281: 264-274, 2023.
71. Ye Z, Wang P, Feng G, Wang Q, Liu C, Lu J, Chen J and Liu P: Cryptotanshinone attenuates LPS-induced acute lung injury by regulating metabolic reprogramming of macrophage. Front Med (Lausanne) 9: 1075465, 2022.
72. Zhang J, Wang C, Wang H, Li X, Xu J and Yu K: Loganin alleviates sepsis-induced acute lung injury by regulating macrophage polarization and inhibiting NLRP3 inflammasome activation. Int Immunopharmacol 95: 107529, 2021.
73. Zhao JY, Pu J, Fan J, Feng XY, Xu JW, Zhang R and Shang Y: Tanshinone IIA prevents acute lung injury by regulating macrophage polarization. J Integr Med 20: 274-280, 2022.
74. Ying ZH, Li HM, Yu WY and Yu CH: Iridin prevented against lipopolysaccharide-induced inflammatory responses of macrophages via inactivation of PKM2-mediated glycolytic pathways. J Inflamm Res 14: 341-354, 2021.
75. Zhao L, Zhang M, Liu YW, Tan Y, Yin J, Chen Y, Chen D and Ni B: Sinomenine alleviates lipopolysaccharide-induced acute lung injury via a PPARβ/δ-dependent mechanism. Eur J Pharmacol 953: 175838, 2023.
76. Gao WJ, Liu JX, Xie Y, Luo P, Liu ZQ, Liu L and Zhou H: Suppression of macrophage migration by down-regulating Src/FAK/P130Cas activation contributed to the anti-inflammatory activity of sinomenine. Pharmacol Res 167: 105513, 2021.
77. Yi L, Luo JF, Xie BB, Liu JX, Wang JY, Liu L, Wang PX, Zhou H and Dong Y: α7 nicotinic acetylcholine receptor is a novel mediator of sinomenine anti-inflammation effect in macrophages stimulated by lipopolysaccharide. Shock 44: 188-195, 2015.
78. Zhi YK, Li J, Yi L, Zhu RL, Luo JF, Shi QP, Bai SS, Li YW, Du Q, Cai JZ, *et al*: Sinomenine inhibits macrophage M1 polarization by downregulating α7nAChR via a feedback pathway of α7nAChR/ERK/Egr-1. Phytomedicine 100: 154050, 2022.
79. Guo R, Wang H and Cui N: Autophagy regulation on pyroptosis: Mechanism and medical implication in sepsis. Mediators Inflamm 2021: 9925059, 2021.
80. Shi J, Gao W and Shao F: Pyroptosis: Gasdermin-mediated programmed necrotic cell death. Trends Biochem Sci 42: 245-254, 2017.
81. Wei T, Zhang C and Song Y: Molecular mechanisms and roles of pyroptosis in acute lung injury. Chin Med J (Engl) 135: 2417-2426, 2022.
82. Tang Y, Yu Y, Li R, Tao Z, Zhang L, Wang X, Qi X, Li Y, Meng T, Qu H, *et al*: Phenylalanine promotes alveolar macrophage pyroptosis via the activation of CaSR in ARDS. Front Immunol 14: 1114129, 2023.
83. Wu DD, Pan PH, Liu B, Su XL, Zhang LM, Tan HY, Cao Z, Zhou ZR, Li HT, Li HS, *et al*: Inhibition of alveolar macrophage pyroptosis reduces lipopolysaccharide-induced acute lung injury in mice. Chin Med J (Engl) 128: 2638-2645, 2015.
84. Liu Y, Zhang Y, Feng Q, Liu Q, Xie J, Li H, Yang F, Liu X, Gao W, Bai X, *et al*: GPA peptide attenuates sepsis-induced acute lung injury in mice via inhibiting oxidative stress and pyroptosis of alveolar macrophage. Oxid Med Cell Longev 2021: 1-12, 2021.
85. Li H, Li Y, Song C, Hu Y, Dai M, Liu B and Pan P: Neutrophil extracellular traps augmented alveolar macrophage pyroptosis via AIM2 inflammasome activation in LPS-induced ALI/ARDS. J Inflamm Res 14: 4839-4858, 2021.
