Perioperative Precision Medicine

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REVIEW ARTICLE

Mechanisms of traditional Chinese medicine extracts in ameliorating sepsis-induced myocardial injury

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Abstract

Sepsis-related myocardial dysfunction significantly increases patient mortality and remains a major challenge in critical care medicine. Its pathological mechanisms involve uncontrolled inflammation, excessive oxidative stress, and impaired stress tolerance of cardiomyocytes. Currently, no specific treatment methods are available. Although supportive treatment remains the mainstream in clinical practice, effective interventions for septic myocardial injury are still lacking. This review systematically summarizes the cardioprotective effects of traditional Chinese medicine (TCM) preparations, including Xuebijing injection (containing safflower, red peony root, and *salvia miltiorrhiza*) and Shenfu Injection (containing ginseng and aconite), in cell and animal models. The mechanisms include antioxidation, anti-inflammation, and enhancement of cardiomyocyte resistance to injury. Some of these preparations have been recommended in the "Guidelines for the Diagnosis and Treatment of Sepsis" in China and are used as adjunctive treatments in intensive care units (ICUs). Preliminary clinical studies suggest that these agents may improve microcirculation and potentially enhance survival rates. This review not only highlights the multi-target potential of TCM in sepsis-induced myocardial injury but also provides a direction for future high-quality mechanistic research and international multicenter randomized controlled trials, thereby facilitating the integration of traditional medicine into modern critical care practice.

Keywords: Sepsis-induced myocardial injury, Traditional Chinese medicine extracts, Anti-inflammatory agents, Antioxidants, Herbal cardioprotection, Clinical trials

Highlights

- This review presents a comprehensive overview of the pharmacological effects of traditional Chinese medicine (TCM) in sepsis-induced myocardial injury.
- It systematically summarizes the molecular mechanisms and recent research advancements regarding protective effects of TCM in sepsis.
- It proposes a novel "temporal treatment" strategy for Perioperative Sepsis, aligning TCM interventions with the dynamic pathophysiological stages of the disease.

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1 INTRODUCTION

Sepsis is a life-threatening syndrome triggered by dysregulated host immune response to infection and is characterized by uncontrolled systemic inflammation and progressive multi-organ dysfunction. The heart, as a highly metabolically active and richly perfused organ, is particularly vulnerable to injury during sepsis. Clinical data show that approximately 40%-50% of critically ill patients develop detectable myocardial injury, manifested by decreased left ventricular ejection fraction and reduced cardiac output among others, significantly prolonging ICU stay and increasing mortality risk [1-5]. The pathological mechanisms of sepsis are complex and multifactorial, involving excessive pro-inflammatory factor release, mitochondrial oxidative stress, abnormal calcium acc umulation, and impaired myocardial energy metabolism, all of which jointly lead to inhibited myocardial contractility [6-10].

Although significant progress has been made in anti-infection, fluid resuscitation, and organ support treatments, there are still no specific drugs that can directly target sepsis-induced myocardial damage. This unmet clinical need has prompted growing interest in therapeutic strategies with pleiotropic properties, including anti-inflammatory, antioxidative, and cardioprotective effects. Traditional Chinese Medicine (TCM) has demonstrated potential value in this context. Over thousands of years, TCM has accumulated clinical experience in managing acute and severe syndromes that similar to modern sepsis, such as “heat toxins” and “warm diseases” [11-14]. More importantly, TCM emphasizes the “holistic view” and “diagnosis-based treatment”, achieving systemic regulation through the synergistic effect of multiple components, multiple targets, and multiple pathways, which precisely aligns with the high heterogeneity and network-based pathological characteristics of sepsis [15-20].

In recent years, a large number of high-quality preclinical studies have provided mechanistic evidence supporting the cardioprotective effects of TCM. For instance, baicalin from *Scutellaria baicalensis* and paeonol from *Paeonia lactiflora* have been proven to simultaneously inhibit the NF-κB-mediated inflammatory cascade and activate the Nrf2/HO-1 antioxidant pathway, thereby attenuating cardiomyocyte apoptosis and functional impairment [21-28]. Furthermore, the application of modern technologies, including network pharmacology, transcriptomics, and gene-edited animal models, has facilitated the transformation of traditional empirical prescriptions into evidence-based therapies with increasingly defined molecular mechanisms [29, 30]. Notably, the core TCM principle of “strengthening vital qi and eliminating pathogenic factors while harmonizing yin and yang” is highly consistent with the current international trend of sepsis management, which is evolving from simple pathogen eradication toward reconstruction of immune homeostasis and organ function maintenance [31-33].

Given the increasingly solid experimental and preliminary clinical evidence supporting the myocardial protective effects of TCM in sepsis, a systematic synthesis of current findings is urgently needed. This review aims to comprehensively summarize recent advances in TCM-derived extracts and compound preparations in this field, with particular emphasis on their bioactive components, molecular targets, signaling pathways, and translational potential [34, 35].

The structure of this review is as follows. First, the core pathophysiology of septic cardiomyopathy is briefly outlined. Second, single herbs and active compounds with reliable preclinical evidence (e.g., Scutellaria baicalensis, Salvia miltiorrhiza, and ginsenosides) and their cardioprotective mechanisms are systematically reviewed. Third, the efficacy and safety of clinically applied TCM injections (e.g., Xuebijing injection and Shenfu injection) are analyzed. Finally, key challenges—including compositional complexity, insufficient quality standardization, and limited high-level clinical evidence—are discussed, and future research directions are proposed to promote the scientific, standardized, and internationalized development of TCM in modern critical care medicine (**Figure 1**).

2 RESEARCH PROGRESS ON THE MECHANISMS BY WHICH TCM EXTRACTS IMPROVE SEPSIS-INDUCED MYOCARDIAL INJURY

In recent years, substantial progress has been made in elucidating the mechanisms by which TCM extracts ameliorate sepsis-induced myocardial injury. Several preclinical studies have shown that multiple bioactive components derived from TCM can effectively suppress excessive inflammatory responses, eliminate reactive oxygen species (ROS), improve mitochondrial function, and regulate cardiomyocyte energy metabolism through multi-target and multi-pathway modulation, thereby exerting cardioprotective effects [36-38]. These mechanisms not only provide biological support for the holistic framework of TCM, but also offer mechanistic insights and potential candidate compounds for the development of novel cardioprotective strategies. This section systematically reviews the mechanisms of action of representative TCM extracts and summarizes the corresponding experimental evidence, laying the foundation for a deeper understanding of their therapeutic potential.

2.1 Pathological mechanisms of sepsis-induced myocardial injury

Sepsis is characterized by dysregulated host response to infection, leading to multiple organ dysfunction and high mortality [39]. Among the various organ complications, sepsis-induced myocardial injury represents a clinically significant manifestation that contributes substantially to disease severity and mortality [40]. The pathogenesis of sepsis-induced myocardial injury is multifactorial and involves a complex interplay of

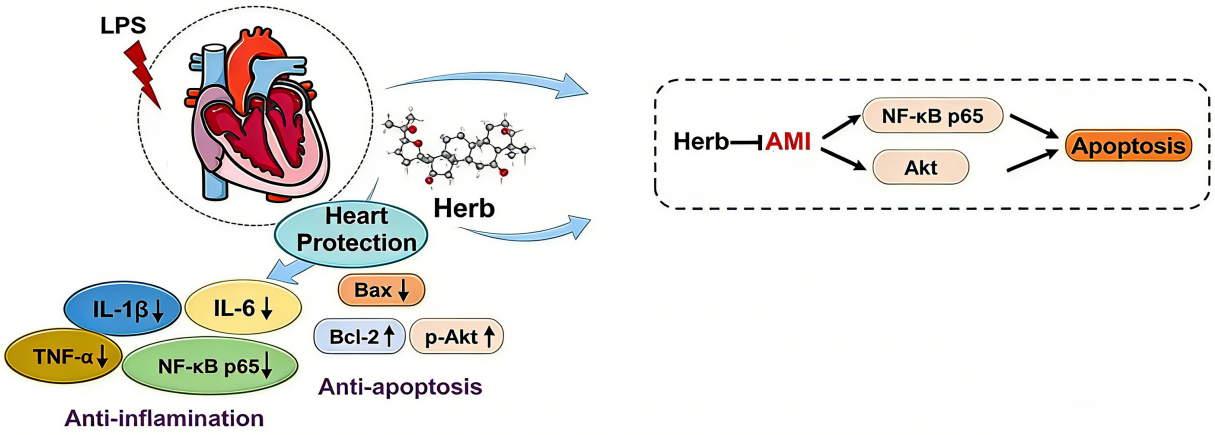

Figure 1. The mechanism of the effect of TCM extracts on improving myocardial injury caused by sepsis. Herbal intervention (labeled "Herb") exerts protective effects on the heart following insult by lipopolysaccharide (LPS) or other AMI-inducing stimuli. The herb modulates key signaling pathways to suppress inflammation and apoptosis. Specifically, it downregulates pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and inhibits NF-κB p65 activation, thereby attenuating inflammatory responses. Concurrently, the herb promotes cell survival by activating the Akt pathway (increasing p-Akt), upregulating anti-apoptotic Bcl-2, and downregulating pro-apoptotic Bax. These coordinated actions converge to inhibit apoptotic cell death via suppression of NF-κB p65 and Akt-mediated signaling cascades. Overall, this multi-targeted mechanism contributes to myocardial protection in the context of acute cardiac injury. The figure created with Microsoft PowerPoint 2019. AMI, acute sepsis-induced myocardial injury.

inflammatory responses, oxidative stress, and cardiomyocyte apoptosis [41, 42]. A comprehensive understanding of these mechanisms is essential for the development of effective therapeutic strategies to alleviate sepsis-related cardiac dysfunction.

2.1.1 Association between inflammatory responses and myocardial injury

Excessive inflammatory activation represents a major mechanism underlying sepsis-induced myocardial injury, characterized by the massive release of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, and IL-6 [43-47]. While these mediators are essential for pathogen clearance, their excessive production exerts opposite effects on cardiac tissue [48]. The increase in these inflammatory cytokines are associated with myocardial dysfunction, decreased cardiomyocyte contractility, and increased susceptibility to apoptosis, all of which contribute to cardiac dysfunction [49].

Nuclear factor-κB (NF-κB) plays a crucial role in mediating sepsis-related cardiac injury. Upon activation, it induces the transcription of numerous pro-inflammatory genes, thereby amplifying cytokine production and sustaining the inflammatory cascade, which directly impairs cardiomyocyte function and promotes structural damage. Experimental studies have shown that inhibition of NF-κB pathway signaling attenuates myocardial injury and protects cardiac function in sepsis models, highlighting this pathway as a potential therapeutic target [50]. In addition to systemic cytokine release, during sepsis, activated immune cells (especially macrophages) accumulate in cardiac tissue and secrete additional inflammatory mediators, thereby intensifying local inflammation and contributing to myocardial dysfunction [51, 52].

The interplay between inflammation and myocardial injury is further amplified by oxidative stress. Excessive inflammatory activation promotes the generation of ROS, which disrupt cellular homeostasis and damage lipids, proteins, and nucleic acids within cardiomyocytes [53, 54]. Importantly, oxidative stress further enhances inflammatory signaling, forming a vicious cycle. In sepsis, this vicious cycle contributes to progressive cardiac dysfunction. Therefore, targeted modulation of inflammatory responses represents a critical strategy for interrupting this pathogenic loop and protecting myocardial function.

2.1.2 Role of oxidative stress in sepsis-induced myocardial injury

Oxidative stress is a critical mechanism contributing to myocardial injury during sepsis, characterized by excessive ROS production and insufficient antioxidant capacity. Upon activation, neutrophils and macrophages generate substantial amounts of ROS as part of the host immune response [55, 56]. When ROS production exceeds the endogenous antioxidant

capacity, oxidative damage to cardiomyocytes ensues. Due to the high metabolic demand and dense mitochondrial content, myocardial tissue is particularly susceptible to oxidative injury. Excessive ROS attack cellular lipids, proteins and DNA, leading to mitochondrial dysfunction, disruption of calcium homeostasis, and activation of cardiomyocyte death pathways [57, 58]. In addition, ROS can activate the NLRP3 inflammasome, thereby promoting the release of inflammatory factors and further aggravating the inflammatory response, establishing a vicious cycle of "oxidative stress - inflammation" [59-61]. Therefore, attenuation of oxidative stress may help interrupt this pathogenic cascade, protect cardiac function, and improve clinical outcomes.

Antioxidant therapy has been proposed as a promising approach to mitigate oxidative injury in sepsis. Early studies in cellular and animal models have shown that antioxidants like N-acetylcysteine (NAC) can effectively reduce ROS accumulation, attenuate myocardial injury, and improve cardiac function [62, 63]. However, clinical translation yielded inconsistent results. Some clinical trials have failed to demonstrate significant benefits, suggesting that antioxidant therapy may not be universally effective. Factors such as timing of application, dosage, and disease severity, and patient heterogeneity likely influence therapeutic efficacy.

2.1.3 Mechanisms of myocardial cell apoptosis and injury

Cell apoptosis is a highly regulated process of programmed cell death. In sepsis-induced myocardial injury, apoptosis plays a critical role: a physiological mechanism for eliminating damaged or old cells is exploited by the disease, ultimately contributing to myocardial damage.

In sepsis, myocardial cells are not simply overwhelmed by inflammation or toxins; rather, intrinsic cellular processes are disrupted. These disruptions include signaling pathway alterations, mitochondrial dysfunction, activation of death-associated proteins. It's like an "insurrection" initiated from within, gradually leading the cells towards self-destruction. The seemingly quiet apoptosis actually exacerbates myocardial damage in an insidious manner. Inflammatory cytokines, oxidative stress, and mitochondrial dysfunction act synergistically to trigger apoptotic signaling pathways [64, 65]. Both intrinsic and extrinsic apoptotic pathways are mobilized, leading to the sequential activation of caspase, which orchestrate the degradation of cellular architecture, ultimately leading to the irreversible loss of functional cardiomyocytes [66, 67].

At the molecular front line, the balance between pro-survival and pro-apoptotic signals is tightly regulated by proteins such as Bax and Bcl-2. In the context of sepsis, this equilibrium is disrupted, with Bax, a pro- apoptotic protein, prevailing over Bcl-2, the key anti-apoptotic protein, resulting in an elevated Bax/Bcl-2 ratio that promotes widespread cardiomyocyte death [68, 69]. In addition, the NF-κB pathway, which is centrally involved in inflammation, further amplifies myocardial cell apoptosis by upregulating the expression of pro-apoptotic genes, thereby contributing to myocardial injury beyond its role in immune activation [70].

The strategic inhibition of apoptosis has therefore emerged as a compelling avenue for cardiac protection in sepsis. Preclinical investigations have shown that targeting caspase activation or reinforcing mitochondrial resilience can significantly reduce cardiomyocyte death and preserve cardiac function under septic conditions [71, 72]. However, despite these advances, clinical translation remains elusive.

In conclusion, sepsis-induced myocardial injury is not the result of a single factor but rather a complex interplay between inflammation, oxidative stress, and cell apoptosis. These factors act synergistically, exacerbating each other's effects and contributing to the progressive decline in cardiac function.

2.2 Mechanisms of action of TCM extracts

TCM has been practiced for centuries, emphasizing holistic management rather than targeting individual symptoms. Nowadays, many studies have demonstrated the efficacy of TCM extracts in eliminating free radicals, slowing down cellular aging, and reducing inflammation, rather than simply masking the symptoms [73-75]. More impressively, some of these extracts have demonstrated cardioprotective effects, such as improving blood circulation, stabilizing blood pressure, and protecting myocardial cells from injury. Commonly used herbs like *Salvia miltiorrhiza*, *Astragalus membranaceus*, and *Panax notoginseng* have long been recognized by modern medicine for their cardiovascular benefits [76-78].

