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Research progress on mitochondrial autophagy in sepsis-related acute lung injury

Kecheng Zhai[1,2], Yangmengna Gao[1,2], Yu Xiang[1,2], Jiameng Liu[1,2], Shangping Fang[1,2]

[1]School of Anesthesiology, [2]Anesthesia Laboratory and Training Center, Wannan Medical College, Wuhu 241002, Anhui Province, China.

Corresponding author: Shangping Fang.

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Highlights

- Mitochondrial autophagy is essential for maintaining mitochondrial health by selectively degrading damaged mitochondria. This process involves two main pathways: ubiquitin-dependent and ubiquitin-independent autophagy.
- Sepsis causes organ dysfunction due to infection, with acute lung injury (ALI) being a common secondary condition. ALI is characterized by excessive inflammation in the lungs, leading to mitochondrial dysfunction.
- Understanding the mechanisms of mitochondrial autophagy can provide new insights for treating sepsis-associated ALI. Continued research could identify novel therapeutic targets to improve outcomes for patients with ALI and sepsis.
- In the early stages of sepsis-related ALI, mitochondrial autophagy is enhanced. In severe or prolonged cases, excessive mitochondrial autophagy may occur. In the later stages, particularly in severe or chronic cases, mitochondrial autophagy may be impaired or completely lost.
- Mitochondrial autophagy holds therapeutic potential for the perioperative assessment and management of sepsis-related ALI. Further investigation into this potential is warranted.

Abstract

Sepsis is a systemic inflammatory response syndrome caused by infection, leading to acute lung injury and acute respiratory distress syndrome, which are common life-threatening complications in intensive care units. Mitochondrial autophagy, a process that selectively removes damaged mitochondria, is essential for maintaining the stability of the intracellular environment and cellular function. In recent years, the role of mitochondrial autophagy in sepsis-associated acute lung injury and acute respiratory distress syndrome has garnered significant attention. This review summarizes the research progress of mitochondrial autophagy in sepsis-associated acute lung injury and acute respiratory distress syndrome, focusing on its mechanism, influencing factors, and potential therapeutic agents.

Keywords: Mitochondrial autophagy, sepsis, acute lung injury

Introduction

Sepsis is a clinical complication resulting from infection-induced organ dysfunction, which is associated with high morbidity and mortality rates. It is the leading cause of death among critically ill patients [1]. In 2017, there were approximately 48.9 million cases of sepsis globally, with 11 million sepsis-related deaths, accounting for 19.7% of all deaths worldwide [2]. Acute lung injury (ALI) is the most common disease associated with sepsis [3]. ALI is characterized by an excessive inflammatory response in the lungs, involving immune cell activation, secretion of pro-inflammatory mediators, and disruption of membrane function [4]. During

Address correspondence to: Shangping Fang, Anesthesia Laboratory and Training Center, Wannan Medical Collegem, No. 22, Wenchang West Road, Higher Education Park, Wuhu 241002, Anhui Province, China. E-mail: 20180041@wnmc.edu.cn.

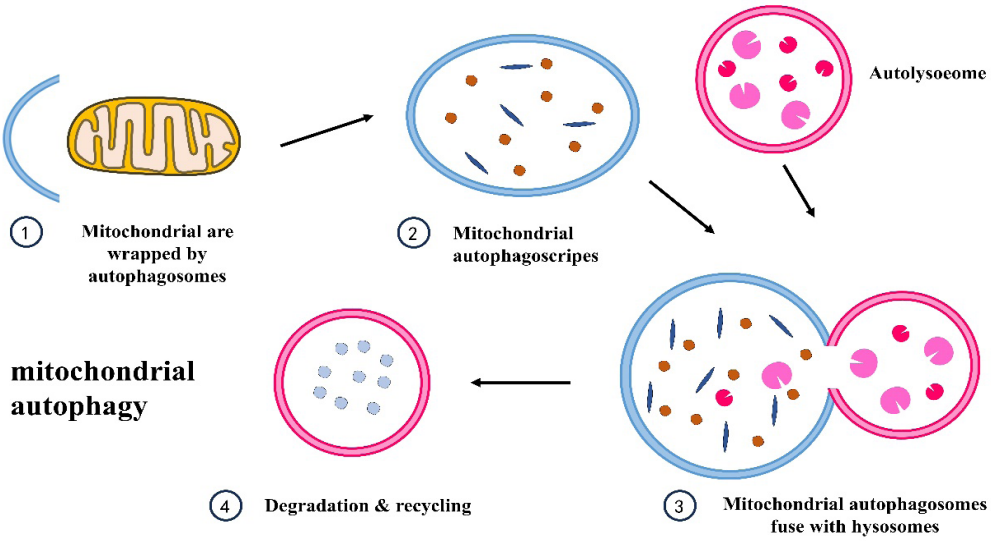


Figure 1. The main processes of mitophagy.

ALI, mitochondria lose their ability to regulate calcium and reactive oxygen species (ROS) levels, leading to excessive mitochondrial free radical leakage, mitochondrial DNA damage, and the production of mitochondrial ROS. The accumulation of mitochondrial ROS activates NOD-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasomes, which in turn trigger caspase-1-dependent pyroptosis, a key driver of cellular focal death in ALI [5]. In contrast, mitochondrial autophagy, a cellular process that maintains mitochondrial health, plays a critical role in the development and progression of ALI. In this process, damaged mitochondria due to pathological conditions such as hypoxia, oxidative stress, and inflammation, are selectively cleared and degraded, thereby maintaining homeostasis and normal lung tissue function [6]. This paper aims to elucidate the molecular mechanisms underlying mitochondrial autophagy and the pathogenesis of mitochondrial autophagy disorders in sepsis-associated ALI, providing new insights for clinical treatment strategies.

Mitochondrial autophagy

Mitochondria are bioenergetic, biosynthetic, and signaling organelles that play a key role in stress perception, enabling cellular adaptation to environmental changes [7]. Many mitochondrial components and metabolites act as damage-associated molecular patterns, promoting inflammation when released into the cytoplasmic lysate or extracellular space. To prevent harmful inflammatory responses, organisms employ mitochondrial quality control systems, including the autophagic clearance of damaged mitochondria. However, when these systems' homeostatic capacity is overwhelmed or defective, mitochondria-induced inflammatory responses may become pathogenic and contribute to the development of various diseases such as neurodegenerative diseases, cardiovascular diseases, cancers, metabolic disorders, and infections [8].

