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REVIEW

# PANoptosis in Sepsis: A Central Role and Emerging Therapeutic Target

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**Abstract:** The pathogenesis of sepsis is intricately linked to regulated cell death. As a novel form of regulated cell death, PANoptosis plays a critical role in driving the inflammatory response, impairing immune cell function, and contributing to multi-organ dysfunction in sepsis. This review explores the molecular mechanisms underlying PANoptosis and its involvement in sepsis. By activating multiple pathways, PANoptosis promotes the release of inflammatory cytokines, triggering a cytokine storm that disrupts immune cell homeostasis and exacerbates organ damage. Emerging therapeutic strategies targeting PANoptosis, including chemotherapeutic agents and herbal remedies, are showing potential for clinical application. The concept of targeting PANoptosis offers a promising avenue for developing innovative treatments for sepsis.

**Keywords:** PANoptosis, regulated cell death, sepsis, therapeutic target

## Introduction

Sepsis is a life-threatening condition characterized by organ dysfunction caused by a dysregulated host response to infection. The 2016 Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) clarified this concept, highlighting the critical role of infection as a trigger and the importance of the host's dysregulated response.[1] Sepsis remains a major global health challenge, with millions of cases reported annually. It is estimated that approximately 31.5 million cases of sepsis occur worldwide each year, leading to around 5.3 million deaths. Even survivors often experience long-term health complications.[2] The incidence and mortality rates vary by region. In low-income countries, sepsis poses a heavier burden due to the high prevalence of infectious diseases such as malaria, Human Immunodeficiency Virus (HIV), and dengue fever. In high-income countries, despite advanced healthcare systems, sepsis remains a leading cause of mortality.[2,3]

Sepsis affects multiple organ systems, leading to a wide range of clinical manifestations. Patients with sepsis often experience arterial hypotension, which results from a combination of factors such as reduced blood volume, vascular tone loss, and myocardial suppression.[4] Hypotension reduces cardiac output, leading to inadequate tissue perfusion and impaired organ function. Sepsis-induced myocardial injury manifests as decreased myocardial contractility and diastolic dysfunction.[5,6] Increased apoptosis and necroptosis of cardiomyocytes are key contributors to cardiac dysfunction, likely driven by inflammatory cytokines, oxidative stress, and mitochondrial dysfunction.[7,8] Respiratory abnormalities such as tachypnea and hypoxemia are also common in sepsis. Pulmonary inflammation damages the alveolar-capillary membrane, disrupting gas exchange and causing respiratory distress. Severe cases may develop acute respiratory distress syndrome (ARDS), severely impairing lung ventilation and gas exchange, often requiring mechanical ventilation to sustain life.[9,10] Sepsis frequently causes kidney damage, presenting as oliguria or anuria, along with elevated serum creatinine and blood urea nitrogen levels. Acute kidney injury (AKI) is a common complication, driven by inflammation, oxidative stress, apoptosis, and necrosis. AKI not only impairs renal excretory function but also exacerbates systemic

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inflammation and multi-organ dysfunction, significantly increasing mortality.[11–13] Beyond these, sepsis impacts the nervous, hematologic, and hepatic systems, contributing to its complex and multifaceted clinical presentation.[14–17] In sepsis, various forms of regulated cell death (RCD)—including apoptosis, necroptosis, and pyroptosis—play critical roles in disease progression.[18] PANoptosis, a recently proposed concept that integrates apoptosis, necroptosis, and pyroptosis, has also been found to be closely associated with sepsis. Apoptosis, a classical RCD pathway, is characterized by membrane blebbing, DNA fragmentation, and a lack of inflammatory response.[19] Pyroptosis, on the other hand, involves inflammasome activation and membrane pore formation, leading to the release of inflammatory cytokines.[20] Necroptosis features molecules like Receptor-Interacting Protein Kinase 1 (RIPK1), Receptor-Interacting Protein Kinase 3 (RIPK3), and Mixed Lineage Kinase Domain-Like Protein (MLKL), resulting in membrane rupture and inflammatory responses.[21] In contrast, PANoptosis represents a more intricate RCD pathway. It integrates key molecules from these pathways, such as inflammasome sensors, Caspase-8, RIPK1/3, and GSDMD, forming a multifunctional molecular platform known as the PANoptosome. This platform orchestrates the cell death process by regulating the interactions and cross-talk among these pathways.[22] The molecular mechanisms of PANoptosis are significantly more complex, involving not only the activation of individual pathways but also their dynamic interplay. This interplay allows for a more precise and adaptive regulation of cell death, highlighting the unique role of PANoptosis in cellular processes.

## Sepsis and Regulated Cell Death

RCD plays a critical role in the progression of sepsis. During the pathophysiology of sepsis, apoptosis is prevalent in various cell types, including lymphocytes, monocytes, neutrophils, endothelial cells, and epithelial cells.[23–26] Factors such as pathogen infection, inflammatory cytokine release, oxidative stress, and mitochondrial damage can activate apoptotic pathways. Apoptosis has a dual role in sepsis: moderate levels help eliminate infected and damaged cells, reducing pathogen replication and alleviating inflammation.[27] However, excessive apoptosis depletes cell populations, impairs immune function, increases infection risk, exacerbates tissue damage, and contributes to multi-organ dysfunction.[25,28] Necroptosis, a regulated form of cell death with necrotic characteristics, combines the programmed nature of apoptosis with necrosis-like morphology.[21,27] In sepsis, necroptosis pathways are activated, leading to cell death. Studies suggest that inhibiting necroptosis can reduce inflammation, limit cell death, improve organ function, and lower mortality, making it a potential therapeutic target.[29] Pyroptosis, an inflammatory form of RCD, is mediated by inflammatory caspases (caspase-1, −4, −5, and −11).[27] In sepsis, pathogen infections induce inflammasome assembly, activating these caspases to cleave substrates such as Gasdermin D (GSDMD) and Gasdermin D (GSDME). This results in cell swelling, rupture, and the release of inflammatory cytokines and intracellular contents, triggering inflammatory responses. While moderate pyroptosis helps control infection and clear pathogens, excessive pyroptosis leads to uncontrolled inflammation, worsening tissue damage.[30,31] Pyroptosis is also closely linked to sepsis-associated organ dysfunction, including injuries to the kidneys, liver, and lungs.[32]

