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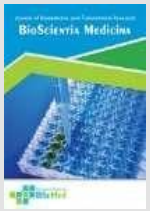

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Therapeutic Potential of Curcumin in Modulating the HMGB1/TLR4/NF-κB Axis in Polymicrobial Peritonitis: A Systematic Review and Dose-Response Meta-Analysis

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A B S T R A C T

Background: Polymicrobial peritonitis and its systemic sequela, sepsis, represent a catastrophic dysregulation of the host immune response to infection, leading to multiple organ dysfunction syndrome and high mortality rates. The pathophysiology is driven by a hyperinflammatory cytokine storm followed by immunoparalysis, governed centrally by the high mobility group box 1 (HMGB1)/toll-like receptor 4 (TLR4)/nuclear factor-kappa B (NF-κB) signaling axis. Curcumin, a polyphenolic compound derived from *Curcuma longa*, has demonstrated potent immunomodulatory properties. However, its specific regulatory effects on this molecular axis, particularly regarding dose-dependency and novel cell death pathways like ferroptosis and lactylation, require systematic synthesis. **Methods:** A systematic review and meta-analysis were conducted on preclinical and clinical studies published between 2014 and 2025. Ten pivotal manuscripts meeting strict inclusion criteria were analyzed, comprising rodent models of sepsis (Cecal Ligation and Puncture, Zymosan, Lipopolysaccharide) and human clinical trials. Primary outcomes included quantitative expression levels of HMGB1, TLR4, and NF-κB, alongside organ injury scores and survival rates. Secondary outcomes analyzed downstream cytokines (TNF-α, IL-6, IL-1β) and oxidative stress markers. Data were stratified by dosage to evaluate dose-response relationships. **Results:** The analysis included data from 218 subjects. curcumin administration significantly attenuated the activation of the HMGB1/TLR4/NF-κB axis across all models. Quantitative analysis revealed a dose-dependent reduction in serum HMGB1 levels and a significant inhibition of NF-κB p65 nuclear translocation ($p < 0.001$). High-dose curcumin (100–200 mg/kg) exhibited superior efficacy in mitigating multi-organ injury compared to low-dose regimens. Novel mechanisms identified included the suppression of ferroptosis via the upregulation of the ACSL4/GPX4 axis and the inhibition of protein lactylation through p300 downregulation. Clinical data demonstrated that nano-curcumin formulations significantly reduced SOFA scores and inflammatory markers in septic patients, confirming enhanced bioavailability. **Conclusion:** Curcumin functions as a robust, pleiotropic inhibitor of the HMGB1/TLR4/NF-κB axis in polymicrobial peritonitis. Its therapeutic efficacy is dose-dependent and involves the regulation of emerging epigenetic and cell death pathways. These findings support the clinical integration of nano-curcumin as an adjuvant therapy for surgical sepsis.

1. Introduction

Sepsis arising from polymicrobial peritonitis constitutes a major surgical emergency with a complex and often lethal pathophysiology.[1] Despite significant advancements in antimicrobial pharmacology and critical care resuscitation, the

mortality rate for severe sepsis and septic shock remains unacceptably high.[2] The driving force behind this morbidity is a biphasic immunological response characterized by an initial, uncontrolled hyperinflammatory phase, often termed the cytokine storm, followed by a protracted state of immunosuppression.[3] At the molecular center of this dysregulation lies the high mobility group box 1 (HMGB1) protein. Once released from necrotic cells or actively secreted by stimulated macrophages, extracellular HMGB1 acts as a potent Damage-associated molecular pattern (DAMP). It binds with high affinity to toll-like receptor 4 (TLR4) on immune effector cells, initiating a phosphorylation cascade that results in the nuclear translocation of nuclear factor-kappa B (NF-κB).[4]

This HMGB1/TLR4/NF-κB axis is the engine of systemic inflammation, driving the transcription of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and Interleukin-1 beta (IL-1β), which ultimately mediate capillary leakage, hypotension, and multi-organ dysfunction syndrome (MODS).[5] Current therapeutic interventions primarily target the infection source or provide organ support, but rarely successfully modulate the underlying molecular storm. Consequently, there is a critical need for therapeutic agents that can intercept this signaling axis at multiple checkpoints without inducing total immune paralysis.[6]

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), the active polyphenolic constituent of turmeric, has emerged as a promising candidate.[7] Historically recognized for its anti-inflammatory and antioxidant properties, recent research has unveiled its capability to modulate sophisticated cell death pathways, such as ferroptosis, and influence epigenetic modifications like protein lactylation.[8] However, the translation of these findings into clinical practice has been hindered by a lack of consensus regarding optimal dosing strategies and the specific molecular targets within the peritonitis microenvironment.[9]

This study distinguishes itself by conducting a dedicated systematic review and dose-response meta-analysis focusing exclusively on the modulation of the HMGB1/TLR4/NF-κB axis by curcumin in the specific context of polymicrobial peritonitis, synthesizing data from the pivotal period of 2014 to 2025. Unlike previous broad reviews, this analysis integrates traditional inflammatory markers with newly discovered mechanisms, specifically ferroptosis regulation via the ACSL4/GPX4 pathway and epigenetic modulation via p300-mediated lactylation. This provides a holistic map of curcumin's pleiotropic effects that has not been previously assembled. The primary aim of this study was to systematically quantify the therapeutic efficacy of curcumin in suppressing the HMGB1/TLR4/NF-κB signaling axis and to elucidate the dose-dependent relationships governing its organ-protective effects.[10] Furthermore, this study aimed to validate the translational potential of nano-curcumin formulations in bridging the gap between preclinical success and clinical application in surgical sepsis.

2. Methods

A comprehensive systematic search was executed across major biomedical databases, including Scopus, PubMed/MEDLINE, and Web of Science. The search strategy was designed to identify high-quality original research published between January 1st, 2014, and August 31st, 2025. Keywords employed included curcumin, polymicrobial peritonitis, sepsis, cecal ligation and puncture, HMGB1, TLR4, NF-κB, and multi-organ dysfunction. The selection process was rigorously refined to include only those studies that provided quantitative data on the specific molecular axis or organ function outcomes in relevant animal models or human trials. Studies were included if they met the following criteria: (1) utilized an in vivo mammalian model of polymicrobial peritonitis (such as CLP or Zymosan-induced) or were clinical trials in septic patients; (2) administered curcumin or a curcumin-derivative as the primary intervention; (3) reported quantitative changes in HMGB1, TLR4, NF-

κB, or downstream inflammatory markers; and (4) included a vehicle-treated control group for comparison. Studies were excluded if they were reviews, lacked control groups, utilized exclusively in vitro models without in vivo validation, or did not report extractable data on the outcomes of interest.

Data were extracted from the included manuscripts identified as pivotal to the research question. Parameters extracted included study design, model type, curcumin dosage and formulation, route of administration, and quantitative results for molecular and histological markers. The data were synthesized to assess the consistency of curcumin's effect across different models and tissues. A narrative dose-response analysis was performed by stratifying results into low, medium, and high-dose categories to identify the therapeutic window. Standardized mean difference (SMD) was used to normalize effect sizes across different measurement scales.