Mitochondrial autophagy plays a critical role in eliminating dysfunctional mitochondria and maintaining mitochondrial homeostasis. Under conditions such as starvation, hypoxia, and endoplasmic reticulum stress, the damaged mitochondria depolarize and lose membrane potential, initiating selective autophagy of damaged mitochondria [9]. These mitochondria are engulfed by autophagosomes, forming mitochondrial autophagosomes (a double-membrane structure). The mitochondrial autophagosomes then fuse with lysosomes to form autophagic lysosomes, where the mitochondrial contents are degraded by lysosomal enzymes and subsequently recycled for cellular use (**Figure 1**).

Molecular mechanisms of mitochondrial autophagy

Mitochondrial autophagy mechanisms are generally divided into two categories: ubiquitin-dependent mitophagy and ubiquitin-independent mitophagy.

Ubiquitin-dependent mitochondrial autophagy

As the name suggests, ubiquitin-dependent autophagy involves the extensive ubiquitination of damaged mitochondria, which are then recognized and degraded by the proteasome. Current research highlights that the Phosphatase and tensin homolog (PTEN)-induced putative kinase 1 (PINK1)/Parkin pathway is a key regulator

of mitochondrial autophagy [10]. PINK1 is a mitochondrial serine/threonine protein kinase containing mitochondrial-targeting sequences that direct its localization to the mitochondria. Under normal mitochondrial conditions, PINK1 is imported into mitochondria via the outer membrane translocase and inner membrane translocase complexes. Upon translocation to the inner mitochondrial membrane, PINK1 is cleaved by matrix processing peptidase and the inner membrane protease PINK1/Phosphoglycerate mutase family member 5 (PGAM5)-associated rhodopsin-like protease and subsequently degraded by the proteasome via the N-terminal rule pathway.

However, when mitochondria are damaged, the loss of membrane potential prevents PINK1 from being imported into the inner membrane, causing the accumulation of PINK1 on the outer mitochondrial membrane (OMM), where it undergoes autophosphorylation and dimerization. PINK1 then phosphorylates Parkin, activating its E3 ubiquitin ligase activity. In turn, Parkin ubiquitinates several outer membrane proteins, forming polyubiquitin chains that are subsequently phosphorylated by PINK1, acting as "eat-me" signals for the core autophagy machinery [11].

Parkin, an E3 ubiquitin ligase encoded by the PARK2 gene, ligates ubiquitin to substrate proteins. The proteasome recognizes the ubiquitin tag and degrades the substrate protein. After mitochondrial damage, PINK1 promotes a conformational change of Parkin into an active E3 ubiquitin ligase, which enhances mitochondrial autophagy. Simultaneously, PINK1 phosphorylates ubiquitin on substrates of OMM proteins, recruiting Parkin from the cytoplasm to the OMM with high affinity. Activated Parkin can then ubiquitinate OMM proteins, such as mitofusin-2 and voltage-dependent anion channel 1, promoting the formation of polyubiquitin chains [12]. Parkin ubiquitinates OMM protein substrates, and PINK1 phosphorylates the ubiquitin chains, further recruiting and activating Parkin, thus creating a feedback loop that amplifies the phosphorylation of ubiquitin [13].

Autophagy receptors, including Optineurin, NDP52, Sequestosome 1 (SQSTM1)/p62, NBR1, and TAX1BP1, recognize the phosphorylated polyubiquitin chains and anchor the mitochondria to autophagosomes by binding to microtubule-associated protein 1 light chain 3 (LC3). The formation of autophagosomes is initiated by the recruitment of autophagy initiation factors, including unc-51-like autophagy-activating kinase 1 (ULK1), WD-repeat domain, phosphatidylinositol-interacting protein 1 (WIPI1), and double FYVE domain-containing protein 1 (DFCP1). TANK-binding kinase 1 is also activated and phosphorylated, enhancing the binding of NDP52 and Optineurin to polyubiquitinated chains. These receptors further promote the synthesis of phagocytic vesicles, the precursors of autophagosomes that eventually fuse with lysosomes for degradation, by recruiting key autophagosome biogenesis components (WIPI1, ULK1, and DFCP1) [5].

In addition to the PINK1-Parkin pathway, other E3 ubiquitin ligases, such as Gp78, SMURF1, Siah1, MUL1, and ARIH1, play roles in regulating mitochondrial autophagy independent of Parkin [14-18]. Once localized on the mitochondrial surface, these ligases generate ubiquitin chains. The autophagy receptor then recognizes the phosphorylated polyubiquitin chains and anchors the mitochondria to the autophagosome by binding to LC3 (**Figure 2**).

Ubiquitin-independent mitochondrial autophagy

Ubiquitin-independent mitochondrial autophagy is mediated by a set of OMM proteins that act as mitochondrial autophagy receptors. These include Nip3-like protein X (NIX), BCL2-interacting protein 3-like (BNIP3L), BCL2-interacting protein 3 (BNIP3), and FUN14 Domain Containing 1 (FUNDC1). These receptors initiate mitochondrial autophagy by binding directly to LC3, independent of ubiquitylation. NIX, also known as BNIP3L, was initially identified when mice with NIX gene deletion exhibited impaired maturation of reticulocytes, leading to the accumulation of excessive mitochondria due to defective mitochondrial autophagy, ultimately resulting in anemia [19]. NIX proteins can directly bind to LC3 through their BH3 structural domain, inducing mitochondrial autophagy. Similarly, BNIP3, which also contains the BH3 structural domain, shares 56% homology with NIX, as both belong to a subfamily of the anti-apoptotic B-cell lymphoma-2 (Bcl-2) family, characterized by the presence of the BH3 domain [20]. BNIP3 deficiency significantly inhibits mitochondrial autophagy, thereby exacerbating apoptosis. FUNDC1, another conserved mitochondrial autophagy receptor, also binds to LC3. It induces Parkin-independent mitochondrial autophagy in mammalian cells under hypoxic conditions (**Figure 2**).

