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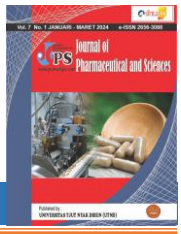

Preclinical Evaluation of Ascorbic Acid in Experimental Sepsis and the Research Gap for *Centella asiatica* in *Staphylococcus aureus*-Induced Sepsis: A Systematic Literature Review

Evaluasi Praklinis Asam Askorbat pada Sepsis Eksperimental dan Kesenjangan Penelitian *Centella asiatica* pada Sepsis Terinduksi *Staphylococcus aureus*: Tinjauan Literatur Sistematis

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Abstract

Background: Adjunctive antioxidant therapy has been extensively investigated in experimental sepsis; however, evidence regarding the combined effects of *Centella asiatica* extract and ascorbic acid on survival outcomes remains limited. This systematic review aimed to evaluate preclinical evidence on the survival benefits of *C. asiatica* extract and/or ascorbic acid in experimental sepsis, particularly in *Staphylococcus aureus*-induced models, and to identify research gaps. **Methods:** A systematic review was conducted following PRISMA guidelines. Comprehensive literature searches were performed in Scopus (n=126) and Google Scholar (n=467) to identify controlled in vivo rat studies evaluating *C. asiatica* extract and/or ascorbic acid supplementation in sepsis models with reported survival outcomes. Data extraction covered intervention characteristics, sepsis models, survival endpoints, inflammatory markers, oxidative stress parameters, organ injury indicators, and statistical analyses. **Results:** Of 593 initial records, 403 were screened after duplicate removal, and five studies met eligibility criteria. All included studies evaluated ascorbic acid monotherapy in sepsis models induced by lipopolysaccharide (LPS), cecal ligation and puncture (CLP), or fecal intraperitoneal injection (FIP); none used *S. aureus* and none evaluated *C. asiatica* extract. Ascorbic acid monotherapy consistently improved survival: 48-hour survival increased from 5.5% to 61% ($p<0.0007$) and 7-day survival from 30% to 45% ($p<0.05$) in CLP models, accompanied by reduced pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, CRP), decreased oxidative stress, and attenuated multiorgan injury. **Conclusion:** This review identifies a critical research gap: no preclinical study has evaluated *C. asiatica* extract, alone or in combination with ascorbic acid, in *S. aureus*-induced sepsis. The available evidence is limited to ascorbic acid monotherapy in alternative sepsis models, which cannot be directly generalized to staphylococcal sepsis due to pathophysiological differences. Direct experimental studies using validated *S. aureus* sepsis models are urgently needed before any therapeutic recommendation can be made.

***Keywords*: Centella asiatica; Ascorbic acid; Staphylococcus aureus; Sepsis**

Abstrak

Latar Belakang: Terapi antioksidan adjuvan telah banyak diteliti pada sepsis eksperimental; namun, bukti mengenai efek kombinasi ekstrak *Centella asiatica* dan asam askorbat terhadap luaran kelangsungan hidup masih terbatas. Tinjauan sistematis ini bertujuan untuk mengevaluasi bukti praklinis mengenai manfaat kelangsungan hidup dari ekstrak *C. asiatica* dan/atau asam askorbat pada sepsis eksperimental, khususnya pada model yang diinduksi *Staphylococcus aureus*, serta mengidentifikasi kesenjangan penelitian. **Metode:** Tinjauan sistematis ini dilakukan sesuai pedoman PRISMA. Pencarian literatur komprehensif dilakukan pada Scopus (n=126) dan Google Scholar (n=467) untuk mengidentifikasi studi terkontrol *in vivo* pada tikus yang mengevaluasi suplementasi ekstrak *C. asiatica* dan/atau asam askorbat pada model sepsis dengan luaran kelangsungan hidup yang dilaporkan. Ekstraksi data mencakup karakteristik intervensi, model sepsis, luaran survival, penanda inflamasi, parameter stres oksidatif, indikator cedera organ, serta analisis statistik. **Hasil:** Dari 593 rekaman awal, 403 disaring setelah penghapusan duplikat, dan lima studi memenuhi kriteria kelayakan. Seluruh studi yang memenuhi kriteria mengevaluasi monoterapi asam askorbat pada model sepsis yang diinduksi oleh lipopolisakarida (LPS), *cecal ligation and puncture* (CLP), atau injeksi intraperitoneal feses (FIP); tidak ada yang menggunakan *S. aureus* dan tidak ada yang mengevaluasi ekstrak *C. asiatica*. Monoterapi asam askorbat secara konsisten meningkatkan kelangsungan hidup: survival 48 jam meningkat dari 5,5% menjadi 61% ($p<0,0007$) dan survival 7 hari meningkat dari 30% menjadi 45% ($p<0,05$) pada model CLP, yang disertai dengan penurunan sitokin proinflamasi (TNF-α, IL-1β, IL-6, CRP), penurunan stres oksidatif, dan perbaikan cedera multiorgan. **Kesimpulan:** Tinjauan ini mengidentifikasi kesenjangan penelitian yang kritis: belum ada studi praklinis yang mengevaluasi ekstrak *C. asiatica*, baik tunggal maupun kombinasi dengan asam askorbat, pada sepsis yang diinduksi *S. aureus*. Bukti yang tersedia terbatas pada monoterapi asam askorbat pada model sepsis alternatif, yang tidak dapat digeneralisasikan secara langsung ke sepsis stafilokokus karena perbedaan patofisiologis. Studi eksperimental langsung menggunakan model sepsis *S. aureus* yang tervalidasi sangat diperlukan sebelum rekomendasi terapeutik dapat diberikan.

***Kata Kunci*: Centella asiatica; asam askorbat; Staphylococcus aureus; sepsis.**

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Introduction

Sepsis remains one of the most critical causes of morbidity and mortality worldwide. It is characterized by a dysregulated host response to infection, leading to life-threatening organ dysfunction [1]. Although advances in antimicrobial therapy, mechanical ventilation, and renal replacement therapy have improved clinical management, mortality remains high, especially in septic shock and severe bacterial infection [2]. The burden of sepsis is also not limited to acute death. Survivors may experience persistent weakness, cognitive impairment, repeated hospitalization, and reduced quality of life. These consequences highlight the need for adjunctive therapies that can complement antimicrobial treatment by modulating excessive host responses, reducing tissue injury, and improving survival.

