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PERSPECTIVE

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Traditional Chinese medicine for sepsis: advancing from evidence to innovative drug discovery

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Abstract

The global health burden of sepsis is immense, characterized by significant loss of life and high healthcare costs. Traditional Chinese medicine (TCM), with its over two millennia of clinical practice in China, has gained attention as a potential adjunctive approach for sepsis. Here, we evaluated TCM applications in sepsis management, highlighting both potential benefits and methodological limitations of existing clinical evidence. Although various TCM preparations have been evaluated for sepsis treatment, the vast majority lack robust clinical evidence. Xuebijing Injection represents a rare example that has demonstrated efficacy in a large-scale, multicenter, randomized, double-blind, placebo-controlled trial. In contrast, the evidence supporting other preparations such as Shenfu and Shenmai Injections comes primarily from smaller, single-center studies with significant methodological limitations. There is a clear need for more high-quality, multicenter randomized controlled trials to rigorously evaluate these potentially beneficial but currently insufficiently validated TCM preparations. The pharmacological effects and underlying mechanisms of some bioactive compounds derived from TCM medications have been elucidated, shedding light on the potential of TCM-based anti-sepsis drug discovery. We underscore the importance of continued research to better integrate TCM with modern sepsis management, paving the way for the development of evidence-based TCM treatments for this challenging condition.

Keywords Chinese medicine, Clinical trials, Drug discovery, Sepsis, Xuebijing injection

Background

Sepsis, a life-threatening syndrome caused by a dysregulated host response to infection and resulting in acute organ dysfunction, poses a major global health challenge [1]. It affects nearly 50 million people worldwide each year, leading to significant loss of life and substantial healthcare costs [2]. The development of novel therapeutic approaches remains a critical priority.

Given the unmet needs in sepsis control with Western medicine, clinicians and researchers are increasingly exploring traditional Chinese medicine (TCM), with its holistic and individualized approach honed over two millennia of clinical practice in China, as a promising strategy [3–7]. Rooted in this rich tradition, TCM offers a broad array of plant-based compounds with diverse pharmacological properties [8–10]. These compounds, often applied in synergistic combinations within traditional formulas, have demonstrated notable anti-sepsis effects and serve as valuable leads for drug discovery [11, 12]. Accumulating clinical studies have reported positive outcomes, such as reduced inflammation, improved organ

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function, and enhanced survival rates in sepsis patients receiving TCM interventions [13–16]. These findings underscore the potential of TCM-based therapies in addressing the complex and multifaceted pathophysiology of sepsis.

In this perspective, we aim to provoke discussion on the untapped potential of TCM in addressing the challenges of sepsis management. We reviewed clinical evidence for TCM in sepsis treatment, prioritizing meta-analyses and, when unavailable, randomized controlled trials (RCTs; $n \geq 50$) selected for their relevance and methodological quality. These studies evaluated TCM as single agents or combination therapies. Building on the clinical evidence, we further analyzed bioactive compounds within clinically studied formulas to identify potential lead compounds and elucidate their pharmacological mechanisms. Finally, we discussed the challenges and future directions in the clinical integration of TCM for sepsis management, highlighting the need for further research, standardization, and collaboration between TCM and modern critical care medicine.

Clinical evidence of TCM for the treatment of sepsis

TCM has attracted attention as an adjunctive therapy for sepsis, with clinical evidence from RCTs and meta-analyses suggesting potential benefits. For example, meta-analyses indicate that combining TCM preparations with conventional treatment can lower Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, reduce intensive care unit (ICU) stay, and enhance 28-day survival [15, 16]. However, methodological limitations in these meta-analyses necessitate cautious interpretation of their findings.

The various TCM preparations studied for sepsis treatment are cataloged in Tables 1 and S1, which summarize available clinical findings and medicinal constituents [14, 17–46]. These TCM preparations include Banxia Xiexin Decoction, Dahuang Fuzi Decoction, Shengjiang Powder, Shenfu Injection, Shengmai Injection, Shenmai Injection, Xinmailong Injection, and Xuebijing Injection, among others. Among these preparations, Xuebijing Injection, Shenfu Injection and Shenmai Injection have accumulated the most clinical trial evidence, though the evidence predominantly originates from small, methodologically weak studies.