Sepsis-induced myocardial injury (SIMI) is a life-threatening complication of systemic infection, characterized by reversible biventricular dilation, reduced ejection fraction, and elevated cardiac biomarkers—despite adequate fluid resuscitation. Unlike ischemic cardiomyopathy, SIMI is not caused by coronary occlusion, but rather by a cascade of biochemical insults (e.g., excessive ROS, uncontrolled inflammatory cascades, mitochondrial dysfunction, and programmed cell death). Conventional supportive therapies often fail to address these intertwined mechanisms, creating an urgent need for multi-target interventions. In this context, TCM extracts—long used in East Asia for "qi deficiency" and "blood stasis" syndromes resembling circulatory collapse—are gaining increasing scientific attention. These extracts are shown to simultaneously modulate oxidative, inflammatory, and apoptotic pathways with remarkable precision.

2.2.1 Targeting oxidative stress pathways

Oxidative stress is a foundational driver of SIMI. During sepsis, activated neutrophils and dysfunctional mitochondria pro-

duce excessive ROS (e.g., superoxide, hydrogen peroxide), while antioxidant defenses—such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx)—become overwhelmed and depleted. This redox imbalance results in oxidative damage of lipids, proteins, and DNA, impairing myocardial contractility and initiating downstream injury cascades.

TCM herbs counteract oxidative stress through a dual strategy: direct free radical scavenging and, more importantly, transcriptional upregulation of endogenous antioxidant systems. For example, *Astragalus membranaceus* (Huang Qi) and *Panax ginseng* (Ren Shen) have been shown to enhance SOD and GPx activity, accelerating ROS clearance, and reducing malondialdehyde (MDA)—a marker of lipid peroxidation—in both animal models and clinical cohorts [79, 80]. Notably, their effects extend far beyond enzymatic support. For instance, *Astragalus polysaccharides* (APS) exerts a cardioprotective effect by targeting the endoplasmic reticulum (ER) stress signaling pathway to inhibit cardiomyocyte apoptosis in diabetic cardiomyopathy. APS downregulates the phosphorylation level of protein kinase R-like ER kinase (PERK) and inhibits the oligomerization and autophosphorylation of inositol-requiring enzyme 1α (IRE1α), thereby blocking two critical ER stress signaling cascades (PERK-eIF2α-ATF4 and IRE1α-XBP1-CHOP). Meanwhile, this regulatory effect reduces the activation of Caspase-12, a specific apoptotic protease in ER stress-induced apoptosis and blocks its cross-talk with the mitochondrial apoptotic pathway, providing a clear molecular basis for APS's application in perioperative myocardial protection for diabetic patients [81].

The core regulator of this adaptive response is nuclear factor erythroid 2–related factor 2 (Nrf2). Normally sequestered in the cytoplasm by Keap1 and targeted for degradation, Nrf2 is liberated upon oxidative challenge or pharmacological stimulation. Once translocated to the nucleus, it binds to antioxidant response elements (AREs), driving the expression of over 200 cytoprotective genes—including HO-1, NQO1, and glutathione synthetase—that collectively enhance cellular resilience to oxidative stress [82, 83]. *Salvia miltiorrhiza* (Danshen), a cornerstone herb in cardiovascular TCM formulas, activates Nrf2 via its diterpenoid (tanshinones) and phenolic acid (salvianolic acids) constituents, which not only scavenge free radicals but also preserve membrane integrity by inhibiting lipid peroxidation [84, 85].

Remarkably, some TCM compounds achieve target specificity comparable to that of synthetic drugs. For instance, hyperoside—a flavonoid derived from *Hypericum perforatum*—though not classical TCM herb but increasingly studied in integrative contexts—binds covalently to cysteine residues on Keap1, preventing Nrf2 ubiquitination and enabling sustained nuclear accumulation. This structurally precise interference with protein–protein interactions reveals a level of mechanistic sophistication once thought exclusive to small-molecule pharmaceuticals [86-88]. Thus, TCM extracts function not merely as passive antioxidants but as dynamic "redox rheostats", recalibrating cellular defense architecture in real time.

2.2.2 Targeting inflammatory signaling pathways

While inflammation is essential for pathogen clearance, its dysregulation in sepsis leads to a self-amplifying cytokine storm that directly depresses myocardial contractility through mechanisms such as nitric oxide–mediated calcium desensitization and β-adrenergic uncoupling. Rather than broadly immunosuppressing—a strategy that increases the risk of secondary infections, TCM emphasizes restoring immune homeostasis, which aligns with the classical TCM principle of "harmonizing the defensive qi".

Two key inflammatory signaling pathways are targeted by TCM: NF-κB and the NLRP3 inflammasome. NF-κB, often referred to as the "master switch" of immune responses, regulates the transcription of TNF-α, IL-6, IL-1β, and adhesion molecules. TCM interventions selectively modulate these pathways, applying molecular brakes without impairing host defense. For instance, *Scutellaria barbata* (Ban Zhi Lian) inhibits IκB kinase (IKK), preventing IκB degradation and subsequent NF-κB nuclear translocation, thereby dampening inflammatory mediator production [89]. Gossypin, a flavonoid derived from *Hibiscus* species and structurally similar to several TCM flavonoids, exerts dual control by suppressing both cytokine mRNA stability and NF-κB activation, positioning it as a candidate for precision immunomodulation in hyperinflammatory states [90, 91].

In addition to NF-κB, the NLRP3 inflammasome plays a critical role in sepsis-induced inflammation. It senses damage-associated molecular patterns (DAMPs) and catalyzes the caspase-1–dependent maturation of IL-1β and IL-18. The clinically approved *Xuebijing* injection, a five-herb formula (Carthamus, Paeonia, Ligusticum, Salvia, Angelica) has demonstrated efficacy in randomized controlled trials (RCTs) for sepsis, significantly reducing serum IL-1β levels and improving cardiac index [92]. Its active components, such as hydroxysafflor yellow A and ferulic acid, inhibit NLRP3 oligomerization and ASC speck formation, effectively disrupting "disconnecting" the inflammasome's activation and subsequent inflammatory amplification.

Beyond cytokine suppression, TCM also reprograms the innate immune response. Macrophages, key mediators of cardiac inflammation, can polarize into either a pro-inflammatory M1 phenotype (producing TNF-α, ROS) or a reparative M2 phenotype (secreting IL-10 and TGF-β) [93, 94]. Quercitrin—a flavonoid abundant in *Rhus chinensis* and other TCM herbs—shifts macrophage polarization toward M2 phenotype via STAT6

activation, transforming the cardiac microenvironment from destructive to regenerative [95]. This functional plasticity reflects a higher-order strategy: not only blocking mediators but also reshaping the immune landscape to favor tissue resolution and repair.

2.2.3 Targeting apoptosis and mitochondrial dysfunction

Cardiomyocyte apoptosis, though limited in absolute number, disproportionately impairs cardiac output due to the post-mitotic nature of heart cells. In sepsis, apoptosis is primarily triggered by ROS, TNF-α, and calcium overload, which converge on mitochondrial outer membrane permeabilization (MOMP) and caspase activation. Consequently, preserving mitochondrial integrity is paramount.

TCM extracts protect mitochondria through multiple mechanisms. Ginsenoside R1, a protopanaxatriol saponin from red ginseng, activates AMP-activated protein kinase (AMPK), a central energy sensor that enhances mitochondrial biogenesis (via PGC-1α), promotes mitochondrial fusion via Mfn2 and stimulates mitophagy to remove damaged organelles. This multifaceted action alleviates cardiac lipotoxicity and prevents the release of cytochrome c, a key event in apoptosis [96]. Clinically, *Shenmai* injection (red ginseng + Ophiopogon japonicus) has been shown to reduce troponin levels and improves left ventricular ejection fraction in patients receiving anthracycline chemotherapy or suffering from septic cardiomyopathy, partly by modulating Bcl-2/Bax ratios and inhibiting caspase-3 cleavage [97, 98].

Guanxin Ning injection (Salvia miltiorrhiza+Ligusticum chuanxiong) has demonstrated robust protection against ischemia–reperfusion injury—a model highly relevant to SIMI—by enhancing electron transport chain efficiency (Complexes I and III), stabilizing mitochondrial membrane potential, and delaying mitochondrial permeability transition pore (mPTP) opening [99]. Moreover, several TCM formulations have been shown to promote angiogenesis via VEGF/PI3K/Akt signaling. Xuebijing injection, for instance, increases capillary density in peri-infarct zones and improves myocardial perfusion, thereby mitigating hypoxia-driven apoptosis and supporting functional recovery [100, 101].

Critically, the effects of these TCM extracts are synergistic: by reducing oxidative stress, TCM limits NF-κB/NLRP3 activation; by tempering inflammation, it preserves mitochondrial function; and by stabilizing mitochondrial integrity, it blocks intrinsic apoptosis—thereby enhancing tissue repair. This systems-level action mirrors the TCM diagnostic framework, where "deficiency" (e.g., qi deficiency) and "excess" (e.g., heat-toxin) coexist and must be addressed concurrently.

2.3 Related research progress

2.3.1 Research in animal models

Recent animal experiments have provided valuable insights into the potential of TCM in treating sepsis. For instance, *Bai Pu Da* (BBD) showed significant therapeutic effects in mice with sepsis caused by lipopolysaccharide (LPS): not only prolonged the survival but also significantly reduced inflammatory factors such as IL-1β and TNF-α [102]. This suggests that BBD may help stabilize excessive inflammation and reduce organ damage.

Further studies have shown that MLG, extracted from chrysanthemum, showed efficacy in a cecal ligation and puncture (CLP) sepsis model, which better mimics human septic conditions. MLG not only inhibited the inflammatory response in macrophages but also increased the survival rate of mice. Its effectiveness is attributed to its ability to "switch off" two key inflammatory signaling pathways, TAK1-NF-κB and MAPK, thereby reducing systemic inflammation and organ damage [103].

Furthermore, "Xingbi Jing" (XBJ), which has been approved for use in treating sepsis in China, has also been found to alleviate acute lung injury in rats caused by sepsis. This therapeutic effect was achieved by regulating oxidative stress and inflammatory responses, which are key contributors to the high mortality associated with sepsis [104].

Overall, these animal experiments not only enhance our understanding of the mechanisms through which TCM exerts its therapeutic effects but also highlight its potential in clinical applications. Without these models, the mechanism of TCM might remain partially understood rather than fully elucidated.

2.3.2 Preliminary results of the clinical trial

A systematic review of multiple RCTs has indicated that TCM interventions, decoction or injection, can significantly improve inflammatory markers and renal function in patients with sepsis with concomitant kidney damage [105].

For instance, the well-known "Xuebijing" injection has been reported to improve the renal microcirculation of patients with sepsis, while reducing inflammatory factors that exacerbate the inflammatory cascade. These findings suggests that *Xuebijing* may serve as a reliable alternative therapy apart from antibiotics [106]. The key outcome indicators of Xuebijing injection in perioperative sepsis were shows in **Table 1**.

Additionally, a compound preparation named *Hongrun Injection*, which contains several herbal ingredients, has been

Table 1. Key outcome indicators of Xuebijing injection in perioperative sepsis

Indicator category	Specific indicator	Effect size (mean difference/odds ratio)	95% confidence interval (CI)	*P* Value	Effect direction (role of Xuebijing)	Reference
Microcirculation Parameters	Mean Arterial Pressure (MAP)	+4.00 mmHg	[1.20, 6.80]	<0.05	Improvement (Increased)	[107, 108]
	Perfused Small Vessel Density (PVD)	+6.43 mm/mm^2	[4.15, 8.71]	<0.01	Improvement (Increased)	
	Microvascular Flow Index (MFI)	0.61	[0.48, 0.74]	<0.01	Improvement (Increased)	
Oxygenation Status	Pimonidazole Adduct (Hypoxia)	-35.20% (Staining Area)	[-48.60, -21.80]	<0.05	Improvement (Decreased)	[109]
Inflammatory Factors	Interleukin-1β (IL-1β)	-28.60 pg/mL	[-39.40, -17.80]	<0.05	Inhibition (Decreased)	[110-112]
	Interleukin-6 (IL-6)	-34.10 pg/mL	[-45.70, -22.50]	<0.05	Inhibition (Decreased)	
	Tumor Necrosis Factor-α (TNF-α)	-21.30 pg/mL	[-30.90, -11.70]	<0.05	Inhibition (Decreased)	
	High Mobility Group Box 1 (HMGB-1)	-19.80 pg/mL	[-28.50, -11.10]	<0.05	Inhibition (Decreased)	
Kidney Injury Biomarkers	Urinary TIMP-2*IGFBP-7	-1.80 ng/mL	[-2.50, -1.10]	<0.05	Protection (Decreased)	[113, 114]
	Urinary NGAL	-42.70 ng/mL	[-56.30, -29.10]	<0.05	Protection (Decreased)	
	Serum Creatinine (SCr)	-83.40 μmol/L	[-112.60, -54.20]	<0.01	Protection (Decreased)	
Histopathology	Paller Score (Renal Tubular Injury)	-12.70 Points	[-16.90, -8.50]	<0.01	Protection (Decreased)	[115]
Survival Status	7-Day Survival Rate	+0.02 (Odds Ratio)	[0.85, 1.19]	>0.05	No Significant Effect	[116]

Note: MAP, Mean arterial pressure; PVD, Perfused small vessel density; MFI, Microvascular flow index; IL-1β, Interleukin-1β; IL-6, Interleukin-6; TNF-α, Tumor necrosis factor-α; HMGB-1, High mobility group box 1; TIMP-2, Tissue inhibitor of metalloproteinase 2; IGFBP-7, Insulin-like growth factor-binding protein 7; NGAL, Neutrophil gelatinase-associated lipocalin; SCr, Serum creatinine.

shown to significantly reduce the mortality rate in patients with sepsis compared to those receiving conventional treatment alone [117].

2.3.3 Comparative study of different Chinese medicinal herbal extracts

Various Chinese medicinal herbs possess distinct therapeutic "specialties" and modes of action when dealing with sepsis. For example, the extract of *Sophora flavescens* demonstrated a potent anti-inflammatory effect in an LPS-induced sepsis model. It not only outperformed other herbal remedies but also significantly reduced the levels of pro-inflammatory factors such as TNF-α and IL-6 [118]. On the other hand, the polysaccharides of *Ganoderma lucidum* take a different approach: they not only enhance immune function but also reduces oxidative damage, showing promising potential in sepsis management [119].

Take two commonly used TCM injections in clinical practice for example: BBD mainly "extinguishes the fire" by inhibiting the NLRP3 inflammasome; while XBJ protects organs and reduces damage by regulating ferroptosis and alleviating oxidative stress.

These examples clearly demonstrate that TCM treatments are not a "single formula that can cure all diseases". Instead, each herbal extract has its own mechanism and distinct advantages. To optimize the use of TCM in treating sepsis, it is crucial to understand the specific therapeutic targets of each component and how their combination can be optimized for better results.

2.4 Application prospects of TCM extracts in sepsis treatment

2.4.1 Challenges in clinical application

Although TCM extracts hold considerable promise for the treatment of sepsis, several challenges remain before they can be widely applied in clinical practice. Sepsis is an inherently complex condition—once the immune system becomes dysregulated, systemic inflammation and organ failure ensue, resulting in high mortality rate [120]. While TCM has several centuries of experience in treating infections, translating these experiences into therapies recognized by modern medicine remains a significant hurdle [121].

One major obstacle is the lack of standardization in TCM. Different manufacturers produce varying formulations, often with significant differences in batches, extraction methods, and even the chemical composition of the same herbal remedy, preventing the establishment of consistent, reliable data on the efficacy and safety of these treatments.

The scientific community generally relies on high-quality evidence, especially RCTs. However, most TCM prescriptions consist of multiple ingredients, each targeting various molecular pathways, emphasizing holistic regulation. This is fundamentally different from the "one drug, one target" paradigm of Western medicine. Therefore, applying the RCT methodology to evaluate TCM is extremely challenging. This has resulted in a rather awkward situation: although many clinicians and patients believe in the efficacy of TCM, the lack of solid data, commonly available for Western medicine, makes it difficult to

substantiate its benefits with scientific evidence [122, 123]. Furthermore, the integration of TCM into sepsis treatment requires collaboration between Western medicine and TCM practitioners. However, due to their differing approaches, communication and collaboration remain difficult.

