From spice to sepsis therapy: Mechanistic perspectives on the anti-sepsis therapeutic potential of curcumin (Review)

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Abstract. Curcumin, a key and abundant polyphenol found in turmeric (*Curcuma longa*), is one of the oldest spices recognized for its medicinal properties. Curcumin exhibits beneficial effects in various ailments, including anxiety, arthritis, metabolic syndrome, inflammatory diseases and hyperlipidemia. The present review discusses the mechanistic basis of the anti-inflammatory, immunomodulatory, antibacterial and organ-protective potential of curcumin in alleviating sepsis-induced hyperinflammation. Current treatments for sepsis, including the use of non-steroidal anti-inflammatory drugs and immunosuppressants, have limitations, including the need for long-term use and severe side-effects, such as gastrointestinal issues. Search engines, including Scopus and PubMed, were used to identify relevant literature for compiling the review. Original research and review articles containing the key words curcumin, sepsis, hyperinflammation, cytokine storm, anti-inflammatory, oxidative stress, clinical translation and organ protection were included. Curcumin influences the key pathways involved in sepsis-induced hyperinflammation by inhibiting pro-inflammatory cytokines, reducing oxidative stress, modulating immune responses and exerting organ-protective effects. Thus, curcumin exhibits potential in reducing the severity of sepsis, improving outcomes and mitigating serious complications, such as organ failure. However, future studies focusing on its bioavailability, delivery, dosage and synergistic potential are warranted to establish its clinical role in sepsis management.

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Key words: curcumin, sepsis, hyperinflammation, organ protection, neutrophils, neutrophil extracellular traps, free radicals

Contents

1. Introduction

Sepsis. Sepsis is a severe condition characterized by a dysregulated host inflammatory response to infection, resulting in organ damage. The latest Global Burden of Disease 2021 analysis estimated 166 million cases of sepsis worldwide in 2021 and ~21.4 million sepsis-related deaths, collectively accounting for almost 31.5% of the total global mortality (1). A constant decline in sepsis-related mortality between 1990 and 2019 was followed by a sharp trend reversal in 2020 and 2021 globally, which was significantly attributed to the coronavirus disease 2019 (COVID-19) pandemic and increased susceptibility in elderly populations. The incidence of sepsis increased by 230% and mortality increased by 26.3% since 1990 among adults aged ≥15 years, with the highest mortality rates being reported among the oldest age group (≥70 years; 9.28 million deaths in 2021). Although the incidence of sepsis-related deaths from infectious conditions, such as diarrheal diseases, tuberculosis, measles and lower respiratory infections has considerably decreased over the past three decades, fatalities related to non-infectious underlying conditions such as stroke, chronic obstructive pulmonary disease, cirrhosis, and ischemic heart disease have increased, highlighting the shift in sepsis epidemiology toward complications of chronic diseases (1). A previous study found that children aged <5 years constituted 26.4% (2.9 million) of the global sepsis death toll and 41.5% (20.3 million) of the cases of sepsis. The incidence of sepsis was lower among children and the younger population aged 5-19 years, accounting for 10% (4.9 million) and 4.1% (0.45 million associated deaths), respectively. Adults aged ≥20 years accounted for the majority of incident cases of sepsis,

representing 48.5% (23.7 million), and for 70% (7.7 million) of associated deaths. Men had a higher sepsis-related mortality rate than women (164 vs. 134 per 100,000, respectively), whereas women had a higher incidence of sepsis globally at 717 vs. 643 cases per 100,000 (2). Moreover, significant geographical and economic disparities have been reported, with high rates in low- and middle-income countries or countries with an intermediate sociodemographic index, such as those located in sub-Saharan Africa and South-East Asia (3). The frequency of sepsis greatly varies by location. The aforementioned scenario supports the view that the incidence of sepsis has decreased in children and is no longer mainly driven by infections; however, the overall global burden of sepsis is high and mostly driven by aging populations, chronic diseases, and new infections such as COVID-19 (1). It poses a major challenge globally, owing to its increasing incidence and high mortality rates, and also poses a tremendous financial burden on healthcare systems. The higher rates in low- and middle-income countries are attributable to inferior medical facilities that are devoid of the necessary tools and resources required for the diagnosis, prevention and treatment of sepsis (Fig. 1). Furthermore, age is a critical determinant wherein the proportionate mortality from sepsis is the highest in neonates, declines during middle adulthood, and then re-increases in the older age groups (3).

Curcumin, a principal constituent of turmeric rhizomes, demonstrates a broad spectrum of physiological and pharmacological properties, and has long been used in traditional medicine. Although turmeric has been used for thousands of years for its medicinal benefits, research related to its precise mechanisms of action and elucidation of its bioactive components is relatively recent (4). Curcumin is used to treat various chronic diseases owing to its potent anti-inflammatory and antioxidant properties.

For the purposes of the present review, search engines, including Scopus and PubMed, were used to identify relevant literature. Original research and review articles with key words such as curcumin, sepsis, hyperinflammation, cytokine storm, anti-inflammatory, oxidative stress, clinical translation and organ protection have been included in the present review. Only studies published in the English language were considered for this review. All identified publications were assessed, but only those that were relevant to curcumin and its potential role in mitigating sepsis were included.

