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REVIEW

Mechanisms and Clinical Application Prospects of Curcumin in the Treatment of Sepsis

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Abstract: Sepsis is a systemic inflammatory response syndrome caused by pathogenic microorganisms such as bacteria, fungi, viruses, and parasites invading the body. It is primarily characterized by an immune dysregulation in response to infection, leading to severe complications such as dysfunction of vital organs, shock, and disseminated intravascular coagulation (DIC), thereby threatening the patient's life. Additionally, approximately 3 million surviving patients suffer from cognitive impairment, severely affecting their quality of life. Curcumin, a monomer of traditional Chinese medicine, has extensive pharmacological activity. Numerous studies have shown that curcumin can counteract the inflammatory response in sepsis and protect against organ damage caused by sepsis, suggesting that curcumin may become a new direction for sepsis treatment. In this review, we summarize the therapeutic effects and detailed mechanisms of curcumin in the treatment of sepsis based on current research.

Keywords: sepsis, curcumin, inflammation, pyroptosis, oxidative stress

Introduction

Sepsis is a life-threatening disease caused by immune dysregulation in response to infection by pathogens such as bacteria and fungi, resulting in multiple organ dysfunction.[1] It is a severe global public health issue, with approximately 5.3 million deaths annually due to sepsis.[2] Most patients require admission to intensive care units (ICU) for comprehensive treatment. Sepsis treatment methods mainly include etiological treatment, supportive treatment, and immunomodulatory therapy. Etiological treatment primarily involves the early removal of infection sources and the use of effective antibiotics. Supportive treatment aims to maintain physiological functions, including early circulatory resuscitation, mechanical ventilation, and renal replacement therapy. Immunomodulatory therapy refers to treatments targeting the immune-inflammatory response. Additionally, sepsis treatment measures include early goal-directed therapy and fluid therapy, the use of vasopressors and hormones, organ function support, and the application of blood products, which impose significant economic burdens on families and society,[3,4] and negatively impact the patients' physical and psychological well-being.[5] Therefore, new treatment strategies and methods await research and proposals from scholars.

Curcumin is a natural small-molecule polyphenolic compound extracted from the rhizome of turmeric,[6] chemical formula: C21H20O6. Curcumin is widely used as a food additive and colorant, and has been qualified as a safe product by the United States Food and Drug Administration (FDA).[7] Numerous studies have shown that curcumin has a wide range of pharmacological effects, including anti-inflammatory,[8,9] antioxidant,[10,11] anticancer,[12,13] immunomodulatory,[14,15] and cardiovascular protective properties.[16,17] Extensive research indicates that curcumin can counteract the inflammatory response in sepsis and protect against organ damage caused by sepsis, suggesting that curcumin may become a new direction for sepsis treatment. This article reviews the therapeutic effects and mechanisms of action of curcumin in the treatment of sepsis (Figure 1 and Tables 1 and 2).

Anti-Inflammatory

The inflammatory response is the main foundation for the occurrence and development of sepsis (Figure 2). It leads to immune dysregulation in response to infection, resulting in multiple organ damage.[35] Therefore, early suppression of the inflammatory response and elimination of inflammatory mediators are key to treating sepsis.