The complexity of sepsis itself adds another layer of difficulty, as TCM extracts often exert multiple effects, such as anti-inflammatory, antioxidant, and immune regulation. Although this is an advantage, it also complicates identification of specific components responsible for therapeutic effects. Questions arise about potential interactions with antibiotics or other conventional treatments [124, 125].

Therefore, more rigorous and comprehensive research is needed in the future. Not only should we investigate whether TCM can improve patient outcomes, but we also need to determine the precise mechanisms through which TCM works and how it can be combined with existing treatments. Only by solving these problems can TCM truly fulfill its potential in the treatment of sepsis and provide broader benefits to patients.

2.4.2 Future research directions

For TCM extracts to truly "establish a firm foothold" in the treatment of sepsis, research efforts should be directed towards several key areas.

First of all, we need to employ more robust scientific methodologies to elucidate how TCM extracts work. For instance, modern technologies such as molecular biology, network pharmacology, and high-throughput screening can help identify the active TCM ingredients and determine which specific targets they modulate within the immune system [126-128]. Only by understanding the mechanism can we explain clearly how TCM regulates inflammation, enhances immunity, and protects organs - rather than simply stating "it works", without being able to provide a rationale.

Second, the extraction and formulation of TCM must be standardized. A major challenge currently is the variability in the effects of different batches of herbal medicines, which significantly hinders their clinical promotion. Therefore, it is essential to establish unified and stable production processes and quality control standards [129]. Furthermore, clear medication guidelines should be formulated, including dosage and administration timing, to support the conduct of high-quality clinical trials.

Regarding experimental research, future studies should focus on designing rigorous RCTs, especially to evaluate the combined effects of TCM extracts and existing therapies (such as antibiotics and fluid resuscitation). It is possible that TCM could generate a synergistic effect when used in conjunction with conventional treatments [130]. Additionally, the timing of administration and optimal dosage are crucial aspects that need to be addressed through systematic research.

Safety considerations are equally important. TCM extracts may interact with Western medications, potentially affecting their metabolism or elimination. In critical conditions such as sepsis, extra caution is necessary. Therefore, pharmacokinetic and pharmacodynamic profiles of TCM extracts must to be specifically evaluated, and adverse reactions should be closely monitored in clinical settings [131].

In addition, beyond focusing solely on treating diseases, it is also worth exploring whether TCM can actually prevent diseases. TCM has long emphasized "preventing diseases before they occur". In high-risk populations for sepsis (such as patients with severe infections), could the use of certain TCM extracts serve as a preventive measure, or act as an auxiliary intervention in the early stages of the disease? This could potentially reduce the risk of progression and warrants further exploration [132].

In conclusion, the integration of ancestral wisdom with modern scientific research methods is crucial. By fostering interdisciplinary collaboration and respecting the holistic perspective of TCM, while also explaining its mechanisms and clinical value in scientific language, TCM extracts can truly be integrated into the modern treatment system for sepsis.

2.4.3 Exploration of comprehensive treatment strategies

Combining TCM extracts with conventional treatments may offer a particularly promising approach to improving the management of sepsis [133]. After all, sepsis is not a single issue but rather a complex interplay of issues, including immune dysfunction, inflammatory storms, and organ damage. Addressing this multifaceted condition with a single medication is challenging. However, TCM's emphasis on holistic conditioning can precisely fill this gap.

Many studies have shown that TCM herbal extracts are effective in regulating the immune system, suppressing excessive inflammation, and protecting organs. These properties make them particularly suitable as adjunctive treatment in sepsis management.

A promising approach is to combine TCM extracts with conventional treatments such as antibiotics, fluid resuscitation, and life support. For instance, some TCM formulations not only enhance the efficacy of antibiotics in killing bacteria but also improve microcirculation, reduce inflammation, and alleviate oxidative stress. These combined effects may improve overall treatment outcome and potentially reduce the risk of developing antibiotic resistance.

Table 2. Summary of pharmacological studies on TCM extract

TCM name (latin name)	Active components	Core targets/signaling pathways	Study type	Results	Reference
Astragalus membranaceus	Astragalus polysaccharides (APS), Astragaloside IV	Nrf2-ARE, NF-κB, PERK/IRE1α, Bcl-2/Bax	Cell experiment, Animal experiment, Clinical RCT	1. Enhances SOD and GPx activities and reduces MDA levels; 2. Inhibits ER stress-mediated cardiomyocyte apoptosis; 3. Improves $CD4^+/CD8^+$ ratio, reduces postoperative sepsis incidence by 35%	[136, 137]
Salvia miltiorrhiza	Tanshinone IIA, Salvianolic acid A/B	Nrf2, AMPK, VEGF/PI3K/Akt, NF-κB	Cell experiment, Animal experiment, Clinical RCT	1. Activates Nrf2 pathway to enhance antioxidant capacity; 2. Promotes mitochondrial biogenesis and autophagy; 3. Improves myocardial perfusion, reduces 90-day readmission rate by 25%	[138, 139]
Scutellaria baicalensis	Baicalin, Baicalein	NF-κB, JAK-STAT, NLRP3 inflammasome	Cell experiment, Animal experiment, Clinical RCT	1. Inhibits cytokine storm (IL-6 and TNF-α reduced by 55%); 2. Stabilizes vascular endothelium and improves MAP; 3. Exhibits synergistic bacteriostatic effect with antibiotics	[140, 141]
Panax ginseng	Ginsenoside R1, Rg1, Rb1	AMPK/PGC-1α, eNOS, Bcl-2/Bax	Cell experiment, Animal experiment, Clinical RCT	1. Enhances myocardial mitochondrial function and reduces apoptosis; 2. Improves myocardial oxygen consumption, reduces postoperative troponin I level by 40%; 3. Regulates neuro-endocrine-immune network	[141, 142]
Panax notoginseng	Ginsenoside Rg1, Rb1	eNOS, Mitochondrial apoptotic pathway	Animal experiment, Clinical RCT	1. Increases NO production and protects endothelial function; 2. Alleviates myocardial ischemia-reperfusion injury; 3. Improves myocardial oxygenation in patients undergoing cardiovascular surgery	[143, 144]
Carthamus tinctorius	Hydroxysafflor yellow A	NLRP3, NF-κB	Cell experiment, Animal experiment	1. Inhibits NLRP3 inflammasome activation and reduces IL-1β release; 2. Improves microcirculation and reduces vascular permeability	[145, 146]
Xuebijing Injection (Compound)	Hydroxysafflor yellow A, Ferulic acid, etc.	TLR4/NF-κB, HO-1, Coagulation pathway	Clinical RCT, Animal experiment	1. Reduces 28-day mortality by 18% and improves SOFA score; 2. Inhibits coagulation disorders and reduces microthrombus formation; 3. Improves renal microcirculation and reduces SCr	[147, 148]
Shenmai Injection (Compound)	Ginsenosides, Ophiopogon polysaccharides	Bcl-2/Bax, caspase-3	Clinical RCT, Animal experiment	1. Reduces troponin level in sepsis patients; 2. Improves left ventricular ejection fraction; 3. Alleviates myocardial mitochondrial damage	[149, 150]

Note: APS, Astragalus polysaccharides; Nrf2-ARE, Nuclear factor erythroid 2-related factor 2-antioxidant response element; NF-κB, Nuclear factor kappa-B; PERK/IRE1α, Protein kinase R-like endoplasmic reticulum kinase/Inositol-requiring enzyme 1α; Bcl-2/Bax, B-cell lymphoma-2/Bcl-2-associated X protein; RCT, Randomized controlled trial; SOD, Superoxide dismutase; GPx, Glutathione peroxidase; MDA, Malondialdehyde; AMPK, Adenosine 5'-monophosphate-activated protein kinase; VEGF/PI3K/Akt, Vascular endothelial growth factor/Phosphatidylinositol 3-kinase/Protein kinase B; JAK-STAT, Janus kinase-signal transducer and activator of transcription; NLRP3, NOD-like receptor thermal protein domain associated protein 3; IL-6/TNF-α, Interleukin-6/Tumor necrosis factor-α; MAP, Mean arterial pressure; PGC-1α, Peroxisome proliferator-activated receptor gamma coactivator 1-α; eNOS, Endothelial nitric oxide synthase; TLR4, Toll-like receptor 4; HO-1, Heme oxygenase-1; SOFA, Sequential Organ Failure Assessment; SCr, Serum creatinine.

Moreover, TCM may help mitigate the side effects of conventional treatments. For instance, antibiotics often cause gastrointestinal damage. Some Chinese herb combinations or interventions (such as acupuncture) may help alleviate gastrointestinal discomfort and maintain intestinal barrier function - an essential consideration for sepsis patients, as their intestines are often damaged [134]. Additionally, therapies focusing on overall condition, such as acupuncture and tonic herbs, can supplement conventional treatments, facilitating faster recovery and improving patients' quality of life.

Another key direction for future research is personalized treatment. TCM has long emphasized "treating each patient individually". By taking into account a patient's background (such as underlying diseases, genetic characteristics, and immune status), and combining this information with the disease stage, the most appropriate combination of TCM and Western medicines could be selected, potentially enhancing treatment precision [135]. This approach necessitates the identification of reliable biomarkers to guide treatment decisions, including when and which TCM intervention to use for optimal results.

In conclusion, integrating TCM extracts into the comprehensive treatment of sepsis should not aim to replace existing therapies, but to achieve a "synergistic effect". The summary of pharmacological studies and basic characteristics of included clinical studies on TCM extract were shown in **Tables 2** and **3**, respectively.

Table 3. Basic characteristics of included clinical studies on TCM extract

Study design	Sample size (intervention/control)	Intervention measures	Control measures	Primary outcomes	Secondary outcomes	References
Multicenter RCT	600/600	Preoperative oral Astragalus polysaccharides (100 mg/day) for 2-4 weeks + Standard perioperative care	Standard perioperative care (antibiotic prophylaxis, fluid resuscitation)	Incidence of postoperative sepsis (primary); 30-day mortality	ICU length of stay, $CD4^+/CD8^+$ ratio, serum IL-6/TNF-α levels	[151]
Single-center RCT	100/100	Intraoperative Xuebijing Injection (20-40 mL/h continuous infusion) + Sepsis Bundle Therapy	Sepsis Bundle Therapy (early antibiotics, source control, organ support)	28-day mortality (primary); Change in SOFA score at 72 hours	Lactate clearance rate, coagulation parameters (INR, platelet count), renal function (SCr)	[152]
Single-center RCT	40/40	Intraoperative baicalin (100 mg bolus + 50 mg/h maintenance) + Conventional therapy	Conventional therapy (antibiotics, vasopressors, fluid resuscitation)	Change in mean arterial pressure (MAP) at 6 hours; Serum IL-6 level reduction	Incidence of septic shock, 14-day mortality, adverse events (hypotension, allergy)	[153]
Single-center RCT	75/75	Preoperative oral Panax notoginseng extract (50 mg/day) for 2 weeks + CABG perioperative care	CABG perioperative care (cardiopulmonary bypass management, antiplatelet therapy)	Postoperative troponin I level at 24 hours; Myocardial oxygen consumption	Left ventricular ejection fraction (LVEF), length of hospital stay, surgical site infection rate	[154]
Multicenter RCT	150/150	Postoperative Salvia miltiorrhiza Injection (20 mL/day) for 7-10 days + Standard rehabilitation	Standard rehabilitation (nutritional support, physical therapy)	90-day readmission rate (primary); LVEF improvement at 1 month	Myocardial fibrosis markers, inflammatory factors (CRP, procalcitonin), quality of life score	[155]
Systematic review + Meta-analysis	12 RCTs (n=1,280 total)	Xuebijing Injection (100-200 mL/day) + Conventional sepsis treatment	Conventional sepsis treatment (antibiotics, renal replacement therapy if needed)	Change in serum creatinine (SCr); Renal microcirculation parameters (PVD, MFI)	Urinary NGAL/TIMP-2*IGFBP-7 levels, Paller score (renal tubular injury), 30-day survival	[156]
Single-center RCT	50/50	Postoperative Shenmai Injection (20 mL/day) for 5-7 days + Septic cardiomyopathy management	Septic cardiomyopathy management (inotropic agents, diuretics)	Change in LVEF at 1 week; Serum troponin level reduction	BNP level, myocardial mitochondrial function markers, length of ICU stay	[157]
Meta-analysis	15 RCTs (n=1,500 total)	Postoperative Astragalus Injection (20 mL/day) for 5-7 days + Standard postoperative care	Standard postoperative care (infection surveillance, wound care)	Infection recurrence rate (primary); Quality of life score	Macrophage phagocytic activity, serum IFN-γ level, adverse events (hyperkalemia)	[158]

Note: RCT, Randomized controlled trial; ICU, Intensive care unit; IL-6, Interleukin-6; TNF-α, Tumor necrosis factor-α; SOFA, Sequential Organ Failure Assessment; INR, International normalized ratio; SCr, Serum creatinine; MAP, Mean arterial pressure; CABG, Coronary artery bypass grafting; LVEF, Left ventricular ejection fraction; CRP, C-reactive protein; PVD, Perfusion vessel density; MFI, Microvascular flow index; NGAL, Neutrophil gelatinase-associated lipocalin; TIMP-2, Tissue inhibitor of metalloproteinase 2; IGFBP-7, Insulin-like growth factor-binding protein 7; BNP, Brain natriuretic peptide; IFN-γ, Interferon-γ.

3 PERIOPERATIVE SEPSIS: EPIDEMIOLOGY, PATHOPHYSIOLOGICAL FEATURES, AND TEMPORAL STRATEGIES FOR TCM INTERVENTIONS

Perioperative sepsis remains a critical global health concern, characterized by high morbidity, mortality, and imposing significant economic burden on healthcare systems. Its development reflects a complex interplay among patient vulnerability, surgical stress responses, and potential microbial exposure. A comprehensive understanding of its epidemiological distribution, underlying pathophysiological cascades, stage-specific therapeutic strategies is essential for improving clinical outcomes. TCM, with its holistic philosophy and emphasis on syndrome differentiation, offers a complementary approach within contemporary perioperative care. This section systematically reviews the epidemiological characteristics of perioperative sepsis, delineates its distinct pathophysiological mechanisms from community-acquired sepsis, and proposes a structured temporal framework for integrating TCM interventions across perioperative phases.

3.1 Epidemiological characteristics of perioperative sepsis

The epidemiology of perioperative sepsis is heterogeneous and involves multiple determinants, including patient-specific factors, surgical characteristics, institutional protocols, and broader socio-economic conditions. Its incidence and clinical impact vary substantially across different contexts, necessitating a multidimensional analytical perspective.

3.1.1 Incidence and variability across surgical specialties

Systematic reviews of global data from the past decade reported an overall incidence of perioperative sepsis ranging from 2% to 15%, though the true figure may be underestimated due to inconsistent diagnostic criteria [159, 160]. The most striking feature is the immense variability across surgical disciplines. High-risk procedures, particularly those involving the gastrointestinal tract, are associated with substantially elevated incidence rates. Abdominal surgeries, including bowel resections, procedures for perforated viscus, and pancreatic operations, frequently report sepsis rates exceeding 10%, and can be as high as 20-30% in complicated or contaminated cases [161, 162]. These elevated rates are attributed to the disruption of colonized luminal organs, significant tissue trauma, prolonged operative duration, and the risk of anastomotic leakage. In contrast, "clean" surgeries such as elective orthopedic procedures (e.g., joint replacements, spinal surgeries) generally exhibit lower sepsis rates, typically below 5%. Nevertheless, the risk is not negligible, particularly in elderly patients or those with multiple comorbidities undergoing prolonged procedures. Cardiothoracic and major vascular surgeries represent an intermediate-risk category, with sepsis rates influenced by factors such as cardiopulmonary bypass time, intraoperative hypothermia, and the implantation of prosthetic material. Neurosurgical procedures, while primarily clean, carry a unique risk related to surgical site infection, which may progress to meningitis or intracranial abscess, potentially progressing to systemic sepsis. This disparity underscores the critical importance of surgical site characteristics and the degree of physiological trespass in determining sepsis risk. The concept of surgical wound classification (clean, clean-contaminated, contaminated, dirty/infected) remains a fundamental, though imperfect, tool for predicting postoperative infectious complications and subsequent sepsis.