Pathophysiology of hyperinflammation-induced sepsis. Sepsis represents a dynamic immune dysregulation, where an initial hyperinflammatory phase driven by excessive cytokine release leads to tissue injury and organ dysfunction. This is followed by a dysfunctional immunosuppressive phase characterized by lymphocyte apoptosis and impaired immune responses, increasing the propensity to secondary infections and poor clinical outcomes (5).

The clinical manifestations of sepsis include fever, tachycardia, tachypnea and organ dysfunction. These processes are driven by a state of hyperinflammation, which involves complex interactions between immune cells and vascular cells, including leukocytes, cytokines, reactive oxygen species (ROS), endothelial cells, complement and the coagulation system (Fig. 2). An imbalance in the immune response of the host during sepsis is the core of persistent inflammation. Prolonged exposure to pathogen-associated molecular patterns and damage-associated molecular patterns may stimulate a cascade of events, leading to leukocyte infiltration and the activation of the endothelium and the complement system. The accelerated synthesis and the secretion of acute-phase proteins and pro-inflammatory cytokines in the early stages of the progression of sepsis reinforce the immune response further into a cycle of self-sustaining inflammation. The participation of interleukin (IL)-17 by T-helper and innate lymphoid cells increases the release of tumor necrosis factor (TNF)-a and IL-1β, potentiating the inflammatory response (5,6). High-mobility group box 1 is a molecule that functions both as a cytokine and damage-associated molecular pattern. It is highly upregulated in sepsis and mediates inflammation via the activation of multiple pathogen recognition receptors (PRRs) (8). As it exhibits promising therapeutic potential, its clinical evaluation is in the preclinical stages.

Neutrophils constitute the first line of defense in the immune system. A recent study found that a population of elderly neutrophils may effectively deliver antigens to T-cells, which, in turn, trigger interferon (IFN)-γ production (9). Neutrophils form neutrophil extracellular traps (NETs) consisting of DNA, histones, myeloperoxidase and elastase, which help neutralize pathogens. NETs are generated by neutrophils upon stimulation by bacteria, viruses, or cancer cells (10,11), and they can occur as self-destructive or vital processes (12). Although extracellular traps are also produced by macrophages, their role in sepsis remains unclear (13). The uncontrolled formation and improper clearance of NETs shift their function from tissue protection to tissue damage, causing hyperinflammation and thrombosis (10,14).

The complement system is vital in the innate immune response (15) and is activated via the following three pathways: The classical pathway initiated by C1 binding to antibodies, an alternative pathway through the activation of the hydrolysed C3 on microbial surfaces, and the lectin pathway, wherein the mannose-binding lectin binds to pathogen carbohydrates. The secretion of chemotactic agents, such as C3a and C5a, leads to the recruitment of leukocytes and changes in vascular flow, permeability and adhesion. Moreover, the terminal complement complex facilitated by the complement system causes bacterial lysis (16). During sepsis, the activation of the complement contributes to hyperinflammation (17), and increased C5a levels are associated with worse outcomes (18). Although preclinical studies have shown promise, complement-targeted therapies, including C5a inhibitors, have not yet been translated to clinical use for sepsis (19).

In sepsis, the activation of the coagulation system is also very common, ranging from mild activation to disseminated intravascular coagulation (DIC) (20). DIC may lead to defective hemostasis due to the consumption of clotting factors and platelets (21). The term immunothrombosis describes a coordinated association between the immune and coagulation systems to trap pathogens through a combination of fibrin, neutrophils, monocytes and platelets (22). However, it may become dangerous when microvascular thrombosis is uncontrolled and could lead to hypoxia and organ failure (23). NETs engage the coagulation cascade via factor XII and transcription factor and cleave antithrombotic proteins, while further activating platelets along with cell-free DNA and histones,