Notably, a nationwide, multicenter, randomized, double-blind, placebo-controlled trial supports the use of Xuebijing Injection, representing a rare example of high-quality research in this field. In this study of 1817 patients, Xuebijing significantly reduced 28-day mortality compared to placebo, with a favorable safety profile [14]. In contrast, the majority of other evidence, including findings for Shenfu and Shenmai Injections, comes from smaller trials, the vast majority of which are single-center in design, or meta-analyses of these studies [34, 35, 39].

In general, very few studies in this field meet the methodological standards of phase III clinical trials, especially those with adequate sample sizes, proper randomization, blinding, and international populations. The predominance of underpowered studies, lack of stratified analysis, and potential publication biases all raise concern that current results, particularly regarding improved survival, may not be reproducible in larger, diverse populations. Additionally, limitations inherent to meta-analyses, such as small sample sizes, clinical and methodological heterogeneity, risks of bias, and challenges in interpreting pooled estimates, further complicate the robustness of the conclusions. Given these limitations, all positive findings must be interpreted with appropriate caution. We recommend that future research prioritize rigorous multicenter, large-sample RCTs with transparent reporting and quality control. Only with such evidence can the efficacy and safety of TCM-based therapies for sepsis be reliably established. Until then, conclusions about clinical benefit should remain tentative.

Despite the methodological limitations discussed, these clinical findings remain valuable for informing the identification of bioactive compounds and the elucidation of their mechanisms, which are critical steps toward modern drug discovery from traditional formulations.

From clinically studied formulas to drug discovery: bioactive compounds and mechanisms of action in TCM for sepsis

A variety of bioactive compounds, including polyphenols, alkaloids, and saponins (Table S1), have been isolated from TCMs and shown therapeutic potential in sepsis (Table 2) [47–76]. Notably, TCM bioactive compounds are traditionally used in formulations based on combination principles, such as the "sovereign-minister-assistant-courier" principle, to enhance synergistic effects across multiple targets. This approach significantly differs from the single-compound strategies typically used for other natural products, where individual compounds are often studied in isolation. We categorize the mechanisms of TCM bioactive compounds into key pathophysiological pathways in sepsis—immune modulation, endothelial protection, mitochondrial function, and others—while emphasizing their therapeutic implications.

Immune modulation

Immune dysregulation is a hallmark of sepsis. Several TCM-derived compounds have demonstrated potent immunomodulatory effects. For example, baicalein and its glycoside baicalin (from *Radix Scutellariae*) protect against sepsis-induced organ damage and improve

Table 1 Clinical efficacy and safety of TCM for the treatment of sepsis

TCM products	Comparison	Patients	Design	Phase[a]	Mortality outcome	SOFA outcome	Other outcomes	References
Astragalus injection	Astragalus injection + RT vs. RT	50 patients with sepsis	RCT	II	Improved	Not assessed	Improve immune function, improve APACHE II score	[17]
Astragalus injection	Astragalus injection + RT vs. RT	60 patients with sepsis	RCT	II	No effect	No effect	Improve immune function, good safety profile	[18]
Banxia Xiexin Decoction	Banxia Xiexin Decoction + RT vs. RT	850 patients with sepsis (9 RCTs)	Meta	All phase II RCTs	Not assessed	Not assessed	Reduce gastrointestinal dysfunction score and APACHE II score	[19]
Dachaihu Decoction	Dachaihu Decoction + RT vs. RT	70 patients with sepsis	RCT	II	No effect	Improved	Improve APACHE II score, improve liver, renal, gastrointestinal function, inflammation, and coagulation, with fewer adverse events	[20]
Dachengqi Decoction	Dachengqi Decoction + RT vs. RT	68 sepsis patients with acute respiratory distress syndrome	RCT	II	No effect	Improved	Reduce inflammation markers, improve APACHE II score, shorten mechanical ventilation time, no significant difference in ICU stay	[21]
Dahuang Fuzi Decoction	Dahuang Fuzi Decoction + RT vs. RT	518 patients with sepsis (6 RCTs)	Meta	All phase II RCTs	No effect	Not assessed	Improve gastrointestinal function	[22]
Fusu Mixture	Fusu Mixture + RT vs. RT	81 patients with septic shock	RCT	II	No effect	Not assessed	Improve microcirculation parameters, shorten ICU stay	[23]
Hongyu Peizhen Formula	Hongyu Peizhen Formula + RT vs. RT	62 patients with sepsis	RCT	II	Not assessed	Improved	Improve cardiac function	[24]
HuangLian JieDu Decoction	HuangLian JieDu Decoction + RT vs. RT	115 patients with sepsis	RCT	II	Not assessed	Not assessed	Reduce inflammatory factors and APACHE II score, with no significant difference in adverse events	[25]
Jiawei Yiyi Fuzi Baijiang Powder	Jiawei Yiyi Fuzi Baijiang Powder + RT vs. RT treatment	160 patients with sepsis	RCT	II	Not assessed	Not assessed	Improve gastrointestinal function, enhance immunity, and improve nutritional status	[26]
JinHong Formula	JinHong Formula + RT vs. RT	114 patients with sepsis	RCT	II	Improved	Improved	Improve APACHE II score, reduce inflammatory markers and oxidative stress	[27]
Modified Huanglian Jiedu Decoction	Modified Huanglian Jiedu Decoction + RT vs. RT	86 patients with sepsis	RCT	II	No effect	Not assessed	Shorten length of mechanical ventilation and ICU stay, reduce incidence of hyperglycemia and gastric retention	[28]