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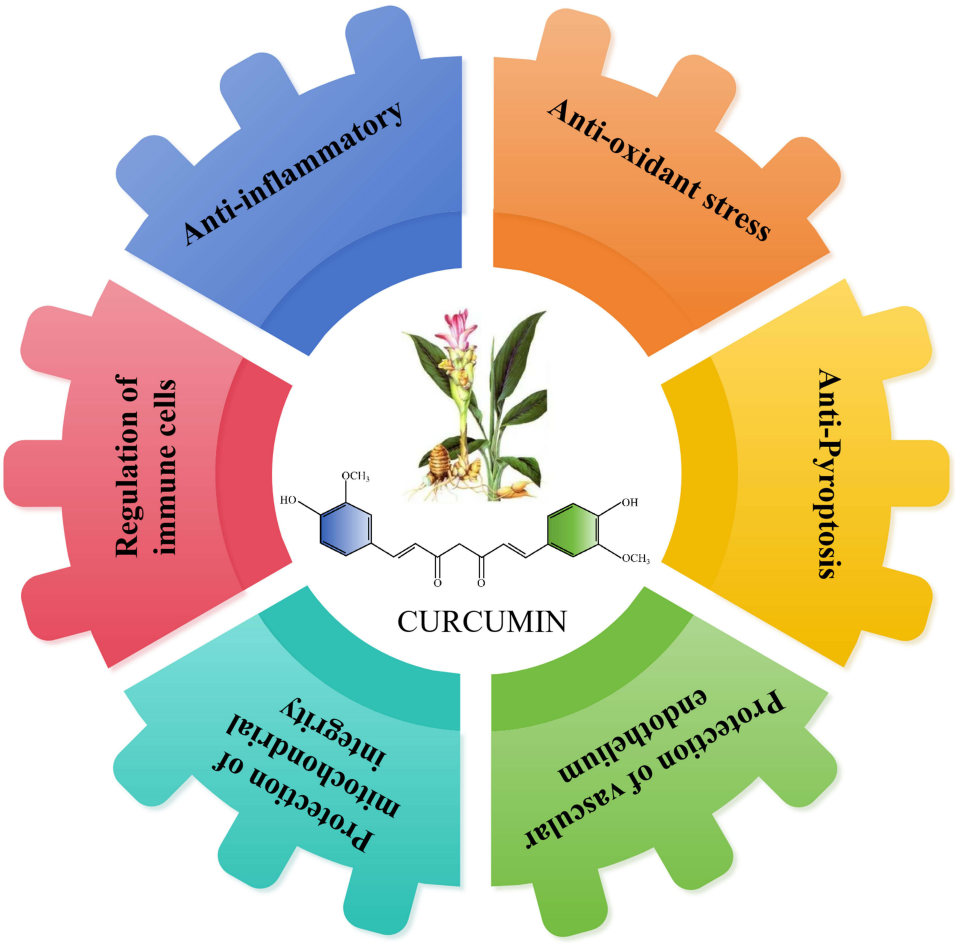

Figure 1 The Therapeutic Effects of Curcumin in Sepsis. The molecular structure of curcumin and its therapeutic effects on sepsis-induced injury, which mainly include Anti-inflammatory, Antioxidant stress, Anti-Pyroptosis, Protection of vascular endothelium, Protection of mitochondrial integrity, and Regulation of immune cells.

Extensive experiments have demonstrated that curcumin has a strong anti-inflammatory effect, which has been validated in various sepsis models.[36] However, due to the complexity of the inflammatory pathways, the detailed anti-inflammatory mechanisms of curcumin in sepsis are still being explored. NF-κB, an important regulatory protein in the inflammatory pathway, plays a crucial role in the inflammatory response. Continuous activation of NF-κB can promote

Table 1 The Protective Mechanism of Curcumin on Vital Organs

Organ	Model	Dosage and Duration of Treatment	Mechanism	References
Liver	Hepatic stellate cells(HSCs)	0, 0.5, 1, 2μM curcumin, 24h of treatment	Curcumin significantly alleviates LPS-induced liver injury in mice by inhibiting the PI3K/AKT and CYP2E1/Nrf2/ROS signaling pathways.	[18]
	C57BL/6 mice	20, 40, 80mg/Kg (i.p), 4weeks of treatment		
Liver	SD rats	100mg/kg (i.p), 2, 6, 12, 24h of treatment	Curcumin can inhibit inflammatory responses and reduce hepatocyte apoptosis.	[19]

(*Continued*)

Table 1 (Continued).

Organ	Model	Dosage and Duration of Treatment	Mechanism	References
Liver	SD rats	100mg/kg (p.o), 7 days of treatment	Curcumin exerts its regulatory effect on mitochondrial permeability transition by reducing intracellular Ca^{2+} concentration, promoting the expression of the anti-apoptotic gene Bcl-2, and inhibiting the activation of caspase-3 and the expression of the Bax gene.	[20]
Kidney	SD rats	100mg/kg (i.p), 12, 24h of treatment	Curcumin can alleviate acute kidney injury in rats by improving renal microcirculation perfusion and reducing inflammation.	[21]
Kidney	HK-2 cells	0, 5, 10, 20μmol/L curcumin Treat HK-2 cells, 12h of treatment	Curcumin can reduce the secretion of inflammatory cytokines, alleviate renal injury, and protect renal function by inhibiting the NF-κB and JAK2/STAT3 signaling pathways.	[22]
Kidney	C57BL/6 mice	50, 100, 200mg/kg (p.o), 7 days of treatment	Curcumin alleviates LPS-induced septic acute kidney injury in mice by inhibiting the lncRNA PVT1-mediated JNK/NF-κB pathway.	[23]
Lung	SD rats	50, 200mg/kg (i.p), 6, 12, 24h of treatment	Curcumin alleviates sepsis-induced acute lung injury by reducing inflammatory cell infiltration and inhibiting the production of reactive oxygen species (ROS) and proinflammatory cytokines.	[24]
Lung	SD rats	200mg/kg (i.p), 0, 6, 12, 24, 48h of treatment	Curcumin alleviates sepsis-induced acute lung injury by inhibiting the expression of the TGF-β1/SMAD3 pathway.	[25]
Heart	Wistar rats	100mg/kg (i.p), 12h of treatment	Curcumin alleviates myocardial damage in sepsis by downregulating TLR1 expression and inhibiting NF-κB phosphorylation in cells.	[26]
Heart	C57BL/6 mice	12.5mg/animal (s.c), 24, 120h of treatment	Curcumin alleviates sepsis-induced myocardial damage by modulating the mTOR pathway.	[27]
Heart	C57BL/6 mice	80mg/kg (i.p), 48h of treatment	Curcumin improves mitochondrial quality by activating SIRT1 to promote mitochondrial biosynthesis and inhibit mitochondrial fragmentation, thereby reducing oxidative stress in cardiomyocytes and mitigating sepsis-induced cardiac dysfunction.	[28]
Heart	C57BL/6 mice	100, 120mg/kg (i.p), 5 days of treatment	Curcumin alleviates sepsis-induced damage by modulating JNK/ERK signaling to reduce oxidative stress and inflammation.	[29]