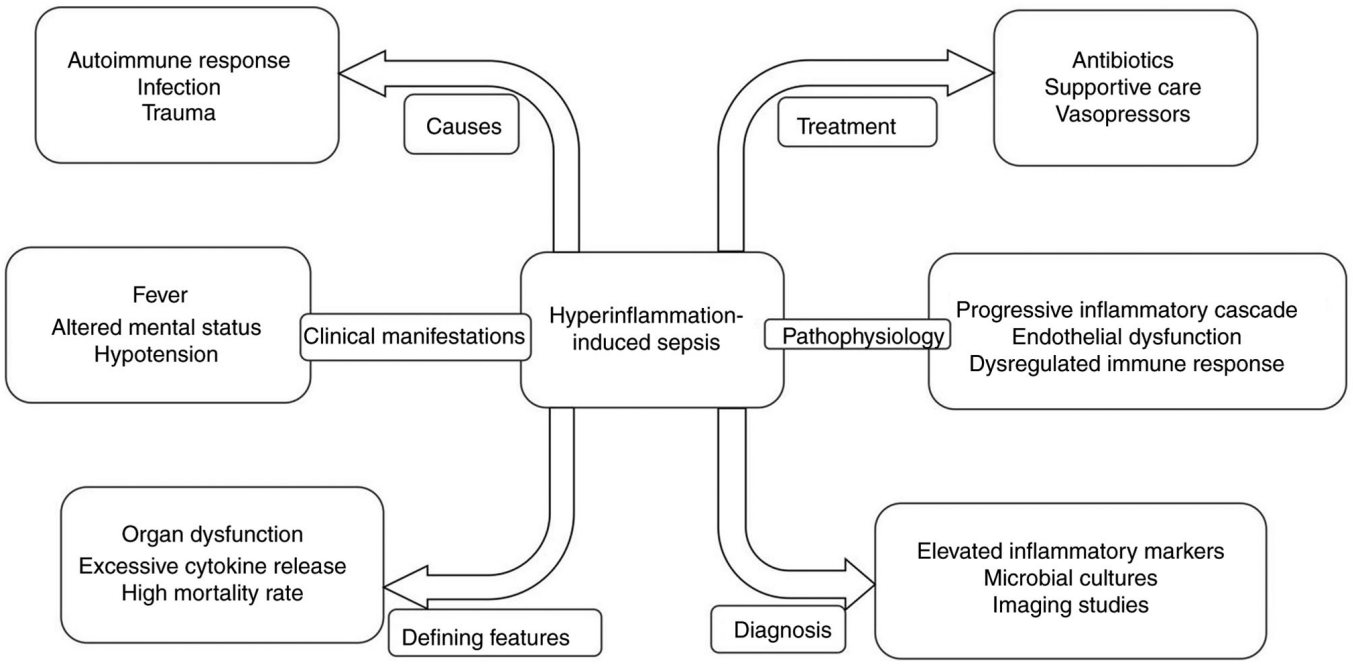

Figure 1. Aspects of the clinical management of hyperinflammation-induced sepsis. The schematic illustrates the major causes, clinical manifestations, diagnostic approaches, underlying pathophysiology, and treatment strategies in hyperinflammation-induced sepsis.