Among bacterial pathogens, Staphylococcus aureus is an important gram-positive organism associated with bloodstream infection, pneumonia, endocarditis, septic shock, and multi-organ failure [3]. This pathogen is clinically important because it possesses multiple virulence factors that promote immune evasion, tissue invasion, and systemic inflammatory activation. Unlike gram-negative sepsis, which is commonly associated with lipopolysaccharide-mediated activation, *S. aureus*-induced sepsis involves distinct pathogen-associated molecular patterns and secreted toxins. Peptidoglycan, lipoteichoic acid, hemolysins, leukocidins, exotoxins, and superantigens may trigger intense immune activation and cytokine release. Superantigen-mediated T-cell activation can produce inflammatory responses that differ substantially from those induced by endotoxin. These differences may influence cytokine kinetics, oxidative stress responses, endothelial dysfunction, coagulation disturbances, organ injury, and survival outcomes [4]. Therefore, therapeutic findings from lipopolysaccharide or polymicrobial models cannot automatically be generalized to *S. aureus*-induced sepsis. Pathogen-specific evaluation is necessary, particularly when survival is used as a major endpoint.

The interaction between uncontrolled inflammation and oxidative stress strongly influences the progression of sepsis. During infection, activation of innate immune cells is required for microbial clearance. However, excessive or prolonged activation may cause systemic release of pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and acute-phase proteins including C-reactive protein. These mediators promote endothelial activation, vascular leakage, leukocyte recruitment, microvascular dysfunction, and mitochondrial impairment [5]. At the same time, activated neutrophils and macrophages, as well as damaged mitochondria, produce large amounts of reactive oxygen species (ROS). Under physiological conditions, ROS support antimicrobial defense and cell signaling. In sepsis, however, excessive ROS overwhelms endogenous antioxidant systems and causes lipid peroxidation, protein oxidation, DNA damage, mitochondrial dysfunction, and cellular injury. Oxidative damage further amplifies inflammation, reduces energy production, impairs vascular responsiveness, and contributes to acute lung injury, hepatic dysfunction, renal injury, and circulatory failure. Thus, oxidative stress is a central mechanism linking immune dysregulation to organ failure and death.

This pathophysiological background supports the investigation of antioxidant-based adjunctive therapy in experimental sepsis. Ascorbic acid, or vitamin C, has received particular attention because it acts as a water-soluble antioxidant, an enzymatic cofactor, an endothelial stabilizer, and an immunomodulatory molecule [6]. It can scavenge ROS, regenerate other antioxidants, preserve nitric oxide bioavailability, and reduce oxidative injury to endothelial and epithelial barriers. Vitamin C is also involved in catecholamine synthesis and may support vascular tone during septic shock. In addition, it may modulate nuclear factor-kappa B signaling, thereby reducing the transcription of inflammatory mediators. Experimental studies have reported that vitamin C supplementation can reduce levels of TNF-α, IL-1β, IL-6, and other inflammatory markers, attenuate oxidative damage, improve microvascular function, and enhance survival in certain sepsis

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models. However, differences in dose, timing, route of administration, observation period, and method of sepsis induction make interpretation challenging. Survival benefit observed in cecal ligation and puncture or endotoxin models may not necessarily predict efficacy in *S. aureus*-induced sepsis.

In parallel with vitamin-based interventions, medicinal plants have gained attention as sources of multi-target bioactive compounds. Plant extracts often contain diverse secondary metabolites that may act simultaneously on inflammation, oxidative stress, immune regulation, endothelial function, and tissue repair. *Centella asiatica* is a medicinal plant widely used in traditional medicine and has been studied for wound healing, neuroprotection, hepatoprotection, anti-inflammatory activity, antioxidant activity, and tissue regeneration. Its major bioactive constituents include pentacyclic triterpenoids such as asiaticoside, madecassoside, asiatic acid, and madecassic acid [7]. These compounds have been reported to modulate inflammatory signaling, reduce oxidative injury, improve collagen synthesis, and protect tissues from damage in several experimental models. The pharmacological profile of *C. asiatica* is therefore biologically relevant to sepsis, in which inflammatory injury, oxidative stress, microvascular dysfunction, and impaired tissue recovery occur simultaneously.

Experimental evidence suggests that *C. asiatica* extract can suppress the production of pro-inflammatory mediators and improve antioxidant defense. Several studies have reported that *C. asiatica* preparations reduce TNF-α, IL-1β, IL-6, nitric oxide, and other inflammatory markers in models of tissue injury or inflammation [8]. Other studies indicate that the extract may increase endogenous antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, while reducing malondialdehyde and other lipid peroxidation markers [9]. These effects may help preserve mitochondrial function and limit cellular damage. *C. asiatica* has also been associated with improved histological tissue architecture, suggesting tissue-protective activity [10]. Although these mechanisms are highly relevant to sepsis pathophysiology, most evidence has been generated from non-sepsis models or from disease models that do not evaluate survival. Therefore, the translational relevance of *C. asiatica* extract in experimental sepsis remains uncertain.

The combination of *C. asiatica* extract and ascorbic acid could theoretically provide complementary protection. Ascorbic acid may rapidly reduce circulating oxidative stress, stabilize the endothelium, and support vascular responsiveness, whereas *C. asiatica*-derived triterpenoids may offer broader anti-inflammatory, antioxidant, and tissue-protective effects. Together, these interventions may reduce cytokine storm, limit ROS-mediated injury, preserve microcirculatory function, attenuate organ damage, and improve survival in bacterial sepsis. Nevertheless, biological plausibility does not automatically confirm therapeutic efficacy. Drug–extract interactions, dose-response relationships, treatment timing, route of supplementation, and pathogen-specific immune responses may influence outcomes. In *S. aureus*-induced sepsis, exotoxins and superantigens may induce immune activation patterns that differ from those in lipopolysaccharide, cecal ligation and puncture, or fecal intraperitoneal injection models. Therefore, evidence from these models should be interpreted cautiously.