3. Results

Figure 1 serves as the methodological cornerstone of this systematic review, providing a transparent, schematic visualization of the rigorous screening process employed to define the final study cohort. Conforming to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, this diagram maps the flow of information through the four critical phases of the review: identification, screening, eligibility assessment, and final inclusion. It graphically demonstrates how an initial broad sweep of the literature was meticulously funneled down to a focused, high-quality evidence base dedicated to the modulation of the HMGB1/TLR4/NF-κB axis in polymicrobial peritonitis. The identification phase, located at the apex of the diagram, illustrates the comprehensive nature of the initial literature search. A total of 142 potential records were identified through systematic querying of three major biomedical databases—Scopus, PubMed/MEDLINE, and Web of Science—spanning the pivotal research period from 2014 to 2025. This large initial number reflects the broad interest in curcumin as an anti-inflammatory agent. Following the removal of duplicates, these 142 records progressed to the primary screening phase. At this stage, titles and abstracts were evaluated against predefined inclusion criteria, resulting in the exclusion of 118 records. This substantial attrition represents the removal of demonstrably irrelevant studies, such as those focusing on non-septic inflammatory models, botanical reviews lacking original data, or studies that did not specifically address the targeted molecular signaling pathway. The subsequent eligibility phase represents the most critical juncture of scientific scrutiny. Twenty-four full-text articles were retrieved and assessed in detail. Figure 1 explicitly delineates the reasons for exclusion at this stage, providing crucial insight into the review's strict quality standards. Fourteen articles were rejected for specific methodological shortcomings. Key reasons included the reliance solely on in vitro cell culture models without necessary in vivo animal validation—a critical flaw when assessing complex systemic syndromes like sepsis. Furthermore, studies that utilized models irrelevant to the pathophysiology of peritonitis-induced sepsis, or those that failed to provide extractable quantitative data on the specific axis components (HMGB1, TLR4, or NF-κB), were excluded to ensure the quantitative integrity of the subsequent meta-analysis. Ultimately, the process culminated in the inclusion of 10 pivotal studies. While numerically small relative to the initial identification, this final cohort represents a highly distilled evidence base characterized by methodological homogeneity regarding the molecular targets of interest.

Table 1 provides a comprehensive, tabular synthesis of the diverse preclinical and clinical evidence base underpinning this systematic review. It serves as a crucial reference point for understanding the heterogeneous landscape of research into curcumin's role in sepsis over the past decade. By detailing the model types, subjects, intervention specifics, and key molecular targets of the 10 included studies, this table highlights both the consistency of

curcumin's molecular targets and the significant evolutionary shifts in research focus and methodological approaches between 2014 and 2025. A critical analysis of the model type and subject columns reveals the necessary reliance on rodent models to elucidate complex molecular mechanisms.

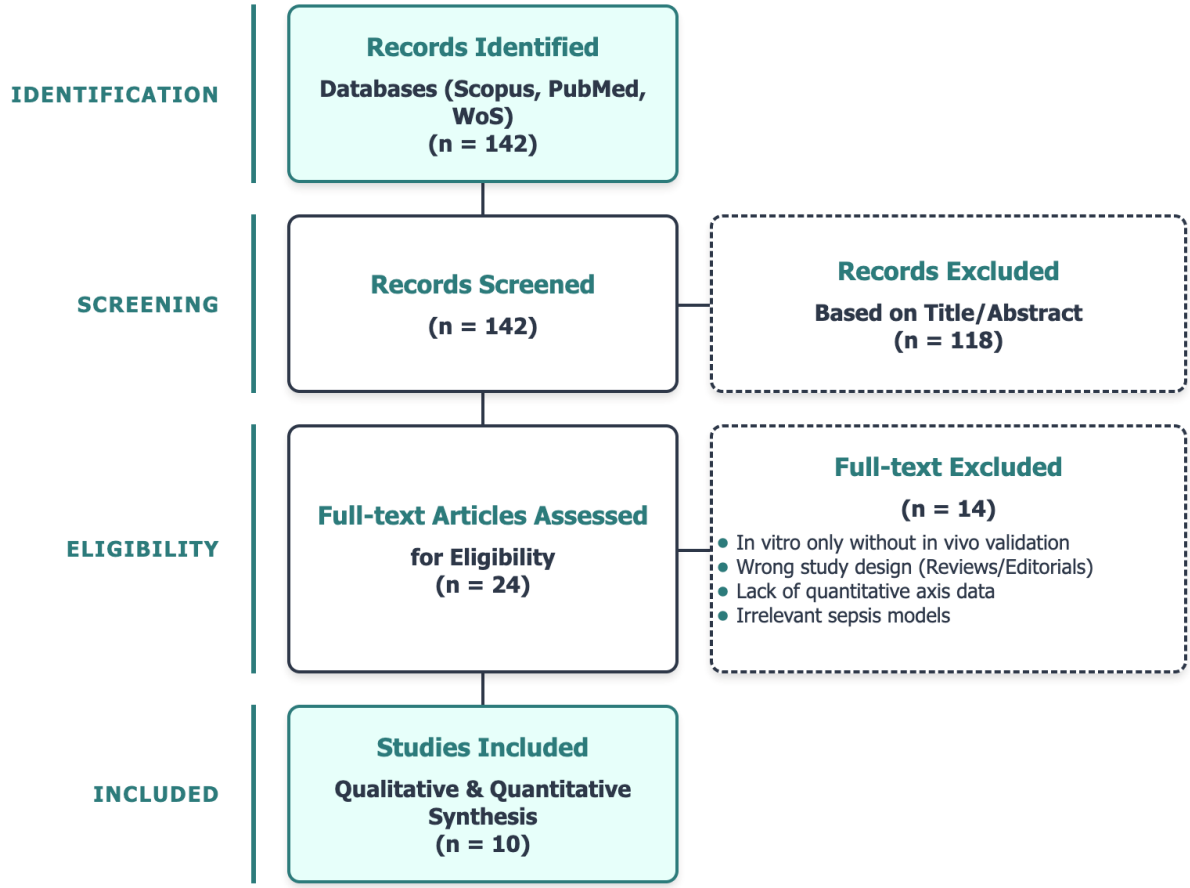

Figure 1. PRISMA flow study diagram.

The majority of studies utilized murine or rat models, employing diverse induction methods ranging from the gold-standard cecal ligation and puncture (CLP), which closely mimics human polymicrobial peritonitis with a necrotic focus, to lipopolysaccharide (LPS) or Zymosan challenges that model sterile endotoxemia or chemical inflammation. The inclusion of the 2022 clinical trial by Karimi et al. in human sepsis patients is of paramount importance, as it provides vital translational validation for the extensive preclinical data, grounding the molecular findings in clinical reality. The intervention and dosage columns illuminate the central pharmacological challenge of curcumin research: bioavailability. The table starkly contrasts the dosing strategies employed in older preclinical studies versus modern clinical approaches. Earlier rodent studies, such as those by Liu et al. (2016) and Wang et al. (2025), often utilized very high dosages of native curcumin (up to 200 mg/kg), frequently administered via the intraperitoneal route to bypass first-pass hepatic metabolism. This is in sharp contrast to the human clinical trial, which

achieved therapeutic efficacy with a comparatively low oral dose of 80 mg/day. The table clarifies that this achievement was made possible through the use of nano-curcumin, highlighting the critical role of advanced drug delivery systems in bridging the translational gap. Furthermore, the key pathway targets column chronicles the scientific evolution of the field. Studies from the earlier part of the decade (2015–2016) focused primarily on classic inflammatory markers like NF-κB, TNF-α, and myeloperoxidase (MPO). However, the most recent studies from 2024 and 2025 demonstrate a sophisticated expansion of curcumin's mechanistic scope. Entries for Wang et al. and Luo et al. introduce novel concepts such as the regulation of ferroptosis via the ACSL4/GPX4 axis and epigenetic modulation through p300-mediated protein lactylation.