3.1.2 Patient-specific risk factors

Beyond surgical factors, patient demographics and baseline physiological reserves are major determinants of sepsis susceptibility.

Advanced age is one of the most consistent and potent risk factors. Age-related immune remodeling, commonly referred to as immunosenescence, is characterized by reduced naive T-cell output, impaired neutrophil function, and a chronic, low-grade pro-inflammatory state ("inflammaging"). This diminishes effective pathogen clearance while simultaneously increasing the risk of a dysregulated, hyperinflammatory response. A large retrospective cohort study involving more than 5,000 surgical patients demonstrated that individuals over 65 years old had a 2.5-fold higher risk of developing perioperative sepsis compared to younger adults [163]. Furthermore, sepsis in the elderly often presents atypically, without classic signs of fever or leukocytosis, leading to delays in diagnosis and treatment, which contributes to poorer clinical outcomes.

Pre-existing chronic diseases significantly amplify sepsis risk. Diabetes mellitus is a prototypical example, with evidence showing approximately a 1.8-fold higher incidence in postoperative sepsis among diabetic patients [164]. The underlying mechanisms are multifactorial: hyperglycemia impairs neutrophil chemotaxis and phagocytosis, induces endothelial dysfunction, and promotes a pro-inflammatory milieu. Additionally, diabetic neuropathy and microangiopathy may delay infection recognition. Chronic obstructive pulmonary disease (COPD) is associated with impaired mucociliary clearance and chronic airway colonization by pathogenic bacteria, thereby increasing the risk of postoperative pneumonia, a common precursor to sepsis. End-stage renal disease contributes to uremia-associated immunosuppression, while chronic liver disease impairs protein synthesis (including coagulation factors and opsonins) and Kupffer cell function. Malignancy, especially in patients receiving cytotoxic chemotherapy, predisposes to bone marrow suppression and neutropenia. The concept of "frailty", a syndrome of decreased physiological reserve across multiple organ systems, is increasingly recognized as a powerful integrative predictor of vulnerability to surgical stress and postoperative complications, including sepsis.

Malnutrition, particularly protein-calorie malnutrition, weakens both cellular and humoral immunity, impairs wound healing, and reduces respiratory muscle strength, thereby increasing vulnerability to pneumonia and surgical site infection. Obesity, on the other hand, is associated with chronic adipose tissue inflammation, technical surgical complexity, higher rates of deep wound infection, and altered antibiotic pharmacokinetics. Chronic alcohol consumption suppresses immune function and increases intestinal permeability, while smoking compromises pulmonary defense mechanisms and tissue oxygenation.

Suboptimal adherence to evidence-based perioperative protocols directly affects sepsis incidence, including delayed or inappropriate administration of surgical antibiotic prophylaxis, breaches in sterile technique, suboptimal perioperative glycemic control, and inappropriate management of invasive devices like urinary catheters and central venous lines, which serve as potential portals for infection. The increasing prevalence of multidrug-resistant organisms (MDROs) within healthcare settings, including methicillin-resistant *Staphylococcus aureus*

and carbapenem-resistant Enterobacteriaceae, has significantly complicated the management of postoperative infections and contributed to increased sepsis-related mortality.

The burden of perioperative sepsis is disproportionately concentrated in low- and middle-income countries. A multi-center study conducted across sub-Saharan Africa reported alarmingly high perioperative sepsis rates ranging from 18 to 22%, with associated mortality rates exceeding 40%, compared to approximately 10-15% in high-income countries [165]. The reasons for these disparities are multifactorial and systemic, including limited access to sterile surgical environments and reliable sterilization equipment, shortages of essential antimicrobial agents, delayed or unavailable microbiological diagnostics, advanced disease severity at presentation due to delayed healthcare access, and fewer critical care capacity for organ support. These disparities highlight that perioperative sepsis represents not only a clinical challenge but also a manifestation of healthcare inequality, demanding targeted interventions at the health system level.

3.1.3 Temporal dynamics of onset

Early-onset sepsis (Within 48 hours) is most commonly linked to intraoperative events. Causes include gross contamination from a perforated viscus, inadequate antisepsis of the surgical field, contamination from operating room personnel or the environment, and—although rare—contamination of intravenous fluids or anesthesia equipment. The rapid onset typically suggests exposure to a high microbial inoculum or infection with highly virulent organisms.

Delayed-onset sepsis (7-14 days postoperatively) is more commonly associated with postoperative complications occurring during the wound-healing phase. The most frequent source is surgical site infection, which may involve the superficial incision layer, deep soft tissues, or an organ/space compartment (e.g., intra-abdominal abscess). Other sources include hospital-acquired pneumonia (often ventilator-associated pneumonia), catheter-associated urinary tract infections, and infections related to intravascular devices. Hematogenous dissemination from a distant and occasionally occult infectious focus is also possible. Recognizing this temporal distribution is essential for optimizing postoperative surveillance, guiding diagnostic evaluation, and informing the selection of empirical antibiotic therapy.

3.2 Pathophysiological mechanisms of perioperative sepsis

The pathophysiology of perioperative sepsis shares fundamental features with sepsis from other etiologies; however, it is distinguished by a planned surgical insult, which precedes and conditions the infectious event. This "two-hit" paradigm, where operative trauma acts upon a potentially vulnerable host, results in a unique and often more unstable clinical trajectory.

3.2.1 The "first hit": surgical trauma

Even in the absence of infection, major surgery induces a profound systemic inflammatory response syndrome. Tissue injury and cellular necrosis leads to the release of endogenous DAMPs, including high-mobility group box 1 (HMGB1), heat shock proteins (HSPs), mitochondrial DNA (mtDNA), and adenosine triphosphate (ATP). These molecules are recognized by pattern recognition receptors (PRRs) on immune cells, such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs). TLR4, for instance, recognizes HMGB1, initiating a signaling cascade that converge on NF-κB, a central transcriptional regulator of pro-inflammatory gene expression, resulting in a massive release of early response cytokines including TNF-α and IL-6. This sterile inflammation priming alters endothelial function and contributes to postoperative organ dysfunction. Simultaneously, the surgical stress response, mediated by activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, results in elevated circulating cortisol and catecholamines, which have complex, often immunosuppressive effects in the later phases.

3.2.2 Microbial invasion and the "second hit"

In perioperative sepsis, the sterile inflammatory "first hit" is rapidly amplified by a "second hit" of pathogenic invasion. Unlike community-acquired sepsis, commonly originating from pneumonia or UTI, the infectious source in perioperative sepsis is directly related to the operative site or perioperative complications. Microbial components, such as LPS from Gram-negative bacteria and lipoteichoic acid from Gram-positive bacteria, act as pathogen-associated molecular patterns (PAMPs), providing a potent second signal through PRRs, thereby exponentially amplifying the inflammatory cascade. A critical and often underrecognized factor is the disruption of the gut barrier. Surgical stress, perioperative ischemia–reperfusion injury, opioid use, and alterations in mesenteric perfusion increase intestinal permeability, allowing translocation of bacteria and endotoxins from the gut lumen into the systemic circulation and lymphatic system. This not only provides a source of pathogens but also intensifies systemic inflammation, creating a vicious cycle.

3.2.3 The unique role of coagulation dysregulation

The convergence of surgical trauma and sepsis creates a prothrombotic milieu, predisposing patients to profound hemostatic disturbance. Surgery inherently induces endothelial injury, resulting in exposure of tissue factor (TF) and activation of the extrinsic coagulation pathway. Platelets are activated by both damaged endothelium and inflammatory cytokines. Sepsis further exacerbates coagulation abnormalities by causing widespread endothelial dysfunction, suppressing natural anticoagulant pathways (e.g., protein C, antithrombin III), and impairing fibrinolysis. The cumulative effect results in a shift

toward a hypercoagulable state, manifested as disseminated intravascular coagulation (DIC) in its early pro-thrombotic phase. Microvascular thrombosis develops in vital organs (e.g., lungs and kidneys), contributing to tissue hypoxia and multiple organ dysfunction syndrome (MODS). This thrombotic tendency is often more pronounced in perioperative sepsis compared to medical sepsis. The histopathological study of patients with sepsis revealed that in surgical sepsis cases, there were diffuse microthrombi in the lung and kidney tissues, while in non-surgical sepsis cases, this proportion significantly decreased. This highlights the synergistic pro-coagulant effect of tissue damage and systemic inflammation [166].

3.2.4 Myocardial dysfunction in the perioperative context

Sepsis-induced myocardial dysfunction, often termed septic cardiomyopathy, presents a particular challenge in postoperative patient. It is characterized by biventricular dilatation, reduced left ventricular ejection fraction (LVEF), and attenuated responsiveness to fluid resuscitation and catecholamines. In the perioperative setting, septic cardiomyopathy occurs against a background of additional cardiac stressors, including intraoperative myocardial ischemia–reperfusion injury (particularly in cardiac surgery), fluid shifts, perioperative blood loss, and the increased metabolic demands associated with wound healing and systemic inflammation. Echocardiographic studies reveal that patients undergoing perioperative sepsis may experience acute reductions in LVEF of 20-30%. While often reversible within 7-10 days following effective infection control, acute deterioration can precipitate circulatory collapse [167]. The mechanisms are multifactorial and include circulating myocardial depressant factors (e.g., TNF-α and IL-1β), direct bacterial toxin effects, mitochondrial dysfunction with impaired energy production, disruption of intracellular calcium handling, and excessive production of nitric oxide leading to pathological vasodilation and direct cardiotoxicity.

3.2.5 The immunological paradox and sepsis-induced immunosuppression

Following the initial hyperinflammatory phase, many sepsis patients enter a state of sustained immunosuppression, which is increasingly recognized as a major driver of late morbidity and mortality due to secondary infections. This immunosuppressive phenotype is characterized by widespread lymphocyte apoptosis (particularly affecting B cells and $CD4^+$ T helper cells), expansion of immunosuppressive regulatory T cells and myeloid-derived suppressor cells (MDSCs), and monocyte deactivation (reduced HLA-DR expression). In perioperative patient, this immunosuppressive phase may be further exacerbated by anesthesia-related immunomodulation, blood transfusion, and postoperative pain management. Collectively, these factors predispose patients to delayed-onset nosocomial infections and complicating postoperative recovery.

3.3 Temporal framework for TCM interventions in perioperative sepsis

A distinctive strength of TCM lies in its dynamic, stage-based therapeutic framework, aligning with the evolving pathophysiological trajectory of perioperative sepsis. The principle of "treatment according to temporal stage" (Yishi Zhifa) provides a structured paradigm for tailoring interventions across the perioperative continuum, with interventions directed toward the dominant pathological patterns at each phase.

3.3.1 Preoperative phase (prevention): immune priming and metabolic conditioning

The TCM principle of "treating the undiseased" (Zhi Weibing) parallels the modern strategy of prehabilitation. The goal is to strengthen Zhengqi (upright qi, or host defensive/adaptive capacity) to better withstand the upcoming surgical trauma (Xieqi or pathogenic factor). This involves fortifying the immune system, stabilizing metabolic homeostasis, and improving organ functional reserve.

Astragalus membranaceus (Huang Qi) is regarded as the foundational herb for preoperative fortification. Its bioactive constituents—APS and saponins (astragalosides)—exhibit remarkable immunomodulatory properties. APS can enhance the phagocytic activity of macrophages, promote lymphocyte proliferation and differentiation, and modulates the Th1/Th2 balance toward immune homeostasis. APS has also been reported to increase regulatory T cells, which may help modulate the postoperative inflammatory response and prevent excessive tissue damage. Furthermore, Astragalus exhibits anti-inflammatory effects by inhibiting the NF-κB pathway, thereby reducing the production of TNF-α, IL-6, and other pro-inflammatory cytokines. Several meta-analyses of randomized controlled trials, primarily conducted in China, have indicated that preoperative supplementation with Astragalus (typically for 1-4 weeks) may significantly reduce the incidence of postoperative infectious complications (including sepsis) by approximately 30-40% and shorten hospital stays in patients undergoing major surgery [168].

Panax notoginseng (San Qi), renowned for its ability to invigorate blood and resolve stasis without increasing hemorrhagic risk, is particularly suitable for preoperative microcirculatory optimization. Its principal ginsenosides (Rg1, Rb1) exert antioxidant effects, scavenging ROS generated during ischemia-reperfusion injury. These compounds also protect endothelial function by promoting nitric oxide release and reducing endothelial adhesion molecule expression. A study demonstrated that preoperative administration of Panax notoginseng significantly reduced postoperative myocardial injury biomarkers, with troponin I levels approximately 40% lower than controls [169]. Improvements in indices of myocardial oxygen utiliza-

tion were also observed, suggesting cardioprotection mediated through mitochondrial stabilization and suppression of apoptosis-related signaling pathways [170, 171].

Effective implementation of preoperative TCM conditioning requires adequate lead time. Clinical guidelines and studies suggest initiating preoperative TCM conditioning 2-4 weeks before elective major surgery to allow measurable modulation of immune parameters and metabolic parameters. A dose-response study on APS indicated that the preoperative optimization approach should be personalized based on TCM pattern diagnosis [172]. For example, supplementing Qi and Yin may be appropriate for frail elderly patient characterized by Qi-Yin Deficiency, while clearing damp-heat and strengthening the spleen may be indicated in patient with chronic gastrointestinal dysfunction.

3.3.2 Intraoperative and immediate postoperative phase (hyperinflammatory stage): anti-inflammatory and organ protection

This phase corresponds to the peak of sterile and infection-driven systemic inflammatory responses and early development of organ dysfunction. In TCM theory, this stage is often characterized as *Heat Toxin Blazing Internally* (Redu Neisheng), accompanied by Qi Stagnation and blood stasis, and in severe cases, impending Yang collapse. Accordingly, the TCM strategy shifts to clearing heat, detoxifying, cooling the blood, and protecting organ function, while cautiously preserving Zhengqi.

Herbs like *Scutellaria baicalensis* (Huang Qin), Forsythia suspensa (Lian Qiao), and *Isatis indigotica* (Ban Lan Gen) have strong antibacterial and endotoxin-neutralizing properties. Baicalein, derived from Scutellaria, inhibits pro-inflammatory enzymes such as cyclooxygenase-2 (COX-2) and lipoxygenase (LOX) and suppresses NF-κB activation, thereby attenuating transcription of TNF-α, IL-6, and related cytokines. Salvia miltiorrhiza (Dan Shen) and Carthamus tinctorius (Hong Hua) are particularly relevant in addressing sepsis-associated microcirculatory dysfunction and DIC. Tanshinones derived from Salvia improve blood flow, inhibit platelet aggregation, and exert endothelial antioxidant effects, thereby mitigating thromboinflammatory injury.

Modern injectable TCM formulations represent a key interface between traditional pharmacotherapy and modern intensive care practice. Xuebijing Injection, a compound containing extracts of Carthamus, Paeonia, Ligusticum, Salvia, and Angelica, has been extensively studied in sepsis management. Multiple RCTs and meta-analyses suggest that adjunctive administration of Xuebijing to standard sepsis care accelerates reductions in circulating TNF-α, IL-6, and PCT, improves coagulation parameters, shortens vasopressor duration, and may reduce 28-day mortality [173, 174]. Mechanistically, its effects involve anti-endotoxin, anti-inflammatory, immunomodulatory, and microcirculation-improving activities. Another example is Shenmai injection, derived from Panax ginseng and Ophiopogon japonicus. Traditionally indicated for supplementing Qi and nourishing Yin, Shenmai injection has shown potential benefits in septic shock, including improving hemodynamic stability and protecting myocardial function.