Sepsis involves additional forms of cell death, such as autophagy and ferroptosis, which also play significant roles in its progression.[30,33] Research has shown that cuproptosis is associated with the onset of septic cardiomyopathy and immune infiltration.[34] The pathological process of sepsis promotes cuproptosis in cardiomyocytes, resulting in cardiac toxicity.[35] Cuproptosis also plays a critical role in the human immune response, with several key genes closely related to the prognosis of sepsis patients.[36,37] Immune cells such as macrophages, T cells, and B cells undergo ferroptosis, which leads to their reduced number and function. Ferroptotic cells can be recognized by immune cells, triggering a cascade of inflammatory or specific immune responses.[38] Ferroptosis also contributes to septic myocardial injury. Inhibiting ferroptosis can significantly alleviate LPS-induced cardiac damage and inflammation in mice.[39] It has been confirmed that ferroptosis plays a key role in LPS-induced acute lung injury.[40] Ferroptosis is also critically involved in diseases such as acute kidney injury and sepsis-associated encephalopathy (SAE).[41] Autophagy, closely linked to inflammation and immunity, provides protective effects in sepsis by negatively regulating abnormal macrophage activation, modulating macrophage polarization, reducing inflammasome activation, and limiting the release of inflammatory cytokines.[42,43] Autophagy supports antigen presentation and T cell homeostasis, influencing T cell function and polarization.[44] However, excessive autophagy may lead to autophagic death of macrophages, exacerbating the inflammatory response.[42] Some studies have shown that autophagy also contributes to mitochondrial damage induced by sepsis, potentially resulting in

harmful effects on the body.[45] Excessive autophagy increases regulated cell death.[46] Enhanced autophagy in pulmonary endothelial cells can lead to increased vascular permeability, worsening septic lung injury.[47] Understanding the mechanisms of RCD in sepsis is essential for identifying novel therapeutic targets.

## PANoptosis and the Maintenance of Homeostasis

PANoptosis is a recently identified form of RCD, first proposed by Malireddi et al in 2019.[48] This concept emerged from extensive research into cell death mechanisms, particularly the crosstalk between apoptosis, pyroptosis, and necroptosis (Figure 1). These three RCD pathways are not entirely independent but form an intricate network of interactions and regulatory mechanisms.[49] The hallmark of PANoptosis is its involvement of key molecular components from these three pathways while defying full classification under any single one. Its introduction marks a significant breakthrough in understanding cell death mechanisms, establishing a new framework to study the role of cell death in diseases. Recent studies have demonstrated the crucial role of PANoptosis in the progression of various diseases, including infections, inflammation, and cancer. This emerging concept offers novel perspectives for exploring the impact of cell death on disease mechanisms and potential therapeutic interventions.

