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Mechanisms and Efficacy of Traditional Chinese Medicine in the Management of Sepsis with Multiple Organ Dysfunction

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ABSTRACT

Sepsis is increasingly recognized not just as an infection-triggered systemic inflammatory response but as a life-threatening condition marked by organ dysfunction resulting from a dysregulated host response. Among its most severe consequences is multiple organ dysfunction syndrome (MODS), which significantly worsens patient prognosis. Currently, effective pharmacological interventions for sepsis and sepsis-induced MODS are limited, and mortality remains high. Traditional Chinese medicine (TCM) offers extensive experience in both preventing and managing sepsis, with its diverse bioactive compounds, molecular targets, and pathways contributing to therapeutic effects. This review systematically searched CNKI, Wanfang, PubMed, and Web of Science using the keywords 'Sepsis,' 'Organ dysfunction,' and 'Traditional Chinese medicine' to examine the role of TCM formulations in addressing sepsis with MODS. The study summarizes the current understanding of TCM strategies, providing insights to support clinical practice and guide the development of novel therapeutic agents.

Keywords: Multiple organ dysfunction syndrome, Sepsis, Traditional Chinese medicine, Therapeutic strategies

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Introduction

Sepsis is a life-threatening condition characterized by organ dysfunction resulting from a dysregulated host response to infection, which can originate in any part of the body [1]. In the United States, epidemiological data indicate that sepsis affects roughly 1.7 million adults annually, contributing to around 250,000 deaths each year [2]. In contrast, comprehensive epidemiological data on sepsis in mainland China remain limited. A 2023 study in Beijing reported that 13.1% of hospitalized patients developed sepsis, with an in-hospital mortality rate of 28.4%. After adjustment for age and sex, the standardized incidence was 421.85 per 100,000, with a mortality rate of 19.16 per 100,000 [3].

Effective management of sepsis requires early recognition of clinical signs and identification of the infectious source, followed by timely intervention to control the immune response. Untreated or delayed treatment can lead to septic shock and multiple organ dysfunction syndrome (MODS), which represents the severe end of systemic inflammatory dysregulation and accounts for more than 5.3 million deaths worldwide annually [4]. Research by Xue *et al*. [5] found that the incidence of secondary MODS within 28 days among hospitalized sepsis patients was 13.33%. Moreover, mortality in sepsis patients who develop MODS can reach 60%–80% [6], highlighting the critical need for effective prevention and treatment strategies.

The high morbidity and mortality associated with sepsis-induced MODS, coupled with the lack of optimal clinical therapies, make it a major focus of research. Conventional Western medicine primarily relies on antibiotics and supportive care [7]. However, antibiotic therapy may disrupt the systemic microbiota and contribute to the emergence of antibiotic resistance [8].

Advances in modern medicine and molecular biology have expanded the application of traditional Chinese medicine (TCM) in the management of sepsis. In TCM, sepsis falls under the category of febrile diseases [9] and is classified based on severity into sepsis, severe sepsis, and septic shock. TCM is increasingly integrated with standard antibiotic therapy as a complementary approach [10]. Evidence from meta-analyses indicates that herbal medicines play a significant role in mitigating sepsis by modulating inflammatory responses and reducing cytokine production [11]. TCM interventions have been shown to improve organ function and help maintain systemic homeostasis [12].

This review aims to summarize the current understanding of TCM strategies and their bioactive components in the treatment of sepsis and MODS, providing a theoretical foundation for their clinical application.

Pathological mechanisms of sepsis with multiple organ dysfunction syndrome

The pathophysiology of sepsis and multiple organ dysfunction syndrome (MODS) is highly intricate, involving the interplay of inflammatory responses, oxidative stress, and autophagy [13]. Two central host defense mechanisms against infection are the inflammatory response and the activation of coagulation pathways [13]. These processes are not isolated; rather, they interact synergistically and dynamically to respond to pathogenic challenges [13].