Mitochondrial autophagy and sepsis-related ALI

Under normal physiological conditions, cells

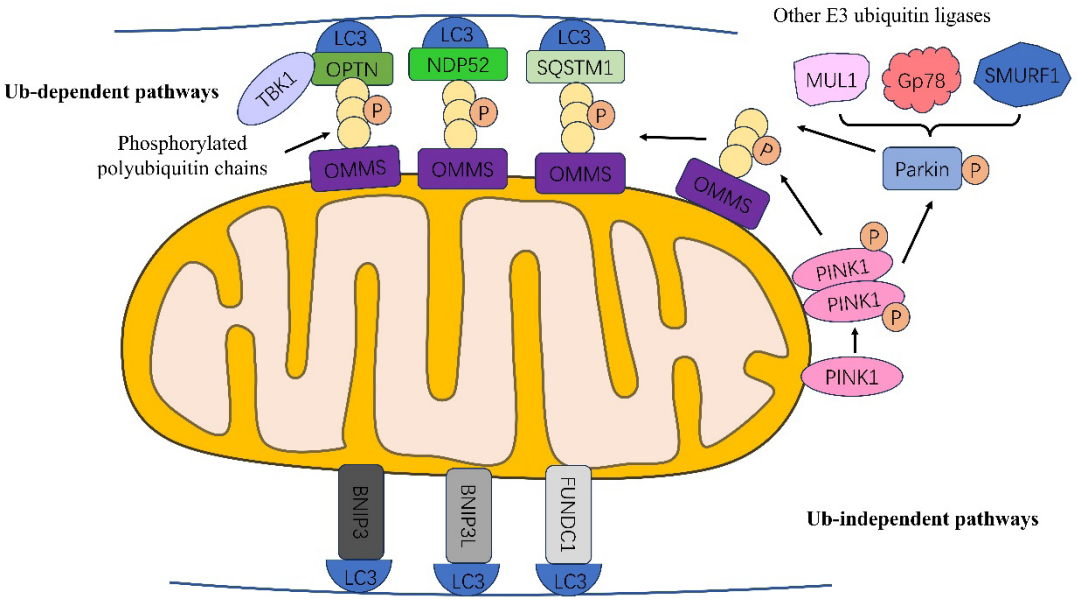


Figure 2. Mechanistic overview of mitophagy. TBK1, TANK-Binding Kinase 1; OPTN, Optineurin; NDP52, Nuclear dot protein 52; SQSTM1, Sequestosome 1; LC3, Microtubule-associated protein 1 light chain 3; PINK1, PTEN-induced kinase 1; Parkin, Parkinson protein 2, E3 ubiquitin protein ligase; MUL1, Mitochondrial E3 Ubiquitin Ligase 1; Gp78, Glucose-regulated protein 78; SMURF1, SMAD specific E3 ubiquitin protein ligase 1; BNIP3, BCL2 Interacting Protein 3; BNIP3L, BCL2 Interacting Protein 3 Like; FUNDC1, FUN14 Domain Containing 1.

maintain mitochondrial quality control through basal levels of autophagy. In lung cells, mitochondrial autophagy plays a crucial role in eliminating damaged or dysfunctional mitochondria, thereby preventing the accumulation of ROS and preserving cellular homeostasis. This basal process is regulated by the PINK1/Parkin pathway and mitochondrial autophagy receptors, such as NIX/BNIP3, ensuring lung tissue integrity and proper cellular function, especially in lung epithelial and endothelial cells.

The balance between pro- and anti-inflammatory mediators governs the progression of the inflammatory response following sepsis-associated ALI. Maintaining this balance is critical for controlling infection in patients. However, disruption of this homeostasis results in the release of pro-inflammatory mediators into the bloodstream, triggering a broader inflammatory cascade and organ dysfunction [21]. The lungs, which play a key role in gas exchange by oxygenating the blood and removing carbon dioxide, receive large amounts of blood and are therefore primary sites for the diffusion of inflammatory mediators during sepsis [22]. These mediators can cause inflammation, increase oxidative stress, and damage lung tissue.

Oxidative phosphorylation in mitochondria is a major route for ROS production due to abnormal electron leakage [23]. Although mitochondria possess antioxidant proteins that can neutralize ROS, excessive ROS production can impair the endothelial barrier function in the pulmonary vasculature and alveolar epithelium, leading to immune cell infiltration (e.g., neutrophils) secretion of cytotoxic substances, and mitochondrial damage. In sepsis-induced ALI, ultrastructural changes in mitochondria include reduced mitochondrial mass, disrupted cristae, and extensive mitochondrial swelling [24]. Mitochondrial autophagy removes aged and damaged mitochondria through selective segregation and lysosomal degradation, thus limiting ROS production.

ROS-induced mtDNA damage reduces mitochondrial membrane potential and leads to protein and lipid oxidation. In response, mitochondrial autophagy plays a critical role in maintaining mitochondrial function and facilitating DNA repair. Inhibition of mitochondrial autophagy has been shown to disrupt mitochondrial Ca2+ homeostasis, impair ATP production, and hinder DNA repair [25]. Suliman et al. observed widespread activation of mitochondrial autophagy in the alveolar region of a mouse model of S. aureus-induced pneumonia [26]. This quality control process contributes to the removal and replacement of damaged mitochondria in lung cells, thereby enhancing cell survival and supporting alveolar function.

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that regulates mitochondrial quality, cytoprotective gene expression, oxidative stress response, and an-

ti-inflammatory and anti-apoptotic processes through downstream factors such as HO-1, Bcl-2, and B-cell lymphoma-extra large [27]. Nrf2 activation has been shown to reduce ROS production by counteracting mitochondrial toxins and regulating the production of reduced glutathione [28]. Additionally, Nrf2 deficiency may impair mitochondrial fatty acid oxidation and reduce ATP production [29]. Downregulation of classical autophagy during sepsis exacerbates lung inflammation, whereas Nrf2 activation promotes mitochondrial autophagy in the alveolar region. This process selectively removes damaged mitochondria, facilitates tissue repair, and enhances cell survival, thereby attenuating sepsis-induced ALI and acute respiratory distress syndrome (ARDS).

However, in cases of severe or prolonged ALI, excessive mitochondrial autophagy can lead to cellular energy depletion and impaired mitochondrial biogenesis. This can cause significant mitochondrial loss, leading to further energy deficits and worsening tissue damage. Additionally, excessive mitochondrial autophagy also releases damage-associated molecular patterns, which amplify the inflammatory response, creating a vicious cycle of damage. In the later stages of ALI, especially in severe or chronic cases, mitochondrial autophagy may become impaired or absent. This dysfunction leads to the accumulation of damaged mitochondria, increased ROS production, mitochondrial fragmentation, and heightened oxidative stress.

The time-dependent effects of mitochondrial autophagy in ALI are critical for determining the trajectory of injury and recovery. Early mitochondrial autophagy is protective, as it removes damaged mitochondria and limits inflammation. However, in cases of prolonged or excessive injury, mitochondrial autophagy becomes detrimental, leading to mitochondrial depletion and further tissue damage. In the later stages, mitochondrial autophagy dysfunction exacerbates oxidative stress and hinders cellular repair. Therefore, interventions should focus on enhancing mitochondrial autophagy during the early stages of injury, controlling excessive mitochondrial autophagy during prolonged injury, and restoring mitochondrial autophagy function in later stages to optimize recovery from sepsis-induced ALI and ARDS [30].