TCM interventions during this acute phase must be implemented strictly as adjunctive therapies and should not replace evidence-based standard-of-care measures, including early antibiotic administration, source control, and organ support. The optimal timing of administration (preferably early within the first 24 hours of diagnosis) and patient selection based on TCM pattern differentiation remain areas requiring active research.

3.3.3 Recovery and post-sepsis phase (immunosuppressive/prolonged inflammation stage): restoring homeostasis and functional recovery

After the acute hyperinflammatory phase, patients often face a prolonged period characterized by immune dysregulation, catabolic depletion, and functional decline. In TCM theory, this stage is commonly described as deficiency of both Qi and Yin (Qi-Yin Liangxu), accompanied by residual blood stasis and phlegm-damp accumulation. Therapeutic focus shifts to tonification, elimination of residual pathogenic factors, and promotion of tissue repair.

Formulas such as Shengmai San (composed of Ginseng, Ophiopogon, Schisandra) or Liuwei Dihuang Wan are commonly used to replenish vital energy and fluids that depleted by the hypercatabolic state of sepsis. Clinically, such approaches aim to ameliorate fatigue, anorexia, and generalized weakness. Atractylodes macrocephala (Bai Zhu) and Poria cocos (Fu Ling) are used to strengthen spleen function and resolve dampness, addressing anorexia and digestive weakness. Mild blood-activating herbs may be continued judiciously to facilitate recovery of organ function.

Emerging evidence suggests that several TCM herbs have prebiotic effects and can modulate gut microbial composition and associated gut–lung and gut–brain axes. Restoring intestinal barrier integrity and microbial homeostasis aligns with the TCM concept of fortifying the "acquired foundation" (Spleen-Stomach system), which is crucial for overall recovery and immune reconstitution. Adjunctive non-pharmacological modalities, such as acupuncture and moxibustion, can further support recovery. Acupuncture at points like Zusanli (ST-36), Guanyuan (CV-4), and Qihai (CV-6) can help regulate immune function, improve gastrointestinal motility, reduce residual inflammatory burden, and address symptoms like pain, insomnia, and cognitive dysfunction associated with post-sepsis syndrome.

In conclusion, perioperative sepsis is a time-sensitive, pathophysiologically complex condition requiring stage-specific management strategies. TCM, with its rich pharmacopeia and sophisticated diagnostic framework centered on pattern differentiation and temporal progression, offers valuable tools for modulating the host response across each stage. When applied as evidence-informed adjunctive therapy within a standardized perioperative care pathway, TCM interventions may contribute to improved immune regulation, microcirculatory stability, and functional recovery. Future research should focus on high-quality, multicenter RCTs incorporating standardized biomarker panels and outcome assessments to further refine this integrative temporal strategy and solidify its role in evidence-based sepsis management.

4 CONCLUSION

In recent years, accumulating evidence has elucidated the multi-dimensional mechanism by which TCM extracts alleviates sepsis-associated myocardial injury, demonstrating unique advantages beyond conventional single-target pharmacotherapies [175-177]. These natural compound preparations exert synergistic regulatory effects by concurrently modulating oxidative stress, suppressing excessive inflammation, maintaining mitochondrial function, and enhancing the anti-apoptotic ability of cardiomyocytes. More importantly, this holistic regulatory concept is highly consistent with the evolving trend in critical care medicine, which is shifting from a predominantly "pathogen-eradication–oriented" strategy to an "immune homeostasis reconstruction and organ protection" paradigm. Collectively, these findings suggest that TCM may serve not only as an auxiliary means but also as a source of novel theoretical frameworks and intervention paths for the treatment of sepsis.

However, there are still substantial translational bottlenecks. Most supportive data are derived from animal models, such as LPS or CLP models. Although these models are convenient to operate, they inadequately recapitulate the dynamic evolution of human sepsis - especially late-stage immune suppression, metabolic reprogramming, and interdependent multi-organ failure. The resulting "efficacy illusion" may lead to an overestimation of clinical value. Moreover, the inherent chemical complexity of TCM extracts—some formulations containing dozens of bioactive constituents—poses challenges in identifying definitive pharmacologically active components, characterizing pharmacokinetic profiles, and predicting drug–drug interactions (such as vancomycin, norepinephrine) in the intensive care setting. Without standardized extraction processes, rigorous quality control metrics, and reliable PK/PD models, even formulations with robust preclinical performance may face significant barriers to precise clinical application.

Safety considerations are equally critical. The assumption that "natural equates safe" should be avoided. Reports indicate that astragalus injection may be associated with immediate hypersensitivity reactions, the components of danzhenyuan may inhibit the CYP3A4 enzyme and thereby affect the metabolism of antibiotics, and long-term use of Xuebijing may occasionally lead to an increase in transaminase or creatinine levels in patients with liver and kidney dysfunction [178-180]. Although the overall incidence of such adverse events appears relatively low, even rare complications may have serious consequences in critically ill patients. Therefore, it is urgent to establish dedicated pharmacovigilance system for TCM injections, develop organ function–based individualized medication guidelines, and clearly delineate potential adverse reactions and contraindications in the product labeling.

Looking forward, advancing this field from empirical exploration to evidence-based integration requires breakthroughs in at least three key domains. First, high-quality multicenter RCTs should be designed with patient-centered outcomes, not only focusing on 28-day mortality rates, but also including comprehensive endpoints such as the speed of cardiac function recovery, length of ICU stay, and quality of life at 6 months; Second, an integrated research framework linking mechanistic studies, clinical trials and real-world data should be established. Emerging technologies such as organoids, single-cell sequencing, and artificial intelligence may facilitate systematic characterization of the multi-component, multi-target properties of TCM formulations; Third, interdisciplinary collaboration among experts in TCM, critical care medicine, pharmacology, toxicology, and regulatory science is essential to jointly formulate a research path for TCM compound preparations that conforms to international standards. Only in this way can the thousand-year wisdom of TCM be transformed into repeatable, scalable, and reliable modern critical care strategies, providing more effective and more humanistic care options for patients with sepsis worldwide.

DECLARATIONS

Author contributions

Yutong Sun, Qin Zhang, and Yan Zhang, contributed to the conception of the study and wrote the manuscript draft; Jiayin Wang, Weiqi Lin, Sixu Chen, Haiyi Qian, Xinyi Xie, Qixiang Xu and Xiaolong Yuan contributed to the information collection and analysis; Cuifeng Zhang helped perform the analysis by having constructive discussions and revising the manuscript.

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Competing interests

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REFERENCES

[1] Lin H, Wang W, Lee M, Meng Q, Ren H. Current status of septic cardiomyopathy: Basic science and clinical progress. Front Pharmacol. 2020 Mar 3;11:210. https://doi.org/10.3389/fphar.2020.00210

[2] Leoni D, Rello J. Cardiac arrest among patients with infections: Causes, clinical practice and research implications. Clin Microbiol Infect. 2017 Oct;23(10):730-735. https://doi.org/10.1016/j.cmi.2016.11.018

[3] Lahiri S, Rashid O, Goel A, Moondhra A. Septic myocarditis masquerading as acute inferior st-elevation myocardial infarction. Cureus. 2025 Dec;17(12):e98607. https://doi.org/10.7759/cureus.98607

[4] Chehab O, McGuire E, Wani RLS, Weerackody R. Acute myopericarditis caused by salmonella enterica serovar enteritidis: A case report. Eur Heart J Case Rep. 2020 Aug;4(4):1-5. https://doi.org/10.1093/ehjcr/ytaa173

[5] Daghestani MH. Septicemia caused by enterococcus coli in a pregnant woman after cerclage-a case report. SAGE Open Med Case Rep. 2024;12:2050313x241254990. https://doi.org/10.1177/2050313x241254990

[6] Li B, Xia Y, Mei S, Ye Z, Song B, Yan X, et al. Histone h3k27 methyltransferase ezh2 regulates apoptotic and inflammatory responses in sepsis-induced aki. Theranostics. 2023;13(6):1860-1875. https://doi.org/10.7150/thno.83353

[7] Yang H, Feng L, Jiang Z, Deng R, Wu X, Zeng K. Establishment of a novel in vitro model of sepsis-induced myocardial injury using septic serum: A comprehensive comparative study. J Inflamm Res. 2025 Jun 17;18:8015-8031. https://doi.org/10.2147/jir.S523124

[8] Zheng Y, Peng X, Zhang Y, Liu R, Long J. Elf4 improves sepsis-induced myocardial injury by regulating sting signaling-mediated t cells differentiation. Cell Biol Toxicol. 2025 May 7;41(1):82. https://doi.org/10.1007/s10565-025-10029-3

[9] Hu Y, Xu Y, Gao J, Ling B, Pan S, Liu S, et al. Integrated metabolomics and network pharmacology reveal the mechanisms of xuebijing in counteracting sepsis-induced myocardial dysfunction. J Ethnopharmacol. 2025 May 12;347:119729. https://doi.org/10.1016/j.jep.2025.119729

[10] Li W, Lin M, Li J, Ding Q, Chen X, Chen H, et al. Xijiao dihuang decoction protects against murine sepsis-induced cardiac inflammation and apoptosis via suppressing tlr4/nf-κb and activating pi3k/akt pathway. J Inflamm Res. 2024 Feb 8;17:853-863. https://doi.org/10.2147/jir.S428305

[11] Bian Z, Zhao A, Wang Q, Li Y, Liu Y, Yang W, et al. Advancements in research on the anti-metabolic dysfunction-associated steatotic liver disease effects and mechanisms of action of traditional chinese medicine polysaccharides: A review. Int J Biol Macromol. 2025 Sep;321(Pt 3):146292. https://doi.org/10.1016/j.ijbiomac.2025.146292

[12] Jiang C, Zeng X, Wang J, Wu X, Song L, Yang L, et al. Andrographolide sulfonate alleviates rheumatoid arthritis by inhibiting glycolysis-mediated activation of pi3k/akt to restrain th17 cell differentiation. Chin J Nat Med. 2025 Apr;23(4):480-491. https://doi.org/10.1016/s1875-5364(25)60855-7

[13] Liu J, Shi J, Niu S, Liu Z, Cui X, Song Y, et al. Genistein alleviates rheumatoid arthritis by inhibiting fibroblast-like synovial exosome secretion regulated by the rab27/nsmase2/mfge8 pathway. Food Funct. 2025 Feb 17;16(4):1407-1422. https://doi.org/10.1039/d4fo05730a

[14] Han Y, Xu J, Zhu Q, Yang L, Wang Y, Luo H, et al. Study on basic and clinical application of shufeng jiedu capsule in treating respiratory tract infection. Chin Med. 2023 Apr 25;18(1):45. https://doi.org/10.1186/s13020-023-00749-1

[15] Wu J, Tang G, Cheng CS, Yeerken R, Chan YT, Fu Z, et al. Traditional chinese medicine for the treatment of cancers of hepatobiliary system: From clinical evidence to drug discovery. Mol Cancer. 2024 Oct 1;23(1):218. https://doi.org/10.1186/s12943-024-02136-2

[16] Zhai Y, Liu L, Zhang F, Chen X, Wang H, Zhou J, et al. Network pharmacology: A crucial approach in traditional chinese medicine research. Chin Med. 2025 Jan 12;20(1):8. https://doi.org/10.1186/s13020-024-01056-z

[17] Su J, Burgoyne JR. Non-canonical pkg1 regulation in cardiovascular health and disease. Br J Pharmacol. 2025 Jul 18. https://doi.org/10.1111/bph.70148

[18] Chen X, Shao M, Liu Y, Zhou J, Cao F, Liu Y, et al. Role of the renin-angiotensin-aldosterone system in sepsis and its therapeutic targets. Int Immunopharmacol. 2025 Sep 23;162:115192. https://doi.org/10.1016/j.intimp.2025.115192

[19] Fu CF, Li JL, Chen JW, Liang H, Zhao WR, He SY, et al. Mechanism and therapeutic potential of traditional chinese medicine extracts in sepsis. Front Pharmacol. 2024 Jul 3;15:1365639. https://doi.org/10.3389/fphar.2024.1365639

[20] Song Y, Lin W, Zhu W. Traditional chinese medicine for treatment of sepsis and related multi-organ injury. Front Pharmacol. 2023 Jan 19;14:1003658. https://doi.org/10.3389/fphar.2023.1003658

[21] Zhao F, Cheng W, Wu D, Gong Z, Ma W, Xu J, et al. Hydroxysafflor yellow a ameliorates myocardial ischemia/reperfusion injury by promoting mdh1-mediated mitochondrial metabolic homeostasis. Phytomedicine. 2025 Aug;144:156868. https://doi.org/10.1016/j.phymed.2025.156868

[22] Li L, Huang K, Wang D, Yang D, Gao K, Tang J, et al. Chlorogenic acid and ferulic acid in smyad alleviate diabetic cardiomyopathy by inhibiting cardiac lipotoxicity via gcgr/pparα and gcgr/ampk pathways. Phytomedicine. 2025 Jul 25;143:156906. https://doi.org/10.1016/j.phymed.2025.156906

[23] Pan D, Chen P, Zhang H, Zhao Q, Fang W, Ji S, et al. Mitochondrial quality control: A promising target of traditional chinese medicine in the treatment of cardiovascular disease. Pharmacol Res. 2025 May;215:107712. https://doi.org/10.1016/j.phrs.2025.107712

[24] Zhou Z, Li M, Zhang Z, Song Z, Xu J, Zhang M, et al. Overview of panax ginseng and its active ingredients protective mechanism on cardiovascular diseases. J Ethnopharmacol. 2024 Nov 15;334:118506. https://doi.org/10.1016/j.jep.2024.118506

[25] Li Y, He L, Song H, Bao X, Niu S, Bai J, et al. Cordyceps: Alleviating ischemic cardiovascular and cerebrovascular injury - a comprehensive review. J Ethnopharmacol. 2024 Oct 5;332:118321. https://doi.org/10.1016/j.jep.2024.118321

[26] Lan Y, Wang H, Jing L, Li R, Sun J, Meng X, et al. Jatrorrhizine alleviates cytokine storm secondary lung injury via regulating cd39-dominant purinergic braking and downstream nlrp3 inflammasome. Phytother Res. 2025 May;39(5):2374-2392. https://doi.org/10.1002/ptr.8062

[27] Liu Z, Gao J, Ban Y, Wan TT, Song W, Zhao W, et al. Synergistic effect of paeoniflorin combined with luteolin in alleviating lipopolysaccharides-induced acute lung injury. J Ethnopharmacol. 2024 Jun 12;327:118022. https://doi.org/10.1016/j.jep.2024.118022

[28] Zou F, Zou J, Du Q, Liu L, Li D, Zhao L, et al. Xuebijing injection improves the symptoms of sepsis-induced acute lung injury by mitigating oxidative stress and ferroptosis. J Ethnopharmacol. 2025 Jan 30;337(Pt 1):118732. https://doi.org/10.1016/j.jep.2024.118732

[29] Qi LY, Xing JX, Ouyang BQ, Li YF, Lei M. [Role of mitophagy affecting macrophage polarization in immunomodulationin sepsis and traditional chinese medicine intervention:A review]. Zhongguo Yi Xue Ke Xue Yuan Xue Bao. 2024 Oct;46(5):720-731. https://doi.org/10.3881/j.issn.1000-503X.15849

[30] Ding W, Qian K, Bao W, Wang Z. Phellodendrine inhibits oxidative stress and promotes autophagy by regulating the ampk/mtor pathway in burn sepsis-induced intestinal injury. Toxicol Res (Camb). 2025 Feb;14(1):tfae233. https://doi.org/10.1093/toxres/tfae233

[31] Fan X, Xu J, Gao J, Zhang J, Wang Y, Shan Y, et al. Ferroptosis in pulmonary fibrosis: Pathogenesis and traditional chinese medicine-driven therapeutic approaches. Front Cell Dev Biol. 2025 Jul 18;13:1598924. https://doi.org/10.3389/fcell.2025.1598924