When an infectious agent is introduced, it triggers an acute immune reaction, primarily through macrophage activation and the release of pro-inflammatory cytokines, which can escalate into a cytokine storm. This response is mediated by pattern recognition receptors (PRRs), with Toll-like receptors (TLRs) being the most extensively studied [14]. TLRs recognize pathogen-associated or damage-associated molecular patterns and initiate several signaling cascades, including the mitogen-activated protein kinase (MAPK) and nuclear factor-kappa B (NF-κB) pathways, resulting in the production of inflammatory mediators [14]. The NF-κB pathway serves as a central hub linking inflammation and thrombosis [15]. It is expressed in vascular and circulating cells involved in thromboinflammatory processes and regulates the expression of cytokines, chemokines, and coagulation factors [15]. Through mechanisms such as neutrophil extracellular trap (NET) formation or endothelial injury caused by mechanical stress, the interconnection between inflammation and thrombosis can prompt rapid platelet activation and aggregation, contributing to thromboinflammatory complications observed in sepsis [15].

Oxidative stress, primarily induced by reactive oxygen species such as superoxide and hydrogen peroxide, disrupts mitochondrial dynamics, impairs adenosine triphosphate (ATP) production, and promotes neuronal damage [16]. These oxidative effects elevate caspase-3 and caspase-9 activation, alter the Bax/Bcl2 ratio in hippocampal and cortical neurons, and contribute to cognitive deficits seen in sepsis-associated encephalopathy [16].

Autophagy constitutes another essential host defense mechanism, protecting against invading pathogens and harmful stimuli [17]. It regulates inflammatory responses in innate immune cells and plays a pivotal role in sepsis progression. Protective effects of autophagy include pathogen clearance, neutralization of microbial toxins, modulation of cytokine release, inhibition of apoptosis, and enhancement of antigen presentation [17]. Specifically, upregulation of Beclin-1 has been shown to attenuate cardiac inflammation and tissue damage, preserve mitochondrial content, and improve cardiac function following lipopolysaccharide-induced injury [18]. Enhanced Beclin-1 signaling can also suppress mitochondrial reactive oxygen species generation, thereby maintaining autophagic activity even under severe septic conditions **(Figure 1)** [18].