PINK1/Parkin signaling pathway and acute lung injury

The PINK1/Parkin pathway is a classical mitochondrial autophagy signaling pathway that plays a crucial role in ALI. It has been shown that resveratrol may improve ALI in mice by inhibiting the activation of NLRP3 inflammasomes, activating the PINK1/Parkin pathway, and promoting mitochondrial autophagy [31]. In the absence of PINK1, mitochondrial autophagy was found to be halted; However, resveratrol upregulated the expression of PINK1, Parkin, Beclin-1, autophagy-related 5, and microtubule-associated protein 1A/1B light chain 3B, which enhanced mitochondrial autophagy, offering a new therapeutic target for the treatment of ALI.

In addition, targeting Bcl-2 family proteins, including Bcl-2 and Bad, can modulate sepsis-induced ALI through the PINK1/Parkin signaling pathway. The anti-apoptotic role of Bcl-2 in various apoptotic cells and animal models is well documented [32, 33]. Bad, an upstream member of the Bcl-2 family, acts as a sensor for cellular stress, injury, infection, growth factor deprivation, and apoptosis [34]. Bad is a BH3-like protein that interacts with Bcl-2. The BH1-BH4 structural domains of Bcl-2 form a hydrophobic groove that binds to Bad, thus regulating autophagy. Hollville et al. demonstrated that Bcl-2 family proteins can inhibit mitochondrial autophagy by preventing translocation of Parkin to depolarized mitochondria in HeLa and HEK293T cells [35]. Additionally, in lipopolysaccharide (LPS) induced A549 cell injury and ALI in mice, elevated apoptosis, enhanced mitochondrial autophagy, decreased Bcl-2 expression, increased Bad expression, and activation of the PINK1/Parkin pathway were observed in both cells and lung tissues [36]. However, both Bcl-2 overexpression and Bad knockdown attenuated LPS-induced injury, inhibited apoptosis and mitochondrial autophagy, and increased survival. Furthermore, Bcl-2 family proteins regulated mitochondrial autophagy by promoting the recruitment of Parkin from the cytoplasm to the mitochondria through direct protein interactions [36].

Mitochondrial autophagy receptors and sepsis-related ALI

Mitochondrial autophagy, mediated by receptors such as BNIP3L/NIX and FUNDC1, plays a vital role in mitochondrial network reorganization during cell differentiation. Knockdown of these receptors during differentiation results in sustained mitochondrial fission and the formation of damaged mitochondria, thereby increasing the likelihood of cell death [37]. Therefore, mitochondrial autophagy receptors are crucial for maintaining the integrity and health of lung cells.

FUNDC1

FUNDC1 is a key receptor for mitochondrial autophagy. Under normoxic conditions, FUNDC1 is phosphorylated by the protein kinase Src, which reduces the interaction between phosphorylated FUNDC1 and LC3, thereby inhibiting FUNDC1-mediated mitochondrial autophagy [38]. Under hypoxic conditions, reduced Src kinase activity leads to decreased phosphorylation of FUNDC1, which facilitates the interaction between dephosphorylated FUNDC1 and LC3, thus promoting mitochondrial autophagy [39]. Autophagy is significantly increased in response to ALI, especially in alveolar epithelial cells and pulmonary vascular endothelial cells. Study has shown that autophagy is activated under hypoxic conditions, making FUNDC1 a key molecule involved in hypoxia-induced mitochondrial autophagy [40]. Following LPS intervention, the autophagic proteins FUNDC1 and LC3-II were elevated, while P62/SQSTM1 was decreased. Notably, FUNDC1 knockdown led to reduced autophagic activity and more severe lung injury following LPS treatment. Additionally, survival curves showed higher mortality in FUNDC1 knockout mice compared to wild-type mice [41].

BNIP3 and BNIP3L/NIX

BNIP3 and BNIP3L/NIX are target genes of HIF-1 that contain an LC3-interacting region. These proteins can recruit LC3 autophagosomes, thereby inducing mitochondrial autophagy [42]. BNIP3 has a dual function: it can promote cell survival through autophagy or induce cell death via apoptosis. BNIP3 binds to Bcl-2, which activates Beclin1 from its inactivation complex, initiating autophagy.

Simultaneously, BNIP3 interacts with mitochondrial fusion protein optic atrophy 1 to promote cell death [43]. It has been shown that inhibiting mitochondrial autophagy and apoptosis by regulating BNIP3 with the HIF-1α inhibitor YC-1 significantly reduces lung injury [44]. Luo et al. identified the transcription factor Runt-related transcription factor 1 (RUNX1) as a key regulator of injury-induced mitochondrial autophagy, and silencing RUNX1 significantly suppressed the expression of BNIP3 and BNIP3L. RUNX1 regulates mitochondrial autophagy by upregulating the expression of mitochondrial autophagy receptors [45]. The transcription factor RUNX1 plays a crucial role in regulating injury-induced mitochondrial autophagy, activating autophagy, and reducing lung inflammation during acute lung injury.

Drugs that ameliorate ALI by affecting mitochondrial autophagy

Small molecule modulators of mitochondrial autophagy are valuable pharmacological tools for studying complex biological processes and translating these insights into potential therapeutic drugs. In recent years, pharmacological modulation of mitochondrial autophagy has demonstrated promising therapeutic effects in ALI models. This section summarizes the current state of research on mitochondrial autophagy modulators, analyzes the available chemical tools, and discusses their advantages, limitations, and current applications (**Table 1**).

Nrf2 inducers

Radish thiols

Radish thiols, found in broccoli, possess significant biological properties. One of the most notable compounds is Sulforaphane, a potent natural activator of the transcription factor Nrf2, which is known for its antioxidant and anti-inflammatory effects [46]. Sulforaphane promotes the translocation of Nrf2 to the nucleus, thereby activating the expression of antioxidant enzymes. Interestingly, activation of the Nrf2 pathway can also increase the production of ROS in mitochondria. At moderate levels, ROS acts as a signaling molecule for mitochondrial damage and trigger the process of mitochondrial autophagy. In an animal model of oleic acid-induced ARDS, sulforaphane treatment was found to reduce lung injury and exert a protective effect by upregulating NRF2 expression [47].

