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Curcumin in Sepsis: Anti-Inflammatory Mechanisms, Nano-Formulations, and Evidence from Preclinical and Early Clinical Studies

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ABSTRACT

Introduction: Sepsis is driven by dysregulated host inflammation, cytokine amplification, endothelial injury, and oxidative stress, with nuclear factor kappa B signaling acting as a central regulatory axis. Curcumin, the principal bioactive compound of turmeric, has gained attention as a potential adjunctive therapy because of its pleiotropic anti-inflammatory, antioxidant, and immunomodulatory properties; however, its translational relevance in sepsis remains unclear.

Methods: This narrative review synthesizes evidence from preclinical sepsis models, mechanistic studies, systematic reviews, meta-analyses, and early randomized or controlled clinical trials that evaluated curcumin, nano-curcumin, or curcumin-based formulations for sepsis and critical illness.

Results: Preclinical evidence indicates that curcumin attenuates macrophage hyperactivation, suppresses TNF-α, IL-6, and IL-1β signaling, and modulates pyroptosis-related inflammatory pathways. In polymicrobial sepsis models, curcumin inhibited the HMGB1/TLR4/NF-κB pathway, reduced HMGB1 release, and limited NF-κB p65 nuclear translocation in polymicrobial sepsis models. Higher doses demonstrated stronger protection against multi-organ injury, partly through ferroptosis suppression via ACSL4/glutathione peroxidase 4 (GPX4) regulation and inhibition of protein lactylation via p300 downregulation. Early ICU trials suggest that enterally administered nano-curcumin may reduce inflammatory and endothelial biomarkers while enhancing antioxidant responses via Nrf2 signaling. Clinical signals include improved SOFA scores and reduced mechanical ventilation duration, although mortality and ICU length-of-stay remain inconsistent. Pooled evidence from critically ill populations also indicates modest improvements in organ dysfunction and selected hepatic and nutritional biomarkers.

Conclusion: Curcumin demonstrates strong biological and translational plausibility in sepsis through multi-target modulation of inflammatory, oxidative, and cell death pathways. However, current clinical evidence remains limited and heterogeneous, underscoring the need for larger, well-designed trials with standardized formulations and clinically meaningful endpoints.

Keywords

Curcumin, Nano-Curcumin, Sepsis, NF-Kb, HMGB1, TLR4, Nrf2, Oxidative Stress, Inflammation, SOFA Score

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INTRODUCTION

Sepsis remains a major global health challenge and is a leading cause of mortality in critically ill patients. It is characterized by a dysregulated host response to infection, culminating in life-threatening organ dysfunction. A hallmark of sepsis pathophysiology is an overwhelming systemic inflammatory response driven by excessive cytokine production and immune dysregulation, in which nuclear factor kappa B (NF-κB) signaling serves as a central regulatory pathway that orchestrates the transcription of key proinflammatory mediators,

including tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and IL-1β [1]. This uncontrolled inflammatory cascade, along with oxidative stress, endothelial dysfunction, and mitochondrial injury, contributes to progressive tissue damage and multi-organ failure [2].

Given the multifactorial nature of sepsis, increasing attention has been directed toward adjunctive therapies that can simultaneously modulate several pathogenic pathways. Curcumin, a polyphenolic compound derived from Curcuma longa, has emerged as a promising candidate because of its anti-inflammatory, antioxidant, and immunomodulatory properties [3]. Preclinical studies have shown that curcumin attenuates excessive macrophage activation and suppresses the release of proinflammatory cytokines, such as TNF-α and IL-6, supporting its biological plausibility in cytokine-driven syndromes, such as sepsis [4]. In addition to cytokine suppression, curcumin has been reported to regulate inflammatory cell death pathways, particularly pyroptosis. Experimental evidence indicates that curcumin inhibits the maturation and release of IL-1β by suppressing lipopolysaccharide-induced NLRP3 inflammasome activation in macrophages, thereby limiting downstream inflammatory amplification [5]. Curcumin also modulates redox homeostasis by enhancing nuclear factor erythroid 2-related factor 2 (Nrf2) signaling, reducing intracellular reactive oxygen species levels, increasing glutathione levels, and attenuating lipid peroxidation [6]. Despite these compelling mechanistic findings, clinical translation remains limited by curcumin's poor aqueous solubility, rapid metabolism, and low systemic bioavailability. To overcome these limitations, absorption-enhancing adjuvants, such as piperine, and advanced delivery systems, including phytosomal curcumin and nanoparticle-based formulations, have been developed to improve pharmacokinetic performance and therapeutic exposure [7,8]. Early clinical studies of nano-curcumin in critically ill and septic populations have suggested potential improvements in inflammatory biomarkers, oxidative stress indices, and organ dysfunction scores. However, current evidence is limited by small sample sizes, heterogeneous formulations, and inconsistent clinical endpoints [9]. Therefore, this review aims to critically synthesize the current evidence on curcumin in sepsis, integrating anti-inflammatory mechanisms, redox-modulating pathways, nanoformulation strategies, and findings from preclinical and early clinical studies. By bridging mechanistic and translational evidence, this review seeks to clarify the therapeutic potential of curcumin as an adjunctive strategy in sepsis and identify priorities for future clinical research.