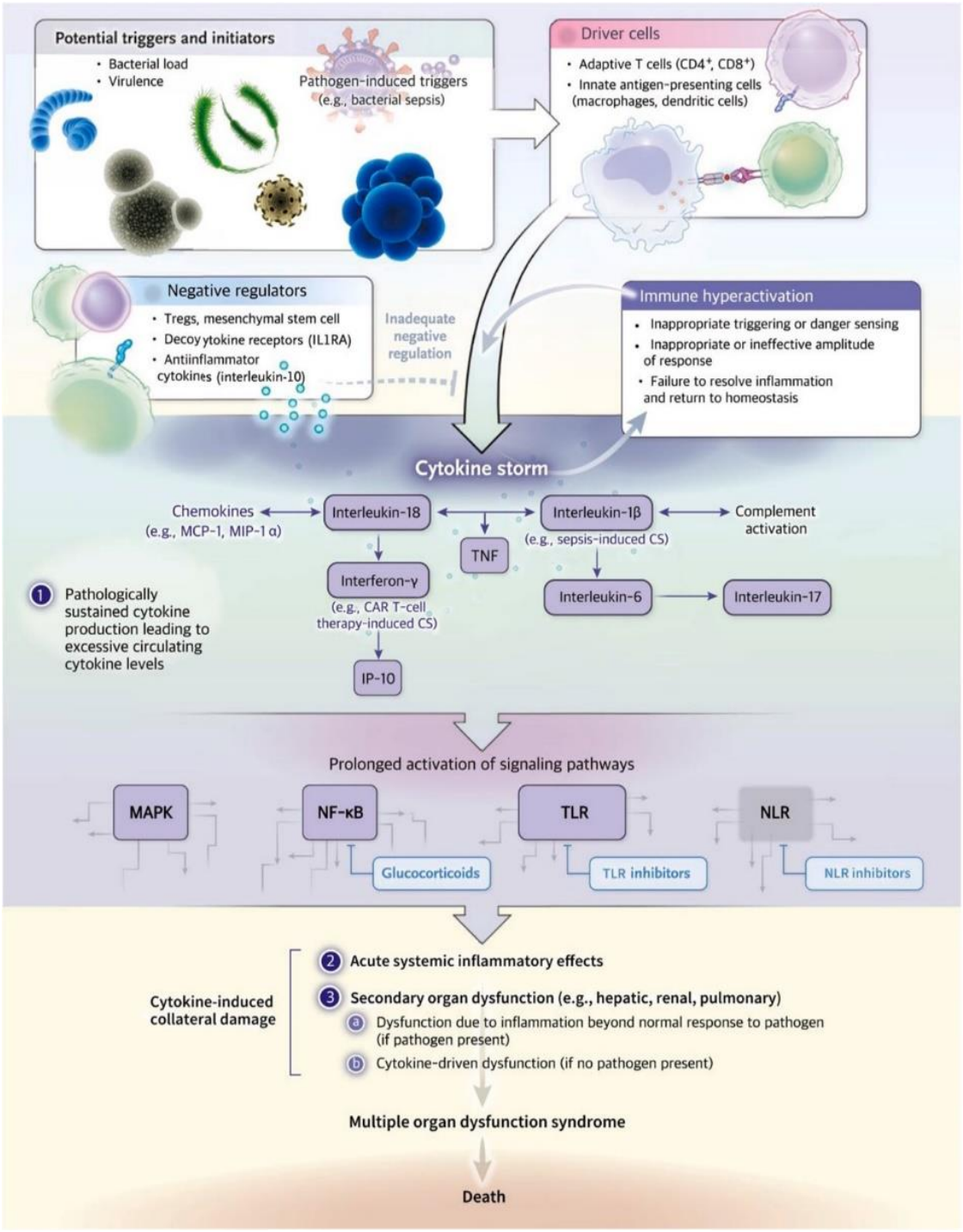

Figure 1. Pathological mechanisms of sepsis and MODS.

Coagulation abnormalities and traditional chinese medicine in sepsis with MODS

Coagulation activation is a fundamental defense mechanism against infection; however, in patients with sepsis, coagulation processes are frequently dysregulated [19]. Such coagulation disorders can contribute to the development of multiple organ dysfunction via microvascular thrombosis [19]. Consequently, maintaining proper coagulation function and minimizing the impact of coagulation abnormalities on organ systems are critical strategies for preventing and managing MODS in sepsis.

The etiology and pathogenesis of sepsis are complex, and traditional Chinese medicine (TCM) emphasizes treatment based on syndrome differentiation. Wang summarized sepsis pathogenesis under the principle of "three syndromes and three methods," which include: toxin-heat syndrome treated with heat-clearing and detoxifying methods, blood stasis syndrome treated with approaches to promote blood circulation and remove stasis, and acute

deficiency syndrome addressed with Fu Zheng–Gu Ben prescriptions [20, 21]. In clinical practice, TCM typically utilizes compound formulations rather than single herbs, with treatment tailored to the patient's syndrome presentation [22]. Furthermore, TCM and its active components have demonstrated potential in combating antibiotic-resistant bacteria, offering novel strategies to overcome resistance associated with conventional antibiotic therapy in sepsis with MODS [22].

Traditional Chinese medicine for diagnosis and management of sepsis with MODS

Toxic-fever symptoms and heat-clearing/detoxifying methods

In sepsis with MODS, toxic-fever symptoms manifest as persistent high fever, dizziness, nausea, vomiting, red tongue with yellow or dry coating, and a weak and rapid pulse [23]. The TCM approach for these symptoms primarily involves heat clearance and detoxification [23].

Rhubarb-derived anthraquinones

A literature search using the terms "sepsis," "organ dysfunction," and "heat clearing and detoxification" across PubMed and China National Knowledge Infrastructure identified rhubarb as the most frequently used herb in heat-clearing and detoxifying TCM formulations. Rhubarb contains diverse bioactive constituents, including anthraquinones, organic acids, volatile oils, glycosides, and tannins [24]. It has demonstrated wide-ranging therapeutic effects, such as regulating the digestive and circulatory systems, enhancing metabolism, supporting kidney function, reducing pain, preventing lung injury, mitigating oxidative stress, and exerting anti-inflammatory, antibacterial, antiviral, and antitumor actions [24].