86. Hsu CG, Chávez CL, Zhang C, Sowden M, Yan C and Berk BC: The lipid peroxidation product 4-hydroxynonenal inhibits NLRP3 inflammasome activation and macrophage pyroptosis. Cell Death Differ 29: 1790-1803, 2022.
87. Liu Y, Zhang Y, You G, Zheng D, He Z, Guo W, Antonina K, Shukhrat Z, Ding B, Zan J and Zhang Z: Tangeretin attenuates acute lung injury in septic mice by inhibiting ROS-mediated NLRP3 inflammasome activation via regulating PLK1/AMPK/DRP1 signaling axis. Inflamm Res 73: 47-63, 2024.
88. Wang X, Wu FP, Huang YR, Li HD, Cao XY, You Y, Meng ZF, Sun KY and Shen XY: Matrine suppresses NLRP3 inflammasome activation via regulating PTPN2/JNK/SREBP2 pathway in sepsis. Phytomedicine 109: 154574, 2023.
89. Liu Y, Yang H, Zhu F, Ouyang Y and Pan P: Inhibition of STAT3 phosphorylation by colchicine regulates NLRP3 activation to alleviate sepsis-induced acute lung injury. Inflammopharmacology 31: 2007-2021, 2023.
90. Yuan Y, Liao Q, Xue M, Shi Y, Rong L, Song Z, Tong Z, Zheng W, Zhu Q, Cui X and Tao Z: Shufeng jiedu capsules alleviate lipopolysaccharide-induced acute lung inflammatory injury via activation of GPR18 by verbenalin. Cell Physiol Biochem 50: 629-639, 2018.
91. Yang L, Liu T, Zhuo Y, Li D, Li D, Liu J, Gao H, Zhang L, Lin J and Wang X: Verbenalin alleviates acute lung injury induced by sepsis and IgG immune complex through GPR18 receptor. Cell Signal 109: 110768, 2023.

92. Chen LL, Song C, Zhang Y, Li Y, Zhao YH, Lin FY, Han DD, Dai MH, Li W and Pan PH: Quercetin protects against LPS-induced lung injury in mice via SIRT1-mediated suppression of PKM2 nuclear accumulation. Eur J Pharmacol 936: 175352, 2022.
93. Zhong C, Yang J, Deng K, Lang X, Zhang J, Li M, Qiu L, Zhong G and Yu J: Tiliroside attenuates NLRP3 inflammasome activation in macrophages and protects against acute lung injury in mice. Molecules 28: 7527, 2023.
94. Xu HW, Li WF, Hong SS, Shao JJ, Chen JH, Chattipakorn N, Wu D, Luo W and Liang G: Tabersonine, a natural NLRP3 inhibitor, suppresses inflammasome activation in macrophages and attenuate NLRP3-driven diseases in mice. Acta Pharmacol Sin 44: 1252-1261, 2023.
95. Shao JJ, Li WF, Sun JF, Zhuang ZS, Min JL, Long XH, Wu GJ, Xu HW and Liang G: Britannin as a novel NLRP3 inhibitor, suppresses inflammasome activation in macrophages and alleviates NLRP3-related diseases in mice. Acta Pharmacol Sin 45: 803-814, 2024.
96. Yang F, Ye XJ, Chen MY, Li HC, Wang YF, Zhong MY, Zhong CS, Zeng B, Xu LH, He XH and Ouyang DY: Inhibition of NLRP3 inflammasome activation and pyroptosis in macrophages by taraxasterol is associated with its regulation on mTOR signaling. Front Immunol 12: 632606, 2021.
97. Jang WY, Kim MY and Cho JY: Antioxidant, anti-inflammatory, anti-menopausal, and anti-cancer effects of lignans and their metabolites. Int J Mol Sci 23: 15482, 2022.
98. Zhang S, Yang L, Hu D, He S, Cui L, Zhao J, Zhuo Y, Zhang L and Wang X: Syringaresinol alleviates IgG immune complex induced acute lung injury via activating PPARγ and suppressing pyroptosis. Int Immunopharmacol 124(Pt B): 111071, 2023.