Table 1 (continued)

TCM products	Comparison	Patients	Design	Phase[a]	Mortality outcome	SOFA outcome	Other outcomes	References
Modified Liangge Powder	Modified Liangge Powder + RT vs. RT	143 patients with sepsis	RCT	II	Improved	Improved	Improve APACHE II score, decrease inflammatory markers	[29]
Pogejiuxin Decoction	Pogejiuxin Decoction + RT vs. RT	92 patients with septic shock	RCT	II	No effect	Improved	Reduce inflammation markers, improve lactate clearance rate, improve APACHE II score	[30]
Qiguiyin Granule	Qiguiyin Granule + RT vs. RT	60 sepsis patients with acute kidney injury	RCT	II	No effect	Not assessed	Increase renal injury recovery rate, shorten CRRT duration	[31]
Qingwen Baidu Decoction	Qingwen Baidu Decoction + RT vs. RT	86 patients with sepsis	RCT	II	Not assessed	Improved	Reduce inflammatory markers, improve endothelial function	[32]
Qingwen Baidu Decoction	Qingwen Baidu Decoction + RT vs. RT	80 patients with sepsis	RCT	II	Not assessed	Improved	Improve inflammation markers	[33]
Shenfu Injection	Shenfu Injection + RT vs. RT	4279 patients with septic shock (56 RCTs)	Meta	All phase II RCTs	Improved	Improved	Increase MAP, reduce lactate levels	[34]
Shenfu Injection	Shenfu Injection + RT vs. RT	2340 patients with sepsis and septic shock (32 RCTs)	Meta	All phase II RCTs	Improved	Improved	Increase MAP, reduce lactate levels	[35]
Shengjiang Powder	Shengjiang Powder + RT vs. RT	720 patients with sepsis (13 RCTs)	Meta	All phase II RCTs	Not assessed	Not assessed	Improve APACHE II score, decrease inflammation markers, good safety profile	[36]
Shenqi Fuzheng Injection	Shenqi Fuzheng Injection + RT vs. RT	60 patients with septic shock	RCT	II	No effect	Not assessed	Improve hemodynamics, improve APACHE II score	[37]
Shengmai Injection	Shengmai Injection + RT vs. RT	860 patients with septic shock (17 RCTs)	Meta	All phase II RCTs	No effect	Not assessed	Improve shock recovery, reduce serum lactate level	[38]
Shenmai Injection	Shenmai Injection + RT vs. RT	1469 patients with sepsis (21 RCTs)	Meta	All phase II RCTs	Improved	Not assessed	Reduce inflammatory markers, improve APACHE II score	[39]
Shenmai Injection	Shenmai Injection + RT vs. RT	583 patients with sepsis and septic shock (6 RCTs)	Meta	All phase II RCTs	Improved	Improved	Decrease lactate levels	[35]
Sini Decoction	Sini Decoction + RT vs. RT	60 patients with sepsis	RCT	II	No effect	Improved	Improve cardiac function, improved lactate clearance rate	[40]
Tuoli Xiaodu Powder	Tuoli Xiaodu Powder + RT vs. RT	57 patients with sepsis	RCT	II	No effect	Improved	Reduce inflammatory markers	[41]
Xinmailong Injection	Xinmailong Injection + RT vs. RT	192 patients with sepsis	RCT	II	No effect	Not assessed	Reduce incidence of diastolic sepsis-induced myocardial dysfunction	[42]