The primary active anthraquinones—emodin, rhein, and chrysophanol—are also found in other commonly used TCM plants, such as *Polygonum cuspidatum* and *Polygonum multiflorum*, and have been extensively studied for both clinical and experimental applications [25]. Xu *et al*. [26] reported that emodin mitigates myocardial damage in septic rats by reducing oxidative stress, apoptosis, and inflammatory factor levels in cardiac tissue. Similarly, Dong *et al*. [27] demonstrated that emodin pretreatment in mice with lipopolysaccharide-induced sepsis-associated brain injury significantly decreases inflammatory cytokines such as IL-6 and markers of neuronal injury, likely through cholinergic pathway activation and suppression of inflammatory responses. Chrysophanol has been shown to induce M2 macrophage polarization, reduce lung injury, inhibit NF-κB p65 and ERK1/2 signaling pathways, and downregulate cleaved caspase-3 and -9 in septic rats [28].

Furthermore, intraperitoneal administration of emodin in septic rats reduces oxidative stress and inflammatory infiltration in heart, liver, lung, and kidney tissues, providing organ-protective effects [29]. Lin *et al*. [30] observed that septic rats initially display hypocoagulability, with reduced fibrin and platelet activity, followed by compensatory hypercoagulability. Emodin enhances endogenous coagulation factor activity and fibrinogen function, thereby lowering 48-hour mortality rates in septic animals. These findings highlight emodin's therapeutic potential in modulating coagulation disturbances, particularly in the context of sepsis-induced multiple organ dysfunction.

Berberine

Coptis chinensis is a widely used TCM herb for heat clearing and detoxification, ranking second only to rhubarb in frequency of use for sepsis-related prescriptions [31]. Berberine, a major bioactive alkaloid extracted from *C. chinensis*, exhibits significant anti-inflammatory effects in both acute and chronic contexts [31]. Both berberine and *C. chinensis* can enhance leukocyte phagocytic activity in vitro and in vivo, thereby partially modulating the inflammatory response [31]. Administration of berberine in mice with *Escherichia coli*-induced sepsis increased survival rates and enhanced the efficacy of antibiotics, primarily through regulation of T lymphocytes and reduction of inflammatory cytokines such as IL-6, suggesting its utility in both prevention and treatment of sepsis [32].

Berberine also demonstrates protective effects against sepsis-induced multiple organ dysfunction. In mice with sepsis and acute respiratory distress syndrome, berberine pretreatment resulted in lower lung injury scores, reduced serum inflammatory markers, and significantly decreased NF-κB p65 levels in lung tissue, indicating inhibition of aberrantly activated NF-κB signaling as a potential mechanism [33]. Chen *et al*. [34] reported that berberine mitigates septic cardiomyopathy in rats by suppressing TLR4/NF-κB pathway activation, improving left ventricular end-diastolic pressure, and reducing lipopolysaccharide-induced cardiomyocyte swelling.

Experimental and clinical evidence indicates that berberine protects the intestinal epithelium during sepsis by modulating both intrinsic and extrinsic apoptosis pathways, thereby preserving intestinal mucosal integrity [35, 36]. High-mobility group protein 1 (HMGB1), a damage-associated molecular pattern (DAMP) protein, acts as a chemotactic cytokine in conditions such as infection, sepsis, hypoxia, and ischemia-reperfusion, serving as a key alarm signal for systemic imbalance [37]. Berberine may exert part of its protective effect through HMGB1-related pathways; Shi *et al*. [38] showed that berberine inhibits AGE-mediated HMGB1 signaling, reduces microglia-induced A1 astrocyte stress, and mitigates sepsis-associated cognitive impairment, preventing sepsis-related encephalopathy.

Tetramethylpyrazine

Ligusticum chuanxiong is traditionally used in TCM to promote blood and Qi circulation, alleviate liver stagnation, expel wind, and relieve pain [39]. Ligustrazine, a non-volatile alkaloid derived from *Rhizoma chuanxiong*, represents a major active component with significant pharmacological activity [39]. Clinical investigations have primarily focused on Danshen ligustrazine injections, while animal studies have explored ligustrazine's effects on sepsis-related organ dysfunction [40–44].