It remains unclear whether preclinical studies provide direct evidence supporting the survival benefit of *C. asiatica* extract, ascorbic acid, or their combination in *S. aureus*-induced sepsis. Many experimental studies emphasize biochemical markers, histopathological improvement, or inflammatory modulation, whereas survival outcomes are not always reported. Studies that report survival also use different sepsis induction methods, treatment regimens, and observation periods. This creates uncertainty regarding the strength and applicability of the evidence. This systematic review, therefore, aims to critically evaluate controlled *in vivo* animal studies investigating *C. asiatica* extract and/or ascorbic acid supplementation in experimental sepsis, with particular emphasis on survival outcomes, inflammatory biomarkers, oxidative stress parameters, organ injury indicators, and pathogen specificity. By distinguishing direct evidence from biologically plausible indirect evidence, this review seeks to clarify the current research gap and provide a scientific basis for future studies evaluating combined antioxidant and plant-derived adjunctive therapy in staphylococcal sepsis.

Methods

Study Design

This study was conducted as a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11,12]. The review was designed to identify, evaluate, and synthesize available preclinical evidence regarding the effects of *Centella asiatica* extract and/or ascorbic acid supplementation on survival outcomes in experimental sepsis. Particular attention was given to

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controlled *in vivo* rat studies reporting survival-related endpoints, including mortality rate, survival time, or survival analysis. Because the proposed therapeutic concept involved antioxidant and anti-inflammatory modulation in bacterial sepsis, this review also considered secondary outcomes related to inflammation, oxidative stress, organ injury, and histopathological alterations.

PICO Framework and Research Question

The research question was formulated using the PICO framework to clarify the eligibility criteria and guide the synthesis of evidence. The population comprised rats with experimentally induced sepsis, including *Staphylococcus aureus*-induced sepsis where available, as well as other established experimental sepsis models. The intervention included *Centella asiatica* extract, ascorbic acid (vitamin C), or their combination. The comparator included untreated septic controls, vehicle-treated controls, placebo groups, or standard therapy groups. The primary outcome was survival-related, including survival rate, mortality rate, survival time, time-to-death analysis, or survival curve. Secondary outcomes included inflammatory biomarkers, oxidative stress parameters, microcirculatory changes, organ injury markers, and histopathological findings.

The PICO-based research question was: "Does administration of *Centella asiatica* extract and/or ascorbic acid improve survival outcomes in septic rats compared with control treatment?"

Literature Search Strategy

A comprehensive literature search was conducted using two electronic databases, Scopus and Google Scholar, to identify relevant preclinical studies. The search was designed to capture experimental investigations evaluating the effects of *Centella asiatica* extract and/or ascorbic acid supplementation on survival outcomes in animal models of sepsis. The search yielded 593 records in total, comprising 126 from Scopus and 467 from Google Scholar.

A literature search was conducted using two electronic databases, Scopus and Google Scholar, on 18 February 2026. The search was limited to studies published within the last 10–15 years to improve methodological relevance, while older studies were considered only when they provided important survival-related evidence. The search terms included "*Centella asiatica*", "ascorbic acid", "vitamin C", "sepsis", "septic shock", "*Staphylococcus aureus*", "lipopolysaccharide", "cecal ligation and puncture", "fecal intraperitoneal injection", "rats", "animal model", "survival", "mortality", and "survival analysis". Boolean operators such as "AND" and "OR" were used to combine intervention-, disease model-, animal model-, and outcome-related terms.

All retrieved records were exported and organized using a reference management system. Duplicate records were identified and removed before title and abstract screening. The remaining records were then assessed according to predefined eligibility criteria. Full-text articles were retrieved for potentially relevant studies and evaluated for final inclusion in the qualitative synthesis.

Study Selection and PRISMA Flow

The study selection process is summarized in Figure 1. A total of 593 records were identified through database searches, including 126 from Scopus and 467 from Google Scholar. After duplicate removal, 403 records remained for screening, indicating that 190 duplicate records were excluded. Titles and abstracts were screened to remove studies that were clearly unrelated to the research question, including non-sepsis studies, non-animal studies, purely *in vitro* studies, review articles, editorials, conference abstracts without full data, and studies that did not evaluate *Centella asiatica*, ascorbic acid, vitamin C, or relevant antioxidant interventions.

Potentially eligible articles were then assessed in full text. Studies were further excluded if they did not report survival-related outcomes, did not use a controlled experimental design, did not involve rat models, or did not provide sufficient methodological and outcome data. Following screening and eligibility assessment, five studies met the inclusion criteria and were included in the qualitative review. The PRISMA flow diagram was used to illustrate the identification, screening, eligibility, and inclusion stages of the review process.

Eligibility Criteria

Studies were included if they fulfilled the predefined eligibility criteria [14]. Eligible studies were controlled in vivo experimental studies conducted in rat models of sepsis. Sepsis induction could involve established experimental methods, including *Staphylococcus aureus* inoculation, lipopolysaccharide administration, cecal ligation and puncture, or fecal intraperitoneal injection. The intervention had to involve

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Centella asiatica extract, ascorbic acid (vitamin C), or a clearly defined antioxidant intervention relevant to the review question. Survival-related outcomes, including survival rate, mortality rate, survival time, time-to-death analysis, or survival curves, were considered the primary outcomes of interest.

Controlled experimental designs were prioritized to allow comparison between intervention and control groups [15]. Acceptable comparators included untreated septic controls, vehicle-treated septic controls, placebo groups, or standard therapy groups. Studies were excluded if they were conducted only in vitro, used non-rat models that were not sufficiently relevant to the review objective, were review articles, editorials, letters, case reports, or conference abstracts without complete experimental data [16]. Studies were also excluded when the intervention effect could not be clearly attributed to *Centella asiatica* extract or ascorbic acid because of unclear intervention composition, inseparable combination therapy, or major confounding co-interventions.

Because direct evidence on the combined use of *Centella asiatica* extract and ascorbic acid in *S. aureus*-induced sepsis was expected to be limited, this review distinguished between direct survival evidence and secondary mechanistic evidence. Direct evidence was defined as controlled rat studies evaluating *Centella asiatica* extract and/or ascorbic acid in *S. aureus*-induced sepsis with survival-related outcomes. Studies that did not report survival but evaluated relevant secondary outcomes, such as inflammatory cytokines, oxidative stress parameters, microcirculatory changes, organ injury markers, or histopathological findings, were retained only as secondary mechanistic evidence. These studies were not interpreted as direct evidence of survival benefit.