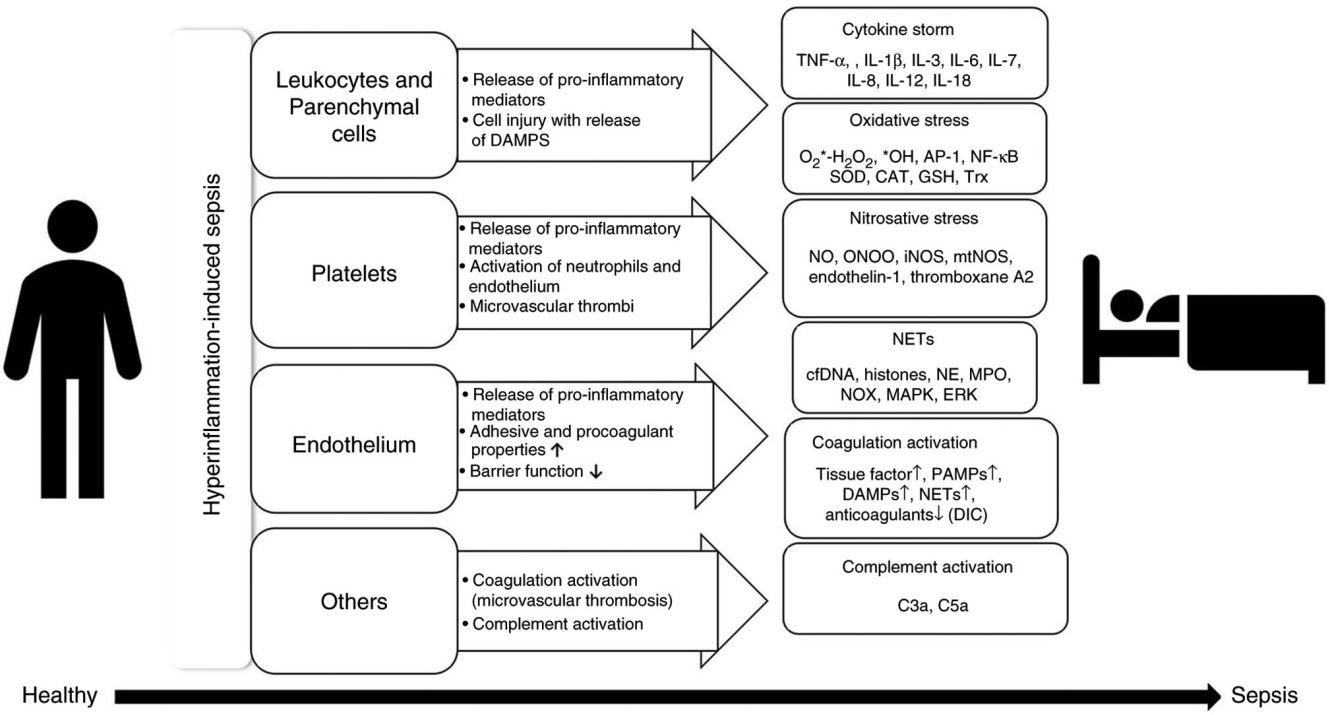

Figure 2. Hyperinflammation-induced sepsis pathophysiology. The image depicts the series of cellular and molecular events occurring during hyperinflammation-induced sepsis and highlights the involvement of leukocytes, platelets, and endothelial cells in the cascade of reactions that include cytokine release, oxidative and nitrosative stress, NET formation, complement and coagulation activation. DAMPS, damage-associated molecular patterns; NET, neutrophil extracellular trap; SOD, superoxide dismutase; CAT, catalase; GSH, glutathione; NO, nitric oxide; iNOS, inducible nitric oxide synthase; mtNOS, mitochondrial nitric oxide synthase; cfDNA, cell-free DNA; NE, neutrophil elastase; MPO, myeloperoxidase; NOX, NADPH oxidase.

supporting fibrin generation and promoting the amplification and further generation of NETs (24,25). However, high levels of NETs, as noted in the case of severe sepsis, can lead to tissue deterioration and a hypercoagulant response, causing complications such as DIC, thrombosis and organ failure (10,14).

The complement and coagulation systems are also functionally redundant and function synergistically. Complement factors facilitate the expression of tissue factor on leukocytes, activate platelets and release von Willebrand factor from endothelial cells (26). This relationship was established using

a primate model of *Escherichia coli*-induced sepsis, where the administration of compstatin, a C3 inhibitor, significantly reduced microvascular thrombosis (27). Pyroptosis is a pro-inflammatory form of programmed cell death that is also connected with immunothrombosis. Pyroptosis is activated by PRRs, and it triggers the formation of the inflammasome and the cleavage of gasdermin D, which forms pore-releasing inflammatory cytokines and tissue factors (28). Understanding these interactions will help further identify novel therapeutic strategies that would help reduce the severity of hyperinflammation-related complications in sepsis.

The current management of sepsis includes controlling the underlying infection, stabilizing hemodynamic factors and modulating the host immune response. Significant challenges still exist despite the success of antibiotics in treating sepsis. These include the development of antibiotic resistance when several antibiotics are used incorrectly, further complicating the treatment (29). Antibiotics have a negative effect on the beneficial microflora, which may lead to diarrhea and the occurrence of secondary infections (30). Moreover, treatment outcomes achieved using immunomodulators, including hydrocortisone, are not always favorable (31,32). Several side-effects have been reported in response to vasopressin (33).

2. Curcumin

Curcumin [(1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is the major polyphenol present in the turmeric plant (*Curcuma longa*), which is one of the oldest known medicinal spices. Curcumin is also present in other *Curcuma* species, including *Curcuma domestica* (34), *Curcuma aromatica* and *Curcuma xanthorrhiza* (35). *Curcuma longa*, a rhizome from the Zingiberaceae family, is largely cultivated in India (36,37). Upon consumption, curcumin is biotransformed into major biliary metabolites, including dihydrocurcumin, tetrahydrocurcumin and hexahydrocurcumin, which are further metabolized to monoglucuronide conjugates (37-39). Curcumin exerts several biological and pharmacological effects, including antispasmodic (37), anticancer, antibacterial and antirheumatic effects (36,40). Curcumin also shows benefits in treating anxiety, arthritis, metabolic syndrome, inflammatory diseases and hyperlipidemia. Furthermore, curcumin may control post-exercise inflammation and muscular pain, enhancing recuperation and, in turn, performance in athletes (41). Chronic inflammatory diseases, such as rheumatism, atherosclerosis, type II diabetes, Alzheimer's disease and inflammatory bowel disease have also been treated or managed with curcumin (42-44). Curcumin exerts these health benefits by modulating various signaling pathways and altering gene expression. It is a partial inhibitor of protein kinase and is known to affect the activity of protein kinase C (45), protein tyrosine kinase (46), cyclooxygenase (COX)-1 and COX-2 (43,47), inhibiting lipoxygenase, TNF-α, IFN-γ, inducible nitric oxide synthase and transcriptional nuclear factor κB (NF-κB) (43). Curcumin is also a potent ROS scavenger that protects hemoglobin from nitrite-induced oxidation to methemoglobin and is also known to inhibit lipid peroxidation (48). Treatment with curcumin can increase fibronectin and collagen expression, and it is accompanied by the infiltration of numerous cells such as macrophages, neutrophils and fibroblasts (49). The presence of myofibroblasts facilitates more rapid wound contraction (48). The pharmacological derivatives of curcumin, its molecular weight and formula are presented in Table SI.