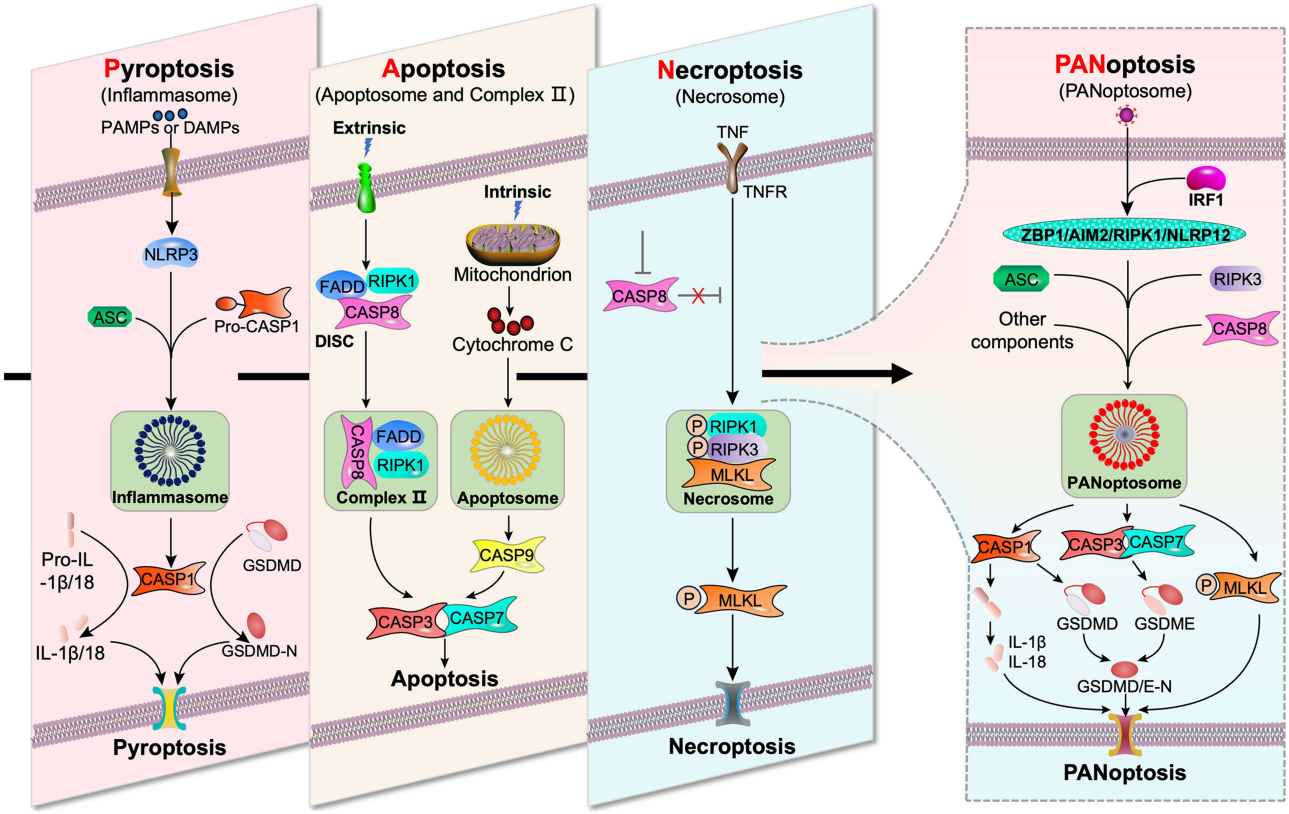


**Figure 1** Molecular Mechanisms of Pyroptosis, Apoptosis, Necroptosis, and PANoptosis. (1) Pyroptosis: Pyroptosis involves inflammasome formation, typically the Nucleotide-Binding Domain, Leucine-Rich Repeat, and Pyrin Domain Containing Protein (NLRP) 3 inflammasome comprising the NLRP3 sensor, Apoptosis-Associated Speck-Like Protein Containing a CARD (ASC) adaptor, and Pro-Caspase-1. Activated inflammasomes cleave Caspase-1, which then processes Interleukin (IL)-1β/18 and Gasdermin D (GSDMD). The N-terminal fragment of GSDMD oligomerizes on the plasma membrane, forming pores that execute cell death. (2) Apoptosis: Apoptosis operates via extrinsic and intrinsic pathways: In the extrinsic pathway, external stimuli activate death receptors, forming the Fas-Associated protein with Death Domain (FADD)/Caspase-8/Receptor-Interacting Protein Kinase (RIPK1) complex. This activates Caspase-8, which cleaves Caspase-3/-7 to execute cell death. In the intrinsic pathway, mitochondrial outer membrane permeability changes, releasing cytochrome C. This promotes apoptosome formation, activating Caspase-9, which subsequently cleaves Caspase-3/-7 to execute cell death. (3) Necroptosis: When Caspase-8 is absent or inhibited, necroptosis occurs. Tumor Necrosis Factor-alpha (TNF-α) binding to its receptor forms the necrosome, containing RIPK1 and RIPK3. Phosphorylated RIPK1/RIPK3 recruits and phosphorylates Mixed Lineage Kinase Domain-Like Protein (MLKL), which disrupts membrane integrity to induce cell death. (4) PANoptosis: PANoptosis is mediated by the PANoptosome, integrating components from other cell death pathways. Pathogens activate sensors such as Z-DNA binding protein 1 (ZBP1), AIM2, RIPK1, or NLRP12, forming a PANoptosome complex that includes inflammasome components (eg, ASC), complex II elements (eg, Caspase-8), and necrosome components (eg, RIPK3). IRF1 further facilitates this process. The PANoptosome induces cell death by activating CASP1 (cleaving GSDMD and IL-1β/18), Caspase-3/-7 (cleaving Gasdermin E), and phosphorylating MLKL.


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PANoptosis plays a critical role in maintaining bodily homeostasis by eliminating pathogen-infected cells and triggering immune responses through the release of inflammatory cytokines, thereby protecting the host from infections. For instance, during viral infections, Z-DNA binding protein 1 (ZBP1) detects viral RNA and activates the PANoptosome, leading to the death of infected cells and limiting viral replication and spread.[50] PANoptosis also contributes to the removal of damaged, aging, or cancerous cells, essential for tissue health and tumor suppression.[51] In the context of disease, PANoptosis plays a dual role. It is involved in various pathological processes, including infectious diseases, inflammatory disorders, cancer, cardiovascular conditions, and neurodegenerative diseases. For example, in infectious diseases, pathogens such as bacteria, viruses, and fungi can induce PANoptosis, limiting pathogen spread. However, excessive PANoptosis can exacerbate tissue damage and inflammation, worsening disease symptoms.[49,52] The process of PANoptosis also plays a crucial role in promoting intervertebral disc degeneration.[53] In inflammatory diseases, PANoptosis-mediated immune cell death releases inflammatory cytokines, intensifying the inflammatory response.[54] Simultaneously, it regulates immune cell activity and function, influencing immune modulation during inflammation.[55,56] In cancer, PANoptosis also exhibits dual effects. Targeting PANoptosis-related molecules can induce cancer cell death and inhibit tumor growth. However, cancer cells may exploit PANoptosis activation to evade immune surveillance and resist chemotherapy.[57]

# Molecular Mechanisms of PANoptosis

## PANoptosome

The PANoptosome is the central molecular platform for executing PANoptosis, enabling cells to initiate PANoptosis instead of a single "classical" RCD pathway. The assembly of the PANoptosome involves three main categories of proteins: (1) sensors for Pathogen-Associated Molecular Patterns (PAMPs) or Damage-Associated Molecular Patterns (DAMPs), such as ZBP1, Absent in Melanoma 2 (AIM2), and Nucleotide-Binding Domain, Leucine-Rich Repeat, and Pyrin Domain Containing Protein (NLRP) 3; (2) adaptor proteins, including Apoptosis-Associated Speck-Like Protein Containing a CARD (ASC) and Fas-Associated protein with Death Domain (FADD); and (3) catalytic effectors, such as RIPK1, RIPK3, Caspase-1, and Caspase-8.[52,58]

Several PANoptosomes have been identified, including ZBP1-PANoptosome, AIM2-PANoptosome, RIPK1-PANoptosome, and NLRP12-PANoptosome.[59–62] ZBP1 was the first PANoptosis sensor identified. It detects Z-DNA or Z-RNA during viral infections, triggering cell death signals. ZBP1 uses its Zα domain to bind the Receptor-Interacting Protein Homotypic Interaction Motif (RHIM) domain of RIPK3, facilitating PANoptosome assembly. AIM2 initiates PANoptosis by detecting cytosolic DNA fragments through its Hematopoietic Interferon-inducible Nuclear proteins with a 200-amino acid repeat (HIN200) domain. It recruits ASC, which activates Caspase-1, driving downstream cell death processes. RIPK1 acts as a central hub for PANoptosome formation and integrates cell death signals. It activates Caspase-8 via FADD to induce apoptosis or interacts with RIPK3 to drive necroptosis or pyroptosis, depending on the signaling context and molecular interactions. NLRP12 senses heme or PAMPs via its Leucine-Rich Repeat (LRR) domain and activates the Caspase-8/RIPK3 axis, assembling the PANoptosome and triggering inflammatory and cell death responses.[63] The PANoptosome represents a highly flexible and efficient cell death platform, orchestrated through the precise cooperation of key proteins. Its dynamic adaptability allows cells to respond to diverse stressors with tailored cell death mechanisms.