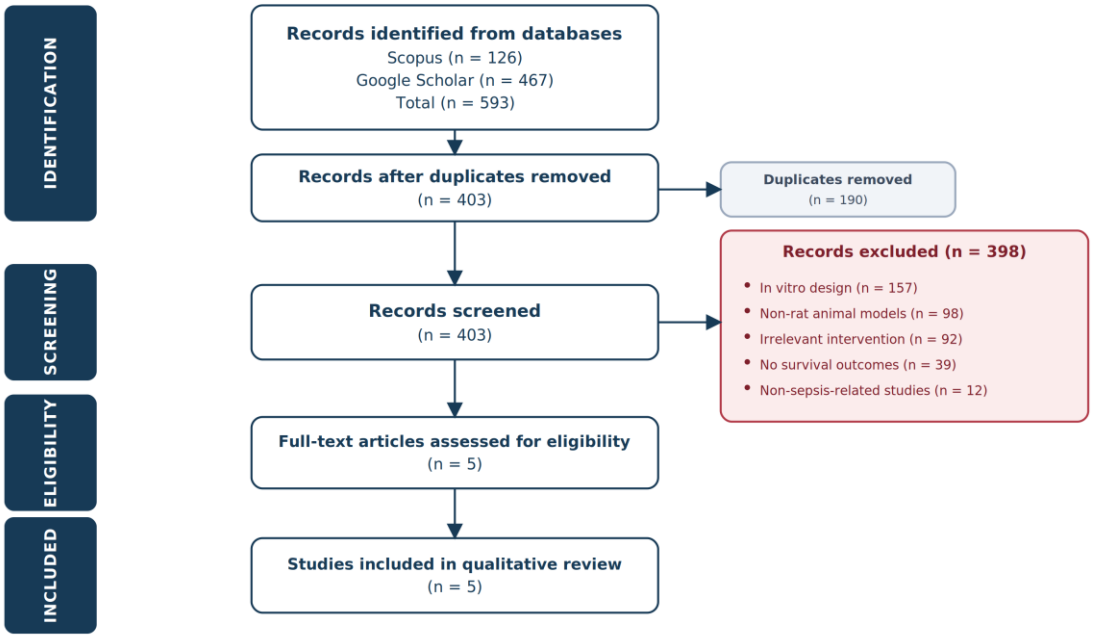

Figure 1. PRISMA flow diagram.

Data Extraction

Data extraction was performed using a structured and standardized form to ensure consistency across all included studies [17]. Extracted information covered study characteristics, intervention details, sepsis induction methods, animal characteristics, survival outcomes, secondary biological outcomes, and statistical analyses.

Study characteristics included the first author, year of publication, study design, experimental setting, number of groups, sample size, duration of observation, and type of comparator. Intervention-related data included the type of substance administered: Centella asiatica extract, ascorbic acid (vitamin C), or a combination therapy. Additional information included dose, route of administration, timing of administration, treatment duration, frequency of administration, and any co-interventions used during the experiment.

Details of sepsis induction were also extracted. These included sepsis models such as *Staphylococcus aureus* inoculation, lipopolysaccharide-induced endotoxemia, cecal ligation and puncture, or fecal intraperitoneal injection. Where available, the dose of the septic stimulus, route of administration, method of

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sepsis confirmation, and timing between sepsis induction and treatment initiation were recorded. Study population characteristics included rat strain, sex, age, body weight, number of animals per group, and total study duration.

The primary outcomes of interest were survival-related endpoints, including survival rate, mortality rate, time to death, Kaplan–Meier survival analysis, and log-rank test results when available. Secondary outcomes included inflammatory biomarkers such as TNF-α, IL-1β, IL-6, and C-reactive protein; oxidative stress parameters such as malondialdehyde, superoxide dismutase, catalase, glutathione, and reactive oxygen species; organ function markers; and histopathological findings in major organs, including the liver, kidney, lung, and intestine. Statistical information, including statistical tests, p-values, confidence intervals, and effect estimates, was also recorded when available [18].

Data Synthesis

Due to heterogeneity in sepsis induction methods, intervention types, doses, treatment timing, survival assessment periods, and reported biological outcomes, meta-analysis was not performed. Instead, the findings were synthesized qualitatively. Included studies were grouped according to intervention type, sepsis model, and survival outcome. Studies evaluating ascorbic acid (vitamin C) were analyzed separately from those evaluating plant-derived interventions. Particular attention was given to whether the included studies directly evaluated *S. aureus*-induced sepsis or only provided indirect evidence from lipopolysaccharide, cecal ligation and puncture, or fecal intraperitoneal injection models.

The synthesis focused on identifying whether the available evidence supported survival benefits and whether improvements in inflammatory, oxidative stress, or organ injury parameters accompanied these effects. The strength of the evidence was interpreted with caution, considering model relevance, the quality of the survival endpoint, intervention timing, and the consistency of findings across studies. Because no eligible study directly evaluated the combined effect of *Centella asiatica* extract and ascorbic acid in *S. aureus*-induced sepsis, the review emphasized the distinction between demonstrated evidence and theoretical biological plausibility.

Results

Characteristics of Included Studies

Table 1. Characteristics of included preclinical studies evaluating ascorbic acid in rat models of sepsis

Study	Rat strain	Sepsis induction method	Ascorbic acid dose and route	Timing relative to sepsis	Comparator agents	Primary endpoint	Sample size per group
Kawade et al. [19]	ODS/Shi Jcl-od/od rats are unable to synthesize ascorbic acid	Intraperitoneal injection of LPS, 15 mg/kg body weight	300 or 3,000 mg/kg dietary oral administration	8 days before LPS injection	Ascorbic acid-deficient diet	48-hour survival rate	18
Bozkurt et al. [20]	Wistar Hannover infant rats, 21 days old, 50–55 g	Intraperitoneal injection of *E. coli* LPS, 30 mg/kg	200 mg/day oral gavage	7 days before LPS injection	Quercetin, untreated sepsis, healthy control	Inflammatory cytokines and antioxidant biomarkers	7
Tyml et al. [21]	Sprague-Dawley rats	Cecal ligation and puncture	7.6 mg/100 g body weight intravenous bolus	1, 6, or 24 hours after CLP	Saline vehicle	Microvascular blood flow distribution	Not reported
Lyu et al. [22]	Sprague-Dawley rats, SPF grade	Cecal ligation and puncture	Intravenous sodium ascorbate; dose not stated	3 hours after CLP	Untreated sepsis, sham, control	7-day survival rate and neurological scores	Not reported
Canbolat et al. [23]	Wistar albino rats, 200–250 g	Fecal intraperitoneal injection, 1 g/kg body weight	500 mg/kg/day intraperitoneal administration	After a 1-hour FIP procedure	Vitamin E, untreated FIP, healthy control	Lung histopathology and inflammatory markers	10