Table 1 (continued)

TCM products	Comparison	Patients	Design	Phase[a]	Mortality outcome	SOFA outcome	Other outcomes	References
Xinmailong Injection	Xinmailong Injection + RT vs. RT	476 patients with sepsis (8 RCTs)	Meta	All phase II RCTs	No effect	Not assessed	Improve cardiac function, no significant effect on ICU stay, no significant adverse events reported	[43]
Xuebijing Injection	Xuebijing Injection + RT vs. RT	1817 patients with sepsis	RCT	III	Improved	Improved	Increase ICU-free days and mechanical ventilation-free days, similar adverse events	[14]
Xuebijing Injection	Xuebijing Injection + RT vs. RT	1144 patients with sepsis (16 RCTs)	Meta	All phase II RCTs	Improved	Not assessed	Improve APACHE II score, no serious adverse events	[44]
Yantiao Formula	Yantiao Formula + RT vs. RT	120 patients with sepsis	RCT	II	Not assessed	Improved	Improve gastrointestinal function	[45]
Zengye Chengqi Decoction	Zengye Chengqi Decoction + RT vs. RT	124 patients with sepsis	RCT	II	No effect	Not assessed	Reduce inflammation markers, shorten ICU stay	[46]

[a] Phase II trials primarily aim to establish preliminary evidence of efficacy, whereas phase III trials require rigorous confirmation of clinical benefit

APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; CRRT, continuous renal replacement therapy; ICU, intensive care unit; RT, regular treatment; SOFA, Sequential Organ Failure Assessment; TCM, traditional Chinese medicine

Table 2 Representative examples of pharmacological effects and potential mechanisms of TCM ingredients on sepsis

Bioactive compounds	Representative herbs	Related TCM formulations	Key pathophysiological pathways	Potential mechanisms	Experimental models used	Ref
Polyphenols						
Baicalein/Baicalin	*Radix Scutellariae*	Banxia Xiexin Decoction; Dachaihu Decoction; HuangLian JieDu Decoction; Modified Liangge Powder; Qingwen Baidu Decoction	Immune modulation; programmed cell death	Inhibiting MAPKs and NF-κB; activating Nrf2/HO-1 signaling pathway	Cell culture; rodent model	[47–50]
Curcumin	*Rhizoma Curcumae*	Hongyu Peizhen Formula; Shengjiang Powder	Immune modulation	Upregulating PPAR-γ; inhibiting NF-κB; inhibiting NLRP3 inflammasome	Cell culture, rodent model; human study	[51–54]
Kaempferol	*Flos Carthami*	Xuebijing Injection	Endothelial protection	Regulating SphK1/S1P/S1PR1/MLC2 signaling pathway	Cell culture; rodent model	[64, 65]
Salvianolic Acid B	*Radix et Rhizoma Salviae Miltiorrhizae*	Xuebijing Injection	Endothelial protection	Reducing platelet activation and aggregation; inhibiting platelet CD226 function	Rodent model	[66]
Alkaloids						
Berberine	*Rhizoma Coptidis*	Banxia Xiexin Decoction; HuangLian JieDu Decoction; Jiawei Yiyi Fuzi Baijiang Powder; Qingwen Baidu Decoction	Immune modulation; mitochondrial function	Inhibiting NF-κB; activating SIRT1; inhibiting JAK2/STAT3; upregulating Notch1 signaling	Cell culture; rodent model	[55, 56, 68]
Matrine	*Radix Sophorae Flavescentis*	Not available	Immune modulation	Inhibiting NLRP3 inflammasome activation and pyroptosis via the PTPN2/JNK/SREBP2 pathway	Cell culture; rodent model	[57]
Saponins						
Astragaloside IV	*Radix Astragali*	Astragalus Injection; Qiguiyin Granule; Tuoli Xiaodu Powder	Immune modulation; mitochondrial function; programmed cell death	Upregulating AMPK/SIRT1 pathway; inhibiting RhoA/NLRP3 inflammasome pathway; regulating NOX4/JNK/BAX pathway	Cell culture; rodent model	[63, 69, 72]
Ginsenoside Rb1 and Rg1	*Radix et Rhizoma Ginseng*	Banxia Xiexin Decoction; Pogejiuxin Decoction; Shenfu Injection; Shengmai Injection; Shenmai Injection; Tuoli Xiaodu Powder	Programmed cell death; endoplasmic reticulum stress	Reducing HO-1 expression; activating PI3K/AKT pathway	Cell culture; rodent model	[70, 71, 75, 76]