## Signaling Pathways of PANoptosis

The initiation of PANoptosis relies on a complex network of upstream signals. These networks detect PAMPs and DAMPs to activate multiple signaling pathways that induce cell death. Pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), nucleotide-binding oligomerization domain-like receptors (NLRs), and ZBP1, are key sensors for PANoptosis.[64,65] PRRs recognize viral RNA and other PAMPs, such as TLR7 detecting Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and RIG-I recognizing influenza virus (IAV) or hepatitis C virus (HCV) RNA.[65–70] The amplification of these signals often depends on type I interferon signaling pathways, which induce ZBP1 expression through the Janus Kinase (JAK)/Signal

Transducer and Activator of Transcription (STAT) pathway. ZBP1, in turn, recognizes viral RNA via its Zα domain, activating the Nucleotide-Binding Domain, Leucine-Rich Repeat, and NLRP3 inflammasome and triggering PANoptosis.[50] Cytokine signals, such as tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ), can also induce nitric oxide production via the JAK/STAT1/Interferon Regulatory Factor(IRF) 1 axis, activating the caspase-8/FADD complex and driving PANoptosis.[54] Additionally, TLRs directly activate NLRP3 and AIM2 inflammasomes and regulate other cell death signals, such as the Stimulator of Interferon Genes (STING) pathway, which promotes ZBP1 and AIM2 activation by inducing IRF3 expression.[71] The Transforming Growth Factor-β-Activated Kinase 1 (TAK1) signaling pathway plays a dual role in PANoptosis: it maintains NLRP3 in a resting state but triggers RIPK1-dependent or independent PANoptosis when inhibited or absent.[48,72,73] Oxidative stress signals also link mitochondrial dysfunction to PANoptosis by activating the NLRP3 inflammasome.[74–76] Through these interconnected networks, molecules and signaling pathways collectively integrate upstream signals to coordinate the induction of PANoptosis.

At the downstream level, PANoptosis integrates and executes multiple RCD pathways through the coordinated activation of various signaling cascades. The caspase signaling pathway plays a pivotal role, with Caspase-1, Caspase-8, and effector caspases (Caspase-3/7) being key mediators. These caspases not only activate inflammasomes but also directly execute apoptosis and necroptosis.[77] The RIPK1/RIPK3/MLKL pathway, central to necroptosis, involves the formation of the necrosome complex through RIPK1-RIPK3 interactions. This activates MLKL, which oligomerizes upon phosphorylation, forming membrane pores that disrupt membrane integrity and lead to cell death.[78] Pyroptosis is mediated by inflammasomes such as NLRP3 and AIM2, which detect viral invasion and activate Caspase-1. Caspase-1 cleaves GSDMD, whose pore formation causes cell lysis while releasing pro-inflammatory cytokines like IL-1β and IL-18.[79,80] A defining feature of PANoptosis is the crosstalk between these pathways. For instance, the ZBP1-PANoptosome complex detects viral RNA and recruits the NLRP3 inflammasome to activate Caspase-1. Simultaneously, it triggers the RIPK1/RIPK3 axis to activate Caspase-8, integrating pyroptosis, necroptosis, and apoptosis into a unified response.[81] Additionally, PANoptosis relies on key effector molecules such as GSDMs and MLKL, which execute membrane disruption in pyroptosis and necroptosis, respectively, ultimately resulting in cell death. These interwoven signaling pathways form a tightly coordinated network, regulated through platforms like the PANoptosome, ensuring efficient execution of PANoptosis.

# PANoptosis in Sepsis

## PANoptosis Related Genes and Sepsis

Research on PANoptosis-related genes (PRGs) in sepsis has identified 16 genes that determine sepsis subtypes. By examining molecular clustering and prognostic features based on PANoptosis, the immune landscape and prognosis of sepsis patients can be predicted. It was also found that PRGs exhibit different expression patterns in various immune cells.[82] One study confirmed that PANoptosis-related genes show significant predictive power for sepsis, with the differential expression of these genes being strongly associated with sepsis prognosis and leading to organ dysfunction.[83] Another study found that PRGs are highly useful in the early detection of pediatric septic shock. This is crucial for understanding the role of immune cell infiltration in the pathophysiology of pediatric septic shock, though further confirmation through basic and clinical research is needed.[84] A diagnostic prediction model based on PRGs was able to effectively distinguish between septic ARDS patients and general sepsis patients. NDRG1 was identified as a potential therapeutic target, and subsequent research in a sepsis mouse model confirmed that inhibiting NDRG1 could alleviate lung injury.[85] A study combining bioinformatics analysis and experimental validation suggested that four PANoptosis genes—CD14, GSDMD, IL-1β, and Fas—are highly involved in the immune response and multiple inflammatory pathways during sepsis-induced acute lung injury.[86] In addition to studies on the association between PANoptosis-related genes and sepsis, PANoptosis is also linked to sepsis through its role in exacerbating inflammatory responses, impairing immune function, and contributing to organ dysfunction (Table 1).

**Table 1** Studies Related to PANoptosis in Sepsis

| Disease | Result | References |
|---|---|---|
| Sepsis | Prediction of the Immune Landscape and Prognosis in Sepsis Patients Based on Molecular Clustering and Prognostic Features of PANoptosis | [82] |
| Sepsis | The differential expression of PANoptosis-related genes (PRGs) is significantly associated with the prognosis of sepsis | [83] |
| Sepsis | PANoptosis-related genes play a crucial role in the early detection and diagnosis of pediatric septic shock patients. | [84] |
| Sepsis | Constructing a diagnostic prediction model based on PRGs can effectively differentiate between sepsis-associated ARDS patients and non-ARDS sepsis patients, while also identifying potential therapeutic targets. | [85] |
| Sepsis | Bioinformatics analysis and experimental validation studies indicate that four PANoptosis feature genes are highly involved in the immune response and multiple inflammatory pathways of sepsis-induced ALI. | [86] |
| Sepsis | High expression levels of S100A8/A9 induce mitochondrial dysfunction by downregulating Nrf1 expression, activating PANoptosis in endothelial cells during sepsis. | [87] |
| Sepsis | Lactic acidosis promotes the release of macrophage-derived eCIRP, which mediates ZBP1-dependent PANoptosis in pulmonary endothelial cells during sepsis. | [88] |
| Sepsis | Piezo1 plays a crucial role in calcium-mediated PANoptosis in Sepsis-induced cardiomyopathy. The inhibition of Piezo1 diminishes LPS-induced PANoptosis by limiting calcium release in cardiomyocytes. | [89] |
| Sepsis | Dachaihu Decoction alleviates sepsis-induced Acute Lung Injury by inhibiting PANoptosis through the regulation of the PI3K/AKT/NF-κB pathway. | [90] |
| Sepsis | Inhibition of cIAP1/2 leads to the upregulation of PANoptosis, including apoptosis, necroptosis, and pyroptosis, in sepsis. | [91] |
| Sepsis | The PANoptosis pathway regulates the oligomerization of neural injury-induced protein 1. Inhibiting the molecule can effectively reduce platelet activation and membrane rupture, thereby suppressing the platelet cascade and contributing to anti-thrombosis and anti-DIC effects in sepsis. | [92] |
| Sepsis | Platelets in sepsis patients undergo PANoptosis, and Myricetin mitigates platelet PANoptosis, which can delay the onset of disseminated intravascular coagulation. | [93] |
| Sepsis | The mechanisms linking PANoptosis and other forms of cell death not only lead to cell death but also increase vascular permeability, disrupt tissue integrity, and recruit inflammatory cells, exacerbating septic lung injury. | [94] |
| Sepsis | MiR-29a-3p can inhibit PANoptosis in alveolar epithelial cells, alleviating acute lung injury. | [95] |
| Sepsis | Dachengqi Decoction Dispensing Granule can suppress excessive inflammation and PANoptosis, thereby alleviating LPS-induced acute lung injury. | [96] |
| Sepsis | TLR9 activates PANoptosis through the p38 MAPK signaling pathway, leading to an increased incidence of sepsis-associated encephalopathy and higher mortality. | [97] |
| Sepsis | PANoptosis in tubular epithelial cells plays a key role in septic acute kidney injury. Inhibiting AIM2-mediated PANoptosis can alleviate kidney injury caused by sepsis. | [98] |
| Sepsis | Echinacea polyphenols inhibit the PANoptosis pathway, improving acute lung injury induced by LPS. | [99] |
| Sepsis | Ursodeoxycholic acid alleviates sepsis-induced lung injury by suppressing PANoptosis through STING pathway inhibition. | [100] |
| Sepsis | In sepsis, immune cells, including T lymphocytes, B lymphocytes, monocytes, and macrophages, exhibit significant reductions in either quantity or function due to PANoptosis-driven impairment. | [54] |
| Sepsis | In sepsis-induced cardiomyopathy, activation of the PANoptosis drives cardiomyocyte loss, impairing cardiac function. XiaoChaiHu Decoction mitigates this pathological process by suppressing PANoptosis, thereby ameliorating sepsis-associated myocardial injury. | [101] |