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A total of five studies met the eligibility criteria and were included in the qualitative synthesis. However, none of the included studies directly addressed the predefined research question. No study evaluated *Centella asiatica* extract as an intervention, and no study used *Staphylococcus aureus* to induce sepsis. All included studies investigated the effects of ascorbic acid (vitamin C) in rat models of sepsis induced by lipopolysaccharide (LPS), cecal ligation and puncture (CLP), or fecal intraperitoneal injection (FIP). Therefore, the available evidence should be interpreted as indirect support for the potential role of antioxidant therapy in experimental sepsis, rather than as direct evidence for combined *Centella asiatica* extract and ascorbic acid therapy in *S. aureus*-induced sepsis.

Based on outcome reporting, the included studies were grouped into two evidence categories. Kawade et al. [19] and Lyu et al. [22] were classified as survival-outcome studies because they reported mortality or survival rates. Bozkurt et al. [20], Tyml et al. [21], and Canbolat et al. [23] were classified as secondary mechanistic studies because they primarily reported inflammatory, oxidative stress, microcirculatory, or organ injury outcomes without formal survival analysis.

Survival Outcomes

Only two of the five included studies formally reported survival outcomes. The reported survival rates, follow-up periods, and statistical comparisons are summarized in Table 2.

Table 2. Reported survival outcomes in preclinical rat models of sepsis treated with ascorbic acid

Study	Follow-up period	Sepsis or untreated control	Ascorbic acid treatment	Statistical comparison
Kawade et al. [19]	48 hours	5.5% survival in the ascorbic acid-deficient group	39% survival with a 300 mg/kg diet and 61% survival with a 3,000 mg/kg diet	$p < 0.0039$ for 300 mg/kg vs deficient group; $p < 0.0007$ for 3,000 mg/kg vs deficient group; log-rank test
Lyu et al. [22]	7 days	30% survival in untreated septic rats	45% survival in sodium ascorbate-treated rats	$p < 0.05$

Kawade et al. [19] demonstrated a clear dose-related improvement in 48-hour survival in LPS-induced septic ODS rats receiving dietary ascorbic acid. Survival in the ascorbic acid-deficient group was only 5.5%. In contrast, survival increased to 39% in rats receiving 300 mg/kg dietary ascorbic acid and to 61% in rats receiving 3,000 mg/kg dietary ascorbic acid. Lyu et al. [22] also reported a survival benefit following therapeutic administration of sodium ascorbate in a CLP-induced sepsis model. In this study, 7-day survival increased from 30% in untreated septic rats to 45% in rats treated with intravenous sodium ascorbate administered three hours after CLP induction. The remaining three studies did not include formal survival analysis as a primary endpoint.

Expanded Survival Outcome Analysis

Evidence of survival was limited to two studies. Kawade et al. [19] reported 48-hour survival in an LPS-induced sepsis model using ODS rats. Survival was 5.5% in the ascorbic acid-deficient group, 39% in the 300 mg/kg dietary ascorbic acid group, and 61% in the 3,000 mg/kg dietary ascorbic acid group. This corresponds to an absolute survival increase of 33.5 percentage points for 300 mg/kg and 55.5 percentage points for 3,000 mg/kg compared with the deficient group. The crude relative survival ratio was approximately 7.1 for 300 mg/kg and 11.1 for 3,000 mg/kg.

Lyu et al. [22] reported 7-day survival in a CLP-induced sepsis model. Survival increased from 30% in untreated septic rats to 45% in sodium ascorbate-treated rats, corresponding to an absolute survival increase of 15 percentage points and a crude relative survival ratio of approximately 1.5. However, because the dose and sample size were not clearly reported, this finding should be interpreted cautiously. The survival endpoints were not directly comparable because the studies differed in sepsis model, treatment regimen, route of administration, and follow-up duration. Kawade et al. [19] evaluated prophylactic dietary ascorbic acid before an LPS challenge and assessed short-term (48-hour) survival, whereas Lyu et al. [22] evaluated therapeutic sodium ascorbate after CLP induction and assessed 7-day survival. Therefore, these findings suggest a possible survival benefit of ascorbic acid in experimental sepsis but do not provide sufficient evidence to estimate pooled effects or to extrapolate directly to Staphylococcus aureus-induced sepsis.

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Inflammatory Markers

Three studies evaluated inflammatory biomarkers following ascorbic acid administration in experimental sepsis models. The effects of ascorbic acid on TNF-α, IL-1β, IL-6, and CRP are summarized in Table 3.

Across the included studies, ascorbic acid consistently reduced pro-inflammatory mediators. Kawade et al. [19] reported that LPS administration increased TNF-α and IL-1β levels, whereas dietary ascorbic acid supplementation suppressed these cytokines in a dose-dependent manner. Bozkurt et al. [20] reported significant reductions in TNF-α, IL-1β, IL-6, and CRP in septic infant rats treated with ascorbic acid. Canbolat et al. [23] also observed lower TNF-α, IL-1β, IL-6, and CRP levels in vitamin C-treated rats compared with untreated FIP-induced septic rats. These findings support the anti-inflammatory potential of ascorbic acid in experimental sepsis, although the evidence remains indirect for *S. aureus*-induced sepsis.