P62-mediated mitochondrial autophagy inducer (PMI)

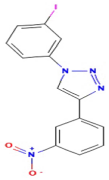
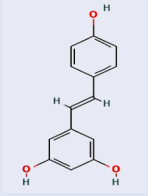
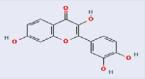
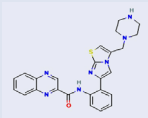
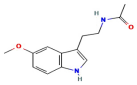
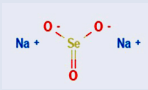
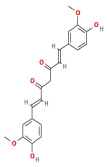
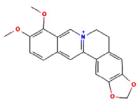
A recently developed compound, PMI, enhances the expression and signaling of the autophagy adaptor protein P62/SQSTM1, which drives mitochondria into autophagy [48]. PMI promotes the accumulation of Nrf2 by targeting the interactions between Nrf2 and Keap1, specifically inhibiting Keap1 and thus enhancing Nrf2 signaling. Importantly, PMI does not disrupt the mitochondrial membrane potential. Therefore, PMI holds significant therapeutic potential for the treatment of ALI [49].

Sirtuin 1 (SIRT1) activators

Sirtuin 1

SIRT1 is a deacetylase that regulates various

Table 1. Drugs that ameliorate acute lung injury by affecting mitochondrial autophagy

Classification	Names	Chemical structure	Mechanisms	Advantages or limitations	References
Nrf2 inducers	Sulforaphane		Activating Nrf2	Low specificity	[46, 47]
	PMI		Inhibiting Keap1	High therapeutic potential; High specificity	[48, 49]
SIRT1 activators	Resveratrol		Activating SIRT1 directly	Low specificity; Induction of general autophagy	[50, 51]
	Fisetin		Activating SIRT1 directly	Non-toxic, and safe	[52, 53]
	SRT1720		Activating SIRT1 directly	High therapeutic potential	[54, 55]
Amine hormone	Melatonin		Upregulating the PINK1/Parkin pathway and inhibiting mTOR.	Strong antioxidant; High safety	[56-59]
Superoxide generator	Sodium selenite		Activating MUL1, ROS-dependent, down-regulation of MCL-1	Nontoxic Low cost Se Supplementation	[17, 60-64]
Natural products	Curcumin		Activation via AMPK	Reference effect on the treatment of ALI. Risk of contact dermatitis with excessive intake	[65-68]
	Berberine		Upregulating the PINK1/Parkin pathway	High therapeutic potential	[69-74]

Note: Nrf2, Nuclear factor erythroid 2-related factor 2; PMI, P62-mediated mitochondrial autophagy inducer; SIRT1, Sirtuin 1; PINK1, PTEN-induced kinase 1; mTOR, mechanistic target of rapamycin; MUL1, Mitochondrial E3 Ubiquitin Ligase 1; ROS, reactive oxygen species; AMPK, AMP-activated protein kinase; MCL-1, Myeloid Cell Leukemia-1ALI, acute lung injury; Se, Selenium.

cellular activities by controlling biological processes such as gene expression, DNA repair, metabolism, and mitochondrial function. SIRT1 may initiate mitochondrial autophagy by promoting the deacetylation and subsequent activation of LC3. The most well-known activators of SIRT1 include resveratrol, fexofenadine, and synthetic small molecules such as SRT1720.

Resveratrol

Resveratrol, a polyphenolic compound found in grapes and peanuts, is renowned for its potent antioxidant and anti-inflammatory properties [50]. As a well-known activator of SIRT1, resveratrol, upon activation, regulates mitochondrial autophagy through deacetylation. Specifically, SIRT1 activates the PINK1/Parkin pathway, enhancing selective mitochondrial autophagy (mitophagy). Additionally, SIRT1 also facilitates autophagy by deacetylating ULK1, a core protein of the autophagy initiation complex [51]. As an antioxidant, resveratrol reduces the production of ROS, which, in excess, can dam-

age mitochondria and inhibit autophagy. By lowering ROS levels, resveratrol helps maintain normal mitochondrial function and promotes the removal of damaged mitochondria, thereby protecting cells from oxidative stress.

Fisetin

Fisetin is a natural flavonoid found abundantly in vegetables and fruits, known for its broad pharmacological effects, including anti-inflammatory, anti-apoptotic, antioxidant, anti-tumor, and anti-angiogenic properties [52]. SIRT1 facilitates the recognition and clearance of damaged mitochondria by deacetylating proteins such as PINK1 and Parkin. Studies have shown that Fisetin enhances the stability and activity of PINK1, enabling its accumulation on damaged mitochondria, which subsequently recruits Parkin [53]. Parkin then ubiquitinates the damaged mitochondria, marking them for degradation. Additionally, laccasein has been reported to accelerate the clearance of damaged mitochondria by modulating this pathway [53].

SRT1720

SRT1720 is a synthetic small molecule that activates SIRT1, leading to the deacetylation of PINK1, which stabilizes PINK1 and enhances its accumulation and function on damaged mitochondria [54]. The accumulation of PINK1 on the mitochondrial membrane recruits Parkin, an E3 ubiquitin ligase, which tags damaged mitochondria for degradation via the autophagy pathway. By deacetylating PINK1, SRT1720 enhances the activity of the PINK1/Parkin pathway, thereby facilitating mitochondrial autophagy (mitophagy) [55].

Melatonin

Melatonin is an indole heterocyclic compound primarily secreted by the pineal gland, well known for its role in regulating sleep and its anti-inflammatory, antioxidant, anti-aging, and antiviral properties [56]. Additionally, melatonin also regulates mitochondrial autophagy. Melatonin inhibits excessive mitochondrial autophagy through the PINK1/Parkin pathway [57]. It reduces oxidative damage and improves mitochondrial function by directly scavenging ROS and activating antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase. Furthermore, melatonin promotes mitochondrial repair and autophagy by upregulating endogenous antioxidants like glutathione. In addition, Melatonin inhibits the mechanistic target of rapamycin (mTOR) pathway, a critical regulator of cell growth, proliferation, and autophagy inhibition. By inhibiting mTOR, melatonin activates the autophagic process, promoting mitochondrial clearance and renewal [58]. Several clinical studies have investigated melatonin's potential in treating ALI and ARDS, focusing on its antioxidant, anti-inflammatory, and lung function-improving effects [59]. These studies have shown that melatonin improves oxygenation, reduces inflammatory markers, and decreases lung injury. However, direct clinical evidence supporting melatonin's ability to ameliorate ALI through mitochondrial autophagy remains limited. Despite this, melatonin has been found to improve the survival rate of critically ill septic patients in the perioperative period.