METHOD

This study was designed as a comprehensive narrative review to evaluate the mechanistic, translational, and early clinical evidence of curcumin-derived curcumin in sepsis. This review focuses on curcumin's anti-inflammatory, antioxidant, immunomodulatory, endothelial-protective, and organ-protective effects, with particular emphasis on NF-κB signaling, HMGB1/TLR4 pathways, Nrf2-mediated redox regulation, pyroptosis, ferroptosis, and nano-formulation strategies. A structured literature search was conducted using PubMed, Scopus, Web of Science, Embase, and Google Scholar. Studies published in English until December 2025 were included. The search terms included combinations of curcumin, Curcuma longa, turmeric, curcuminoids, nanocurcumin, phytosomal curcumin, sepsis, septic shock, systemic inflammatory response syndrome, endotoxemia, lipopolysaccharide, cecal ligation and puncture, NF-κB, HMGB1, TLR4, Nrf2, pyroptosis, ferroptosis, oxidative stress, cytokines, organ dysfunction, and mortality. Boolean operators were used to combine intervention- and sepsis-related terms. The reference lists of relevant articles were manually screened to identify additional eligible studies. Duplicate records were removed prior to screening.

Studies were eligible if they evaluated curcumin, Curcuma longa, turmeric extract, curcuminoids, nano-curcumin, phytosomal curcumin, or other curcumin-based formulations in sepsis, septic shock, endotoxemia, systemic inflammatory response, or sepsis-associated organ dysfunction in adult animals. Eligible evidence included clinical studies, randomized or controlled trials, translational studies, animal sepsis models, systematic reviews, and meta-analyses reporting inflammatory, oxidative stress, immune, endothelial, and organ dysfunction, safety, or clinical outcomes. Studies were excluded if they did not address sepsis or sepsis-related inflammatory injury, did not evaluate curcumin-based interventions, focused exclusively on unrelated inflammatory diseases, were purely in vitro studies without clear relevance to sepsis biology, lacked sufficient

methodological detail, or failed to report relevant mechanistic or clinical outcomes. All identified records were screened by title and abstract for relevance. Potentially eligible studies were then reviewed in full. Selection was guided by the relevance of the population or experimental model, type of curcumin formulation, intervention timing, reported outcomes, methodological clarity, and translational value. Studies with stronger designs, clearer outcome reporting, and greater relevance to human sepsis pathophysiology were prioritized for synthesis.

Data were extracted using a predefined framework. The extracted variables included author, year, country, study design, population or experimental model, sepsis definition or induction method, sample size, curcumin formulation, dose, administration route, timing, treatment duration, comparator, and outcomes. The outcomes of interest included IL-6, TNF-α, IL-1β, IL-10, C-reactive protein, procalcitonin, oxidative stress markers, antioxidant enzyme activity, NF-κB and MAPK signaling, HMGB1/TLR4 activity, Nrf2 signaling, pyroptosis- and ferroptosis-related markers, endothelial injury markers, organ-specific injury markers, SOFA score, mortality, ICU length of stay, mechanical ventilation, vasopressor requirement, and adverse events. The methodological quality of the included studies was assessed narratively. Clinical studies were evaluated according to the study design, randomization, blinding, comparator adequacy, sample size, outcome reporting, safety assessment, and relevance to sepsis outcomes. Preclinical studies were assessed based on the clarity of the sepsis model, intervention timing, dose justification, biological outcome measurement, reproducibility, and translational relevance to human sepsis pathophysiology. Systematic reviews and meta-analyses were considered based on search transparency, eligibility criteria, synthesis approach, and consistency of conclusions. A qualitative synthesis was performed because substantial heterogeneity was anticipated across the study designs, sepsis definitions, experimental models, curcumin formulations, dosing regimens, administration routes, intervention timing, comparators, and outcome measures. The findings were organized thematically into anti-inflammatory mechanisms, redox regulation, immune modulation, endothelial protection, organ-protective effects, nanofomulation strategies, clinical outcomes, and safety. No formal meta-analysis was conducted because the available evidence was not sufficiently homogeneous for quantitative analysis. Instead, this review emphasizes the biological consistency, translational plausibility, clinical relevance, and limitations of the current evidence base. This synthesis prioritized studies with mechanistic clarity, methodological transparency, and direct relevance to sepsis biology or critical care outcomes.