Chemistry of curcumin. Curcuminoids constitute ~1-6% of the dry weight of turmeric. The three major curcuminoids in turmeric are curcumin (60-70% of the crude extract), demethoxycurcumin (20-27%) and bisdemethoxycurcumin (10-15%) (50,51). Curcumin has been extensively studied by researchers in recent times owing to its attractive characteristics, particularly in biological applications. It is considered a good lead molecule in drug discovery programs. However, its poor pharmacokinetic and pharmacodynamic properties restrict its progression to a drug candidate (52). It is water insoluble at room temperature and has a neutral pH (Log P-value, 2.3-3.2); however, it is soluble in solvents such as acetone, methanol and ethanol. Moreover, as it forms phenolates at an alkaline pH, it degrades rapidly in neutral and alkaline conditions via solvolysis and oxidative degradation pathways, thereby not fulfilling the basic stability requirement under physiological conditions. Its chemical instability is the major challenge posed during its development, as it undergoes keto-enol tautomerism due to the presence of a β-diketone moiety. This instability restricts the reproducibility of *in vivo* and *in vitro* findings and further constrains computational models. The chemical instability of curcumin is also responsible for its poor bioavailability (<1%), which further affects studies on the Absorption, Distribution, Metabolism, Excretion, and Toxicity of drug candidates. Several approaches are currently being explored, particularly formulation development, nanoformulation approaches and the use of other additives (e.g., piperine, a known bioavailability enhancer) to improve the stability of curcumin under physiological conditions and enhance bioavailability (53-55). Moreover, curcumin can combine with several biopolymers to enhance wound healing (56). The incorporation of curcumin into nanocarrier systems can enhance its penetration into tissues (57). Its structural components, including a diketone moiety and two phenolic groups, facilitate key reactions including hydrogen donation, nucleophilic addition and hydrolysis. These reactions underpin the diverse biological applications of curcumin, including its potent ROS-scavenging activity, anti-inflammatory effects and immunomodulatory properties, which constitute core mechanisms supporting its potential use in the treatment of sepsis (31,36,51).

3. Pharmacological potential of curcumin in sepsis

The phenolic compound, curcumin, exerts a range of pharmacological effects, including ameliorating hyperinflammation, modulating the immune response and scavenging free radicals (Fig. 3). Curcumin attenuates cytokine storms, excessive inflammation and acute respiratory distress syndrome both *in vitro* and *in vivo* (32,58). Furthermore, curcumin exerts an anti-inflammatory effect by inhibiting ROS formation and normalizing cytokine secretion to block the oxidation pathway. It also prevents the production of inflammatory cytokines and oxidative stress-related proteins, thereby improving the survival rate and reducing alveolar exudation, degeneration and necrotic cell death (58-62).

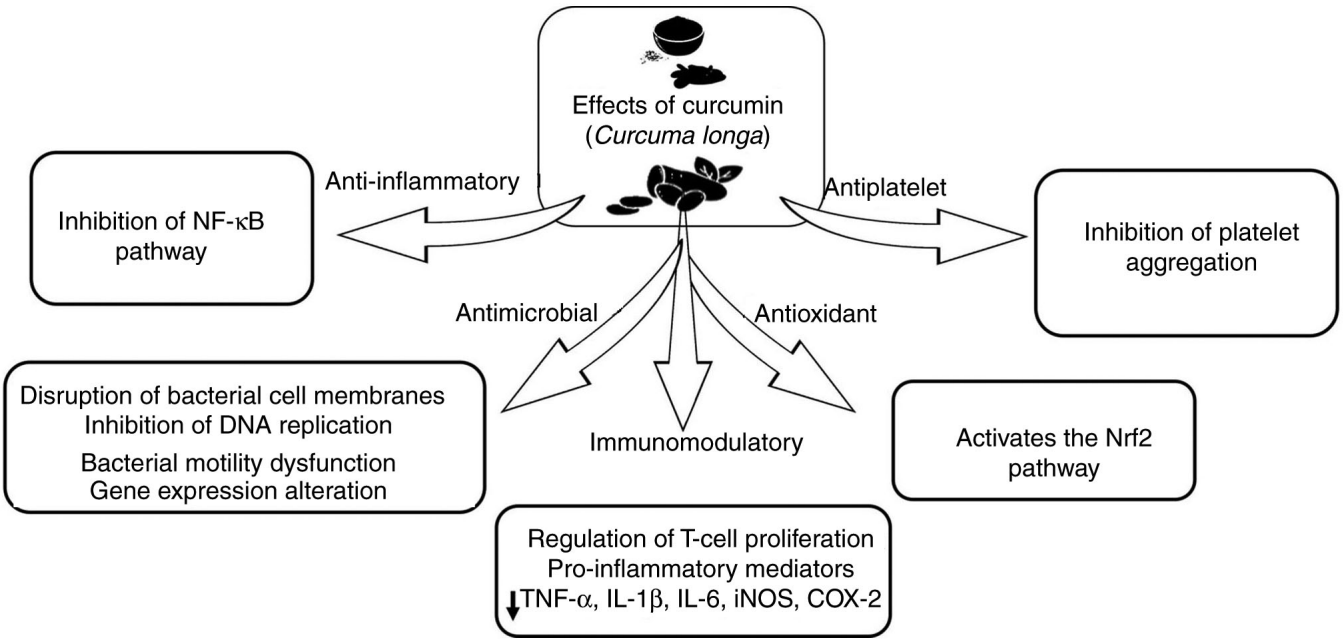

Figure 3. Multifaceted effects of curcumin. The image depicts the biological activities of curcumin, including its anti-inflammatory, antioxidant, antimicrobial, antiplatelet, and immunomodulatory effects, all of which are considered pleiotropic. The synergistic effect of the inhibition of the NF-κB pathway, activation of the Nrf2 pathway, modulation of the gut microbiota, and pro-inflammation mediator suppression by curcumin is shown. Nrf2, nuclear factor erythroid 2-related factor 2; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase 2.