## Effects of PANoptosis on Inflammatory Responses

PANoptosis triggers the release of inflammatory cytokines through multiple mechanisms, leading to inflammatory storms. Under conditions of infection or cellular stress, intracellular PRRs, such as ZBP1 and NOD-like receptor family CARD domain-containing protein 4 (NLRC4), detect PAMPs or DAMPs. This activates inflammasomes, including NLRP3, which leads to the autocleavage and activation of Caspase-1. Activated Caspase-1 catalyzes the maturation and secretion of interleukin (IL)-1β and IL-18 while inducing GSDMD cleavage to form membrane pores that drive pyroptotic cell death.[81,102] These inflammatory cytokines amplify the local and systemic inflammatory responses, playing a significant role in conditions such as infections, trauma, and autoimmune diseases.[103] Second, the combined action of TNF-α and IFN-γ has been shown to induce PANoptosis by activating the IRF1 and nitric oxide synthase 2 (NOS2) axis. This triggers the cleavage of GSDM family members, including GSDMD and GSDME, intensifying cell death and cytokine release.[54] Additionally, the necroptosis pathway mediated by RIPK1/RIPK3 results in the phosphorylation and activation of MLKL. Activated MLKL disrupts membrane integrity by forming pores, and releasing cellular contents, including inflammatory cytokines.[104] Caspase-8, apart from its role in apoptosis, also contributes to pyroptosis and necroptosis, influencing the production and release of inflammatory cytokines through its interactions with other apoptosis-related proteins.[21,105] The excessive production of these inflammatory cytokines not only exacerbates local inflammatory responses but can also spread systemically, resulting in a full-scale inflammatory storm.

PANoptosis-induced activation of inflammasome and necroptosis leads to the release of inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which are elevated in the serum of sepsis patients.[106] These cytokines amplify inflammation, exacerbate tissue damage, and create a vicious cycle. Excessive production of inflammatory cytokines such as IL-1β, IL-6, and TNF-α during a cytokine storm not only directly damages tissues but also disrupts vascular barrier function. These cytokines activate endothelial cells, increase vascular permeability, and promote thrombosis, leading to severe complications like pulmonary edema and ARDS.[107] Additionally, they activate immune cells, particularly neutrophils, which release large amounts of reactive oxygen species (ROS) and neutrophil extracellular traps (NETs), further exacerbating tissue damage.[108,109] Research has demonstrated the critical role of ZBP1, a key component of the PANoptosis in sepsis.[110] The activation of PANoptosis leads to the release of inflammatory cytokines, contributing to AKI and exacerbating renal dysfunction.[98,111] PANoptosis also drives acute lung injury (ALI) through pro-inflammatory pathways and inhibition of PANoptosis has been shown to alleviate ALI symptoms.[94–96,99,100] Moreover, PANoptosis has been implicated in sepsis-associated intestinal dysfunction, myocardial suppression, liver dysfunction, and the development of multiple organ dysfunction syndrome (MODS), significantly increasing mortality in sepsis patients.[54,97,101,111] In addition to pro-inflammatory cytokines, PANoptosis alters the secretion of anti-inflammatory cytokines. IL-10 and Transforming Growth Factor-beta (TGF-β) are known for their immunosuppressive and anti-inflammatory roles. Increased TGF-β expression during PANoptosis in gastric cancer, indicates the complexity of this process.[112] Understanding the mechanisms of PANoptosis and its role in cytokine storms is crucial for developing effective therapeutic strategies to mitigate the severe outcomes of sepsis.

## Effects of PANoptosis on Immune Cells

PANoptosis occurs in various pathological conditions, including sepsis and autoimmune diseases, and is often associated with a reduction in the number of immune cells. For instance, in sepsis, the numbers and functions of immune cells such as T lymphocytes, B lymphocytes, monocytes, and macrophages are significantly diminished due to PANoptosis.[54] These cells are critical for immune responses and inflammation regulation, and their depletion impairs immune function, negatively affecting patient outcomes.[25,106] PANoptosis not only reduces the overall number of immune cells but also impacts their differentiation. In systemic lupus erythematosus (SLE), for example, regulatory T cells (Tregs) decrease, while effector T cells increase, leading to immune imbalance. CD8+ T cells, known for their cytotoxic activity, often exhibit dysfunction in SLE patients, increasing their susceptibility to infections.[113] Studies suggest that PANoptosis in T cells may contribute to the immune dysregulation seen in SLE.[114] Antigen-presenting cells (APCs), such as macrophages and dendritic cells (DCs), are also affected by PANoptosis. DC depletion due to PANoptosis impairs antigen uptake, processing, and presentation, hindering T cell activation and immune responses.[115] For example, DCs induce

cytokine production and PANoptosis while presenting cancer antigens to T cells.[116] In sepsis, DC numbers in peripheral blood are reduced, compromising their antigen-presenting function and impairing T cell proliferation and differentiation.[117,118] B cell subsets are also selectively depleted in sepsis, accompanied by selective Caspase-1, 3, 8 expression.[119] The Caspase family is known to be closely associated with PANoptosis.[105,120]