Table 3. Effects of ascorbic acid on inflammatory markers in preclinical sepsis models

Study	TNF-α	IL-1β	IL-6	CRP	Direction of effect with ascorbic acid
Kawade et al. [19]	Elevated by LPS and suppressed by ascorbic acid	Elevated by LPS and suppressed by ascorbic acid	Not reported	Not reported	Dose-dependent reduction
Bozkurt et al. [20]	Significantly lower with ascorbic acid	Significantly lower with ascorbic acid	Significantly lower with ascorbic acid	Significantly lower with ascorbic acid	Significant reduction, $p < 0.05$
Canbolat et al. [23]	Lower in the vitamin C group compared with the FIP group	Lower in the vitamin C group compared with the FIP group	Lower in the vitamin C group compared with the FIP group	Lower in the vitamin C group compared with the FIP group	Reduction across all markers

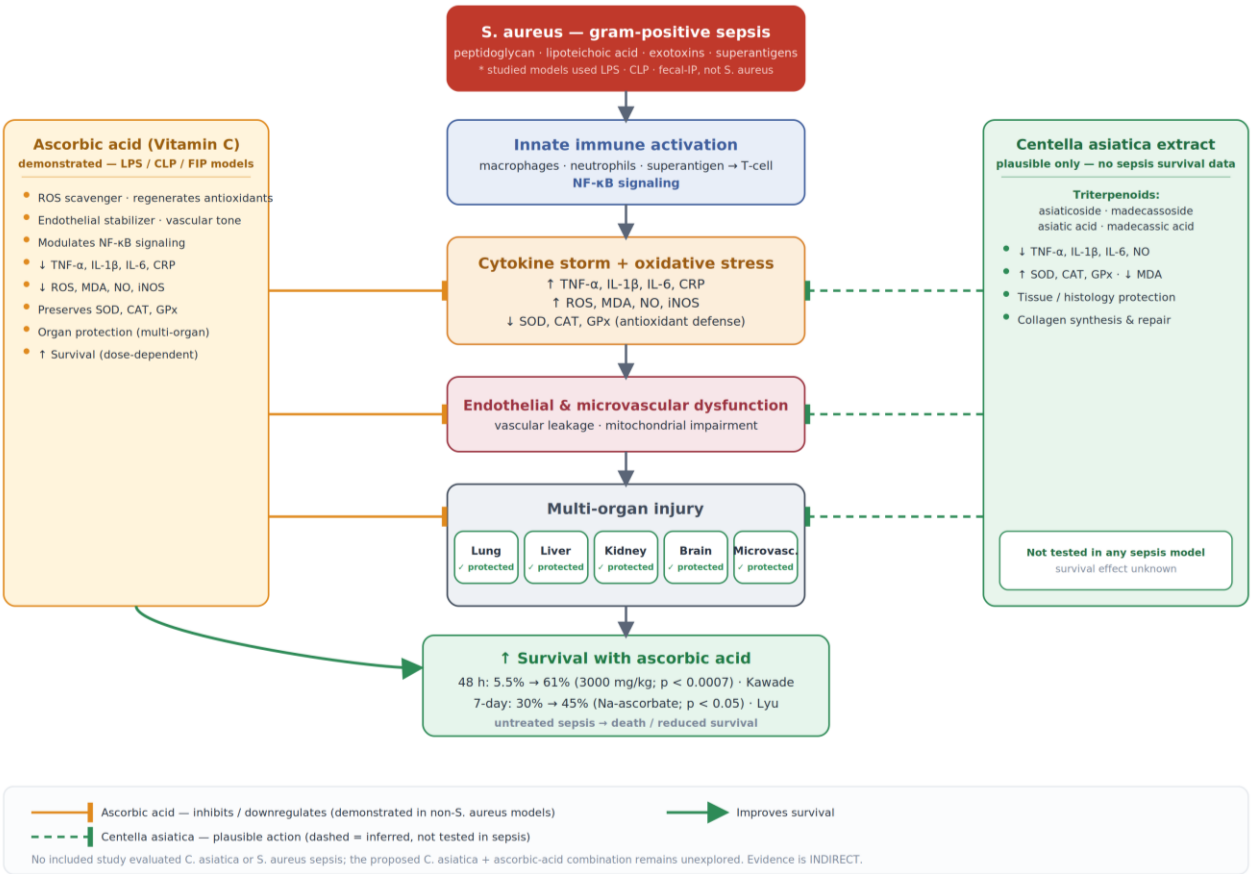

Figure 2. Potential mechanism of Centella asiatica and vitamin C in sepsis condition

The figure summarises the actual evidence identified in this review. Included studies evaluated ascorbic acid or vitamin C in LPS, CLP, or fecal intraperitoneal injection models. No included study evaluated *Centella*

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asiatica extract or *Staphylococcus aureus*-induced sepsis. Survival benefit was reported in two studies, while the remaining studies mainly supported anti-inflammatory, antioxidant, microcirculatory, or organ-protective effects.

Oxidative Stress Markers

Four included studies assessed oxidative stress-related parameters. The oxidative biomarkers and principal findings are summarized in Table 4.

Table 4. Effects of ascorbic acid on oxidative stress markers in preclinical sepsis models

Study	Markers assessed	Key findings
Kawade et al. [19]	Nitrite/nitrate	Oxidative stress-related nitrite/nitrate levels were modulated by dietary ascorbic acid.
Bozkurt et al. [20]	SOD, CAT, GPx	SOD level was significantly higher in the ascorbic acid group compared with the untreated sepsis and quercetin groups
Lyu et al. [22]	ROS, SOD, MDA, NO, iNOS, CAT	ROS, MDA, NO, and iNOS were significantly reduced in the vitamin C group; antioxidant enzyme activity was preserved
Canbolat et al. [23]	MDA	MDA levels were lower in the vitamin C and vitamin E groups compared with the untreated FIP group

Lyu et al. [22] provided the most detailed evaluation of oxidative stress in a CLP model. Vitamin C treatment significantly reduced ROS, MDA, NO, and iNOS levels, while preserving antioxidant enzyme activity. Canbolat et al. [23] reported lower MDA levels in vitamin C- and vitamin E-treated groups compared with untreated septic rats, indicating reduced lipid peroxidation. Bozkurt et al. [20] found that SOD levels were significantly higher in the ascorbic acid group than in untreated septic rats and quercetin-treated rats. Overall, these findings indicate that ascorbic acid may attenuate sepsis-associated oxidative damage by reducing oxidative injury and preserving endogenous antioxidant defense systems.