[32] Yang HS, Mauki DH, Zheng YX, Wang TH, He XY. Terpenoids: A promising traditional chinese medicine for neuropathic pain relief. Pharmacol Res. 2025 Jun;216:107789. https://doi.org/10.1016/j.phrs.2025.107789

[33] Scherer R, Braun-Falco O. Alternative pathway complement activation:A possible mechanism inducing skin lesions in benign gonococcal spesis. Br J Dermatol. 1976 Sep;95(3):303-309. https://doi.org/10.1111/j.1365-2133.1976.tb07018.x

[34] Liu Y, Gao C, Zhang X, Li W, Huang Y, Zhou T, et al. Lipidic prodrug co-crystals: A platform for combination therapy targeting fungal biofilms. Adv Mater. 2025 Oct;37(43):e10382. https://doi.org/10.1002/adma.202510382

[35] Zhang D, Zhu J, Wang Z, Liu Z. Pathogenesis and therapeutic strategy of heat stroke-induced acute kidney injury. Int Immunopharmacol. 2025 Jul 28;160:114969. https://doi.org/10.1016/j.intimp.2025.114969

[36] Wang Y, Yuan H, Shen D, Liu S, Kong W, Zheng K, et al. Artemisinin attenuated ischemic stroke induced pyroptosis by inhibiting ros/txnip/nlrp3/caspase-1 signaling pathway. Biomed Pharmacother. 2024 Aug;177:116894. https://doi.org/10.1016/j.biopha.2024.116894

[37] Liu P, Jiang P, Tan K, Yu Y, Qin G, Liu T, et al. Linarine inhibits inflammatory responses in dry eye disease mice by modulating purinergic receptors. Front Immunol. 2024 Sep 30;15:1463767. https://doi.org/10.3389/fimmu.2024.1463767

[38] Wan S, Cui Z, Wu L, Zhang F, Liu T, Hu J, et al. Ginsenoside rd promotes omentin secretion in adipose through tbk1-ampk to improve mitochondrial biogenesis via wnt5a/ca(2+) pathways in heart failure. Redox Biol. 2023 Apr;60:102610. https://doi.org/10.1016/j.redox.2023.102610

[39] Fox-Robichaud AE. Supplemental prevention of sepsis? Crit Care Med. 2025 Oct 1;53(10):e2092-e2094. https://doi.org/10.1097/ccm.0000000000006823

[40] Yang L, Feng JK, Gong PX, Yao LN, Li P. Advances in research pertaining to biomarkers for myocardial injury in sepsis. Shock. 2026 Feb 1;65(2):134-141. https://doi.org/10.1097/shk.0000000000002678

[41] Zhao L, Zhao H, Sun M, Chen M, Wu X, Deng C, et al. Kudzu celery decoction exerts protection against sepsis-induced myocardial injury. Oxid Med Cell Longev 2022 May 4;2022:2886932. https://doi.org/10.1155/2022/2886932

[42] Zhang J, Liu Y, Liu L. Hyperoside prevents sepsis-associated cardiac dysfunction through regulating cardiomyocyte viability and inflammation via inhibiting mir-21. Biomed Pharmacother. 2021 Jun;138:111524. https://doi.org/10.1016/j.biopha.2021.111524

[43] Liu J, Feng J, Hu J, Chen J, Li FX, Lin N. Exploring the importance of zbp1 in sepsis: A mini review on it's mechanisms and progress. J Inflamm Res. 2025 Jul 25;18:9871-9878. https://doi.org/10.2147/jir.S527506

[44] Cao Z, Meng B, Chen J, Ge R, Liu Y, Li J. B-nicotinamide mononucleotide protects against hypervirulent klebsiella pneumoniae bloodstream infection and liver injury. mSphere. 2025 Aug 26;10(8):e0036125. https://doi.org/10.1128/msphere.00361-25

[45] Abdelsattar S, Al-Amodi HS, Nazih M, Salem EHM, Mostafa RG, Menshawy SS, et al. Genotype-phenotype correlation of

tnf-α (-238, rs361525) and cystatin c for early detection of sepsis-associated aki and its severity in critically ill neonates. Int J Mol Sci. 2025 Jul 14;26(14):6738. https://doi.org/10.3390/ijms26146738

[46] Deng H, Liang WY, Chen LQ, Yuen TH, Sahin B, Vasilescu DM, et al. CETP inhibition enhances monocyte activation and bacterial clearance and reduces streptococcus pneumonia-associated mortality in mice. JCI Insight. 2024 Apr 22;9(8):e173205. https://doi.org/10.1172/jci.insight.173205

[47] Zhou Q, Zeng X, Kang W, Pan X, Wang L, Xia Z. Ciprofol attenuates sepsis-induced cardiomyopathy via α7 nicotinic acetylcholine receptor-dependent modulation of myocardial inflammation and nf-κb/stat3 signaling. Eur J Pharmacol. 2025 Sep 15;1003:177983. https://doi.org/10.1016/j.ejphar.2025.177983

[48] Yu H, Du Q, Wu J, Feng F, Hou S, Liu M, et al. Gastrodin regulates h3k14la through the cdt2-kat2a axis to treat sepsis-induced myocardial dysfunction. Int Immunopharmacol. 2025 Aug 28;161:115065. https://doi.org/10.1016/j.intimp.2025.115065

[49] Wei Z, Liu J, Liu H, Zhang X. Klotho alleviates sepsis-associated myocardial inflammation and apoptosis. Eur J Pharmacol. 2025 Jul 5;998:177653. https://doi.org/10.1016/j.ejphar.2025.177653

[50] Sumneang N, Kobroob A, Phungphong S, Boonhoh W, Punsawad C, Kangwan N. Fermented houttuynia cordata juice exerts cardioprotective effects by alleviating cardiac inflammation and apoptosis in rats with lipopolysaccharide-induced sepsis. Nutrients. 2025 Jan 29;17(3):501. https://doi.org/10.3390/nu17030501

[51] Yang H, Jiang Z, Feng L, Wang C, Xu H, Wu X, et al. Nppb contributes to sepsis-induced myocardial injury by regulating senescence-related genes. Int Immunopharmacol. 2024 Dec 25;143(Pt 2):113461. https://doi.org/10.1016/j.intimp.2024.113461

[52] Kanmani S, Song XM, Kanmani P, Wu XJ, Tan XD, Liu J, et al. Enhancement of autophagy in macrophages via the p120-catenin-mediated mtor signaling pathway. J Immunol. 2024 Dec 1;213(11):1666-1675. https://doi.org/10.4049/jimmunol.2400189

[53] Li W, Peng Y, Liu J, Wu T, Qiang X, Zhao Q, et al. Discovery and synthesis of novel glyrrhizin-analogs containing furanoylpiperazine and the activity against myocardial injury in sepsis. Bioorg Chem. 2024 Dec;153:107846. https://doi.org/10.1016/j.bioorg.2024.107846

[54] Chen R, Zheng A, Wang Y, Guo L, Dou H, Lu L, et al. Salvianolic acid b improves mitochondrial dysfunction of septic cardiomyopathy via enhancing atf5-mediated mitochondrial unfolded protein response. Toxicol Appl Pharmacol. 2024 Oct;491:117072. https://doi.org/10.1016/j.taap.2024.117072

[55] Zhang Q, Wen L, Li J, Liu P, Sun X, Liu Q, et al. Network pharmacology approach to unveiling the mechanism of wolfberry mulberry raspberry decoction in the treatment of sepsis-induced myocardial dysfunction. Drug Des Devel Ther. 2025 Jun 20;19:5293-5310. https://doi.org/10.2147/dddt.S502301

[56] Liu S, Liu FZ, Yan JY, Fang X, Xu ZP, Cai HL, et al. The elabela-apj axis attenuates sepsis-induced myocardial dysfunction by reducing pyroptosis by balancing the formation and degradation of autophagosomes. Free Radic Biol Med. 2024 Nov 1;224:405-417. https://doi.org/10.1016/j.freeradbiomed.2024.09.003

[57] Xie Q, Yi Q, Zhu J, Tan B, Xiang H, Wang R, et al. Protective role of triiodothyronine in sepsis-induced cardiomyopathy through phospholamban downregulation. Int J Mol Med. 2025 Mar;55(3):47. https://doi.org/10.3892/ijmm.2025.5488

[58] Ni L, Lin B, Shen M, Li C, Hu L, Fu F, et al. Pkm2 deficiency exacerbates gram-negative sepsis-induced cardiomyopathy via disrupting cardiac calcium homeostasis. Cell Death Discov. 2022 Dec 23;8(1):496. https://doi.org/10.1038/s41420-022-01287-9

[59] Yu YY, Wang R, Chen GQ, Gui YF, Ma J, Ma JH, et al. Mechanisms and targeted therapeutic strategies in sepsis-induced myocardial dysfunction: The role of NLRP3 inflammasome-mediated inflammation. J Inflamm Res. 2025 Jul 5;18:8875-8897. https://doi.org/10.2147/jir.S521655

[60] Jin Y, Fleishman JS, Ma Y, Jing X, Guo Q, Shang W, et al. NLRP3 inflammasome targeting offers a novel therapeutic paradigm for sepsis-induced myocardial injury. Drug Des Devel Ther. 2025 Feb 14;19:1025-1041. https://doi.org/10.2147/dddt.S506537

[61] Wen L, Quan Z, Guan C, Zheng J, Li Y, Zeng S, et al. Targeted inhibition of nek7 preventing sepsis-induced cardiomyopathy by inhibiting nlrp3 inflammasome. Int Immunopharmacol. 2025 Apr 4;151:114245. https://doi.org/10.1016/j.intimp.2025.114245

[62] Zhu H, Shan L, Peng T. Rac1 mediates sex difference in cardiac tumor necrosis factor-alpha expression via nadph oxidase-erk1/2/p38 mapk pathway in endotoxemia. J Mol Cell Cardiol. 2009 Aug;47(2):264-274. https://doi.org/10.1016/j.yjmcc.2009.05.002

[63] Giustina AD, Bonfante S, Zarbato GF, Danielski LG, Mathias K, de Oliveira AN Jr, et al. Dimethyl fumarate modulates oxidative stress and inflammation in organs after sepsis in rats. Inflammation. 2018 Feb;41(1):315-327. https://doi.org/10.1007/s10753-017-0689-z

[64] Zhang Y, Zhang Y, Deng H, Zeng Q, Zhu Z, Zhang Z, et al. Naringenin exerts antiarrhythmic action in septic cardiomyopathy by downregulating the camkii/drp1/bcl-2 pathway. Phytomedicine. 2025 Sep;145:157006. https://doi.org/10.1016/j.phymed.2025.157006

[65] Lazarević M, Kostić M, Džopalić T, Sokolović D, Lazarević Z, Milovanović J, et al. Melatonin mediates cardiac tissue damage under septic conditions induced by lipopolysaccharide. Int J Mol Sci. 2024 Oct 15;25(20):11088. https://doi.org/10.3390/ijms252011088

[66] Xing Y, Tian T, Zhang X, Yang D, Zhang C, Wang M, et al. Endogenous β 3 -adrenergic receptor activation alleviates sepsis-induced cardiomyocyte apoptosis via pi3k/akt signaling pathway. Shock. 2024 Jun 1;61(6):915-923. https://doi.org/10.1097/shk.0000000000002354

[67] Altmann DR, Korte W, Maeder MT, Fehr T, Haager P, Rickli H, et al. Elevated cardiac troponin i in sepsis and septic shock: No evidence for thrombus associated myocardial necrosis. PLoS

One. 2010 Feb 3;5(2):e9017. https://doi.org/10.1371/journal.pone.0009017

[68] Liu H, Hu Q, Ren K, Wu P, Wang Y, Lv C. Aldh2 mitigates lps-induced cardiac dysfunction, inflammation, and apoptosis through the cgas/sting pathway. Mol Med. 2023 Dec 20;29(1):171. https://doi.org/10.1186/s10020-023-00769-5

[69] Kang XF, Lu XL, Bi CF, Hu XD, Li Y, Li JK, et al. Xuebijing injection protects sepsis induced myocardial injury by mediating tlr4/nf-κb/ikkα and jak2/stat3 signaling pathways. Aging (Albany NY). 2023 Aug 30;15(16):8501-8517. https://doi.org/10.18632/aging.204990

[70] Cui YN, Tian N, Luo YH, Zhao JJ, Bi CF, Gou Y, et al. High-dose vitamin c injection ameliorates against sepsis-induced myocardial injury by anti-apoptosis, anti-inflammatory and pro-autophagy through regulating mapk, nf-κb and pi3k/akt/mtor signaling pathways in rats. Aging (Albany NY). 2024 Apr 19;16(8):6937-6953. https://doi.org/10.18632/aging.205735

[71] Guo NK, Si LN, Li PQ, Gan GF. Nano acacetin mitigates intestinal mucosal injury in sepsis rats by protecting mitochondrial function and regulating TRX1 to inhibit the NLRP3 pyroptosis pathway. Int J Nanomedicine. 2024 Dec 31;19:14125-14141. https://doi.org/10.2147/ijn.S497081

[72] Zhuang H, Li C, Wang L, Zhou B, Guo Z, Huang Y, et al. High-throughput screening of an FDA-approved compound library reveals a novel GAS6 receptor agonist for therapeutic intervention in septic myocardial and microvascular injury via modulation of danger-associated molecular patterns. Int J Biol Sci. 2024 Nov 11;20(15):6222-6240. https://doi.org/10.7150/ijbs.104427

[73] Yang R, Yuan BC, Ma YS, Zhou S, Liu Y. The anti-inflammatory activity of licorice, a widely used chinese herb. Pharm Biol. 2017 Dec;55(1):5-18. https://doi.org/10.1080/13880209.2016.1225775

[74] Yang L, Lai X, Lin F, Shi N, Xu X, Wang H, et al. Revitalising aging oocytes: Echinacoside restores mitochondrial function and cellular homeostasis through targeting gja1/sirt1 pathway. Cell Prolif. 2025 Oct;58(10):e70044. https://doi.org/10.1111/cpr.70044

[75] Liu L, Wen T, Xiao Y, Chen H, Yang S, Shen X. Sea buckthorn extract mitigates chronic obstructive pulmonary disease by suppression of ferroptosis via scavenging ros and blocking p53/mapk pathways. J Ethnopharmacol. 2025 Jan 10;336:118726. https://doi.org/10.1016/j.jep.2024.118726

[76] Wei B, Sun C, Wan H, Shou Q, Han B, Sheng M, et al. Bioactive components and molecular mechanisms of salvia miltiorrhiza bunge in promoting blood circulation to remove blood stasis. J Ethnopharmacol. 2023 Dec 5;317:116697. https://doi.org/10.1016/j.jep.2023.116697

[77] Peng X, Tang F, Yang Y, Li T, Hu X, Li S, et al. Bidirectional effects and mechanisms of traditional chinese medicine. J Ethnopharmacol. 2022 Nov 15;298:115578. https://doi.org/10.1016/j.jep.2022.115578

[78] Wu T, Sun J, Kagota S, Maruyama K, Wakuda H, Shinozuka K. Panax notoginseng saponins ameliorate impaired arterial vasodilation in shrsp.Z-lepr(fa)/lzmdmcr rats with metabolic syndrome. Clin Exp Pharmacol Physiol. 2016 Apr;43(4):459-467. https://doi.org/10.1111/1440-1681.12547

[79] Duan Z, Yuan B, Li H, Yang J, Xiao X, Wei K. Ginsenoside rh2 exerts a therapeutic effect against myocardial infarction via promoting angiogenesis and mitochondrial bioenergetics. J Agric Food Chem. 2025 Jun 18;73(24):15056-15066. https://doi.org/10.1021/acs.jafc.5c00479

[80] Jiang M, Ni J, Cao Y, Xing X, Wu Q, Fan G. Astragaloside IV attenuates myocardial ischemia-reperfusion injury from oxidative stress by regulating succinate, lysophospholipid metabolism, and ROS scavenging system. Oxid Med Cell Longev. 2019 Jun 24;2019:9137654. https://doi.org/10.1155/2019/9137654