Sodium selenite

Selenium is an essential trace element in the human body, and its deficiency is linked to a variety of diseases. It has been reported that serum or plasma selenium levels tend to decrease early in critically ill patients, especially those suffering from sepsis or infectious shock [60]. Research has demonstrated that sodium selenite activates the E3 ubiquitin ligase MUL1 in a ROS-dependent manner. This activation recruits ULK1 to the mitochondria, promoting its autophagic degradation [17]. Additionally, intravenous sodium selenite has been found to restore lung antioxidant capacity, modulate the inflammatory response, and significantly improve respiratory mechanics in ALI patients [61]. Several clinical studies have shown that low selenium status may be associated with the severity of ALI, and that selenium supplementation, including sodium selenite, can help reduce oxidative stress and inflammation [62-64]. By improving the antioxidant defense system, sodium selenite contributes to the alleviation of lung injury [61].

Natural products

Curcumin

Curcumin, a polyphenolic compound found in the rhizome of Curcuma longa, regulates the expression of receptor complexes, growth factors, and other molecules, ultimately exerting biological functions such as anti-inflammatory, anticancer, and antidiabetic properties [65]. In an energy-deficient state (e.g., low ATP/AMP ratio), AMP-activated protein kinase (AMPK) is activated. AMPK, a crucial intracellular energy-sensing enzyme of the serine/threonine kinase family, plays a crucial role in maintaining energy homeostasis by regulating various meta-

bolic pathways [66]. Activated AMPK promotes autophagy by mTOR, a key cellular signaling protein that regulates biological processes such as cell growth, proliferation, and protein synthesis. mTOR exists in two complexes: mTORC1 and mTORC2, with mTORC1 playing a significant role in regulating mitochondrial autophagy. mTORC1 inhibits autophagy by phosphorylating and tinhibiting ULK1, a core enzyme that initiates mitochondrial autophagy [67]. Additionally, the mitochondrial permeability transition pore (mPTP) plays a crucial role in cellular stress responses, particularly during apoptosis and autophagy. Excessive mPTP opening leads to a loss of mitochondrial membrane potential, triggering apoptosis. Curcumin regulates mPTP by reducing oxidative stress, potentially preventing excessive opening and thereby preserving mitochondrial function and integrity. Moderate mPTP opening may also promote mitochondrial autophagy, and curcumin enhances mitochondrial quality control by optimizing this process [68].

Berberine

Berberine, a quaternary isoquinoline alkaloid isolated from several herbs such as Coptis chinensis, is known for its wide range of biological activities, including anti-inflammatory, anti-diarrheal and anti-colitis effects. It is characterized by low toxicity and low cost, which has led to its widespread use over-the-counter for treating gastroenteritis, colitis, diarrhea, and dysentery [69]. Berberine can be oxidized to 8-oxoberberine, known as oxyberberine, which has been found to possess superior anti-inflammatory, antifungal, and antiarrhythmic properties compared to berberine [70]. Studies have shown that oxyberberine reduces lung injury by inhibiting inflammatory responses through the inhibition of Parkin/Pink1-mediated mitochondrial autophagy in LPS-induced ALI [71, 72]. Additionally, oxyberberine inhibits LPS-induced translocation of Parkin1 from cytoplasm to mitochondria [73]. Furthermore, berberine activates the AMPK/mTOR pathway and promotes mitochondrial autophagy by inhibiting mTOR [74].

Conclusion

Modulating mitochondrial autophagy to ameliorate ALI has emerged as a promising therapeutic strategy in recent years. While enhancing mitochondrial autophagy has shown promise in alleviating ALI in animal models, several challenges remain in translating this strategy into effective clinical treatments. For instance, pharmacological interventions targeting mitochondrial autophagy—such as those involving the PINK1/Parkin pathway or small molecules that modulate autophagy factors—are not yet widely used in clinical practice. Moreover, the selectivity and potential side effects of these drugs require comprehensive evaluation. To effectively regulate mitochondrial autophagy, the development of highly selective, low-toxicity drugs remains a critical research focus. Currently, several small molecules capable of modulating mitochondrial autophagy, either by enhancing the PINK1/Parkin pathway or by modulating the NIX/BNIP3 pathway, have been identified. Future advancements may lead to the development of small molecule drugs targeting these pathways, with their efficacy in treating acute lung injury further validated through animal studies.

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References

[1] Singer M, Deutschman C, Seymour C, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315(8):801-810.

[2] Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet 2020;395(10219):200-211.

[3] Matthay MA, Ware LB, Zimmerman GA. The acute respiratory distress syndrome. J Clin Invest 2012;122(8):2731-2740.

[4] Matthay MA, Zimmerman GA. Acute lung injury and the acute respiratory distress syndrome: four decades of inquiry into pathogenesis and rational management. Am J Respir Cell Mol Biol 2005;33(4):319-327.

[5] Mohsin M, Tabassum G, Ahmad S, et al. The role of mitophagy in pulmonary sepsis. Mitochondrion 2021;59:63-75.

[6] Ng MYW, Wai T, Simonsen A. Quality control of the mitochondrion. Dev Cell 2021;56(7):881-905.

[7] Nunnari J, Suomalainen A. Mitochondria: in sickness and in health. Cell 2012;148(6):1145-1159.