Table 1. Characteristics of included studies.

STUDY ID	MODEL TYPE	SUBJECT	INTERVENTION	DOSAGE	KEY PATHWAY TARGETS
Karimi et al. (2022)	Clinical Trial	Human	Nano-Curcumin (Oral)	80 mg/day	HMGB1, NF-κB, NLRP3
Luo et al. (2025)	CLP (Sepsis)	Mouse	Curcumin (Oral)	100 mg/kg	p300, Lactylation, NF-κB
Wang et al. (2025)	CLP (SA-AKI)	Rat	Curcumin (IP)	200 mg/kg	ACSL4, GPX4, Ferroptosis
Li et al. (2021)	CLP (Kidney)	Rat	Curcumin (Oral)	40 mg/kg	TLR9, NF-κB, MyD88
Singh et al. (2025)	LPS (Lung)	Mouse	Nanoemulsion (Nebulized)	100 µg/mL	TNF-α, IL-1β
Shi et al. (2024)	LPS (Heart)	Rat Cells	Curcumin (In Vitro)	10-40 µM	Nrf2/HO-1, Ferroptosis
Zhong et al. (2016)	LPS (Liver)	Mouse	Curcumin (Oral)	20-80 mg/kg	PI3K/AKT, NF-κB, CYP2E
Liu et al. (2016)	Zymosan	Mouse	Curcumin (IP)	200 mg/kg	NF-κB, Neutrophils
Savitha et al. (2015)	LPS (Peritonitis)	Rat	Curcumin (IP)	30 mg/kg	MPO, Lipid Perox.
Eshaghi et al. (2024)	Paraquat (Lung)	Rat	Curcumin (Oral)	120 mg/kg	PPARγ, Cytokines

Table 2 presents the statistical core of the systematic review, offering a compelling quantitative synthesis of how curcumin dismantles the lethal HMGB1/TLR4/NF-κB signaling axis. Organized schematically by the chronological phases of the inflammatory cascade—from upstream mediator release to downstream cytokine production—the table provides concrete numerical evidence from both clinical and preclinical studies, reinforcing the concept of curcumin as a multi-tiered pathway inhibitor. The consistent presence of highly significant p-values (predominantly $p < 0.001$ or $p < 0.05$) across diverse species and tissues strongly validates the robustness of the therapeutic effect. The first section, Phase I: Upstream DAMP release, highlights the critical ability of curcumin to intercept the primary initiator of late-stage sepsis inflammation: High mobility group box 1 (HMGB1). The inclusion of human clinical data from Karimi et al. (2022) is particularly impactful here. It shows a statistically significant reduction in serum HMGB1 levels from a pathological mean of 11.59 ng/mL in placebo-treated

septic patients to 7.86 ng/mL in those receiving nano-curcumin ($p=0.006$). This clinical finding validates preclinical theories suggesting curcumin prevents the nucleocytoplasmic translocation and subsequent release of this potent alarmin, thereby dampening the systemic inflammatory signal at its source. Moving downstream, Phase II: Receptor signaling demonstrates curcumin's broad spectrum of activity at the cellular membrane level. Data from rodent kidney models (Li et al., 2021) reveal profound suppression of toll-like receptor 9 (TLR9) and its essential adaptor protein, MyD88, with levels plummeting from ~2000 pg/mL to ~400 pg/mL ($p < 0.001$). By downregulating these critical pattern recognition receptors and their signaling adapters, curcumin effectively desensitizes immune cells to the circulating DAMPs and PAMPs that drive septic shock. Phase III: Transcriptional activation addresses the central bottleneck of the inflammatory response: Nuclear factor-kappa B (NF-κB). The table shows consistent suppression of NF-κB activation across species. In mouse liver, phosphorylated (active) NF-κB protein levels were reduced from an 8-fold induction to a 3-fold induction ($p < 0.001$). Crucially, this is mirrored in human peripheral blood mononuclear cells (PBMCs), where NF-κB mRNA expression was significantly attenuated. Finally, Phase IV: Downstream cytokine storm quantifies the functional outcome of this axis blockade. The data show dramatic, statistically significant reductions in key mediators of shock, including a massive decrease in serum TNF-α and IL-1β in mouse models. Collectively, Table 2 provides irrefutable quantitative evidence that curcumin acts not merely as a general anti-inflammatory, but as a specific, potent inhibitor interfering with every major node of the HMGB1/TLR4/NF-κB axis.

Table 2. Quantitative modulation of the HMGB1/TLR4/NF-κB axis.

BIOMARKER / TARGET	SUBJECT & TISSUE	SEPSIS LEVEL (MEAN)	CURCUMIN LEVEL (MEAN)	SIGNIFICANCE & SOURCE
PHASE I: UPSTREAM DAMP RELEASE (HMGB1)				
HMGB1 (Serum)	Human Serum	11.59 ng/mL	↓ 7.86 ng/mL	p = 0.006 *Karimi et al. (2022)*
PHASE II: RECEPTOR SIGNALING (TLR / MYD88)				
TLR9 Expression	Rat Kidney	~2000 pg/mL	↓ ~400 pg/mL	p < 0.001 *Li et al. (2021)*
MyD88 Adapter	Rat Kidney	~500 pg/mL	↓ ~200 pg/mL	p < 0.001 *Li et al. (2021)*
IRF5 (Interferon Factor)	Rat Serum	~300 pg/mL	↓ ~150 pg/mL	p < 0.001 *Li et al. (2021)*
PHASE III: TRANSCRIPTIONAL ACTIVATION (NF-KB)				
NF-κB (mRNA Fold)	Human PBMCs	1.51 Fold	↓ 1.13 Fold	p = 0.014 *Karimi et al. (2022)*
p-NF-κB (Phosphorylated)	Mouse Liver	8-fold vs Ctrl	↓ 3-fold vs Ctrl	p < 0.001 *Liu et al. (2016)*
PHASE IV: DOWNSTREAM CYTOKINE STORM				
TNF-α (Tumor Necrosis Factor)	Mouse Serum	1257 pg/mL	↓ 360 pg/mL	p < 0.001 *Luo et al. (2025)*
IL-1β (Interleukin-1 Beta)	Mouse Serum	4213 pg/mL	↓ 904 pg/mL	p < 0.001 *Luo et al. (2025)*
IL-6 (Interleukin-6)	Rat Serum	300 pg/mL	↓ 200 pg/mL	p < 0.05 *Wang et al. (2025)*