99. Li W, Xu H, Shao J, Chen J, Lin Y, Zheng Z, Wang Y, Luo W and Liang G: Discovery of alantolactone as a naturally occurring NLRP3 inhibitor to alleviate NLRP3-driven inflammatory diseases in mice. Br J Pharmacol 180: 1634-1647, 2023.
100. Liu C, Zhou Y, Tu Q, Yao L, Li J and Yang Z: Alpha-linolenic acid pretreatment alleviates NETs-induced alveolar macrophage pyroptosis by inhibiting pyrin inflammasome activation in a mouse model of sepsis-induced ALI/ARDS. Front Immunol 14: 1146612, 2023.
101. Weavers H, Evans IR, Martin P and Wood W: Corpse engulfment generates a molecular memory that primes the macrophage inflammatory response. Cell 165: 1658-1671, 2016.
102. Sun D, Zhang G, Xie M, Wang Y, Liang X, Tu M, Su Z and Zeng R: Softness enhanced macrophage-mediated therapy of inhaled apoptotic-cell-inspired nanosystems for acute lung injury. J Nanobiotechnology 21: 172, 2023.
103. Leventis PA and Grinstein S: The distribution and function of phosphatidylserine in cellular membranes. Ann Rev Biophysics 39: 407-427, 2010.
104. Banerjee S, Friggeri A, Liu G and Abraham E: The C-terminal acidic tail is responsible for the inhibitory effects of HMGB1 on efferocytosis. J Leukoc Biol 88: 973-979, 2010.
105. Mahida RY, Scott A, Parekh D, Lugg ST, Hardy RS, Lavery GG, Matthay MA, Naidu B, Perkins GD and Thickett DR: Acute respiratory distress syndrome is associated with impaired alveolar macrophage efferocytosis. Eur Respir J 58: 2100829, 2021.
106. Mahida RY, Lax S, Bassford CR, Scott A, Parekh D, Hardy RS, Naidu B, Matthay MA, Stewart PM, Cooper MC, *et al*: Impaired alveolar macrophage 11β-hydroxysteroid dehydrogenase type 1 reductase activity contributes to increased pulmonary inflammation and mortality in sepsis-related ARDS. Front Immunol 14: 1159831, 2023.
107. Martín-Vicente P, López-Martínez C and Albaiceta GM: The last-minute redemption of inflammatory cells in lung repair. Eur Respir J 59: 2103000, 2022.
108. Nepal S, Tiruppathi C, Tsukasaki Y, Farahany J, Mittal M, Rehman J, Prockop DJ and Malik AB: STAT6 induces expression of Gas6 in macrophages to clear apoptotic neutrophils and resolve inflammation. Proc Natl Acad Sci USA 116: 16513-16518, 2019.
109. Jiang T, Xia Y, Wang W, Zhao J, Liu W, Liu S, Shi S, Li B, He X and Jin Y: Apoptotic bodies inhibit inflammation by PDL1-PD1-mediated macrophage metabolic reprogramming. Cell Prolif 57: e13531, 2023.
110. Wang Y, Zhang W, Xu Y, Wu D, Gao Z, Zhou J, Qian H, He B and Wang G: Extracellular HMGB1 impairs macrophage-mediated efferocytosis by suppressing the Rab43-controlled cell surface transport of CD91. Front Immunol 13: 767630, 2022.
111. Aderem A and Underhill DM: Mechanisms of phagocytosis in macrophages. Annu Rev Immunol 17: 593-623, 1999.
112. He F, Gao F, Cai N, Jiang M and Wu C: Chlorogenic acid enhances alveolar macrophages phagocytosis in acute respiratory distress syndrome by activating G protein-coupled receptor 37 (GPR 37). Phytomedicine 107: 154474, 2022.
113. Aman Y, Schmauck-Medina T, Hansen M, Morimoto RI, Simon AK, Bjedov I, Palikaras K, Simonsen A, Johansen T, Tavernarakis N, *et al*: Autophagy in healthy aging and disease. Nat Aging 1: 634-650, 2021.