[81] Sun S, Yang S, An N, Wang G, Xu Q, Liu J, et al. Astragalus polysaccharides inhibits cardiomyocyte apoptosis during diabetic cardiomyopathy via the endoplasmic reticulum stress pathway. J Ethnopharmacol. 2019 Jun 28;238:111857. https://doi.org/10.1016/j.jep.2019.111857

[82] Fu D, Zhou J, Xu S, Tu J, Cai Y, Liu J, et al. Smilax glabra roxb. Flavonoids protect against pathological cardiac hypertrophy by inhibiting the raf/mek/erk pathway: In vivo and in vitro studies. J Ethnopharmacol. 2022 Jun 28;292:115213. https://doi.org/10.1016/j.jep.2022.115213

[83] Xiao Z, Liu W, Mu YP, Zhang H, Wang XN, Zhao CQ, et al. Pharmacological effects of salvianolic acid b against oxidative damage. Front Pharmacol. 2020 Nov 11;11:572373. https://doi.org/10.3389/fphar.2020.572373

[84] Li ZM, Xu SW, Liu PQ. Salvia miltiorrhizaburge (danshen): A golden herbal medicine in cardiovascular therapeutics. Acta Pharmacol Sin. 2018 May;39(5):802-824. https://doi.org/10.1038/aps.2017.193

[85] Orgah JO, He S, Wang Y, Jiang M, Wang Y, Orgah EA, et al. Pharmacological potential of the combination of salvia miltiorrhiza (danshen) and carthamus tinctorius (honghua) for diabetes mellitus and its cardiovascular complications. Pharmacol Res. 2020 Mar;153:104654. https://doi.org/10.1016/j.phrs.2020.104654

[86] Xing HY, Liu Y, Chen JH, Sun FJ, Shi HQ, Xia PY. Hyperoside attenuates hydrogen peroxide-induced l02 cell damage via mapk-dependent keap1-nrf2-are signaling pathway. Biochem Biophys Res Commun. 2011 Jul 15;410(4):759-765. https://doi.org/10.1016/j.bbrc.2011.06.046

[87] Wang T, Chen L, Wang A, Xu Y, Zhang Y, Zhao Q, et al. Hyperoside inhibits prrsv proliferation via the tlr4/nf-κb and p62-nrf2-keap1 signaling pathways, mediating inflammation and autophagy. Microbiol Spectr. 2025 Aug 5;13(8):e0310724. https://doi.org/10.1128/spectrum.03107-24

[88] Chen K, Lu S, Shi K, Ali MH, Liu J, Yin F, et al. Hyperoside attenuates sepsis-induced acute lung injury by nrf2 activation and ferroptosis inhibition. Int Immunopharmacol. 2025 Jan 3;145:113734. https://doi.org/10.1016/j.intimp.2024.113734

[89] Pan Y, Ma T, Chen D, Wang Y, Peng Y, Lu T, et al. Scutellaria barbata D.Don and scleromitrion diffusum (Willd.) R.J.Wang inhibits the progression of triple negative breast cancer though the activation inhibition of NF-KB triggered by CAFs-derived

IL6. J Ethnopharmacol. 2024 Dec 5;335:118656. https://doi.org/10.1016/j.jep.2024.118656

[90] Huang H, Wang J, Hussain SA, Gangireddygari VSR, Fan Y. Gossypin exert lipopolysaccharide induced lung inflammation via alteration of Nrf2/HO-1 and NF-KB signaling pathway. Environ Toxicol. 2023 Aug;38(8):1786-1799. https://doi.org/10.1002/tox.23806

[91] Cinar I, Sirin B, Aydin P, Toktay E, Cadirci E, Halici I, et al. Ameliorative effect of gossypin against acute lung injury in experimental sepsis model of rats. Life Sci. 2019 Mar 15;221:327-334. https://doi.org/10.1016/j.lfs.2019.02.039

[92] Niu L, Xiao L, Zhang X, Liu X, Liu X, Huang X, et al. Comparative efficacy of Chinese herbal injections for treating severe pneumonia: A systematic review and bayesian network meta-analysis of randomized controlled trials. Front Pharmacol. 2021 Jan 10;12:743486. https://doi.org/10.3389/fphar.2021.743486

[93] Wu C, Zheng T, Wu L, Lv Z, Li M, Hu L, et al. The tanyu tongzhi formula enhances IL-10 expression and macrophage efferocytosis to alleviate atherosclerosis in mice. Phytomedicine. 2025 Oct;146:157122. https://doi.org/10.1016/j.phymed.2025.157122

[94] Song S, Wen X, Chen F, Li J, Shi K, Lou Y, et al. Qu-zhuo-tongbi decoction exerts gouty arthritis therapy by skewing macrophage polarization through butanoate metabolism. Chin Med. 2025 Jul 22;20(1):115. https://doi.org/10.1186/s13020-025-01162-6

[95] Wang L, Lin S, Wei Q, Li T, Mo Q, Bai R, et al. Preventive administration of quercetin promotes survival and reduces adverse ventricular remodeling after myocardial infarction through facilitating M2-like macrophage polarization. Int Immunopharmacol. 2025 Apr 4;151:114296. https://doi.org/10.1016/j.intimp.2025.114296

[96] Tian X, Chen X, Jiang Q, Sun Q, Liu T, Hong Y, et al. Notoginsenoside R1 ameliorates cardiac lipotoxicity through AMPK signaling pathway. Front Pharmacol. 2022 Mar 17;13:864326. https://doi.org/10.3389/fphar.2022.864326

[97] Yoshikawa N, Hirata N, Kurone Y, Shimoeda S. Red ginseng prevents doxorubicin-induced cardiomyopathy by inhibiting cell death via activating the Nrf2 pathway. Cardiooncology. 2024 Jun 22;10(1):39. https://doi.org/10.1186/s40959-024-00242-0

[98] Wu Z, Zhao X, Miyamoto A, Zhao S, Liu C, Zheng W, et al. Effects of steroidal saponins extract from ophiopogon japonicus root ameliorates doxorubicin-induced chronic heart failure by inhibiting oxidative stress and inflammatory response. Pharm Biol. 2019 Dec;57(1):176-183. https://doi.org/10.1080/13880209.2019.1577467

[99] Xiao G, Liu J, Wang H, He S, Liu J, Fan G, et al. CXCR1 and its downstream NF-KB inflammation signaling pathway as a key target of guanxinning injection for myocardial ischemia/reperfusion injury. Front Immunol. 2022 Oct 17;13:1007341. https://doi.org/10.3389/fimmu.2022.1007341

[100] Pan Z, Shao Y, Dong W, Liu C, Chen Y, Jin H, et al. Xuebijing attenuates hypotension through the upregulation of angiotensin II type 1 receptor-associated protein 1 in rats suffering from heat stroke. Int J Mol Med. 2014 Dec;34(6):1699-1705. https://doi.org/10.3892/ijmm.2014.1950

[101] He JB, Yang X, Luo ZY, Yuan PG, Song D, Xiang BQ, et al. [Effects of xuebijing injection on cardiac function and structure in rats with myocardial hypoxia/reoxygenation injury]. Zhongguo Ying Yong Sheng Li Xue Za Zhi. 2016 Feb 8;32(2):173-176. https://doi.org/10.13459/j.cnki.cjap.2016.02.021

[102] Lu L, Wu C, Lu BJ, Xie D, Wang Z, Bahaji Azami NL, et al. Babaodan cures hepatic encephalopathy by decreasing ammonia levels and alleviating inflammation in rats. J Ethnopharmacol. 2020 Mar 1;249:112301. https://doi.org/10.1016/j.jep.2019.112301

[103] Zhang Y, Zhou S, Zhou J, Wang D, Zhou T. Regulation of nf-κb/mapk signaling pathway attenuates the acute lung inflammation in klebsiella pneumonia rats by mollugin treatment. Microb Pathog. 2019 Jul;132:369-373. https://doi.org/10.1016/j.micpath.2019.05.007

[104] Ling B, Ji J, Huang Q, Xu Y, Hu Y, Pan S, et al. Xuebijing injection alleviates sepsis-induced acute lung injury by inhibition of cell apoptosis and inflammation through the hippo pathway. J Inflamm Res. 2025 Jun 12;18:7717-7733. https://doi.org/10.2147/jir.S523991

[105] Liang LX, Liu ZH, Long DH, Liu HX. [Outcome indicators in randomized controlled trials on traditional chinese medicine intervention of sepsis-induced myocardial injury in recent five years]. Zhongguo Zhong Yao Za Zhi. 2022 Sep;47(18):5088-5096. https://doi.org/10.19540/j.cnki.cjcmm.20220529.503

[106] Liu J, Wang Z, Lin J, Li T, Guo X, Pang R, et al. Xuebijing injection in septic rats mitigates kidney injury, reduces cortical microcirculatory disorders, and suppresses activation of local inflammation. J Ethnopharmacol. 2021 Aug 10;276:114199. https://doi.org/10.1016/j.jep.2021.114199

[107] Shu B, Zhou X, Fan J, Yang C, Deng W, Fang B, et al. Comparative efficacy and safety of xuebijing injection as adjuvant therapy in sepsis-associated acute kidney injury: A systematic review and meta-analysis. Front Pharmacol. 2025 Oct 21;16:1643557. https://doi.org/10.3389/fphar.2025.1643557

[108] Zhang L, Zhang G, Mao W, Sun S, Tao S, Gao Y, et al. Xuebijing injection alleviates septic acute kidney injury by modulating inflammation, mitochondrial dysfunction, and endoplasmic reticulum stress. Ren Fail. 2025 Dec;47(1):2483986. https://doi.org/10.1080/0886022x.2025.2483986

[109] Li X, Ren K, Baran MR, Tang J, Wang L, Tchivelekete GM, et al. Revealing the molecular mechanisms underlying xuebijing against sepsis and septic acute kidney injury via bioinformatics and experimental approaches. PLoS One. 2025;20(10):e0333478. https://doi.org/10.1371/journal.pone.0333478

[110] Gong ZT, Yang HX, Zhu BB, Liu HH, Siri G. Clinical efficacy of xuebijing injection for the treatment of sepsis: A retrospective cohort study. J Integr Med. 2024 Nov;22(6):645-651. https://doi.org/10.1016/j.joim.2024.08.006

[111] Yuan S, Cao Y, Jiang J, Chen J, Huang X, Li X, et al. Xuebijing injection and its bioactive components alleviate nephrotic

syndrome by inhibiting podocyte inflammatory injury. Eur J Pharm Sci. 2024 May 1;196:106759. https://doi.org/10.1016/j.ejps.2024.106759

[112] Li J, Olaleye OE, Yu X, Jia W, Yang J, Lu C, et al. High degree of pharmacokinetic compatibility exists between the five-herb medicine xuebijing and antibiotics comedicated in sepsis care. Acta Pharm Sin B. 2019 Sep;9(5):1035-1049. https://doi.org/10.1016/j.apsb.2019.06.003

[113] Shang T, Yu Q, Ren T, Wang XT, Zhu H, Gao JM, et al. Xuebijing injection maintains GRP78 expression to prevent candida albicans-induced epithelial death in the kidney. Front Pharmacol. 2019 Jan 6;10:1416. https://doi.org/10.3389/fphar.2019.01416

[114] Li CM, Sun Q. Therapeutic effect of xuebijing combined with thymosin on hemorrhagic fever with renal syndrome: A protocol of systematic review and meta-analysis. Medicine (Baltimore). 2020 May;99(20):e20262. https://doi.org/10.1097/md.0000000000020262

[115] Zhou X, Li H, Xie G, Fang J, Lian Y, Fang X. [Protective effect of the use of xuebijing injection during laparotomy on perioperative inflammatory response and organ function]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2014 Apr;26(4):258-263. https://doi.org/10.3760/cma.j.issn.2095-4352.2014.04.012

[116] Chen X, Feng Y, Shen X, Pan G, Fan G, Gao X, et al. Antisepsis protection of Xuebijing injection is mediated by differential regulation of pro- and anti-inflammatory TH17 and T regulatory cells in a murine model of polymicrobial sepsis. J Ethnopharmacol. 2018 Jan 30;211:358-365. https://doi.org/10.1016/j.jep.2017.10.001

[117] Wang Z, Chen W, Li Y, Zhang S, Lou H, Lu X, et al. Reduning injection and its effective constituent luteoloside protect against sepsis partly via inhibition of HMGB1/TLR4/NF-KB/MAPKs signaling pathways. J Ethnopharmacol. 2021 Apr 24;270:113783. https://doi.org/10.1016/j.jep.2021.113783

[118] Chen L, Lin X, Xiao J, Tian Y, Zheng B, Teng H. Sonchus oleraceus Linn protects against LPS-induced sepsis and inhibits inflammatory responses in RAW264.7 cells. J Ethnopharmacol. 2019 May 23;236:63-69. https://doi.org/10.1016/j.jep.2019.02.039

[119] Ding L, Shangguan H, Wang X, Liu J, Shi Y, Xu X, et al. Extraction, purification, structural characterization, biological activity, mechanism of action and application of polysaccharides from ganoderma lucidum: A review. Int J Biol Macromol. 2025 Feb;288:138575. https://doi.org/10.1016/j.ijbiomac.2024.138575

[120] Wang Q, Achour J, Emam L, Louaguenouni Y, Cailleau C, Mercier-Nomé F, et al. Pulmonary delivery of sirna anti-tnfα-loaded lipid nanoparticles for rapid recovery in murine acute lung injury. Adv Healthc Mater. 2025 Nov;14(29):e00695. https://doi.org/10.1002/adhm.202500695

[121] Xu X, Yan Y, Zheng M, Zhang M, Chen T, Qu Z, et al. Emodin alleviates sepsis-induced multiorgan damage by inhibiting netosis through targeting neutrophils bcl-10. Adv Sci (Weinh). 2025 Nov;12(41):e17129. https://doi.org/10.1002/advs.202417129

[122] Wu Z, Wang Z, Chang X, Chen X, Ding Q, Fu R, et al. Prioritizing pathway signature using deep learning approach: A novel strategy for traditional chinese medicine formula generation and optimization. Brief Bioinform. 2025 Jul 2;26(4):bbaf403. https://doi.org/10.1093/bib/bbaf403

[123] Zhou T. Unveiling secrets of traditional Chinese medicine: Cutting-edge techniques in component analysis. Chin Herb Med. 2025 Jul;17(3):484-487. https://doi.org/10.1016/j.chmed.2025.05.006

[124] Rader A, Ruffin F, Fai C, Barton KD, Skalla LA, Wang TW, et al. A systematic review of health-related quality-of-life measurement in patients with complicated intraabdominal infections. Clin Infect Dis. 2025 Aug 6;81(Supplement_1):S40-S47. https://doi.org/10.1093/cid/ciaf299

[125] Zhu B, Sun C, Luo D, Liang Y, Jiang A, Jiang Z, et al. Coptisine improves liver inflammation in sepsis by regulating STAT1/IRF1/GPX4 signaling-mediated kupffer cells ferroptosis. Phytother Res. 2025 Sep;39(9):4308-4326. https://doi.org/10.1002/ptr.70063

[126] Khanal S, Kumar A, Kumar P, Thakur P, Chander AM, Verma R, et al. Unraveling bioactive potential and production in ganoderma lucidum through omics and machine learning modeling. Chin Herb Med. 2025 Jul;17(3):414-427. https://doi.org/10.1016/j.chmed.2025.05.003

[127] Chen Y, Weng D, Shi W, Wei S, Ji W, Wang X, et al. Integrative network pharmacology and multi-omics reveal anisodamine hydrobromide's multi-target mechanisms in sepsis. Sci Rep. 2025 Jul 31;15(1):27996. https://doi.org/10.1038/s41598-025-13187-w

[128] Liu Y, Zhang M, Cai Y, Wu S, Mei C, Wang H, et al. Synergistic antimicrobial efficacy of glabrol and colistin through micelle-based co-delivery against multidrug-resistant bacterial pathogens. Phytomedicine. 2025 Feb;137:156371. https://doi.org/10.1016/j.phymed.2025.156371