Regarding sepsis-induced renal injury, Ying *et al*. [40] demonstrated that ligustrazine significantly reduced renal water content and urinary levels of kidney injury molecule-1 in mice, mitigating renal damage. This protective effect is believed to involve caspase-3 inhibition, downregulation of anti-NMDA receptor activity, and anti-apoptotic properties. For sepsis-related cerebral and pulmonary injury, Huang *et al*. [41] found that ligustrazine attenuated inflammatory cell infiltration and tissue damage in the brain and lungs of septic rats, enhancing the expression of tight-junction proteins claudin-5 and occludin and preserving blood–brain barrier integrity. Wang *et al*. [42] reported that ligustrazine inhibited the p38 MAPK/CREB pathway, reducing hippocampal inflammation in sepsis-associated encephalopathy. Additionally, Liu *et al*. [43] showed that ligustrazine prevented apoptosis of pulmonary microvascular endothelial cells via modulation of the ER stress-associated PERK pathway, improving oxygenation and survival in septic rats with acute lung injury. In liver protection, ligustrazine-pretreated rats exhibited better mitochondrial function and overall hepatic performance in sepsis-induced acute liver injury models [44]. Zhang *et al*. [45] revealed that ligustrazine reduced hepatic iron accumulation by inhibiting JAK/STAT phosphorylation, thereby alleviating systemic inflammatory and liver injury. Similarly, Xiao *et al*. [46] demonstrated hepatoprotective effects of combined *Salvia miltiorrhiza* and ligustrazine injection in septic mice. Clinical studies further confirmed that ligustrazine antagonizes TNF-α, improves microcirculation, and, when combined with standard therapy, mitigates myocardial damage in septic patients [47]. Prophylactic administration of *S. miltiorrhiza* and ligustrazine injections also reduced systemic inflammatory response in severe burn patients, though the incidence of MODS remained unaffected [48]. While numerous animal studies validate ligustrazine's efficacy in sepsis and MODS, clinical evidence remains limited, highlighting the need for further research.

Acute deficiency syndrome and fu Zheng–Gu ben therapy

Acute deficiency syndrome in sepsis manifests as either Yin or Yang deficiency [21]. Yin deficiency is characterized by restlessness, flushed face, oliguria or anuria, a red and dry tongue, and bradycardia. Yang deficiency presents with cold sweats, cold extremities, dizziness, pale or purple tongue, and weak or irregular pulse. Fu Zheng–Gu Ben prescriptions are the primary TCM approach for treating these syndromes [21].

Ginsenosides

Ginseng, a principal Qi-invigorating herb, is frequently used in Fu Zheng–Gu Ben formulations. Its bioactive constituents—including ginsenosides, polysaccharides, volatile oils, and amino acids—exhibit anti-fatigue, anti-aging, antioxidant, and immunomodulatory effects [49]. Multiple studies have investigated ginsenosides in sepsis-related MODS, including liver, lung, myocardial, and neurological injury [50–55].

Wu *et al*. [50] demonstrated that ginsenosides upregulate taurine-upregulated gene 1 and downregulate miR-200a-3p, activating the SIRT1/AMPK pathway to enhance autophagy, thereby improving liver injury and mitochondrial dysfunction in septic models. Ginsenosides also protect type II alveolar epithelial cells from LPS-induced apoptosis by promoting autophagy and inducing Nrf2 expression, contributing to lung injury mitigation [51]. Zhang *et al*. [52] reported reduced pulmonary inflammation, decreased alveolar cytokines, and lowered NF-κB activation in ginsenoside-treated septic mice, confirming their anti-inflammatory effects. Ji *et al*. [53] observed

that LPS-induced autophagy initially increases to reduce apoptosis and that ginsenosides further modulate this response, providing lung protection.

Cardiomyocyte apoptosis and inflammation in sepsis involve TLR4, NF-κB, and NLRP3 pathways [54]. Ginsenosides inhibit these pathways, attenuating myocardial apoptosis and restoring cardiac function. In sepsis-associated encephalopathy, ginsenosides suppress abnormal activation of NF-κB and MAPK signaling, regulating cytokine and chemokine levels to reduce neural damage [55].

Conclusion

As an integral component of complementary and integrative medicine, traditional Chinese medicine (TCM) has demonstrated significant therapeutic potential in managing acute and critical conditions, including sepsis complicated by multiple organ dysfunction syndrome (MODS). This review highlights that TCM exerts multiple beneficial effects in sepsis management, such as anti-inflammatory activity, improvement of microcirculation, mitigation of gastrointestinal dysfunction, immune system modulation, and protection of vital organs, thereby contributing to the alleviation of MODS. Future studies should focus on elucidating the mechanisms and efficacy of TCM in treating sepsis-induced MODS, supporting the development of novel therapeutic agents and the design of prospective, randomized controlled clinical trials to validate the clinical application of its active components.

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