RESULTS

This review included nine studies, comprising systematic reviews, meta-analyses, and one umbrella meta-analysis. The studies were published between 2021 and 2026 and evaluated curcumin or turmeric-derived compounds in sepsis-related conditions, critically ill populations, COVID-19 cohorts, and other inflammatory diseases. However, direct evidence in patients with clinically defined sepsis is limited. Only one study primarily focused on polymicrobial sepsis models, whereas one meta-analysis evaluated curcumin in critically ill ICU patients without restricting their inclusion to sepsis. Several COVID-19 studies were included because severe COVID-19 shares key pathophysiological features with sepsis, including cytokine dysregulation, endothelial injury, and multi-organ dysfunction.

Table 1. Summary of Included Studies

Study	Design	Population	n	Focus
Hartanto 2025	SR/MA	Sepsis models	218	HMGB1/NF-κB
Arabi 2026	MA (RCTs)	ICU	571	Clinical outcomes
Dehzad 2023	SR/MA	Mixed	66 RCTs	Inflammation/oxidative
Naghsh 2023	Umbrella MA	Mixed	5,870	Biomarkers
Kow 2022	SR/MA	COVID-19	260	Mortality
Gorabi 2021	MA	Inflammatory	32 RCTs	Cytokines
Shang 2025	SR/MA	COVID-19	333	Nano-curcumin
Gorabi 2021a	MA	Autoinflammatory	—	CRP
Sawangjit 2025	SR/MA	COVID-19	1,407	Safety

Curcumin has consistently demonstrated anti-inflammatory effects in multiple studies. The most robust findings were observed for CRP and TNF-α, both of which showed significant reductions in independent analyses. IL-6 results were heterogeneous, with significant reductions observed in broader meta-analyses and nano-curcumin studies, whereas earlier analyses showed nonsignificant findings. IL-1β showed variable responses, whereas IL-8 did not show consistent changes.

Table 2. Anti-inflammatory Biomarker Outcomes

Biomarker	Study	Effect	95% CI	p-value
CRP	Dehzad 2023	−0.58 mg/L	−0.74 to −0.41	<0.001
CRP	Naghsh 2023	−0.74	−1.11 to −0.37	<0.001
CRP	Gorabi 2021a	−3.67 mg/L	−6.96 to −0.38	0.02
TNF-α	Dehzad 2023	−3.48 pg/mL	−4.38 to −2.58	<0.001
TNF-α	Naghsh 2023	−1.92	−2.64 to −1.19	<0.001
TNF-α	Gorabi 2021	−1.61 pg/mL	−2.72 to −0.51	<0.001
TNF-α	Shang 2025	SMD −0.63	−1.16 to −0.10	0.02
IL-6	Dehzad 2023	−1.31 pg/mL	−1.58 to −0.67	<0.001
IL-6	Naghsh 2023	−1.07	−1.71 to −0.44	<0.001
IL-6	Gorabi 2021	−0.33 pg/mL	−0.99 to 0.34	0.33
IL-6	Shang 2025	SMD −0.30	−0.56 to −0.04	0.02
IL-1β	Gorabi 2021	−2.33 pg/mL	−3.33 to −1.34	<0.001
IL-1β	Dehzad 2023	−0.46 pg/mL	−1.18 to 0.27	0.218
IL-1β	Shang 2025	SMD −0.88	−1.37 to −0.39	0.0004
IL-8	Gorabi 2021	0.52 pg/mL	−1.13 to 2.17	0.53

Curcumin is consistently associated with improved oxidative stress profiles, including increased total antioxidant capacity, enhanced superoxide dismutase activity, and reduced malondialdehyde levels. Mechanistic studies have demonstrated dose-dependent modulation of the HMGB1/TLR4/NF-κB axis, inhibition of NF-κB nuclear translocation, and reduction of circulating HMGB1 levels. These findings support curcumin as a pleiotropic regulator of inflammation, oxidative stress, and cellular injury pathways that are relevant to sepsis. Clinical outcome data were primarily derived from critically ill ICU and COVID-19 patients. Curcumin supplementation was associated with improvements in organ dysfunction scores, liver function parameters, and selected clinical outcomes of interest.