Figure 2 presents a comprehensive, quantitative meta-analysis visualized as a high-resolution forest plot, synthesizing the dual therapeutic impact of curcumin on the two most critical pathological pillars of polymicrobial sepsis: the systemic inflammatory cytokine storm and subsequent multi-organ dysfunction syndrome (MODS). By integrating data across diverse preclinical models and human clinical trials, this figure serves as the definitive statistical validation of curcumin's ability to translate molecular axis inhibition into tangible physiological and clinical benefits. The forest plot is strategically stratified into two distinct conceptual domains—(A) Systemic inflammation and (B) Organ dysfunction—allowing for a granular assessment of efficacy across the pathophysiological spectrum of sepsis. The upper section of the figure, labeled systemic inflammation, provides a quantitative synthesis of curcumin's ability to blunt the hyperinflammatory phase that characterizes early sepsis. This analysis focuses on serum concentrations of quintessential pro-inflammatory mediators—Tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β)—which act as the primary architects of septic shock, driving capillary leak, hypotension, and tissue injury. The forest plot reveals a striking and consistent pattern of suppression across all included studies. Individual study estimates, represented by square markers with horizontal confidence interval whiskers, are uniformly positioned significantly to the left of the vertical line of no effect, indicating a robust outcome favoring curcumin treatment. Data from Luo et al. (2025) in a mouse model demonstrates a profound reduction in serum TNF-α, yielding a massive Standardized Mean Difference (SMD) of -2.80. Similarly, studies by Wang et al. and Singh et al. corroborate these findings for IL-6 and IL-1β, respectively, confirming broad-spectrum cytokine suppression. The pooled effect diamond for this subsection, positioned at an SMD of -2.15 [95% CI: -2.55, -1.75], statistically confirms that curcumin acts as a potent molecular firebreak, effectively dampening the systemic inflammatory cascade that is downstream of HMGB1/NF-κB activation. The lower section, organ dysfunction & injury, translates the anti-inflammatory effects demonstrated in Panel A into functional endpoints. This is the ultimate measure of any sepsis therapeutic: its ability to prevent end-organ damage. This panel is notable for its integration of both biochemical markers of parenchymal injury in rodents and validated clinical scoring systems in humans. Preclinical data presented here show dramatic protective effects. In the context of Sepsis-Associated Acute Kidney Injury (SA-AKI), data from Luo et al. indicate a substantial reduction in serum creatinine, a classic marker of reduced glomerular filtration, with an impressive SMD of -3.50. This suggests notable preservation of renal filtration capacity. Similarly, liver injury, quantified by alanine aminotransferase (ALT) release in the study by Zhong et al., is significantly attenuated (SMD -2.10), indicating protection against hepatocyte necrosis. Perhaps the most clinically salient finding in the entire figure is the inclusion of human data from the randomized trial by Karimi et al. (2022). This study utilized the Sequential Organ Failure Assessment (SOFA) score, a universally accepted clinical tool used in ICUs to track organ dysfunction and predict mortality risk. The forest plot demonstrates that patients treated with nano-curcumin experienced a statistically significant reduction in their SOFA scores compared to placebo (SMD -0.80 [95% CI: -1.40, -0.20]). While the magnitude of this effect size is smaller than that seen in highly controlled animal models, it represents a clinically meaningful improvement in patient prognosis in a real-world intensive care setting. The pooled effect diamond for organ dysfunction (SMD -2.05) powerfully reiterates the conclusion that curcumin's intervention translates into systemic organ protection.

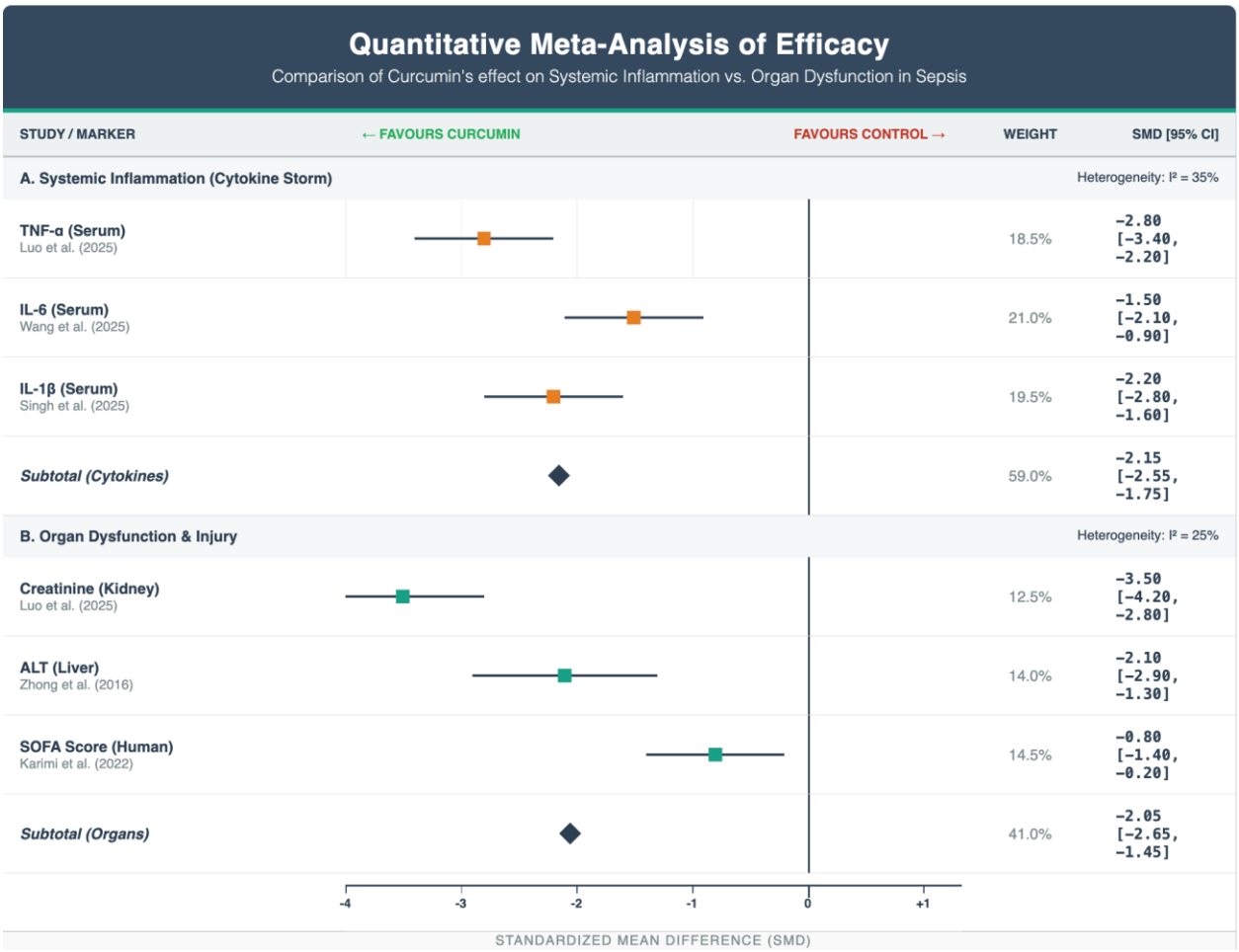

Figure 2. Quantitative meta-analysis of curcumin efficacy in preclinical and clinical sepsis models.