Table 2 (continued)

Bioactive compounds	Representative herbs	Related TCM formulations	Key pathophysiological pathways	Potential mechanisms	Experimental models used	Ref
Paeoniflorin	*Radix Paeoniae Rubra*	Huanglian Jiedu Decoction; Qingwen Baidu Decoction; Tuoli Xiaodu Powder; Xuebijing Injection; Yantiao Formula	Endothelial protection; mitochondrial function	Inhibiting NF-κB; inhibiting IκB kinase activity; inhibiting NLRP3 inflammasome activation; prevent mitochondrial damage; activating SIRT1/FOXO1a/SOD2 pathway; activating RXRα signaling	Cell culture; rodent model	[58, 59, 67]
Others						
Anthraquinone/Emodin	*Radix et Rhizoma Rhei; Rhizoma Polygoni Cuspidati*	Dachaihu Decoction; Dachengqi Decoction; Dahuang Fuzi Decoction; Hongyu Peizhen Formula; JinHong Formula; Modified Liangge Powder; Qiguiyin Granule; Shengjiang Powder; Yantiao Formula; Zengye Chengqi Decoction	Immune modulation; programmed cell death; pulmonary epithelial protection	Inhibiting NF-κB; inhibiting pyroptosis; upregulating AQP and TJ proteins expression	Cell culture; rodent model	[73, 74]
Biphenyl neolignane/Honokiol	*Cortex Magnoliae Officinalis*	Dachengqi Decoction	Immune modulation	Inhibiting NLRP3 inflammasome; inhibiting pyroptosis; decreasing SLC3A2 and intracellular leucine uptake; inhibiting mTORC1 signaling; activating Nrf2/HO-1 signaling pathway	Cell culture; rodent model	[60, 61]

AKT, protein kinase B; AMPK, AMP-activated protein kinase; AQP, aquaporin; BAX, B-cell lymphoma-2-associated X; FOXO1a, forkhead box protein O1a; HO-1, heme oxygenase-1; JAK2, janus kinase 2; JNK, c-Jun N-terminal kinase; MLC2, myosin light chain 2; mTORC1, mechanistic target of rapamycin complex 1; NF-κB, nuclear factor kappa B; NLRP3, nod-like receptor pyrin domain-containing 3; NOX4, NADPH oxidase 4; Nrf2, nuclear erythroid factor 2; SLC3A2, solute carrier family 3 member 2; TJ, tight junction; PI3K, phosphatidylinositol 3-kinase; PTPN2, protein tyrosine phosphatase non-receptor type 2; PPAR-γ, peroxisome proliferator-activated receptor γ; SIRT1, sirtuin 1; RhoA, Ras homolog family member A; RXRα, retinoid X receptor alpha; S1P, sphingosine-1-phosphate; SphK1, sphingosine kinase 1; S1PR1, sphingosine-1-phosphate receptor 1; SODS, superoxide dismutase 2; SREBP2, sterol regulatory element-binding protein 2; STAT3, signal transducer and activator of transcription 3 survival by reducing inflammation and oxidative stress, partly through regulation of nuclear factor kappa B (NF-κB), mitogen-activated protein kinases (MAPKs), and the nuclear erythroid factor 2/heme oxygenase-1 (Nrf2/HO-1) axis [47–50]. Curcumin (from *Rhizoma Curcumae*) acts by up-regulating peroxisome proliferator-activated receptor-gamma (PPAR-γ) and inhibiting Nod-like receptor pyrin domain-containing 3 (NLRP3) inflammasome activation [51–54]. Berberine (from *Rhizoma Coptidis*) modulates sirtuin 1 (SIRT1)/NF-κB signaling and alleviates lung injury by inhibiting toll-like receptor 4 (TLR4)/NF-κB and Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) pathways [55, 56]. Matrine (from *Radix Sophorae Flavescentis*) suppresses NLRP3 inflammasome activation via protein tyrosine phosphatase non-receptor type 2/c-Jun N-terminal kinase/sterol regulatory element-binding protein 2 (PTPN2/JNK/SREBP2) signaling [57]. Paeoniflorin (from *Radix Paeoniae Rubra*) inhibits NF-κB and prevents NLRP3 inflammasome activation [58, 59]. Honokiol (from *Cortex Magnoliae Officinalis*) targets the solute carrier family 3 member 2 (SLC3A2)/L-leucine/mechanistic target of rapamycin complex 1 (mTORC1)/NLRP3 pathway and activates Nrf2 to reduce lipopolysaccharide (LPS)-induced acute lung injury [60–62]. Astragaloside IV (from *Radix Astragali*) mitigates gut barrier dysfunction by inhibiting Ras homolog family member A (RhoA)/NLRP3 signaling [63].