Organ-Specific Outcomes

Several included studies reported organ-specific protective effects of ascorbic acid. The affected organ systems and principal findings are summarized in Table 5.

Table 5. Organ-specific effects of ascorbic acid in preclinical sepsis models

Study	Organ system	Key findings
Kawade et al. [19]	Liver and kidney	LPS-induced increases in bilirubin, AST, ALT, creatinine, and BUN were suppressed proportionally to dietary ascorbic acid dose.
Tyml et al. [21]	Skeletal muscle microcirculation	Ascorbate prevented maldistribution of capillary blood flow at 6 hours post-CLP and mitigated hypotension and fever.
Lyu et al. [22]	Brain	Neurological reflex scores improved in the therapy group compared with septic controls; HE staining showed structural improvement.
Canbolat et al. [23]	Lung	Histological injury scores, Hounsfield unit density, and lung injury markers improved; PaO_2 was higher in vitamin C-treated rats.

Kawade et al. [19] found that LPS-induced increases in hepatic injury markers, including bilirubin, AST, and ALT, and renal dysfunction markers, including creatinine and blood urea nitrogen, were suppressed by dietary ascorbic acid. Tyml et al. [21] demonstrated that intravenous ascorbate prevented maldistribution of skeletal muscle capillary blood flow after CLP and mitigated hypotension and fever. Lyu et al. [22] reported neurological protection, with better neurological reflex scores and improved histological findings in brain tissue. Canbolat et al. [23] reported pulmonary protection, including lower histological injury scores and improved oxygenation. Collectively, these findings suggest that ascorbic acid may protect multiple organ systems during experimental sepsis.

Synthesis

Meta-analysis was not performed because the included studies showed substantial heterogeneity in sepsis induction methods, intervention doses, routes of administration, treatment timing, observation periods, and reported outcomes. Therefore, a structured narrative synthesis was applied.

The synthesis was organized into four domains. First, studies were grouped by sepsis model, including lipopolysaccharide-induced endotoxemia, cecal ligation and puncture, and fecal intraperitoneal injection. Second, studies were classified by treatment timing as prophylactic (administered before sepsis induction) or

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therapeutic (administered after sepsis induction). Third, interventions were compared by route of administration, including oral, intravenous, and intraperitoneal. Fourth, outcomes were grouped into survival-related outcomes, inflammatory biomarkers, oxidative stress parameters, microcirculatory outcomes, and organ-specific injury markers.

Survival outcomes were interpreted as the primary evidence category, whereas inflammatory, oxidative stress, microcirculatory, and organ injury outcomes were interpreted as secondary mechanistic evidence. The consistency of findings across studies was assessed by comparing the direction of effect for each outcome domain rather than by pooling numerical effect estimates. This approach allowed the review to distinguish between demonstrated evidence of survival and supportive mechanistic findings while acknowledging the heterogeneity of the available preclinical studies.

Table 6. Structured narrative synthesis framework and consistency of findings

Synthesis domain	Grouping variable	Studies/model	Main outcome pattern	Interpretation
Sepsis model	LPS-induced endotoxemia	Kawade et al. [19]; Bozkurt et al. [20]	Improved survival in one study; reduced inflammatory and oxidative markers	Supports indirect evidence for ascorbic acid in endotoxin-driven sepsis
Sepsis model	CLP-induced sepsis	Tyml et al. [21]; Lyu et al. [22]	Improved microvascular flow, oxidative stress markers, neurological outcomes, and 7-day survival	Supports indirect evidence in polymicrobial sepsis
Sepsis model	Fecal intraperitoneal injection	Canbolat et al. [23]	Reduced inflammatory markers, oxidative injury, and lung damage	Supports organ-protective mechanistic evidence
Treatment timing	Prophylactic administration	Kawade et al. [19]; Bozkurt et al. [20]	Reduced inflammatory and oxidative responses; survival benefit reported in Kawade et al.	Suggests a possible preventive antioxidant effect
Treatment timing	Therapeutic administration	Tyml et al. [21]; Lyu et al. [22]; Canbolat et al. [23]	Improved microcirculation, oxidative stress, organ injury, and survival in one study	Suggests a possible treatment effect after sepsis induction
Outcome category	Survival	Kawade et al. [19]; Lyu et al. [22]	Survival improved in both studies	Represents the strongest outcome evidence, but remains limited to two studies
Outcome category	Biomarkers and organ injury	Bozkurt et al. [20]; Tyml et al. [21]; Canbolat et al. [23]	Generally favorable anti-inflammatory, antioxidant, microcirculatory, and organ-protective effects	Supports mechanistic plausibility but not direct survival benefit

Model Relevance and Generalisability to *Staphylococcus aureus*-Induced Sepsis

The included studies used LPS, CLP, and fecal intraperitoneal injection models, but none used *Staphylococcus aureus* as the sepsis-inducing pathogen (Table 7).

Table 7. Comparison of sepsis models and relevance to *Staphylococcus aureus*-induced sepsis

Sepsis model	Main trigger	Key characteristic	Relevance to *S. aureus* sepsis
S. aureus-induced sepsis	Live gram-positive *S. aureus*	Involves peptidoglycan, lipoteichoic acid, exotoxins, hemolysins, leukocidins, and superantigens	Direct model
LPS-induced endotoxemia	Gram-negative lipopolysaccharide	Produces rapid endotoxin-driven inflammation and oxidative stress	Low; indirect inflammatory model
Cecal ligation and puncture	Polymicrobial peritonitis	Mimics mixed bacterial infection with systemic inflammation and organ injury.	Moderate; indirect polymicrobial model
Fecal intraperitoneal injection	Fecal polymicrobial contamination	Produces mixed microbial stimulation and septic organ injury	Moderate to low; indirect polymicrobial model

This is an important limitation because these models differ substantially in their immunological triggers, cytokine dynamics, microbial characteristics, patterns of organ injury, and survival trajectories. Therefore, findings from these models should be interpreted as indirect evidence and cannot be directly generalized to *S. aureus*-induced sepsis.