Abbreviations: i.p., intraperitoneal; P.O., per os; s.c., subcutaneous; ROS, reactive oxygen species; LPS, lipopolysaccharide.

Table 2 Curcumin Modulates Various Cell Types Involved in Sepsis

Cell	Mechanism	References
Macrophage	Curcumin promotes macrophage polarization toward an anti-inflammatory phenotype and enhances the secretion of anti-inflammatory cytokines such as IL-10, thereby modulating the balance of the inflammatory response and reducing tissue damage.	[30]
	Curcumin inhibits excessive macrophage activation and reduces the release of pro-inflammatory cytokines such as TNF-α and IL-6.	[31]
T lymphocyte	Curcumin can modulate the activity of T lymphocytes by promoting their proliferation and differentiation, enhancing cellular immune function, and improving the body's ability to resist infections.	[32]

(*Continued*)

Table 2 (Continued).

Cell	Mechanism	References
Neutrophil	Curcumin attenuates the expression of TNF-α, IL-6, and IL-8, as well as the phosphorylation levels of p38 and JNK, thereby reducing neutrophil activation and aggregation, decreasing their adhesion to vascular endothelial cells, and ultimately alleviating the inflammatory response.	[33]
Endothelial cells	Curcumin can inhibit the expression of adhesion molecules on endothelial cells, reduce leukocyte adhesion to the endothelium, decrease vascular permeability, and alleviate tissue edema.	[34]

the massive synthesis and release of cytokines, while curcumin can inhibit NF-κB activation through multiple inflammatory pathways. Chen et al[26] showed that curcumin downregulates TLR1 expression in a dose-dependent manner, thereby inhibiting NF-κB phosphorylation and reducing sepsis-induced myocardial injury. This study also revealed through molecular docking analysis that curcumin interacts with TLR1 via hydrogen bonds, stably binding to inhibit TLR1's biological function. Huang et al[23] found that curcumin can inhibit PVT1 expression, thereby suppressing the activation of the JNK/NF-κB pathway and alleviating sepsis-induced kidney injury. Experiments have shown that curcumin can also inhibit NF-κB phosphorylation through the SIRT1 signaling pathway.[37] Furthermore, studies have found that curcumin significantly inhibits p-JAK2/STAT3 expression, reducing sepsis-induced kidney injury.[22] In sepsis models, curcumin can exert anti-inflammatory effects by downregulating the MAPK-ERK1/2 pathway.[38] Wu et al[39] confirmed the anti-inflammatory activity of curcumin in sepsis models, suggesting that its anti-inflammatory activity may be mediated by the ROS/JNK/p53 signaling pathway.

The anti-inflammatory effects of curcumin in sepsis models have been widely validated by scholars, and further detailed mechanisms are still under exploration.