[129] Cui C, Liu W, Feng L, Zou J, Shi Y, Sun J, et al. Cornus officinalis sieb.: An updated review on the ethnopharmacology, phytochemistry, pharmacology, toxicology, and pharmacokinetics. J Ethnopharmacol. 2025 Sep 25;353(Pt B):120365. https://doi.org/10.1016/j.jep.2025.120365

[130] Lai Y, Chen G, Wu Q, Chen X, Zhang H. Revealing disease-specific medication patterns of wuling powder: A large-scale data mining analysis of randomized controlled trials. J Ethnopharmacol. 2025 Sep 25;353(Pt A):120356. https://doi.org/10.1016/j.jep.2025.120356

[131] Bai H, Hu X, Meng C, Zu W, Qiu X, Liu J, et al. The phytochemistry, pharmacology and modern applications of Cotinus coggygria Scop.-A comprehensive review with future perspectives. J Ethnopharmacol. 2025 Sep 25;353(Pt B):120366. https://doi.org/10.1016/j.jep.2025.120366

[132] Wang Z, Liu Y, Chen F, Liao H, Wang X, Guo Z, et al. Feasibility and mechanism analysis of reduning in the prevention of sepsis-induced pulmonary fibrosis. Front Pharmacol. 2022 Dec 20;13:1079511. https://doi.org/10.3389/fphar.2022.1079511

[133] Xing X, Zhi Y, Lu J, Lei S, Huang L, Zhu M, et al. Traditional chinese medicine bundle therapy for septic acute gastrointestinal injury: A multicenter randomized controlled trial. Complement

Ther Med. 2019 Dec;47:102194. https://doi.org/10.1016/j.ctim.2019.102194

[134] Xiao T, Huang F, Guo Z, Cheng X, Duan J, Dai W, et al. Black raspberry polyphenols shape metabolic dysregulation and perturbation in gut microbiota to promote lipid metabolism and liver regeneration. J Agric Food Chem. 2025 Apr 2;73(13):7833-7856. https://doi.org/10.1021/acs.jafc.5c00702

[135] Ruffin F, Sutton KN, Miller J, Lane H, Schexnayder J, Oakes M, et al. A qualitative secondary analysis of patient health-related quality of life in bloodstream infections by source: Intra-abdominal, urinary tract, and acute bacterial skin and skin structure infection. Clin Infect Dis. 2025 Aug 6; 81(Supplement_1):S48-S54. https://doi.org/10.1093/cid/ciaf295

[136] Shen Z, Cui T, Liu Y, Wu S, Han C, Li J. Astragalus membranaceus and salvia miltiorrhiza ameliorate diabetic kidney disease via the "gut-kidney axis". Phytomedicine. 2023 Dec;121:155129. https://doi.org/10.1016/j.phymed.2023.155129

[137] Fu J, Wang Z, Huang L, Zheng S, Wang D, Chen S, et al. Review of the botanical characteristics, phytochemistry, and pharmacology of astragalus membranaceus (huangqi). Phytother Res. 2014 Sep;28(9):1275-1283. https://doi.org/10.1002/ptr.5188

[138] Lu K, Xia Y, Cheng P, Li Y, He L, Tao L, et al. Synergistic potentiation of the anti-metastatic effect of a Ginseng-salvia miltiorrhiza herbal pair and its biological ingredients via the suppression of CD62E-dependent neutrophil infiltration and NETformation. J Adv Res. 2025 Sep;75:739-753. https://doi.org/10.1016/j.jare.2024.10.036

[139] Liu S, Wang Y, Shi M, Maoz I, Gao X, Sun M, et al. SmbHLH60 and SmMYC2 antagonistically regulate phenolic acids and anthocyanins biosynthesis in salvia miltiorrhiza. J Adv Res. 2022 Dec;42:205-219. https://doi.org/10.1016/j.jare.2022.02.005

[140] Zhang J, Tan B, Wu H, Han T, Fang D, Cai H, et al. Scutellaria baicalensis extracts restrict intestinal epithelial cell ferroptosis by regulating lipid peroxidation and GPX4/ACSL4 in colitis. Phytomedicine. 2025 Jun;141:156708. https://doi.org/10.1016/j.phymed.2025.156708

[141] Fang DN, Zheng CW, Ma YL. Effectiveness of scutellaria baicalensis georgi root in pregnancy-related diseases: A review. J Integr Med. 2023 Jan;21(1):17-25. https://doi.org/10.1016/j.joim.2022.09.005

[142] Liu H, Lu X, Hu Y, Fan X. Chemical constituents of panax ginseng and panax notoginseng explain why they differ in therapeutic efficacy. Pharmacol Res. 2020 Nov;161:105263. https://doi.org/10.1016/j.phrs.2020.105263

[143] Fan S, Zhang Z, Su H, Xu P, Qi H, Zhao D, et al. Panax ginseng clinical trials: Current status and future perspectives. Biomed Pharmacother. 2020 Dec;132:110832. https://doi.org/10.1016/j.biopha.2020.110832

[144] Li S, Zhang R, Wang A, Li Y, Zhang M, Kim J, et al. Panax notoginseng: Derived exosome-like nanoparticles attenuate ischemia reperfusion injury via altering microglia polarization. J Nanobiotechnology. 2023 Nov 10;21(1):416. https://doi.org/10.1186/s12951-023-02161-1

[145] Xu Y, Zhu M, Feng Y, Xu H. Panax notoginseng-microbiota interactions: From plant cultivation to medicinal application. Phytomedicine. 2023 Oct;119:154978. https://doi.org/10.1016/j.phymed.2023.154978

[146] Liang Y, Wang L. Carthamus tinctorius l.: A natural neuroprotective source for anti-alzheimer's disease drugs. J Ethnopharmacol. 2022 Nov 15;298:115656. https://doi.org/10.1016/j.jep.2022.115656

[147] Xue X, Deng Y, Wang J, Zhou M, Liao L, Wang C, et al. Hydroxysafflor yellow a, a natural compound from carthamus tinctorius l with good effect of alleviating atherosclerosis. Phytomedicine. 2021 Oct;91:153694. https://doi.org/10.1016/j.phymed.2021.153694

[148] Cui J, Deng Y, Li X, Gao L, Li J, Li Z, et al. Herbal-based Xuebijing injection ameliorated vascular endothelial dysfunction via inhibiting ACLY/MYB/RIG-I axis in sepsis-associated lung injury. Phytomedicine. 2025 May;140:156573. https://doi.org/10.1016/j.phymed.2025.156573

[149] Ji Y, Song H, Li L. Traditional chinese medicine for sepsis: Advancing from evidence to innovative drug discovery. Crit Care. 2025 May 15;29(1):193. https://doi.org/10.1186/s13054-025-05441-4

[150] Li L, Zhong S, Ye J, Hu S, Xiong X, Chen G, et al. Shenmai injection revives cardiac function in rats with hypertensive heart failure: Involvement of microbial-host co-metabolism. BMC Complement Med Ther. 2025 Jan 24;25(1):24. https://doi.org/10.1186/s12906-024-04737-2

[151] Feize W, Meng L, Yanni L, Yuan L, Liqun J, Tong L, et al. A randomized controlled study to observe the efficacy of external treatment with a traditional Chinese medicine herbal ointment on malignant plural effusion: Outcome report and design review. Integr Cancer Ther. 2017 Dec;16(4):473-478. https://doi.org/10.1177/1534735416660193

[152] Nambiar A, Kellogg D 3rd, Justice J, Goros M, Gelfond J, Pascual R, et al. Senolytics dasatinib and quercetin in idiopathic pulmonary fibrosis: Results of a phase i, single-blind, single-center, randomized, placebo-controlled pilot trial on feasibility and tolerability. EBioMedicine. 2023 Apr;90:104481. https://doi.org/10.1016/j.ebiom.2023.104481

[153] Wen RJ, Dong X, Zhuang HW, Pang FX, Ding SC, Li N, et al. Baicalin induces ferroptosis in osteosarcomas through a novel NRF2/XCT/GPX4 regulatory axis. Phytomedicine. 2023 Jul 25;116:154881. https://doi.org/10.1016/j.phymed.2023.154881

[154] Deng Y, Du J, He X, Dong YX, Wang XL, Zeng YM, et al. Risk assessment of CYP3A induction by ginsenoside's metabolites from oral Panax notoginseng (sanqi) extract. J Ethnopharmacol. 2025 Jun 12;349:119864. https://doi.org/10.1016/j.jep.2025.119864

[155] Xia Z, Gu J, Ansley DM, Xia F, Yu J. Antioxidant therapy with salvia miltiorrhiza decreases plasma endothelin-1 and thromboxane B2 after cardiopulmonary bypass in patients with congenital heart disease. J Thorac Cardiovasc Surg. 2003 Nov;126(5):1404-1410. https://doi.org/10.1016/s0022-5223(03)00970-x

[156] Hao N, Liu Y, Guo L, Li W, Zhao P. Xuebijing injection combined with alprostadil in the treatment of diabetic nephropathy:

A prisma-compliant systematic review and meta-analysis. Medicine (Baltimore). 2024 Jun 14;103(24):e32095. https://doi.org/10.1097/md.0000000000032095

[157] Zhang WL, Chi YL, Wang LZ, Liu H, Zhao LX, Su F. Administrations of preoperative shenmai injection and postoperative shenfu injection, two ginseng containing tcm formulas, improve cognitive dysfunction in aged rats. Am J Chin Med. 2018;46(5):1065-1078. https://doi.org/10.1142/s0192415x18500556

[158] Guo J, Zhao N, Jin P, Yin Y. Effect of astragalus injection on inflammatory mediators in patients with viral myocarditis: A systematic review and meta-analysis. Phytomedicine. Chernow B, Zaloga GP. Pharmacologic management of the critically ill patient in the perioperative period--emphasis on the sepsis syndrome. Med Clin North Am. 1987 May;71(3):541-549. https://doi.org/10.1016/s0025-7125(16)30857-4

[159] Sun M, Li F, Wang Y, Miao M, Lu Z, Chen WM, et al. Postoperative sepsis and its sequential impact on dementia. Crit Care. 2025 Feb 6;29(1):66. https://doi.org/10.1186/s13054-025-05276-z

[160] Rawlings EE, Balgobin B. Complications of laparoscopy. Br Med J. 1975 Mar 29;1(5960):727-728. https://doi.org/10.1136/bmj.1.5960.727

[161] Baron TH, DiMaio CJ, Wang AY, Morgan KA. American gastroenterological association clinical practice update: Management of pancreatic necrosis. Gastroenterology. 2020 Jan;158(1):67-75.e61. https://doi.org/10.1053/j.gastro.2019.07.064

[162] Gravante G, Caruso R, Andreani SM, Giordano P. Mechanical bowel preparation for colorectal surgery: A meta-analysis on abdominal and systemic complications on almost 5,000 patients. Int J Colorectal Dis. 2008 Dec;23(12):1145-1150. https://doi.org/10.1007/s00384-008-0592-z

[163] Trevelin SC, Carlos D, Beretta M, da Silva JS, Cunha FQ. Diabetes mellitus and sepsis: A challenging association. Shock. 2017 Mar;47(3):276-287. https://doi.org/10.1097/shk.0000000000000778

[164] Mortality of emergency abdominal surgery in high-, middle- and low-income countries. Br J Surg. 2016 Jul;103(8):971-988. https://doi.org/10.1002/bjs.10151

[165] Gando S, Levi M, Toh CH. Disseminated intravascular coagulation. Nat Rev Dis Primers. 2016 Jun 2;2:16037. https://doi.org/10.1038/nrdp.2016.37

[166] Parker MM, Shelhamer JH, Bacharach SL, Green MV, Natanson C, Frederick TM, et al. Profound but reversible myocardial depression in patients with septic shock. Ann Intern Med. 1984 Apr;100(4):483-490. https://doi.org/10.7326/0003-4819-100-4-483

[167] Jialiken D, Qian L, Wen S, Ren S, Fan Y, Dong YX, et al. Effect of astragalus injection treatment for viral myocarditis: A systematic review and meta-analysis. Eur J Med Res. 2025 Jan 3;30(1):1. https://doi.org/10.1186/s40001-024-02193-9

[168] Zeng JJ, Shi HQ, Ren FF, Zhao XS, Chen QY, Wang DJ, et al. Notoginsenoside R1 protects against myocardial ischemia/reperfusion injury in mice via suppressing TAK1-JNK/p38 signaling. Acta Pharmacol Sin. 2023 Jul;44(7):1366-1379. https://doi.org/10.1038/s41401-023-01057-y

[169] Wang D, Lv L, Xu Y, Jiang K, Chen F, Qian J, et al. Cardioprotection of panax notoginseng saponins against acute myocardial infarction and heart failure through inducing autophagy. Biomed Pharmacother. 2021 Apr;136:111287. https://doi.org/10.1016/j.biopha.2021.111287

[170] Sun R, Huang WY, Guo ZY, Liu F, Sun Q, Fan WJ, et al. Notoginsenoside R1 ameliorates myocardial ischemia/reperfusion injury by suppressing apoptosis via activating wnt/β-catenin signaling. Am J Chin Med. 2025;53(7):2223-2243. https://doi.org/10.1142/s0192415x2550082x

[171] Li CX, Liu Y, Zhang YZ, Li JC, Lai J. Astragalus polysaccharide: A review of its immunomodulatory effect. Arch Pharm Res. 2022 Jun;45(6):367-389. https://doi.org/10.1007/s12272-022-01393-3

[172] Wu Y, Zhang J, Qi L. [Clinical efficacy and safety of xuebijing injection on sepsis: A meta-analysis]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2020 Jun;32(6):691-695. https://doi.org/10.3760/cma.j.cn121430-20200427-00475

[173] Wang X, Lyu H, Chen M, Lu J, Cheng L, Zhou H, et al. [A clinical research on renal protective effect of xuebijing injection in patients with sepsis]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2015 May;27(5):371-374. https://doi.org/10.3760/cma.j.issn.2095-4352.2015.05.010

[174] Wang J, Pu X, Zhuang H, Guo Z, Wang M, Yang H, et al. Astragaloside IV alleviates septic myocardial injury through DUSP1-prohibitin 2 mediated mitochondrial quality control and er-autophagy. J Adv Res. 2025 Sep;75:561-580. https://doi.org/10.1016/j.jare.2024.10.030

[175] Xie L, Zhang G, Wu Y, Hua Y, Ding W, Han X, et al. Protective effects of wenqingyin on sepsis-induced acute lung injury through regulation of the receptor for advanced glycation end products pathway. Phytomedicine. 2024 Jul;129:155654. https://doi.org/10.1016/j.phymed.2024.155654

[176] Huang N, Tam YH, Zhang Z, Kao X, Yang Z, Xu W, et al. Efficacy and safety of dachaihu decoction for sepsis: A randomized controlled trial. Phytomedicine. 2025 Jan;136:156311. https://doi.org/10.1016/j.phymed.2024.156311

[177] Hong KF, Liu PY, Zhang W, Gui DK, Xu YH. The efficacy and safety of astragalus as an adjuvant treatment for type 2 diabetes mellitus: A systematic review and meta-analysis. J Integr Complement Med. 2024 Jan;30(1):11-24. https://doi.org/10.1089/jicm.2022.0767

[178] Qiu F, Wang G, Zhang R, Sun J, Jiang J, Ma Y. Effect of danshen extract on the activity of CYP3A4 in healthy volunteers. Br J Clin Pharmacol. 2010 Jun;69(6):656-662. https://doi.org/10.1111/j.1365-2125.2010.03624.x

[179] Li Z, Wang D, Zhang Y, Wang S, Wang X, Li Y, et al. Efficacy and safety of xuebijing injection for radiation pneumonitis: A meta-analysis. PLoS One. 2022;17(6):e0268819. https://doi.org/10.1371/journal.pone.0268819

[180] 2022 Dec;107:154436. https://doi.org/10.1016/j.phymed.2022.154436