The mechanisms underlying immune cell exhaustion or dysfunction are complex and multifaceted. Dysregulation of cell death signaling pathways plays a crucial role. Under stimuli such as infection or tissue damage, excessive activation of inflammasomes increases the sensitivity of immune cells to PANoptosis, accelerating immune cell depletion.[54] Key molecules in the inflammasome signaling pathway, including NLRP3, ASC, and Caspase-1, are often implicated. Mutations or abnormal expression of these molecules can disrupt inflammasome pathways, impairing immune cell survival and function. For instance, NLRP3 mutations are strongly associated with autoimmune diseases and can lead to hyperactivation of inflammasomes, resulting in immune cell exhaustion.[52,121] Immune cell metabolic dysregulation is another contributing factor. The metabolic state of immune cells is essential for their function and survival. During PANoptosis, immune cell energy metabolism may become disrupted, leading to reduced Adenosine Triphosphate (ATP) production and mitochondrial dysfunction.[74,75,122] As the primary energy source for cellular activities, ATP depletion affects immune cell proliferation, differentiation, and functionality. Mitochondrial dysfunction further exacerbates the situation by increasing ROS production, which damages cellular structures and functions. PANoptosis may also impact the synthesis and breakdown of metabolites such as amino acids and nucleotides, which are critical for protein synthesis, DNA replication, and repair.[123,124] Dysregulation of these processes can impair immune cell functions and promote exhaustion. In addition, changes in the immune microenvironment play a significant role. PANoptosis-induced cytokine storms result in the excessive release of inflammatory cytokines, altering the immune cell microenvironment.[54] This suppresses immune cell proliferation and differentiation while accelerating exhaustion.[125] PANoptosis may also lead to immune cell exhaustion, such as in T cells, B cells, and macrophages, thereby affecting their interactions. Immune cell interactions are crucial for maintaining immune homeostasis, and their disruption can lead to functional impairment and exhaustion.

## PANoptosis in Organ Dysfunction

In addition to contributing to organ damage through cytokine storms, PANoptosis leads to multi-organ dysfunction via other complex mechanisms (Figure 2). In cardiomyocytes, PANoptosis is activated by PRRs such as ZBP1, which detect

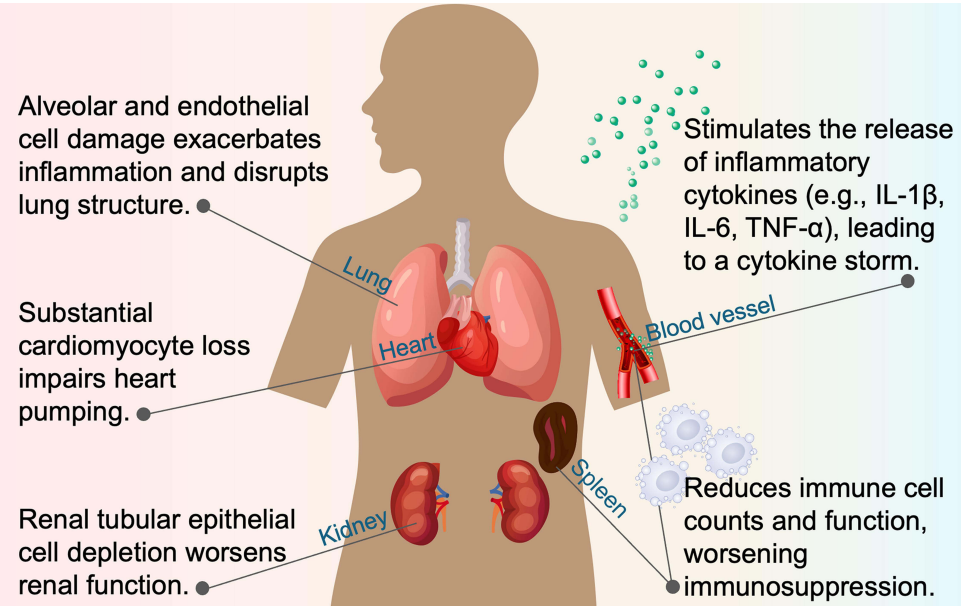


**Figure 2** The immunogenic effects of PANoptosis and its role in sepsis. In sepsis, PANoptosis plays a critical role. It triggers an inflammatory cytokine storm, leading to the massive release of inflammatory factors such as IL-1β, IL-6, and TNF-α into the peripheral blood. It also causes a significant reduction in the number of immune cells in the peripheral blood and spleen, accompanied by functional impairment. Additionally, PANoptosis contributes to multi-organ dysfunction, with conditions such as myocardial depression, lung injury, and kidney injury being closely associated with its effects.

viral-derived Z-nucleic acids or endogenous nucleic acids. This triggers inflammatory cell death, reducing cardiomyocyte numbers and releasing pro-inflammatory mediators that exacerbate local inflammation and impair cardiac function.[101] In sepsis-induced ALI, PANoptosis is driven by the activation of ZBP1, RIPK1, NLRP3 inflammasomes, and STING pathways. This process induces metabolic dysfunction and oxidative stress, exacerbates inflammation and tissue damage, disrupts lung barrier integrity, increases vascular permeability, and leads to pulmonary edema, severely impairing gas exchange. Inhibition of PANoptosis with drugs can reduce inflammation and alleviate ALI.[94–96,99,100] PANoptosis also plays a critical role in AKI. In renal tubular epithelial cells, PANoptosis is primarily mediated by the AIM2-PANoptosome. The formation of the PANoptosome consisting of ZBP1, ASC, and RIPK1 was involved in the development of kidney injury.[98,111] Loss of tubular epithelial cells compromises tubular function, disrupting electrolyte balance and waste excretion, thereby exacerbating kidney failure. Studies have shown that PANoptosis plays a role in sepsis-associated encephalopathy. TLR9 activates PANoptosis through the p38 mitogen-activated protein kinase signaling pathway, leading to the progression of SAE and increased mortality.[97] In summary, PANoptosis significantly impacts organ function by inducing various forms of cell death in sepsis, ultimately worsening patient outcomes.