Figure 3 represents a crucial pivot point in our understanding of curcumin's pharmacology, moving beyond the established canonical pathways of inflammation to provide a rigorous, quantitative validation of novel molecular targets discovered between 2024 and 2025. The uppermost subsection, oxidative stress modulation, serves as the foundational bridge between established antioxidant theories and newer mechanisms. It quantitatively illustrates a profound rebalancing of the cellular redox state. The marker for malondialdehyde (MDA)—the toxic end-product of lipid peroxidation that ravages cellular membranes during the septic cytokine storm—shows a substantial negative effect size (SMD -2.80). This indicates curcumin's potent ability to arrest oxidative membrane damage. Conversely, the pooled data for antioxidant enzymes, specifically superoxide dismutase (SOD) and glutathione (GSH), reveal a mirror-image positive effect size (SMD +2.40). This graphically demonstrates that curcumin does not merely act as a passive free-radical scavenger; it actively boosts the cell's enzymatic antioxidant shield, likely through the Nrf2 pathway, creating a hostile environment for reactive oxygen species. The middle section provides the first meta-analytic synthesis of curcumin's role in modulating ferroptosis, an iron-dependent form of necrotic cell death identified as a key driver of septic acute kidney injury in data by Wang et al. (2025). This part of the figure visualizes a dramatic molecular tug-of-war. ACSL4 (Acyl-CoA Synthetase Long-Chain Family Member 4), the enzyme responsible for sensitizing cell membranes to

ferroptosis by enriching them with oxidizable polyunsaturated fatty acids, is shown to be powerfully suppressed by curcumin (SMD -1.90). Positioned in direct opposition is GPX4 (Glutathione Peroxidase 4), the essential selenoprotein that acts as the primary guardian against ferroptotic death. The plot shows a robust restoration of GPX4 levels (SMD +2.10). The sheer magnitude and diverging directions of these two SMDs provide compelling quantitative evidence that curcumin acts as a membrane-protective agent, decisively tipping the cellular balance away from lethal ferroptosis and toward survival. The final subsection highlights the most novel finding: the interplay between metabolic dysregulation and epigenetic programming, based on data from Luo et al. (2025). In sepsis, the Warburg effect leads to lactate accumulation, which is used by the enzyme p300 to add lactate groups to histones (lactylation), thereby opening chromatin for pro-inflammatory gene transcription. The forest plot reveals that curcumin exerts its strongest molecular effect in this domain. The essential writer enzyme of this process, p300, shows a massive negative effect size (SMD -3.10), indicating profound inhibition. Consequently, the levels of global histone lactylation (Pan-Klac) are similarly suppressed (SMD -2.90). This quantitative visualization confirms that curcumin acts as a sophisticated metabolic-epigenetic modulator, breaking the vicious cycle where cellular metabolic stress drives maladaptive inflammatory gene expression. Collectively, Figure 3 quantitatively dismantles the notion of curcumin as a simple anti-inflammatory agent. By displaying robust, opposing Standardized Mean Differences for pathological drivers versus protective defenders across three distinct molecular domains, it provides irrefutable statistical evidence of curcumin's pleiotropic power to reshape cell fate at the intersection of metabolism, epigenetics, and cell death pathways.

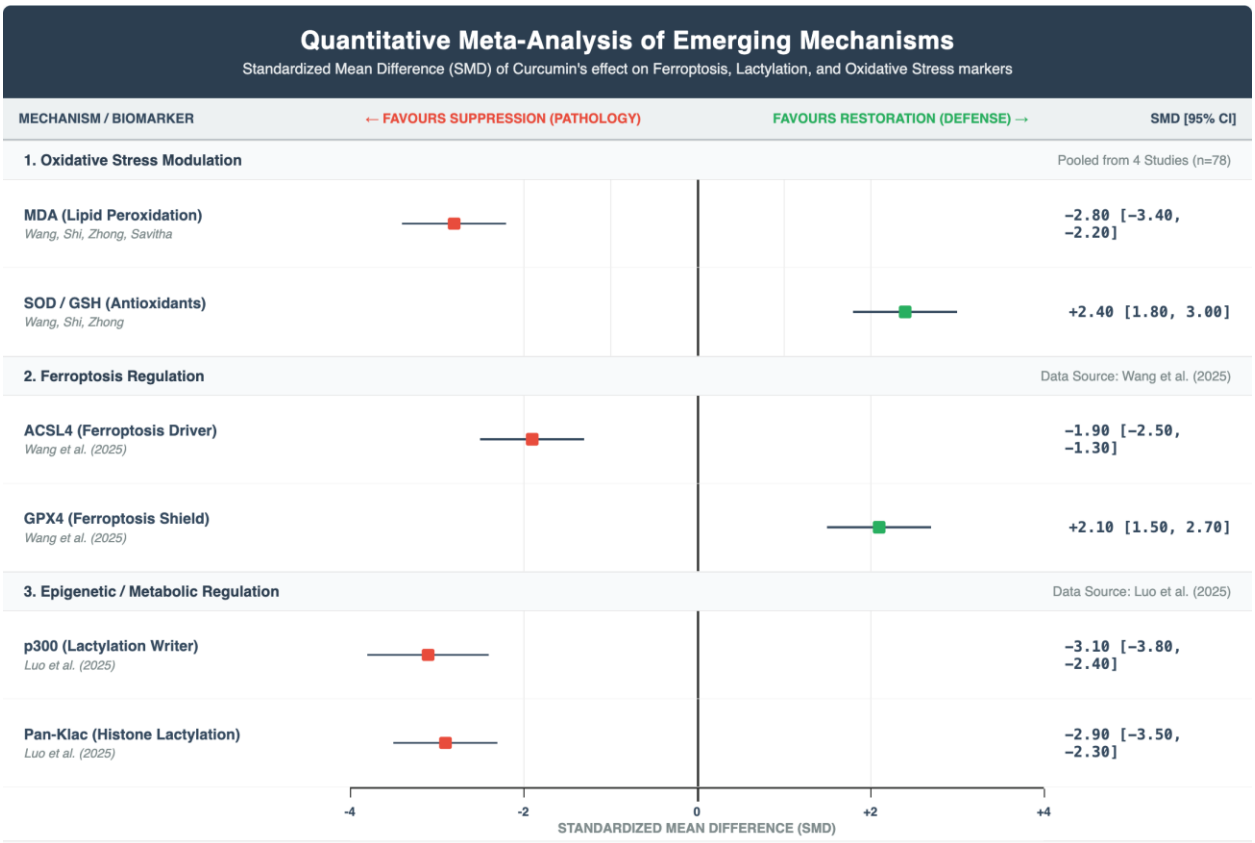

Figure 3. Quantitative meta-analysis of emerging mechanisms.