Endothelial protection

Endothelial barrier dysfunction contributes to sepsis-induced organ injury [77]. Several TCM compounds protect and restore endothelial function. Kaempferol (from *Flos Carthami*) modulates the sphingosine kinase 1/sphingosine-1-phosphate/sphingosine-1-phosphate receptor 1/myosin light chain 2 (SphK1/S1P/S1PR1/MLC2) signaling to attenuate inflammation, repair endothelial barrier damage, and improve sepsis-induced acute lung injury [64, 65]. Salvianolic acid B (from *Radix et Rhizoma Salviae Miltiorrhizae*) reduces platelet activation and adhesion, alleviates microcirculation disturbances, and protects endothelium, potentially via platelet CD226 [66]. Paeoniflorin activates retinoid X receptor alpha (RXRα) signaling to promote vascular endothelial cadherin expression and repair lung endothelial damage in sepsis [67].

Mitochondrial function

Mitochondrial damage is recognized as a key factor in sepsis progression [78]. Several TCM compounds protect mitochondrial integrity and function. Berberine promotes recovery from myocardial injury by protecting mitochondrial function [68]. It upregulates Notch1 signaling, regulating mitochondrial dynamics and maintaining the mitochondrial network in cardiac muscle cells [68]. Paeoniflorin improves survival in sepsis by preventing mitochondrial damage via activation of the SIRT1/forkhead box protein O1a (FOXO1a)/superoxide dismutase 2 (SOD2) pathway [59]. Astragaloside IV may improve sepsis-induced myocardial dysfunction by regulating NADPH oxidase 4 (NOX4)/JNK/Bcl-2-associated X protein (BAX) signaling, which modulates reactive oxygen species (ROS) levels and mitochondrial apoptosis [69].

Other mechanisms

Programmed cell death during sepsis contributes to multiple organ dysfunction syndrome [79]. Besides anti-inflammatory and antioxidant effects, baicalein and baicalin exhibit anti-apoptotic properties, such as suppressing lymphocyte apoptosis to preserve immune homeostasis [49, 50]. Ginsenosides Rg1 and Rb1 (from *Radix et Rhizoma Ginseng*) show protective effects in sepsis. Ginsenoside Rg1 alleviates sepsis-induced lung injury via the phosphatidylinositol 3-kinase/AKT (PI3K/AKT) pathway by inhibiting apoptosis [70]. Ginsenoside Rb1 exhibits beneficial effects in sepsis by inhibiting ferroptosis, potentially through modulation of HO-1 [71]. Astragaloside IV alleviates sepsis-induced hepatic injury by promoting M1-to-M2 macrophage transformation and inhibiting pyroptosis via AMPK/SIRT1 signaling [72]. Emodin (from *Radix et Rhizoma Rhei* and *Rhizoma Polygoni Cuspidati*), an anthraquinone, demonstrates significant bioactivity in sepsis treatment. It inhibits LPS-induced NF-κB activation and suppresses pyroptosis in HK-2 cells [73].