[8] Doblado L, Lueck C, Rey C, et al. Mitophagy

in Human Diseases. Int J Mol Sci 2021;22(8):3903.
[9] Xu Y, Shen J, Ran Z. Emerging views of mitophagy in immunity and autoimmune diseases. Autophagy 2019;16(1):3-17.
[10] Jie L, Dongming Y, Zhiping L, et al. PINK1/Parkin-mediated mitophagy in neurodegenerative diseases. Ageing Res Rev 2022;84:101817.
[11] Dong Y, Zhuang XX, Wang YT, et al. Chemical mitophagy modulators: Drug development strategies and novel regulatory mechanisms. Pharmacol Res 2023;194(0):106835.
[12] Palikaras K, Lionaki E, Tavernarakis N. Mechanisms of mitophagy in cellular homeostasis, physiology and pathology. Nat Cell Biol 2018;20(9):1013-1022.
[13] Pickles S, Vigié P, Youle RJ. Mitophagy and Quality Control Mechanisms in Mitochondrial Maintenance. Curr Biol 2018;28(4):R170-R185.
[14] Alan P, Vandevoorde KR, Joshi B, et al. Basal Gp78-dependent mitophagy promotes mitochondrial health and limits mitochondrial ROS. Cell Mol Life Sci 2022;79(11):565.
[15] Dagar N, Kale A, Steiger S, et al. Receptor-mediated mitophagy: An emerging therapeutic target in acute kidney injury. Mitochondrion 2022;66:82-91.
[16] Abd Elghani F, Safory H, Hamza H, et al. SIAH proteins regulate the degradation and intramitochondrial aggregation of PINK1: Implications for mitochondrial pathology in Parkinson's disease. Aging Cell 2022;21(12):e13731.
[17] Li J, Qi W, Chen G, et al. Mitochondrial outer-membrane E3 ligase MUL1 ubiquitinates ULK1 and regulates selenite-induced mitophagy. Autophagy 2015;11(8):1216-1229.
[18] Howard M, Erickson J, Cuba Z, et al. A secretory form of Parkin-independent mitophagy contributes to the repertoire of extracellular vesicles released into the tumour interstitial fluid in vivo. J Extracell Vesicles 2022;11(7):e12244.
[19] Schweers RL, Zhang J, Randall MS, et al. NIX is required for programmed mitochondrial clearance during reticulocyte maturation. Proc Natl Acad Sci U S A 2007;104(49):19500-19505.
[20] Zhang J, Ney PA. Role of BNIP3 and NIX in cell death, autophagy, and mitophagy. Cell Death Differ 2009;16(7):939-946.
[21] Bosmann M, Ward PA. The inflammatory response in sepsis. Trends Immunol 2012;34(3):129-136.
[22] Park I, Kim M, Choe K, et al. Neutrophils disturb pulmonary microcirculation in sepsis-induced acute lung injury. Eur Respir J 2019;53(3):
[23] Susana C. Mitochondrial uncoupling, ROS generation and cardioprotec-tion. Biochim Biophys Acta Bioenerg 2018;1859(9):1800786.
[24] Tran M, Tam D, Bardia A, et al. PGC-1α promotes recovery after acute kidney injury during systemic inflammation in mice. J Clin Invest 2011;121(10):4003-4014.
[25] Dan X, Babbar M, Moore A, et al. DNA damage invokes mitophagy through a pathway involving Spata18. Nucleic Acids Res 2020;48(12):6611-6623.
[26] Suliman HB, Kraft B, Bartz R, et al. Mitochondrial quality control in alveolar epithelial cells damaged by S. aureus pneumonia in mice. Am J Physiol Lung Cell Mol Physiol 2017;313(4):L699-L709.
[27] Vomund S, Schäfer A, Parnham MJ, et al. Nrf2, the Master Regulator of Anti-Oxidative Responses. Int J Mol Sci 2017;18(12):2772.
[28] Zhu L, Zhang Q, Hua C, et al. Melatonin alleviates particulate matter-induced liver fibrosis by inhibiting ROS-mediated mitophagy and inflammation via Nrf2 activation. Ecotoxicol Environ Saf 2023;268:115717.
[29] Li Y, Feng YF, Liu XT, et al. Songorine promotes cardiac mitochondrial biogenesis via Nrf2 induction during sepsis. Redox Biol 2020;38:101771.
[30] Ajoolabady A, Chiong M, Lavandero S, et al. Mitophagy in cardiovascular diseases: molecular mechanisms, pathogenesis, and treatment. Trends Mol Med 2022;28(10):836-849.
[31] Wu D, Zhang H, Li F, et al. Resveratrol alleviates acute lung injury in mice by promoting Pink1/Parkin-related mitophagy and inhibiting NLRP3 inflammasome activation. Biochim Biophys Acta Gen Subj 2024;1868(7):130612
[32] Zhang Y, Yang X, Ge X, et al. Puerarin attenuates neurological deficits via Bcl-2/Bax/cleaved caspase-3 and Sirt3/SOD2 apoptotic pathways in subarachnoid hemorrhage mice. Biomed Pharmacother 2019;109:726-733.
[33] Jin L, Chen Y, Cheng D, et al. YAP inhibits autophagy and promotes progression of colorectal cancer via upregulating Bcl-2 expression. Cell Death Dis 2021;12(5):457.
[34] Puthalakath H, Strasser A. Keeping killers on a tight leash: transcriptional and post-translational control of the pro-apoptotic activity of BH3-only proteins. Cell Death Differ 2002;9(5):505-512.
[35] Hollville E, Carroll RG, Cullen SP, et al. Bcl-2 family proteins participate in mitochondrial quality control by regulating Parkin/PINK1-dependent mitophagy. Mol Cell 2014;55(3):451-466.
[36] Zhang Z, Chen Z, Liu R, et al. Bcl-2 Proteins

Regulate Mitophagy in Lipopolysaccharide-Induced Acute Lung Injury via PINK1/Parkin Signaling Pathway. Oxid Med Cell Longev 2020;2020:6579696.

[37] Lampert MA, Orogo AM, Najor RH, et al. BNIP3L/NIX and FUNDC1-mediated mitophagy is required for mitochondrial network remodeling during cardiac progenitor cell differentiation. Autophagy 2019;15(7):1182-1198.

[38] Li K, Xia X, Tong Y. Multiple roles of mitochondrial autophagy receptor FUNDC1 in mitochondrial events and kidney disease. Front Cell Dev Biol 2024;12:1453365.

[39] Liu L, Feng D, Chen G, et al. Mitochondrial outer-membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells. Nat Cell Biol 2012;14(2):177-185.

[40] Li G, Li J, Shao R, et al. FUNDC1: A Promising Mitophagy Regulator at the Mitochondria-Associated Membrane for Cardiovascular Diseases. Front Cell Dev Biol 2021;9:788634.

[41] Pan P, Chen J, Liu X, et al. FUNDC1 Regulates Autophagy by Inhibiting ROS-NLRP3 Signaling to Avoid Apoptosis in the Lung in a Lipopolysaccharide-Induced Mouse Model. Shock (Augusta, Ga.) 2021;56(5):773-781.

[42] Zhang Y, Liu D, Hu H, et al. HIF-1α/BNIP3 signaling pathway-induced-autophagy plays protective role during myocardial ischemia-reperfusion injury. Biomed Pharmacother 2019;120:109464.

[43] Liu KE, Frazier WA. Phosphorylation of the BNIP3 C-Terminus Inhibits Mitochondrial Damage and Cell Death without Blocking Autophagy. PloS one 2015;10(6):e0129667.

[44] Jiang H, Huang Y, Xu H, et al. Inhibition of hypoxia inducible factor-1α ameliorates lung injury induced by trauma and hemorrhagic shock in rats. Acta Pharmacol Sin 2012;33(5):635-643.

[45] Tang X, Zhong L, Tian X, et al. RUNX1 promotes mitophagy and alleviates pulmonary inflammation during acute lung injury. Signal Transduct Target Ther 2023;8(1):288.

[46] Mahn A, Castillo A. Potential of Sulforaphane as a Natural Immune System Enhancer: A Review. Molecules 2021;26(3):752.

[47] Sun Z, Niu Z, Wu S, et al. Protective mechanism of sulforaphane in Nrf2 and anti-lung injury in ARDS rabbits. Exp Ther Med 2018;15(6):4911-4915.