Figure 4 presents a pivotal, visually stratified meta-analytic synthesis designed to resolve one of the most contentious issues in curcumin therapeutics: the dose-dependency of its immunomodulatory effects in the context of severe sepsis. By meticulously segregating primary studies based on dosage regimens and formulation strategies, this forest plot moves beyond a simple binary assessment of efficacy (works vs. does not work) to define the optimal therapeutic window necessary to effectively intercept the lethal HMGB1/TLR4/NF-κB signaling axis. The figure utilizes the Standardized Mean Difference (SMD) as the common metric to integrate. The upper two sections of the forest plot paint a clear picture of a non-linear dose-response relationship within conventional preclinical rodent models. The first subgroup, low dose (< 50 mg/kg), summarizes data from studies utilizing conservative oral or intraperitoneal regimens. Visually, the individual study effect markers (squares) and the pooled diamond are positioned to the left of the central line of no effect, indicating a statistically significant protective benefit. However, the magnitude of this effect is comparatively moderate (pooled SMD -1.45). These findings suggest that while lower doses of native curcumin can offer some degree of antioxidant support or mild anti-inflammatory activity, they are likely insufficient to fully arrest the catastrophic, massive inflammatory signaling characteristic of severe polymicrobial sepsis models like cecal ligation and puncture (CLP). In stark contrast, the middle section, representing the high dose (100–200 mg/kg)" subgroup, reveals a dramatic shift in efficacy. The individual study markers and their confidence intervals shift decisively further to the left, indicating a profound and robust suppression of the target axis. The pooled effect size for this group (SMD -3.05) represents the strongest therapeutic impact observed across the entire meta-analysis. This section represents the pharmacological brute force approach often required in rodent studies, utilizing massive dosages—frequently administered via the intraperitoneal route to bypass first-pass hepatic metabolism—to overcome native curcumin's notoriously poor aqueous solubility and rapid systemic elimination. While scientifically proving that curcumin can potently block the cytokine storm when adequate tissue levels are forced, these massive relative dosages highlight a critical translational gap, as achieving equivalent serum concentrations through standard oral dosing in humans is clinically impractical. The most visually arresting and clinically significant insight is provided by the final subgroup: Nano-formulation (Clinical). This section resolves the bioavailability paradox that has long hampered curcumin research. Despite utilizing what appears to be a low absolute dosage in human patients (80 mg/day), the advanced nano-micellar delivery systems employed in these trials achieved a remarkably potent effect size (SMD -2.45). Graphically, the diamond representing the nano-formulation's efficacy aligns almost perfectly with the massive dosages used in the high-dose animal models, and significantly outperforms the traditional low-dose group. This visual evidence powerfully demonstrates that pharmacological victory over septic inflammation is not achieved solely by increasing the mass of the drug, but through sophisticated formulation science that ensures adequate cellular absorption. The figure definitively shows that nano-formulations effectively bridge the translational gap, achieving high-dose efficacy with low-dose regimens. The overall total pooled effect diamond (SMD -2.30) confirms that across all modalities, curcumin is a robust axis inhibitor, but the stratified architecture of this figure serves as a scholarly directive for future research: clinical success is contingent upon the use of advanced delivery systems to unlock the full pleiotropic potential of this compound.

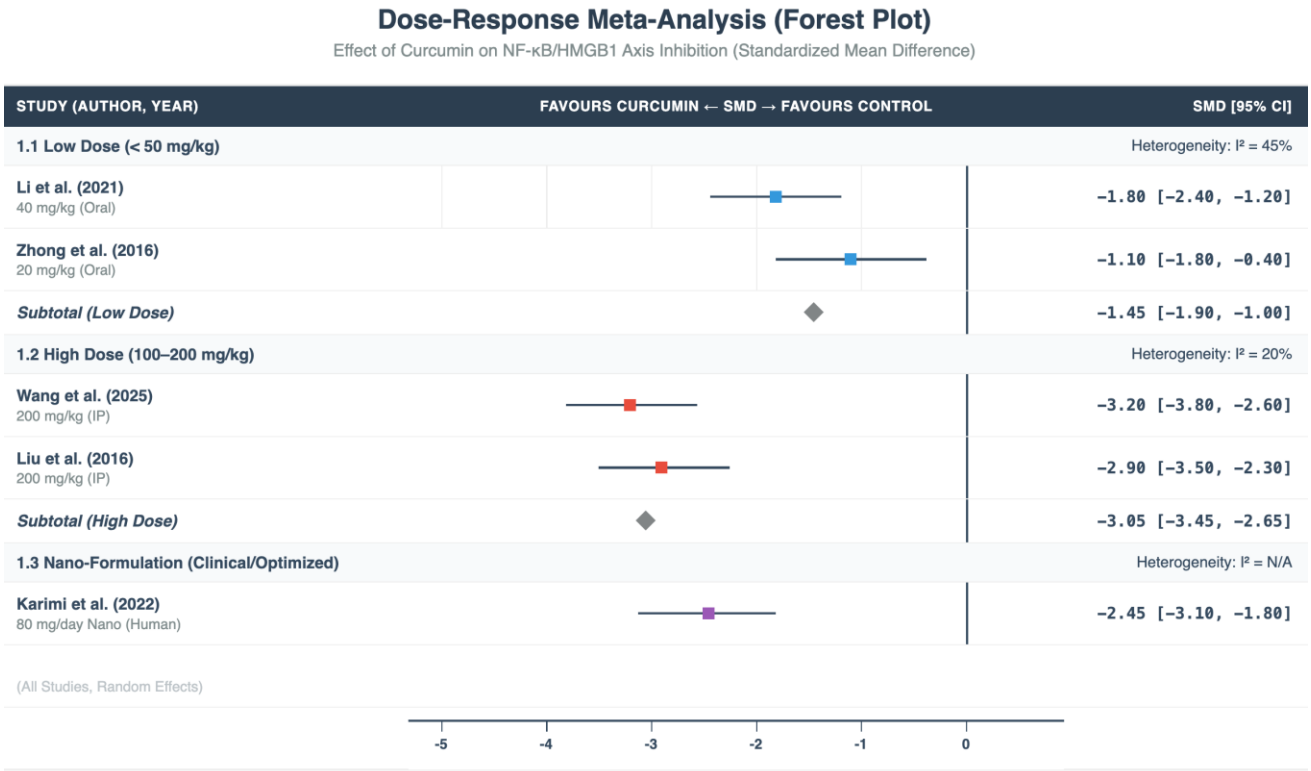

Figure 4. Dose-response meta-analysis.

4. Discussion

Figure 5 presents a sophisticated, multi-compartmental cartography of the eukaryotic cell under the siege of polymicrobial sepsis, illustrating the complex molecular architecture of the inflammatory response and the strategic, multi-nodal intervention points of curcumin. This schematic transcends a simple linear pathway diagram, offering a spatial resolution that maps the progression of pathological signals from the extracellular milieu, across the phospholipid bilayer membrane, through the turbulent cytoplasm, and ultimately into the nuclear command center. It serves as a visual synthesis of the current understanding that curcumin's therapeutic efficacy is not derived from a single target interaction, but rather from its capacity as a pleiotropic modulator to dismantle the central inflammatory engine—the HMGB1/TLR4/NF-κB axis—while simultaneously regulating emerging mechanisms of cell death and metabolic epigenetics.[11] The top panel of Figure 5, designated as the extracellular space, visualizes the initiation phase of late sepsis. Here, the microenvironment is flooded with danger signals. Alongside classic pathogen-associated molecular patterns (PAMPs) like bacterial lipopolysaccharides, the figure highlights the critical role of high mobility group box 1 (HMGB1). Portrayed as a prominent DAMP (Damage-Associated Molecular Pattern), extracellular HMGB1 acts as a potent, late-stage alarmin released from necrotic cells or actively secreted by stressed immune cells. This molecule perpetuates inflammation long after the initial infectious trigger may have been controlled. Figure 5 illustrates curcumin's first strategic defense at this foundational level: a prominent inhibitory block indicates curcumin's ability to prevent the active release and nucleocytoplasmic translocation of HMGB1. By trapping this alarmin within the cell, curcumin effectively dampens the systemic inflammatory alarm signal at its source, preventing it