LPS-induced endotoxemia mainly represents gram-negative endotoxin-mediated inflammation. It is useful for studying acute cytokine release and oxidative stress, but it does not reproduce the complexity of live bacterial infection or gram-positive toxin-mediated immune activation. CLP and fecal intraperitoneal

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injection models better represent polymicrobial peritonitis and systemic infection, but they still do not specifically model staphylococcal virulence mechanisms. In contrast, *S. aureus*-induced sepsis involves pathogen-associated molecular patterns and virulence factors from the gram-positive pathogen, including peptidoglycan, lipoteichoic acid, hemolysins, leukocidins, exotoxins, and superantigens. These factors may produce immune activation patterns that differ from LPS-driven or polymicrobial sepsis models.

Consequently, the protective effects of ascorbic acid observed in LPS, CLP, or FIP models should be considered hypothesis-generating. They support the biological plausibility of antioxidant therapy in experimental sepsis, but they do not establish efficacy in *S. aureus*-induced sepsis. Direct studies using validated *S. aureus* sepsis models are required to determine whether ascorbic acid, *Centella asiatica* extract, or their combination can improve survival and reduce organ injury in gram-positive staphylococcal sepsis.

Limitations of the Included Evidence and Model Relevance

The findings of this review should be interpreted cautiously because the available evidence is indirect and methodologically limited. None of the included studies evaluated *Centella asiatica* extract, either alone or in combination with ascorbic acid, and none used *Staphylococcus aureus* as the sepsis-inducing pathogen. Therefore, the current evidence cannot establish the efficacy of the proposed combination therapy in *S. aureus*-induced sepsis.

Several included studies also had incomplete methodological reporting, including unclear dose information, unreported sample sizes, and limited details on randomization, allocation concealment, or blinding. A formal risk-of-bias appraisal was not performed in this review; therefore, the possibility of methodological bias cannot be excluded. These limitations reduce confidence in the evidence and suggest that the findings should be interpreted as preliminary and hypothesis-generating rather than confirmatory.

The relevance of the animal models should also be considered. Although rat models are useful for studying inflammation, oxidative stress, organ injury, and survival in experimental sepsis, they do not fully reproduce the complexity of human sepsis. Differences in immune regulation, metabolism, cardiovascular responses, comorbidities, pathogen exposure, antimicrobial treatment, and supportive care may limit translation from rats to humans.

Furthermore, the sepsis models included in this review differ substantially from *S. aureus*-induced sepsis. LPS-induced endotoxemia primarily reflects endotoxin-driven inflammatory activation in Gram-negative bacteria. CLP and fecal intraperitoneal injection represent polymicrobial peritonitis models with mixed bacterial exposure. In contrast, *S. aureus*-induced sepsis involves gram-positive pathogen-associated molecular patterns, exotoxins, hemolysins, leukocidins, and superantigens that may trigger distinct immune responses, cytokine kinetics, tissue injury patterns, and survival outcomes. Therefore, findings from LPS, CLP, and fecal intraperitoneal injection models cannot be directly generalized to staphylococcal sepsis.

Overall, the available studies suggest that ascorbic acid may reduce inflammatory and oxidative injury in experimental sepsis models. However, this evidence does not directly support the use of *Centella asiatica* extract or its combination with ascorbic acid in *S. aureus*-induced sepsis. Direct experimental studies using validated *S. aureus* sepsis models are required before stronger conclusions can be made.

Specific Recommendations for Future Preclinical Studies

Future studies should use a controlled in vivo experimental design in Wistar or Sprague-Dawley rats with validated *Staphylococcus aureus*-induced sepsis. The bacterial strain should be clearly reported, such as *S. aureus* ATCC 25923 or a validated clinical isolate, with a standardized inoculum concentration (e.g., 1–2 × 10^8 CFU/mL), adjusted according to pilot lethality testing and ethical considerations.

The intervention groups should include septic control, vehicle control, ascorbic acid alone, *Centella asiatica* extract alone, combined *Centella asiatica* extract and ascorbic acid, and standard therapy or antibiotic comparator where appropriate. Suggested dose ranges may include *Centella asiatica* extract at 50–200 mg/kg orally and ascorbic acid at 50–500 mg/kg via intravenous or intraperitoneal administration, with dose adjustment based on toxicity and pilot efficacy data.

Both prophylactic and therapeutic treatment schedules should be considered. A prophylactic regimen may involve treatment for 7 days before sepsis induction, whereas therapeutic regimens may begin at 1, 6, or 24 hours after sepsis induction. This approach would help determine whether the intervention is more effective as prevention, early adjunctive therapy, or delayed treatment.

Primary outcomes should include survival rate at 24, 48, and 72 hours and 7 days, mortality rate, time-to-death analysis, and Kaplan–Meier survival curves. Secondary outcomes should include bacterial burden in

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blood, liver, spleen, or kidney; inflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-10; oxidative stress markers such as MDA, SOD, CAT, GPx, and GSH; organ function markers such as AST, ALT, creatinine, BUN, and LDH; and histopathological evaluation of the lung, liver, kidney, spleen, and brain.

Conclusions

This systematic literature review found no direct preclinical evidence evaluating *Centella asiatica* extract, either alone or in combination with ascorbic acid, in *Staphylococcus aureus*-induced rat sepsis. None of the included studies used *S. aureus* as the sepsis-inducing pathogen, and none investigated *Centella asiatica* extract as an intervention. Therefore, the current evidence does not support a definitive conclusion regarding the efficacy of *Centella asiatica*, alone or in combination with ascorbic acid, in staphylococcal sepsis. The available evidence is limited to indirect findings from ascorbic acid (vitamin C) monotherapy in alternative experimental sepsis models, including LPS-induced endotoxemia, cecal ligation and puncture, and fecal intraperitoneal injection. Although these studies suggest favorable effects on survival in limited reports, the findings on inflammatory biomarkers, oxidative stress parameters, and organ injury markers cannot be directly generalized to *S. aureus*-induced sepsis. Future studies should directly evaluate standardized *Centella asiatica* extract, ascorbic acid, and their combination in validated *S. aureus*-induced sepsis models. Such studies should include appropriate control groups, dose-response assessment, clearly defined treatment timing, survival analysis, bacterial burden, inflammatory and oxidative stress markers, organ function parameters, and histopathological evaluation before any therapeutic claim can be made.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article. The authors also declare that there are no personal, financial, institutional, or other relationships that could be perceived as inappropriately influencing the representation, interpretation, or reporting of the findings presented in this review.

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