The antioxidant activity of curcumin is due to its ability as a free radical scavenger in reducing oxidative damage (60). The pleiotropic nature of curcumin allows it to modulate multiple signaling pathways, rendering it a potent candidate for treating a wide array of chronic conditions. Experimental evidence from various *in vivo* and *in vitro* disease models ranging from metabolic disorders to neurodegenerative conditions demonstrates its versatile therapeutic efficacy (62-75). A comprehensive summary of these therapeutic effects across different disease models and the pharmacological potential of curcumin is presented Table SII.

Curcumin exerts antimicrobial effects against several pathogens incriminated in sepsis by disrupting bacterial cell membranes, inhibiting DNA replication, inducing bacterial motility dysfunction, and altering gene expression (76,77). Curcumin has shown activity against *Staphylococcus aureus*, *Escherichia coli*, *Salmonella paratyphi*, *Toxoplasma gondii*, *Bacillus subtilis*, *Paenibacillus macerans*, *B. licheniformis* and *Azotobacter* (78) and also against 20 *Candida* species (79,80). Curcumin nanoformulations have been shown to be more effective against *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*, maintaining activity even following 1 month of storage and exhibiting no toxicity, in contrast to antibiotics such as chloramphenicol and gentamicin (76,78). The broad-spectrum antibacterial potential of curcumin has been extensively documented in recent literature (79,80). Specifically, its differential efficacy against various bacterial cell wall structures has been a primary focus of investigation. A comprehensive summary of the inhibitory effects of curcumin and its derivatives against a wide range of Gram-negative and Gram-positive bacteria (29,81-90) is provided in Table SIII.

4. Organ-protective potential of curcumin

Sepsis is a lethal condition that affects one or multiple organs due to hyperinflammation. It is characterized by the overactivation of the host response to an infection, which triggers a complex process through hyperimmune activation, dysregulated immune responses exaggerated ROS production, and finally, NET formation. The factors acting in an integrated manner lead to severe tissue damage and organ failure (36,40), with the lungs, liver, heart, brain and kidneys being the major organs affected due to sepsis (Fig. 4).

Curcumin reduces the initial inflammatory cell infiltration in various organs and tissues, including the lungs, liver, kidneys, brain, heart, spleen and intestines (66,91-109). Curcumin has demonstrated outstanding protective benefits against cardiac ischemia and reperfusion, hyperuricemia and renal endothelial dysfunction, as it inhibits the Janus kinase (JNK)2/signal transducer and activator of transcription 3 pathway (91) and the extracellular signal-regulated kinase/plasmacytoma variant translocation 1/c-Jun N-terminal kinase/NF-kB pathway (92). Curcumin can protect against renal ischemia-reperfusion injury-induced acute kidney injury by upregulating the expression of DCC-interacting protein 13-alpha, which additionally blocks the Akt signaling pathway (93). The anti-apoptotic effects of tetrahydrocurcumin (THC) significantly decreased the expression of Bax and cleaved caspase-3 and increased that of Bcl2, which further decreased the development of diabetic cardiomyopathy by reducing oxidative stress and fibrosis by stimulating the induction of the SIRT1-DRP1/PGC-1α signaling pathway. Some key markers, including serum creatinine, blood urea nitrogen, kidney injury molecule-1 and urine microalbumin/creatinine, were used to assess the decline in renal function (94).

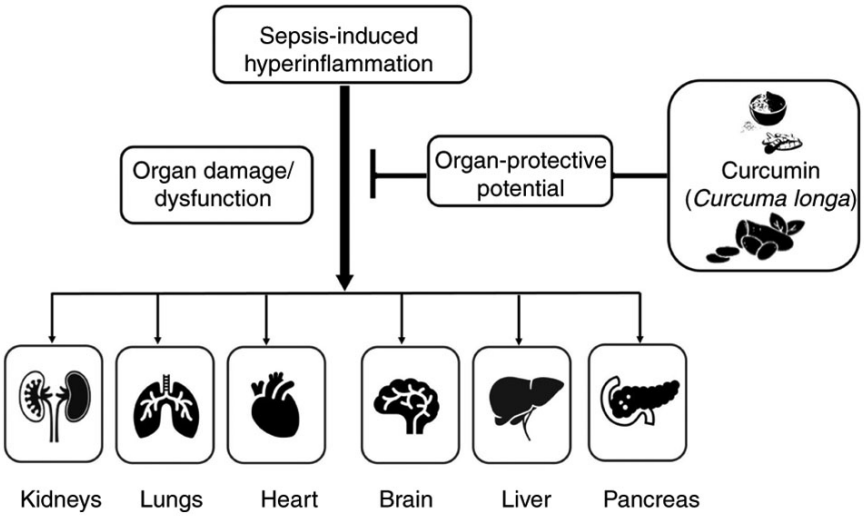

Figure 4. Organ-protective potential of curcumin in sepsis. The image highlights the potential of curcumin in protecting the vital organs, including the kidneys, liver, heart, lungs, brain, and pancreas, against damage from sepsis-induced hyperinflammation.