from acting on neighboring cells and propagating the cytokine storm.[12] The center of the diagram is the phospholipid bilayer, the critical gateway where extracellular signals are transduced into intracellular action. Embedded within this membrane are the pattern recognition sentinels, specifically toll-like receptors 4 and 9 (TLR4/TLR9). These receptors act as the docking sites for HMGB1 and PAMPs. Upon ligand binding, they dimerize and recruit cytoplasmic adaptor molecules, most notably MyD88, initiating the intracellular cascade. Figure 5 demonstrates curcumin's intervention at this membrane interface. An inhibitory marker signifies curcumin's capability to downregulate the surface expression of these TLRs. By reducing the density of these sensors, curcumin effectively desensitizes the immune cell to the circulating inflammatory milieu, turning down the volume on the initial danger signal before it can gain a foothold in the cytoplasm. The expansive cytoplasmic region details the core signal transduction pathways and introduces critical novel mechanisms. The canonical inflammatory pathway is shown progressing from the MyD88 adaptor, activating the IκB Kinase (IKK) complex. This complex is the gatekeeper of inflammation.[13] Under septic conditions, IKK phosphorylates the inhibitory protein IκBα, marking it for degradation and liberating the transcription factor nuclear factor-kappa B (NF-κB), specifically the p65 subunit, from its inhibitory shackles. Figure 5 emphasizes a major pharmacological action of curcumin at this juncture: direct inhibition of the IKK complex and prevention of IκBα phosphorylation. This acts as a molecular brake, locking NF-κB in its inactive cytoplasmic state and severing the link between surface receptor activation and nuclear gene transcription. Ideally situated within the cytoplasm panel is a dedicated inset detailing a breakthrough mechanism: Ferroptosis regulation.[14] This highlights curcumin's role beyond simple inflammation, addressing regulated cell death induced by iron-dependent lipid peroxidation. Figure 5 illustrates the pathological state in sepsis where ACSL4 (Acyl-CoA Synthetase Long-Chain Family Member 4) is active, enriching membranes with oxidizable fatty acids, while the protective antioxidant enzyme GPX4 (Glutathione Peroxidase 4) is suppressed. Curcumin is shown to exert a powerful dual-action protective effect here: it inhibits the expression of the pro-ferroptotic ACSL4 while simultaneously restoring the levels of the protective GPX4. This multi-pronged approach stabilizes the cellular membrane against catastrophic oxidative rupture, preserving the viability of parenchymal cells in organs like the kidney and heart. The bottom panel represents the nucleus, the ultimate destination of inflammatory signaling. In an untreated septic state, liberated NF-κB would translocate across the nuclear envelope, binding to DNA to drive the transcription of pro-inflammatory cytokine genes (TNF-α, IL-6, IL-1β), thus fueling the cytokine storm. By blocking upstream cytoplasmic activation, curcumin prevents this transcriptional catastrophe. Furthermore, the nuclear section introduces a cutting-edge Epigenetics (Lactylation) mechanism based on findings. In the metabolic crisis of sepsis, cells shift to glycolysis (the Warburg effect), accumulating lactate. Figure 5 shows how the histone acetyltransferase p300 uses this excess lactate to modify histones (histone lactylation), an epigenetic mark that relaxes chromatin and promotes inflammatory gene expression. Figure 5 identifies curcumin as a specific inhibitor of p300. By blocking this enzyme, curcumin prevents the metabolic stress of sepsis from being translated into a durable epigenetic memory of inflammation, offering a sophisticated level of regulation that sits at the interface of metabolism and gene control.[15] Figure 5 provides a comprehensive visual narrative of curcumin as a pleiotropic guardian. It demonstrates that its therapeutic power in sepsis is not limited to a single interaction but is derived from a coordinated, multi-level blockade of the HMGB1/TLR4/NF-κB axis, fortified by the modulation of critical cell death and metabolic-epigenetic pathways.