# Therapeutic Strategies Targeting PANoptosis

## Drug Development and Applications

Efforts to develop chemical drugs targeting key molecules or signaling pathways of PANoptosis are ongoing. Significant progress has been made in designing inhibitors for multiple pathways, reducing cell death.[126]

Several small-molecule compounds targeting RIPK1 and RIPK3 have been developed to inhibit necroptosis. Necrostatin and its derivatives (Necrostatin-3, Dimethyl Oxazolone, Necrostatin-4 Series) are specific RIPK1 inhibitors with significant effects in necroptotic diseases and inflammatory conditions.[127–131] Other RIPK1 inhibitors include Sunitinib, Tozasertib, Butylated Hydroxyanisole, KW-244, and Benzoxazepine derivative GSK2982772.[127,132–135] Compounds such as GNF-7, GSK481, and ZJU-37 target both RIPK1 and RIPK3 to suppress necroptosis.[136–138] Molecules like GSK840, GSK843, GSK872, and AZD5423 regulate the RIPK3/MLKL pathway, further expanding the drug repertoire for necroptosis modulation.[139,140] Disulfiram, Dimethyl fumarate (DMF), necrosulfonamide (NSA), and Bioorthogonally ACtivatable Base editor target GSDMD and GSDME to suppress pyroptosis in diseases including sepsis.[94,141–144] VX765 and Acetyl-Tyrosine-Valine-Alanine-Aspartic Acid-Chloromethylketone (Ac-YVAD-CMK) inhibit Caspase-1 activity.[145,146] Additionally, Dickkopf-related protein 1 blocks GSDMD, Caspase-3, and RIPK3 to suppress PANoptosis.[147]

Drugs targeting PANoptosome components have shown promise in reducing cell death and inflammation. Melatonin suppresses PANoptosis by reducing the expression of key components such as NLRP3, ASC, caspase-1, GSDMD, RIPK1, RIPK3, and MLKL.[148] Cucurbitacin E modulates PANoptosis in Adenoid Cystic Carcinoma cells by interacting with the PANoptosome in a ZBP1-dependent manner.[149] Penehyclidine hydrochloride (PHC) decreases myocardial enzyme release and inhibits ZBP1 to alleviate PANoptosis.[150] MiR-29a-3p down-regulates ZBP1, GSDMD caspase-3, caspase-8, and MLKL Reduces alveolar epithelial cell PANoptosis and down-regulates inflammatory factor expression such as TNF-α, IL-1β and IL-6 in the lung.[95] OLT1177, MCC950, Tranilast, β-hydroxybutyrate, and 3,4-Methylenedioxy-β-Nitrostyrene (MNS) effectively inhibit NLRP3 inflammasome activation.[151–156] J114 disrupts NLRP3/AIM2 interactions with ASC, inhibiting inflammasome oligomerization.[157] Obovatol suppresses NLRP3, AIM2 inflammasome activation and mitochondrial ROS production.[158] AR1D1 interacts with ZBP1's Zα2 domain to block its interaction with RIPK3 to inhibit PANoptosis, and drugs targeting this target are worth developing.[159] Drugs targeting inflammatory signaling pathways also inhibit PANoptosis. TNF-α and IFN-γ neutralizing antibodies protect against sepsis and cytokine storm-related damage by preventing their synergistic effects.[125] Emricasan, a broad-spectrum caspase inhibitor, reduces cell death and protects tissues in multiple diseases.[160,161] Inhibitors of the JAK/STAT signaling pathway are considered potential therapeutic targets for PANoptosis. Among them, the JAK1/2 inhibitor Baricitinib, approved for Coronavirus Disease 2019 treatment, has demonstrated significant improvements in patient survival rates.[162,163] Myricetin alleviates disseminated intravascular coagulation (DIC) in sepsis by reducing platelet activation

and PANoptosis.[93] 1-Methoxy-5-Methylphenazinium Methyl Sulfate (MPMS) and DMF inhibit mitochondrial DNA oxidation and PANoptosome formation, mitigating sepsis-related pathology.[111]

While these drugs have shown efficacy in preclinical models, challenges remain in translating them into clinical use. Diseases may require tailored combination therapies to target specific pathways effectively. Long-term effects and potential interference with normal immune responses need careful evaluation. For example, while TNF-α and IFN-γ antibodies reduce inflammation, their immunosuppressive effects may increase infection risk. The NLRP3 inhibitor MCC950 has demonstrated strong anti-inflammatory effects across various inflammatory disease models, effectively reducing cell death.[152] Inhibitors targeting key PANoptosome components, such as Necrostatin, have shown therapeutic potential in models of ischemia-reperfusion injury, neurodegenerative disorders, and lung injury. Promising results in animal models may not directly apply to humans, necessitating rigorous clinical trials. In conclusion, although substantial progress has been made in PANoptosis-targeted drug development, further research is needed to optimize therapies for safe and effective clinical application.

## The Potential Role of Traditional Chinese Medicine

In recent years, traditional Chinese medicine (TCM) and its active components have shown significant potential in regulating PANoptosis due to their multi-target and multi-pathway mechanisms. For instance, XiaoChaiHu Decoction (XCHD) has demonstrated protective effects in sepsis-induced cardiomyopathy. Active components of XCHD have been identified through network pharmacology as potential targets for PANoptosis, significantly suppressing LPS-induced myocardial inflammatory cytokines (eg, IL-6, IL-1β, TNF-α) and reducing PANoptosis-related gene expression.[101] Similarly, ursodeoxycholic acid (UDCA) alleviates sepsis-induced ALI by blocking the STING pathway, accompanied by suppression of PANoptosis.[100] Other TCM components, such as baicalin and ginsenosides, exhibit antioxidant, anti-inflammatory, and anti-cell exhaustion effects. These properties help mitigate sepsis-induced tissue damage and improve prognosis. Baicalin blocks mitochondrial DNA release and oxidation, reducing intracellular ROS and mitochondrial ROS during PANoptosis. It also inhibits ZBP1-related PANoptosome assembly. In macrophages (Kupffer cells), PANoptotic signaling activation leads to liver damage in hemophagocytic lymphohistiocytosis (HLH) mouse models, which baicalin effectively mitigates by suppressing PANoptosis.[59] Ginsenosides suppress NLRP3 inflammasome activation, reduce ASC oligomerization, and downregulate apoptosis, inflammation, and oxidative stress in sepsis models.[164,165] Duhuo Jisheng Decoction may exert its effects in intervertebral disc degeneration by inhibiting the processes of apoptosis, necrosis, and pyroptosis.[166] Scutellarin, another TCM component, protects against systemic inflammation, multi-organ damage, and PANoptosis in HLH mice by inhibiting mitochondrial damage and mtROS generation.[122] Similarly, Shengxian Decoction (SXD) alleviates bleomycin-induced pulmonary fibrosis by inhibiting ZBP1-mediated PANoptosis. It targets pyroptosis, apoptosis, and necroptosis, effectively delaying or reversing early pathological changes.[167] Achyranthes aspera extract, which downregulates genes and pathways related to DNA damage, oxidative stress, inflammation, and PANoptosis, while promoting survival-related signaling.[168] Dachengqi Decoction (DDG), which inhibits excessive inflammation and PANoptosis, particularly upstream regulators like ZBP1 and RIPK1, to protect against LPS-induced ALI.[96] Cranberry-derived exosomes significantly suppress PANoptosis in mice by suppressing ROS release and cytokine expression.[169]