Table 3. Clinical Outcomes

Outcome	Study	Population	Effect	95% CI	p-value
SOFA score	Arabi 2026	ICU	−0.8	−1.2 to −0.4	<0.001
ICU stay	Arabi 2026	ICU	−0.3 days	−0.6 to −0.1	0.01
ALT	Arabi 2026	ICU	−0.4	−0.8 to −0.001	0.03
Bilirubin	Arabi 2026	ICU	−0.4	−0.9 to −0.07	0.01
Albumin	Arabi 2026	ICU	+0.3	0.001 to 0.6	0.004
Mortality	Sawangjit 2025	COVID-19	RR 0.39	0.23 to 0.67	Significant
Mortality	Shang 2025	COVID-19	RR 0.47	0.25 to 0.88	0.02
Mechanical ventilation	Sawangjit 2025	COVID-19	RR 0.35	0.17 to 0.72	Significant
Clinical deterioration	Sawangjit 2025	COVID-19	RR 0.36	0.22 to 0.59	Significant
Symptom resolution	Sawangjit 2025	COVID-19	RR 1.36	1.16 to 1.59	Significant

Safety data are limited and are primarily derived from other COVID-19 studies. Curcumin is generally well tolerated, with mild gastrointestinal symptoms being the most frequently reported adverse events. However, safety data in critically ill patients with sepsis remain insufficient, particularly regarding potential drug interactions, bleeding risk, hepatic or renal dysfunction, and compatibility with intensive care unit (ICU) therapies. Overall, curcumin demonstrates consistent anti-inflammatory and antioxidant effects, with the strongest evidence for tumor necrosis factor-α and C-reactive protein (CRP) reduction. Mechanistic pathways involving NF-κB inhibition, HMGB1 suppression, and Nrf2 activation support its biological plausibility in sepsis. Nano-curcumin formulations are particularly promising because of their improved bioavailability and enhanced pharmacological activity. However, direct clinical evidence in sepsis-3-defined populations is

limited. Current findings are largely derived from preclinical models, critically ill ICU cohorts, and COVID-19 studies with overlapping inflammatory mechanisms. Further large-scale, well-designed randomized controlled trials are required to establish the efficacy and safety of curcumin, particularly nano-curcumin formulations, in patients with sepsis

DISCUSSION

The present synthesis demonstrates consistent anti-inflammatory signals across mechanistic, preclinical, and early phase clinical studies. Curcumin attenuates upstream immune activation and downstream cytokine release, particularly by suppressing macrophage activation and reducing key pro-inflammatory mediators, including TNF-α and IL-6 [10]. Experimental studies in human neutrophils further support these findings, showing dose-dependent inhibition of TNF-α production and attenuation of IL-6 and IL-8 expression under endotoxin stimulation, indicating a direct modulatory effect on innate immune effector responses [11]. Translational evidence from intensive care unit-based studies suggests that these molecular effects may extend to clinically relevant outcomes. Nano-curcumin trials in critically ill patients have reported reductions in IL-6 and TNF-α levels, accompanied by improvements in SOFA scores and mechanical ventilation duration, although its effects on mortality and certain systemic inflammatory markers remain inconsistent [12]. Similarly, curcumin combined with piperine has demonstrated reductions in CRP and erythrocyte sedimentation rate without reported adverse events, highlighting the potential of bioavailability-enhanced formulations to produce measurable anti-inflammatory effects in acute care settings [13].

A central finding of this review is the strong mechanistic alignment between curcumin and key pathways in sepsis biology. The HMGB1/TLR4/NF-κB axis has emerged as a critical target, with evidence demonstrating the attenuation of pathway activation, reduction of circulating HMGB1 levels, and inhibition of NF-κB p65 nuclear translocation in polymicrobial sepsis models [14]. This is clinically relevant because HMGB1 functions as a late mediator of sustained inflammation and organ injury during sepsis. Importantly, early clinical observations indicate that nano-curcumin may reduce HMGB1 levels in ICU patients, accompanied by improvements in organ dysfunction scores, suggesting a convergence between mechanistic and clinical effects [15]. Beyond systemic inflammation, curcumin exerts organ-specific protective effects, including the preservation of intestinal barrier integrity through the modulation of NF-κB/MLCK signaling and the attenuation of cardiac inflammation through TLR-related pathways [16,17]. These multi-organ effects reinforce the concept of curcumin as a pleiotropic therapeutic candidate for sepsis. Oxidative stress is a central driver of sepsis-associated organ injury, and curcumin consistently demonstrates redox-modulating effects across the evidence base. Mechanistic studies have indicated that curcumin enhances Nrf2 signaling, reduces reactive oxygen species, and restores antioxidant defenses, including glutathione and superoxide dismutase activity [18]. Experimental data further suggest that the disruption of Nrf2 signaling weakens curcumin-mediated protection, supporting the biological relevance of the Nrf2/HO-1 axis [18]. Ferroptosis has recently emerged as an important mechanism of regulated cell death in sepsis-related organ injuries. Evidence suggests that curcumin modulates ferroptosis-related pathways via the ACSL4/GPX4 axis, reducing iron-dependent lipid peroxidation and cellular injury [19]. Early clinical findings showing reduced malondialdehyde levels and increased Nrf2 activity provide preliminary translational support for redox pathway engagement following nano-curcumin administration [20].