Curcumin has been reported to decrease inflammation; normalize the levels of hepatic enzymes such as alkaline phosphatase, aspartate transaminase and alanine transaminase (66,95); attenuate hepatocyte damage (96,97) in *in vitro* models; and decrease the extent of cell degeneration and necrosis in an *in vivo* model of lipopolysaccharide-induced sepsis (98). Treatment with curcumin was shown to reduce histological damage, inflammation, degeneration and necrosis in the glomeruli and renal tubules of the kidneys and increase the survival rate by up to 90% in a rat model of cecal ligation/puncture (CLP)-induced sepsis (96-98). Moreover, curcumin can suppress the levels of pro-inflammatory cytokines (IL-1β and IL-6) and increase the expression of the anti-inflammatory cytokine IL-10, thereby attenuating liver dysfunction in an *in vivo* model of CLP-induced and lipopolysaccharide (LPS)-induced endotoxemia model of sepsis (98,99). Furthermore, curcumin plays a crucial role in attenuating the expression of various proteins, including inhibitory κB kinase β, inhibitor κBα, phosphorylated NF-κB, TNF-α, IL-1β and IL-18, in a mouse model of LPS-induced acute liver failure and sepsis (66,97). It was also found to exert a cytoprotective effect on hepatic microvascular inflammatory responses in endotoxemia in an *in vivo* model by inhibiting Kupffer cell activation, reducing the adhesion of neutrophils, and controlling endothelial cell edema (66,100). Furthermore, in an *in vitro* model, some of the hydrogenated metabolites of curcumin, such as THC and octahydrocurcumin, demonstrated hepatoprotective effects against acetaminophen-induced hepatic injury (101). Another study reported the neuroprotective and neurotrophic effects of the curcumin analog, J147, both *in vivo* and *in vitro*. J147 improves memory and prevents depressive-like behavior by modulating neuroinflammation by suppressing the TLR4/NF-κB signaling pathway in the microglia of mice with sepsis. Pre-treatment with J147 significantly reduced the levels of IL-6, IL-1β, TNF-α and ionized calcium-binding adapter protein 1 in microglia (102). Additionally, curcumin was found to attenuate the activation of transcription factors, including NF-κB and activator protein 1, in an *in vivo* model, thereby alleviating hemorrhage (103). Curcumin can also suppress hypoxia-induced mRNA synthesis and the protein levels of hypoxia-inducible factor 1a, interfering with the secretion of vascular endothelial growth factor A in GH3 cells (104). Additionally, curcumin reduces the blood-brain barrier impairment, decreases the severity of edema and apoptosis, and minimizes mitochondrial damage in the brains of mice with sepsis (105).

L48H37 (1-ethyl-3,5-bis(3,4,5-trimethoxybenzylidene) piperidin-4-one) is a selective autophagy inhibitor and an analog of curcumin that can suppress LPS-induced inflammation by reducing TNF-α and IL-6 production in mouse macrophages, thereby improving survival and protecting lung injury in LPS-induced mice with sepsis (106).

Curcumin also mitigates cardiac dysfunction associated with sepsis. It can reduce the decline of cardiac contractility in sepsis, attenuate cardiac inflammation, and decrease the extent of structural damage to myocardial cells in a rat model of CLP surgery-induced sepsis. Curcumin intervention can significantly decrease the levels of the cardiac injury markers, troponin and malondialdehyde, while restoring superoxide dismutase activity in the plasma of rats with sepsis. It also induces contractility and decreases inflammation and structural damage in the heart. Apart from these effects, it decreases the extent of myocardial inflammation while attenuating structural injury to cardiomyocytes (107). It also alleviates LPS-induced cardiac dysfunction in an LPS-induced mouse model of sepsis by attenuating oxidative stress and inflammation by regulating the JNK/ERK signaling pathway (108).

Multiple organ dysfunction syndrome caused by sepsis involves sepsis-induced myocardial dysfunction as a crucial component. In the CLP-induced model of sepsis, treatment with free curcumin and nanocurcumin was found to preserve the structure of the mitochondria and cardiac myofibrils, decrease severe sepsis-induced cardiac lesions, and alter the components of the mTOR pathway, including the mechanistic target of rapamycin complex (mTORC)1, Raptor, mTORC2 and Rictor in the hearts of mice with sepsis (109). Beyond its antimicrobial properties, curcumin exhibits significant

multi-organ protective effects across various physiological systems. Current research has highlighted its efficacy in mitigating oxidative stress and inflammatory damage in the liver, kidneys, heart and lungs (66,110-125). A detailed summary of these organ-protective mechanisms and the specific experimental models used is provided in Table SIV.