[48] East D, Fagiani F, Crosby J, et al. PMI: a ΔΨm independent pharmacological regulator of mitophagy. Chem Biol 2014;21(11):1585-1596.

[49] Georgakopoulos ND, Frison M, Alvarez MS, et al. Reversible Keap1 inhibitors are preferential pharmacological tools to modulate cellular mitophagy. Sci Rep 2017;7(1):10303.

[50] Conte E, Fagone E, Fruciano M, et al. Anti-inflammatory and antifibrotic effects of resveratrol in the lung. Histol Histopathol 2014;30(5):523-529.

[51] Kang RR, Sun Q, Chen KG, et al. Resveratrol prevents benzo(a)pyrene-induced disruption of mitochondrial homeostasis via the AMPK signaling pathway in primary cultured neurons. Environ Pollut 2020;265(Pt A):115331.

[52] Pal HC, Pearlman RL, Afaq F. Fisetin and Its Role in Chronic Diseases. Adv Exp Med Biol 2016;928:213-244.

[53] Jia S, Xu X, Zhou S, et al. Fisetin induces autophagy in pancreatic cancer cells via endoplasmic reticulum stress- and mitochondrial stress-dependent pathways. Cell Death Dis 2019;10(2):142.

[54] Ma Z, Tang P, Dong W, et al. SIRT1 alleviates IL-1β induced nucleus pulposus cells pyroptosis via mitophagy in intervertebral disc degeneration. Int Immunopharmacol 2022;107:108671.

[55] Jiang T, Liu E, Li Z, et al. SIRT1-Rab7 axis attenuates NLRP3 and STING activation through late endosomal-dependent mitophagy during sepsis-induced acute lung injury. Int J Surg 2024;110(5):2649-2668.

[56] Reiter RJ, Tan DX, Rosales-Corral S, et al. Mitochondria: Central Organelles for Melatonin's Antioxidant and Anti-Aging Actions. Molecules 2018;23(2):509.

[57] Zeng L, He J, Liu C, et al. Melatonin Attenuates Ropivacaine-Induced Apoptosis by Inhibiting Excessive Mitophagy Through the Parkin/PINK1 Pathway in PC12 and HT22 Cells. Inflammation 2022;45(2):725-738.

[58] Shen YQ, Guerra-Librero A, Fernandez-Gil BI, et al. Combination of melatonin and rapamycin for head and neck cancer therapy: Suppression of AKT/mTOR pathway activation, and activation of mitophagy and apoptosis via mitochondrial function regulation. J Pineal Res 2017;64(3).

[59] Kang JY, Xu MM, Sun Y, et al. Melatonin attenuates LPS-induced pyroptosis in acute lung injury by inhibiting NLRP3-GSDMD pathway via activating Nrf2/HO-1 signaling axis. Int Immunopharmacol 2022;109:108782.

[60] Manzanares W, Moreira E, Hardy G. Pharmaconutrition revisited for critically ill patients with coronavirus disease 2019 (COVID-19): Does selenium have a place? Nutrition 2020;81:110989.

[61] Mahmoodpoor A, Hamishehkar H, Shadvar K, et al. The Effect of Intravenous Selenium on Oxidative Stress in Critically Ill Patients with Acute Respiratory Distress Syndrome. Immunol Invest 2018;48(2):147-159.

[62] Kočan L, Vašková J, Vaško L, et al. Selenium

adjuvant therapy in septic patients selected according to Carrico index. Clin Biochem 2014;47(15):44-50.

[63] Hafizi M, Kalanaky S, Fakharzadeh S, et al. Beneficial effects of the combination of BCc1 and Hep-S nanochelating-based medicines on IL-6 in hospitalized moderate COVID-19 adult patients: a randomized, double-blind, placebo-controlled clinical trial. Trials 2023;24(1):720.

[64] Mahmoodpoor A, Hamishehkar H, Shadvar K, et al. The Effect of Intravenous Selenium on Oxidative Stress in Critically Ill Patients with Acute Respiratory Distress Syndrome. Immunol Invest 2019;48(2):147-159.

[65] Hay E, Lucariello A, Contieri M, et al. Therapeutic effects of turmeric in several diseases: An overview. Chem Biol Interact 2019;310:108729.

[66] Carling D. AMPK signalling in health and disease. Curr Opin Cell Biol 2017;45:31-37.

[67] Wang X, Jia J. Magnolol improves Alzheimer's disease-like pathologies and cognitive decline by promoting autophagy through activation of the AMPK/mTOR/ULK1 pathway. Biomed Pharmacother 2023;161:114473.

[68] Zheng Q, Liu H, Zhang H, et al. Ameliorating Mitochondrial Dysfunction of Neurons by Biomimetic Targeting Nanoparticles Mediated Mitochondrial Biogenesis to Boost the Therapy of Parkinson's Disease. Adv Sci (Weinh) 2023;10(22):e2300758.

[69] Li C, Ai G, Wang Y, et al. Oxyberberine, a novel gut microbiota-mediated metabolite of berberine, possesses superior anti-colitis effect: Impact on intestinal epithelial barrier, gut microbiota profile and TLR4-MyD88-NF-κB pathway. Pharmacol Res 2019;152:104603.

[70] Li CL, Tan LH, Wang YF, et al. Comparison of anti-inflammatory effects of berberine, and its natural oxidative and reduced derivatives from Rhizoma Coptidis in vitro and in vivo. Phytomedicine 2019;52:272-283

[71] Li X, Bai Y, Ma Y, et al. Ameliorating effects of berberine on sepsis-associated lung inflammation induced by lipopolysaccharide: molecular mechanisms and preclinical evidence. Pharmacol Rep 2023;75(4):805-816.

[72] Liu H, You L, Wu J, et al. Berberine suppresses influenza virus-triggered NLRP3 inflammasome activation in macrophages by inducing mitophagy and decreasing mitochondrial ROS. J Leukoc Biol 2020;108(1):253-266.

[73] Zhao R, Wang B, Wang D, et al. Oxyberberine Prevented Lipopolysaccharide-Induced Acute Lung Injury through Inhibition of Mitophagy. Oxid Med Cell Longev 2021;2021:6675264.

[74] Khater SI, Almanaa TN, Fattah DMA, et al. Liposome-Encapsulated Berberine Alleviates Liver Injury in Type 2 Diabetes via Promoting AMPK/mTOR-Mediated Autophagy and Reducing ER Stress: Morphometric and Immunohistochemical Scoring. Antioxidants (Basel) 2023;12(6):1220.