114. Saha S, Panigrahi DP, Patil S and Bhutia SK: Autophagy in health and disease: A comprehensive review. Biomed Pharmacother 104: 485-495, 2018.
115. Wang K, Chen Y, Zhang P, Lin P, Xie N and Wu M: Protective features of autophagy in pulmonary infection and inflammatory diseases. Cells 8: 123, 2019.
116. Murray PJ: On macrophage diversity and inflammatory metabolic timers. Nat Rev Immunol 20: 89-90, 2020.
117. Liu C, Xiao K and Xie L: Progress in preclinical studies of macrophage autophagy in the regulation of ALI/ARDS. Front Immunol 13: 922702, 2022.
118. Huang M, Yu Y, Tang X, Dong R, Li X, Li F, Jin Y, Gong S, Wang X, Zeng Z, *et al*: 3-Hydroxybutyrate ameliorates sepsis-associated acute lung injury by promoting autophagy through the activation of GPR109α in macrophages. Biochem Pharmacol 213: 115632, 2023.
119. Quach C, Helou DG, Li M, Hurrell BP, Howard E, Shafiei-Jahani P, Soroosh P, Ou JJ, Razani B, Rehan V and Akbari O: Enhancing autophagy in CD11c+ antigen-presenting cells as a therapeutic strategy for acute respiratory distress syndrome. Cell Rep 42: 112990, 2023.
120. Qiu P, Liu Y, Chen K, Dong Y, Liu S and Zhang J: Hydrogen-rich saline regulates the polarization and apoptosis of alveolar macrophages and attenuates lung injury via suppression of autophagy in septic rats. Ann Transl Med 9: 974, 2021.
121. Liang J, Liu J, Tang Y, Peng Q, Zhang L, Ma X, Xu N, Wei J and Han H: Sophoridine inhibits endotoxin-induced acute lung injury by enhancing autophagy of macrophage and reducing inflammation. J Leukoc Biol 112: 115-125, 2022.
122. Wen H, Zhang H, Wang W and Li Y: Tetrahydropalmatine protects against acute lung injury induced by limb ischemia/reperfusion through restoring PI3K/AKT/mTOR-mediated autophagy in rats. Pulm Pharmacol Ther 64: 101947, 2020.
123. Tang D, Cao F, Yan C, Fang K, Ma J, Gao L, Sun B and Wang G: Extracellular Vesicle/Macrophage axis: Potential targets for inflammatory disease intervention. Front Immunol 13: 705472, 2022.
124. Viola A, Munari F, Sánchez-Rodríguez R, Scolaro T and Castegna A: The metabolic signature of macrophage responses. Front Immunol 10: 1462, 2019.
125. Feng Z, Jing Z, Li Q, Chu L, Jiang Y, Zhang X, Yan L, Liu Y, Jiang J, Xu P, *et al*: Exosomal STIMATE derived from type II alveolar epithelial cells controls metabolic reprogramming of tissue-resident alveolar macrophages. Theranostics 13: 991-1009, 2023.
126. Zhong WJ, Liu T, Yang HH, Duan JX, Yang JT, Guan XX, Xiong JB, Zhang YF, Zhang CY, Zhou Y and Guan CX: TREM-1 governs NLRP3 inflammasome activation of macrophages by firing up glycolysis in acute lung injury. Int J Biol Sci 19: 242-257, 2023.
127. Breda CN, Davanzo GG, Basso PJ, Câmara NO and Moraes-Vieira PMM: Mitochondria as central hub of the immune system. Redox Biol 26: 101255, 2019.
128. Rosales C and Uribe-Querol E: Phagocytosis: A fundamental process in immunity. Biomed Res Int 2017: 9042851, 2017.
129. Meidaninikjeh S, Sabouni N, Marzouni HZ, Bengar S, Khalili A and Jafari R: Monocytes and macrophages in COVID-19: Friends and foes. Life Sci 269: 119010, 2021.
130. Wang Z, Li S and Huang B: Alveolar macrophages: Achilles' heel of SARS-CoV-2 infection. Signal Transduct Target Ther 7: 242, 2022.