In summary, TCM offers a promising approach for regulating PANoptosis and mitigating inflammation-related diseases by targeting multiple pathways and key molecules.

# Conclusion and Future Perspectives

Sepsis, a critical global public health challenge, is closely linked to RCD. As an emerging form of RCD, PANoptosis plays a pivotal role in the pathophysiology of sepsis, influencing inflammation, immune cell function, and multi-organ damage. Targeting PANoptosis pathways has thus become a promising direction for developing new therapeutic strategies for sepsis. Both chemical drugs targeting key molecules or signaling pathways of PANoptosis and traditional Chinese medicines with multi-target, multi-pathway mechanisms have shown potential in regulating PANoptosis.

Despite these advances, the precise regulatory mechanisms of PANoptosis remain incompletely understood. Critical questions, such as the specific triggers of PANoptosis under different conditions, the assembly process of the PANoptosome, and its interactions with other cell death pathways, require further investigation. Further research is also needed to identify more precise molecular targets. The development of effective PANoptosis-targeted drugs is

another priority. Although some compounds have shown potential in inhibiting PANoptosis, their mechanisms of action remain unclear, and their safety and efficacy in clinical settings need validation. Future research should focus on identifying high-efficacy, highly specific PANoptosis inhibitors and evaluating their therapeutic potential through animal models and clinical trials. Additionally, integrating advanced technologies such as single-cell transcriptomics and bioinformatics will provide deeper insights into the role of PANoptosis in personalized medicine. This approach could pave the way for precision-targeted therapies, offering tailored treatment options for sepsis patients. In conclusion, as our understanding of PANoptosis continues to grow and innovative technologies advance, targeting PANoptosis holds the potential to significantly improve sepsis treatment outcomes and patient prognosis, offering hope in addressing this global health challenge.

## Abbreviations

Ac-YVAD-CMK, Acetyl-Tyrosine-Valine-Alanine-Aspartic Acid-Chloromethylketone; ALI, Acute Lung Injury; AIM2, Absent in Melanoma 2; APCs, Antigen-Presenting Cells; ARDS, Acute Respiratory Distress Syndrome; ASC, Apoptosis-Associated Speck-Like Protein Containing a CARD; ATP, Adenosine Triphosphate; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2-associated X protein; DCs, Dendritic Cells; DAMPs, Damage-Associated Molecular Patterns; DDG, Dachengqi Decoction; DMF, Dimethyl fumarate; DIC, Disseminated Intravascular Coagulation; FADD, Fas-Associated protein with Death Domain; GSDMD, Gasdermin D; GSDME, Gasdermin E; HIV, Human Immunodeficiency Virus; HLH, Hemophagocytic Lymphohistiocytosis; HIN200, Hematopoietic Interferon-inducible Nuclear proteins with a 200-amino acid repeat; IFN-γ, Interferon-gamma; IL, Interleukin; IRF, Interferon Regulatory Factor; IAV, Influenza Virus; JAK, Janus Kinase; LRR, Leucine-Rich Repeat; MLKL, Mixed Lineage Kinase Domain-Like Protein; MODS, Multiple Organ Dysfunction Syndrome; MPMS, 1-Methoxy-5-Methylphenazinium Methyl Sulfate; MNS, 3,4-Methylenedioxy-β-Nitrostyrene; NLRC4, NOD-like receptor family CARD domain-containing protein 4; NLRP, Nucleotide-Binding Domain, Leucine-Rich Repeat, and Pyrin Domain Containing Protein; NOS2, Nitric Oxide Synthase 2; NSA, Necrosulfonamide; NLRs, Nucleotide-Binding Oligomerization Domain-like Receptors; PAMPs, Pathogen-Associated Molecular Patterns; RCD, Regulated cell death; PHC, Penehyclidine hydrochloride; PRRs, Pattern Recognition Receptors; RHIM, Receptor-Interacting Protein Homotypic Interaction Motif; RIG-I, Retinoic Acid-Inducible Gene I; RIPK1, Receptor-Interacting Protein Kinase 1; RIPK3, Receptor-Interacting Protein Kinase 3; RLR, RIG-I-like receptors; ROS, Reactive Oxygen Species; SAE, sepsis-associated encephalopathy; SLE, Systemic Lupus Erythematosus; STAT, Signal Transducer and Activator of Transcription; STING, Stimulator of Interferon Genes; SXD, Shengxian Decoction; TAK1, Transforming Growth Factor-β-Activated Kinase 1; TCM, Traditional Chinese Medicine; TGF-β, Transforming Growth Factor-beta; TNF-α, Tumor Necrosis Factor-alpha; TLRs, Toll-like receptors; Tregs, Regulatory T Cells; UDCA, Ursodeoxycholic Acid; XCHD, XiaoChaiHu Decoction; ZBP1, Z-DNA binding protein 1.

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## Author Contributions

All authors have read and agreed to the published version of the manuscript. Qi SY. and Wu QQ. searched and collected the literatures. Qi SY. wrote the manuscript and Wu QQ. finished the drawing, revision, and response to reviewers' comments of the paper. Kang ZF., Bai XJ., and Li ZF., evaluated the theoretical basis and conclusions. Dong XJ., and Cheng Jing. supervised and reviewed the manuscript. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Qiqi Wu and Siyuan Qi share senior authorship.

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