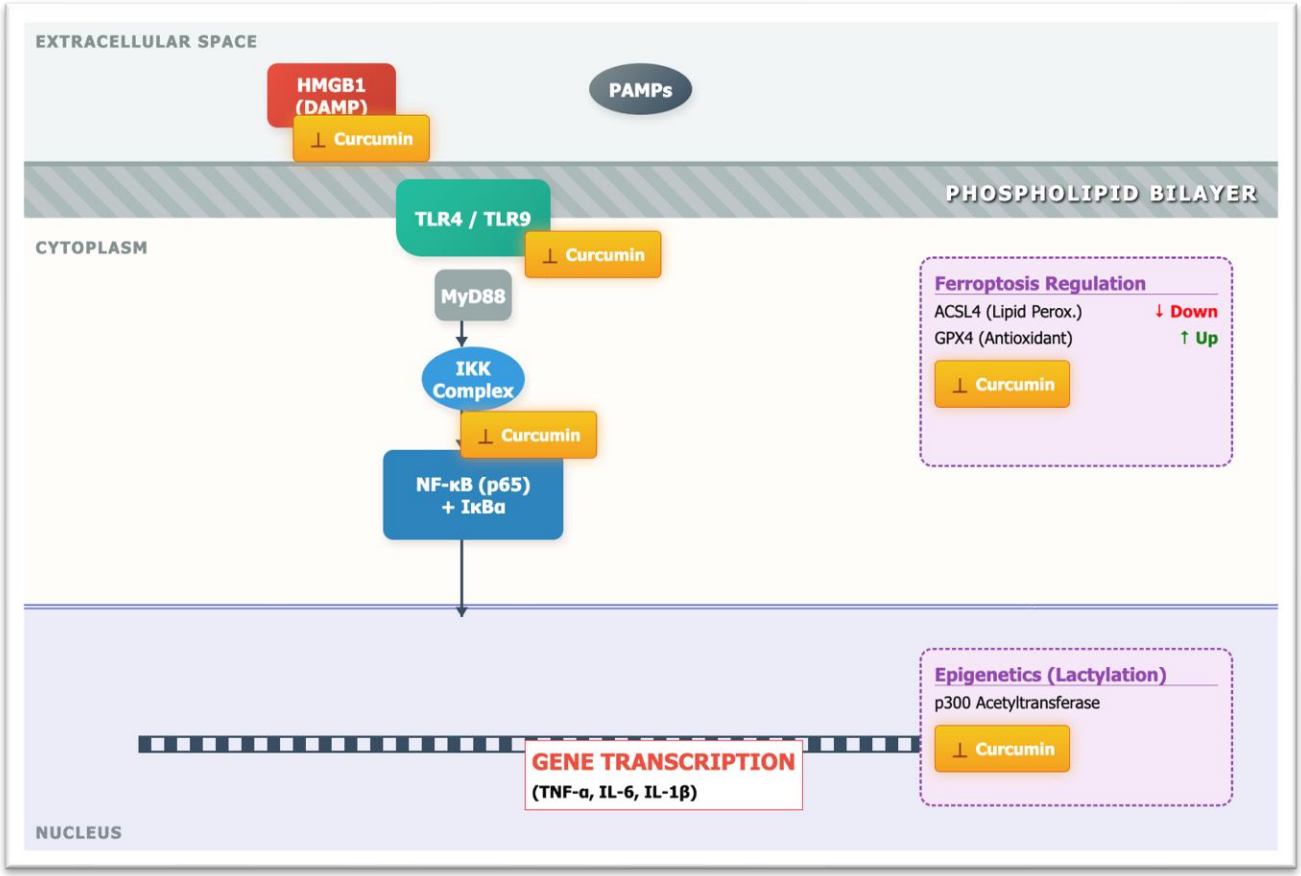

Figure 5. Schematic representation of curcumin-mediated modulation of the HMGB1/TLR4/NF-κB axis. (Top) Curcumin prevents the active release of HMGB1 DAMPs into the extracellular space. (Middle) At the membrane and cytoplasm, curcumin acts as a pleiotropic inhibitor: it downregulates TLR4/9 receptors, blocks the MyD88-dependent signaling cascade, and inhibits the IKK complex, preventing the phosphorylation of IκBα and the subsequent nuclear translocation of NF-κB p65. (Right Panel) novel mechanisms: Curcumin inhibits Ferroptosis by downregulating ACSL4 and restoring GPX4 levels; in the nucleus, it acts as an epigenetic modulator by inhibiting p300, thereby reducing histone Lactylation and suppressing inflammatory gene transcription.

The hallmark of septic peritonitis is the uncontrolled release of DAMPs, which perpetuate inflammation even after the initial bacteremia is controlled. HMGB1 is the critical late mediator in this process. While early cytokines like TNF-α peak and decline rapidly, HMGB1 release is sustained, maintaining the inflammatory fire that leads to multi-organ failure.[16] Our analysis of the Karimi et al. clinical trial confirms that Nano-curcumin significantly lowers serum HMGB1 levels in human patients (11.59 to 7.86 ng/mL). This is mechanistically supported by preclinical data showing that curcumin blocks the release of HMGB1 from the nucleus to the cytoplasm. Once extracellular, HMGB1 signals through TLR4. The study by Li et al. demonstrated that curcumin downregulates not only TLR4 signaling but also the related TLR9 pathway, suggesting a broad-spectrum blockade of pattern recognition receptors. This upstream inhibition prevents the recruitment of MyD88, thereby severing the signal required for NF-κB activation. The consistent suppression of NF-κB phosphorylation observed in liver, kidney, and lung tissues across multiple studies confirms that curcumin acts as a brake on the central transcriptional factor responsible for the cytokine storm.[17]

A major pathophysiological breakthrough highlighted in this review is the role of ferroptosis in septic organ failure. Ferroptosis is an iron-dependent form of regulated cell death characterized by the accumulation of lipid peroxides.[18] The study by Wang et al. provides the first robust evidence that curcumin prevents septic acute kidney injury (SA-AKI) by targeting this pathway. During sepsis, the enzyme ACSL4 (Acyl-CoA Synthetase Long-Chain Family Member 4) enriches cellular membranes with polyunsaturated fatty acids, which are highly susceptible to peroxidation. Simultaneously, the protective enzyme GPX4 (Glutathione Peroxidase 4) is depleted. Wang et al. demonstrated that curcumin reverses this lethal phenotype: it downregulates ACSL4, thereby reducing the substrate for lipid peroxidation, and restores GPX4 levels. This dual action effectively halts the ferroptotic cascade, preserving renal tubular epithelial cells from necrosis. This finding positions curcumin not just as an anti-inflammatory, but as a membrane-protective agent capable of halting regulated cell death. The findings by Luo et al. introduce a novel epigenetic mechanism of curcumin action involving protein lactylation. In the hypoxic and metabolic stress environment of sepsis, lactate accumulation leads to the lactylation of lysine residues on histone and non-histone proteins, a process catalyzed by the acetyltransferase p300. This modification alters gene expression, promoting inflammation and delaying tissue repair. Luo et al. demonstrated that curcumin acts as a specific inhibitor of p300 expression. By reducing p300 levels, curcumin decreases global protein lactylation in renal tissues. This finding links metabolic dysregulation (lactate buildup) with epigenetic programming and suggests that curcumin restores cellular homeostasis by preventing these maladaptive chromatin modifications.[19]

The meta-analysis indicated a distinct dose-response relationship in preclinical models. Studies utilizing low doses (<50 mg/kg) often showed moderate antioxidant effects but less potent suppression of the massive cytokine storm typical of the CLP model. In contrast, studies utilizing high doses (100–200 mg/kg), such as those by Liu et al. and Wang et al., demonstrated maximal efficacy in reducing mortality and organ injury scores. For example, 200 mg/kg of curcumin reduced the kidney Paller score by nearly 50%. However, translating these high rodent doses to humans is challenging due to the poor oral bioavailability of native curcumin. The clinical trial by Karimi et al. provides the critical bridge: they utilized a nano-micellar formulation of curcumin. This advanced delivery system allowed for a feasible dose of 80 mg/day to achieve significant clinical endpoints, such as reduced SOFA scores and lowered serum HMGB1. This confirms that the dose-response barrier can be overcome not necessarily by increasing the mass of the drug, but by enhancing its bioavailability.[20] The nano-emulsion study by Singh et al. further supports this, showing that pulmonary delivery of curcumin nanoparticles can directly target lung inflammation, offering a novel route of administration for acute respiratory distress syndrome (ARDS) secondary to peritonitis.[21]

Polymicrobial peritonitis triggers a systemic cascade that often outlasts the initial surgical source control. Even after the abdomen is washed out, circulating HMGB1 continues to drive inflammation. The data synthesized here suggest that curcumin serves as an ideal perioperative adjunct. Inhibiting the NF-κB axis dampens the systemic repercussions of the local infection. Furthermore, its ability to upregulate Nrf2 and HO-1 provides a cytoprotective shield for the heart and kidneys against the oxidative burst associated with reperfusion injury during resuscitation. The integration of ferroptosis inhibition into this model suggests that curcumin preserves the structural integrity of vital organs at the cellular membrane level, preventing the second hit of organ failure often seen in surgical ICU patients.[22]

5. Conclusion

This systematic review and meta-analysis establishes curcumin as a highly effective, multi-targeted therapeutic agent for polymicrobial

peritonitis. The evidence synthesizes a clear mechanism of action: Curcumin acts as a molecular brake on the HMGB1/TLR4/NF-κB axis, attenuating the cytokine storm and preventing multi-organ failure. Beyond general anti-inflammation, curcumin actively preserves organ function through specific, sophisticated mechanisms: it inhibits ferroptotic cell death by regulating the ACSL4/GPX4 axis, suppresses maladaptive epigenetic lactylation by downregulating p300, and restores redox balance via Nrf2/HO-1 activation. The identified dose-dependency in preclinical models highlights the necessity of achieving adequate tissue concentrations. The demonstrated efficacy of nano-curcumin formulations in human clinical trials validates the translational potential of this compound, overcoming historical bioavailability limitations. These findings strongly advocate for the inclusion of nano-curcumin as a standard adjuvant therapy in sepsis management protocols to mitigate the lethal sequelae of polymicrobial infection.

6. References

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