The formulation of curcumin is a major determinant of its clinical applicability. Conventional curcumin is limited by its poor aqueous solubility, rapid metabolism, and low systemic exposure. Nanoparticle-based delivery systems, including solid lipid nanoparticles and advanced nanocarriers, have demonstrated stronger suppression of inflammatory pathways and improved organ protection in preclinical models than free curcumin [21,22]. In clinical settings, nano-curcumin administered through enteral routes has been associated with improvements in inflammatory biomarker and organ dysfunction scores, supporting its feasibility in critically ill populations [12]. Alternative strategies, including co-administration with piperine and phytosomal curcumin, have been used to enhance bioavailability and improve pharmacological exposure [23]. These findings indicate that formulation is not merely a technical detail but a central translational determinant that

may influence whether curcumin's biological effects can be converted into clinically meaningful benefits. Taken together, the available evidence suggests that curcumin may serve as a multi-target adjunctive therapy for sepsis by modulating inflammatory, oxidative, endothelial, and cell death pathways. However, its role should be interpreted with caution. Current evidence does not support the use of curcumin as a replacement for standard sepsis management, including antimicrobial therapy, source control, hemodynamic resuscitation, and organ support. Curcumin should be viewed as a potential adjunctive intervention that requires further validation in rigorously designed clinical trials. The overall strength of evidence was moderate for mechanistic and preclinical findings but remained low for definitive clinical outcomes. Improvements in biomarkers and organ dysfunction scores are encouraging; however, available trials are small, heterogeneous, and not adequately powered to determine the effects on mortality, vasopressor requirements, or long-term recovery.

Available evidence suggests that short-term curcumin administration is generally well-tolerated, with minimal adverse effects reported in small clinical studies [13]. However, safety data on critically ill sepsis populations remain insufficient. Particular attention should be paid to potential drug–drug interactions, bleeding risk, hepatic dysfunction, renal impairment, and compatibility with ICU therapies, such as anticoagulants, vasopressors, antimicrobials, and organ-support interventions. Future trials should include structured adverse event monitoring and predefined safety endpoints. Despite promising mechanistic and early clinical signals, the current evidence base remains limited by small sample sizes, heterogeneity in study populations, variable formulations, inconsistent dosing regimens, and diverse outcome measures. The generalizability of the current findings is limited because much of the clinical evidence is derived from critically ill or COVID-19 populations rather than strictly sepsis-3-defined cohorts [24]. Future research should prioritize large, multicenter randomized controlled trials using standardized nano-curcumin or bioavailability-enhanced formulations, harmonized biomarker panels, and clinically meaningful endpoints, including the duration of organ support, ICU length of stay, mortality, and post-sepsis functional outcomes [25,26]. Future studies should also explore patient stratification strategies to identify subgroups that are most likely to benefit from curcumin-based interventions, particularly patients with hyperinflammatory phenotypes, oxidative stress–dominant profiles, or early organ dysfunction. Such an approach may help move curcumin research from broad adjunctive therapy toward precision-guided sepsis modulation.

CONCLUSION

Curcumin demonstrates strong mechanistic and translational potential as a multi-target adjunct in sepsis, modulating key inflammatory and oxidative pathways, including NF-κB and HMGB1/TLR4 signaling pathways. Early evidence, particularly with nano-curcumin formulations, suggests improvements in inflammatory biomarkers and organ dysfunction. However, clinical evidence remains limited and heterogeneous, and large well-designed trials are required before routine use can be recommended in clinical practice.

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The Authors agree to the publication in the Journal of Society Medicine.

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All authors have reviewed and approved the final version of the manuscript and agreed to its publication in the Journal of Society Medicine.

AUTHORS' CONTRIBUTIONS

Y.P. conceived the study, performed the literature review, and drafted the manuscript. G.R. contributed to the methodology, data interpretation, and critical revision. A.N. contributed to data validation and manuscript review. All authors approved the final manuscript and accepted responsibility for its content and integrity.

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