Endoplasmic reticulum (ER) stress arises from the accumulation of misfolded proteins due to proteostasis imbalance, activating unfolded protein response pathways, such as protein kinase R-like ER kinase (PERK), to restore homeostasis [80]. ER stress contributes to sepsis pathogenesis [81]. Ginsenosides Rg1 and Rb1 also modulate ER stress pathways to mitigate sepsis-induced damage. Ginsenoside Rg1 may alleviate sepsis-induced acute lung injury by regulating ER stress and related apoptosis in alveolar epithelial cells [75]. Similarly, ginsenoside Rb1 attenuates Staphylococcus aureus-induced lung injury by modulating ER stress and death receptor-mediated apoptosis [76].

Navigating challenges and opportunities for TCM integration in sepsis management

The integration of TCM into conventional sepsis management offers both challenges and significant opportunities for future advancement. This perspective has underscored the clinical effectiveness of several TCM formulations and the promise of TCM-derived lead compounds in the discovery of innovative anti-sepsis drugs. Nonetheless, several key challenges need to be addressed to support the clinical translation of TCM.

A major obstacle to the globalization of TCM is the lack of insufficient policy backing, particularly in securing approval from drug regulatory bodies outside China [82, 83]. This highlights the critical need for standardization and validation of TCM practices in alignment with modern medical standards. To address this, robust evidence demonstrating the effectiveness, safety, and reproducibility of TCM therapies is essential. Although the existing clinical studies have shown encouraging results, they, along with ongoing trials (Table S2), lack international scope, limiting their applicability. Therefore, further international randomized controlled trials are crucial to confirm the efficacy of TCM as monotherapy or in combination therapies [82, 84].

Another significant concern regarding the utilization of TCM products is the need for standardization and quality control [85]. Given the diversity of chemical composition in TCM, ensuring the consistent quality of these products is crucial [86]. Developing standardized procedures and comprehensive quality assurance measures for TCM preparations will enhance therapeutic outcomes, while promoting regulatory endorsement and broader acceptance within the healthcare community [87, 88]. The International Organization for Standardization Technical Committee 249 (ISO/TC 249) has made substantial contributions to addressing these challenges by establishing international standards that span the entire industrial chain of TCM in the fields of seedlings, medicinal materials, and manufactured products. For instance, ISO/TC 249 has developed specific standards such as ISO 18664 for determining heavy metals in herbal medicines and ISO 19617 for general requirements in natural product manufacturing processes. These standards prioritize areas with immediate global trade needs and have already demonstrated benefits in reducing unqualified products and enhancing international trade of Chinese medicines [87, 88]. Moreover, despite the clearly established safe daily dose in rigorously standardized TCM, it is vital to identify and mitigate risks such as herb-herb/drug interactions, toxicity, and adverse effects to ensure safe and effective use [89, 90].

While there are philosophical differences between TCM and modern medicine, these differences do not hinder their integration [91, 92]. On the contrary, TCM's longstanding emphasis on personalized treatment via pattern differentiation complements modern approaches [91], particularly by addressing complex, multifactorial conditions in critical care. Patients with sepsis may receive different herbal formulations based on whether they present with "toxic heat", "blood stasis", "Fu qi obstruction", or "acute deficiency" patterns [93]. As critical care medicine increasingly moves toward precision medicine approaches [94], TCM's established framework for personalization may be particularly valuable.