5. Limitations of curcumin as a therapeutic agent

In addition to its numerous benefits, curcumin also has some drawbacks, such as chemical instability, poor water solubility, rapid clearance and poor absorption, which limit its clinical applications (38). While there is encouraging evidence highlighting the curative effects of curcumin in sepsis-induced complications, the poor bioavailability of curcumin is a key obstacle to the clinical evolution of this captivating chemical, notwithstanding the facts described above that suggest its rational and useful implementation in treating different complications. Curcumin is highly distributed in tissues and undergoes rapid metabolism. The hydrophobicity of curcumin is responsible for its poor bioavailability. Following oral intake, curcumin undergoes conjugation in the liver and intestinal walls and is metabolized into curcumin glucuronide and sulfates (38,126). Several options are currently being explored to enhance the bioavailability of curcumin. One such approach is the use of the bioavailability enhancer piperine from black pepper (38,126,127), an inhibitor of intestinal and hepatic glucuronidation, which increases the bioavailability of curcumin both in animals and humans when co-administered with curcumin. Initiatives such as the design of curcumin-phospholipid complexes, liposomal curcumin and curcumin nanoparticles are attempts that could improve the bioavailability of curcumin (38,128). In the event that the bioavailability of curcumin is successfully enhanced without compromising safety in humans, this naturally occurring polyphenol could be elevated to the forefront of therapeutic medicine to treat a range of illnesses, including malaria (128,129).

Translational challenges related to curcumin. The clinical use of curcumin, which is supported by robust preclinical evidence of its multifaceted properties, still faces some challenges in addition to its poor oral bioavailability. One of the primary challenges is the chemical instability of curcumin and its rapid degradation in the body (e.g., pH-dependent breakdown, sensitivity to light), which reduces its therapeutic availability and complicates formulation stability and storage, thereby limiting the reproducibility of *in vivo* results (130).

Another challenge is the complexity of the pharmacodynamics of curcumin and its biological activity, which has raised concerns about assay interference and nonspecific interactions and, consequently, has categorized this compound as a pan-assay interference compound. Such complexity may not only hinder mechanistic studies, but may also reduce confidence in distinguishing true target engagement, thereby undermining the translational validity of the research (131).

Furthermore, variability in preclinical and clinical trial design (variable dosing regimens, lack of standardized formulations, inconsistent endpoints, and limited statistical power, making direct comparison across studies difficult) has been a reason for mixed or inconclusive results pertaining to its efficacy. Moreover, the interaction of curcumin with drug-metabolizing enzymes and transporters (e.g., inhibition of cytochrome P450 and P-glycoprotein) adds to the problems of polypharmacy, as it may alter the pharmacokinetics of concurrently administered drugs, thereby complicating dose optimization and safety in patients taking multiple medications (132).

6. Conclusions and future perspectives

Sepsis is a severe, life-threatening condition resulting from an overwhelming host response to an infection. It continues to pose a challenge in critical care due to its high morbidity and mortality rates. Sepsis is associated with systemic inflammation, immune dysregulation, and diffuse organ malfunction and requires immediate and appropriate therapeutic interventions. Curcumin has been considered as a supplement in the management of sepsis owing to its anti-inflammatory, antioxidant and immune-modulating effects. As aforementioned, preclinical and early clinical studies have shown that curcumin influences the key pathways of the sepsis cascade by inhibiting proinflammatory cytokines, reducing oxidative stress, and modulating immune responses. Given its multifaceted effects, curcumin may reduce the severity of sepsis, improve outcomes, and reduce serious complications such as organ failure. These results, although encouraging, warrant further studies in terms of their activity and safety profiles to define their optimal role in the management of sepsis, especially in larger clinical trials. In-depth studies are therefore warranted to fully elucidate the therapeutic potential of curcumin in the management of sepsis. Optimization of the bioavailability and delivery methods for curcumin should be the primary focus, as poor absorption and rapid metabolism limit its clinical applications. Improvements in nanoparticle-based delivery systems or formulation advancements may enhance the potency of curcumin. Clinical trials of curcumin may be necessary to define its optimal dosage and duration of therapy and to identify possible interactions with standard sepsis therapies. Furthermore, the synergistic effect of curcumin can be increased when used concurrently with other therapeutic agents, thereby providing a more effective and multidimensional treatment approach. The therapeutic incorporation of curcumin in sepsis management will depend on a deeper understanding of its pharmacokinetics and mechanisms of action, ultimately enabling clinical translation and fostering innovative strategies for more effective treatment.

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Authors' contributions

GA conceptualized the study, searched the literature, and wrote the original draft of the manuscript. SD and AK prepared the tables and figures, and were involved in the literature search. JS, ER and PKV wrote a section of the manuscript and edited the manuscript. AJ conceptualized and supervised the study and edited the manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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