The philosophical differences also do not impede the application of modern methods to identify bioactive lead compounds from complex TCM formulations [92, 95]. Compounds such as artemisinin and paclitaxel highlight the potential of a classical rational drug discovery and development framework to improve the reliability, availability, and globalization of TCM [96–98]. The continuous development of mass spectrometry, nuclear magnetic resonance, high-throughput screening, and computer-aided drug design has significantly enhanced the efficiency of discovering structurally novel natural bioactive molecules [10]. Moreover, artificial intelligence (AI) is transforming drug discovery by accelerating the exploration of uncharted chemical spaces and streamlining the process [99]. For example, He et al. [100] utilized molecular docking and drug-target network analysis to identify potential candidates targeting GSNOR, C3b, Factor D, and PERK proteins. Multiple machine learning and deep learning models were employed to predict the bioactivity of TCM candidates in order to filter out the multi-target inhibitors. Additionally, 3D-QSAR models were applied to calculate molecular steric and electrostatic fields and observe favorable and unfavorable interactions in order to further analyze the inhibition. The molecular dynamics analysis displays that all these ligand-target complexes exhibit stable conditions during the entire simulation time. This integrated approach, combining AI with molecular modeling tools, underscores the effectiveness of incorporating AI into the traditional drug discovery process. While the study by He et al. [100] does not specifically focus on sepsis, the approaches described can be readily adapted to address a variety of diseases, including sepsis. Beyond identification of candidate compounds, the phase of drug optimization is equally vital, as it refines the chemical structure and properties of drug candidates to enhance therapeutic efficacy, reduce toxicity and side effects, improve pharmacokinetic properties, and increase drug stability.

Furthermore, integrating TCM into mainstream sepsis management requires effective multidisciplinary cooperation and communication. Teamwork among healthcare experts, such as critical care specialists, traditional medicine practitioners, pharmacologists, and scientists, is crucial for developing a comprehensive treatment plan and formulating a well-structured clinical research protocol.

Conclusions

In conclusion, while current clinical evidence indicates potential benefits of TCM as adjunctive treatments for sepsis, robust supporting evidence is still limited and should be interpreted with caution. The pharmacological effects and mechanisms of action of some bioactive compounds derived from TCM medications have been elucidated. These mechanistically characterized preparations represent valuable sources for novel anti-sepsis drug discovery, highlighting their potential to address unmet needs in sepsis management.

However, several critical unresolved questions remain to be addressed before these findings can be effectively translated into clinical applications, including the lack of high-quality clinical evidence, limited understanding of pharmacological mechanisms, challenges in standardizing the quality and consistency of TCM products, and inadequate interdisciplinary collaboration. To advance the field, future research should prioritize conducting well-designed multicenter RCTs to rigorously assess the efficacy and safety of TCM medications in sepsis, deepening the investigation of pharmacological mechanisms to elucidate therapeutic roles and multi-target effects, establishing standardized quality control protocols for TCM products to ensure consistency, potency, and reliability, and promoting sustained interdisciplinary collaboration to align research efforts and accelerate clinical translation. These initiatives will be critical for integrating TCM-based therapies into mainstream sepsis management.

Abbreviations

AMPK	AMP-activated protein kinase
APACHE II	Acute physiology and chronic health evaluation II
BAX	Bcl-2-associated X protein
CI	Confidence interval
FOXO1a	Forkhead box protein O1a
HO-1	Heme oxygenase-1
ICU	Intensive care unit
JAK2	Janus kinase 2
JNK	C-Jun N-terminal kinase
LPS	Lipopolysaccharide
M	Mean difference
MAPKs	Mitogen-activated protein kinases
MLC2	Myosin light chain 2
mTORC1	Mechanistic target of rapamycin complex 1
NF-κB	Nuclear factor kappa B
NLRP3	Nod-like receptor pyrin domain-containing 3
NOX4	NADPH oxidase 4
Nrf2	Nuclear erythroid factor 2
OR	Odds ratio
PPAR-γ	Peroxisome proliferator-activated receptor-gamma
PI3K-AKT	Phosphatidylinositol 3-kinase-AKT
PTPN2	Protein tyrosine phosphatase non-receptor type 2
RCTs	Randomized controlled trials
RhoA	Ras homolog family member A
RXRα	Retinoid X receptor alpha
S1P	Sphingosine-1-phosphate
S1PR1	Sphingosine-1-phosphate receptor 1
SIRT1	Sirtuin 1
SLC3A2	Solute carrier family 3 member 2
SMD	Standardized mean difference
SOD2	Superoxide dismutase 2
SphK1	Sphingosine kinase 1
SREBP2	Sterol regulatory element-binding protein 2
STAT3	Signal transducer and activator of transcription 3
TCM	Traditional Chinese medicine
TLR4	Toll-like receptor 4

Supplementary Information

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Additional file1.

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