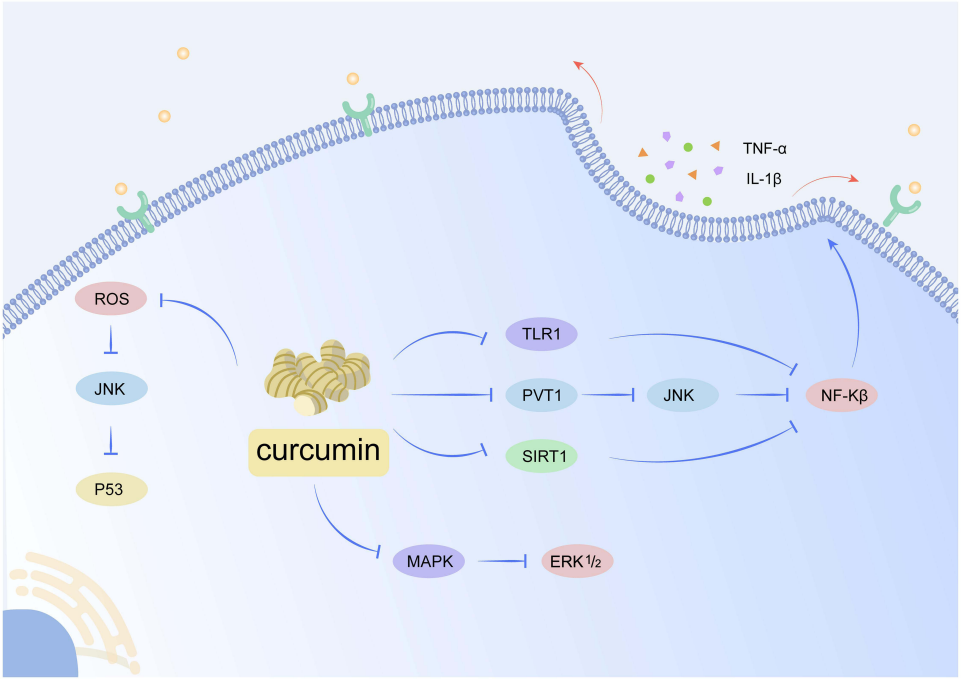

Figure 2 Anti-inflammatory Mechanisms of Curcumin.

Antioxidant Stress

Oxidative stress in sepsis is a complex process wherein the body, when subjected to harmful stimuli, produces excessive amounts of highly reactive molecules such as reactive oxygen species (ROS) and reactive nitrogen species (RNS).[40] This production exceeds the body's ability to eliminate oxidants, leading to an imbalance between oxidative and antioxidant systems. This imbalance causes cells to enter a state of oxidative stress, which may result in cellular damage.[41] Throughout the progression of sepsis, mitochondrial damage, inflammatory responses, and oxidative stress interact and influence each other, creating a vicious cycle.[42] Related toxins and inflammatory mediators can induce oxidative stress responses, which damage the function of endothelial cells throughout the body, increase vascular permeability, impair mitochondrial function, and ultimately lead to dysfunction of various organs and systems in sepsis patients.

Curcumin, as an effective antioxidant, can neutralize oxygen free radicals and enhance the activity of antioxidant enzymes in the body.[43–45] In sepsis models, curcumin promotes the expression of the transcription factor Nrf2 in a concentration-dependent manner,[18] which is an important mechanism for cells to counteract oxidative stress. Through the Nrf2-mediated expression of oxidative stress response element-dependent genes, curcumin can promote the balance of cellular redox reactions, thereby preventing or delaying cellular aging or death. Additionally, curcumin can inhibit the production of intracellular reactive oxygen species,[46] increase mitochondrial membrane potential stability,[42] inhibit lipid peroxidation reactions,[47,48] and increase glutathione levels,[43] demonstrating its capability as a potent scavenger of reactive oxygen species.

Oxidative stress is considered the fundamental mechanism of multi-organ and multi-system damage in sepsis. As an effective antioxidant, curcumin may offer new strategies for the treatment of sepsis.

Anti-Pyroptosis

Pyroptosis is an important process in the pathogenesis of sepsis.[49,50] Pyroptosis, also known as cell inflammatory necrosis, is a form of programmed cell death.[51,52] It leads to the release of a large number of proinflammatory cytokines such as IL-18 and IL-1β into the microenvironment through the activation of Caspase, which then enter the blood circulation and promote systemic inflammatory responses.[29,53,54]

The specific mechanisms by which curcumin affects pyroptosis in sepsis are not yet fully understood. However, according to research reports, curcumin may regulate pyroptosis through the following mechanisms: first, curcumin significantly inhibits the production of mature IL-1β in macrophages triggered by LPS and various NLRP3 inflammasome activators. Curcumin suppresses the activation of inflammasomes, reducing the production of pro-inflammatory factors and thereby alleviating the inflammatory response.[29] Second, curcumin may regulate intracellular signaling pathways, inhibiting the expression of pyroptosis-related proteins and reducing the upregulation of caspase-1, caspase-3, NLRP3, IL-1β, and GSDMD, thereby inhibiting pyroptosis and weakening the cascade reaction of pro-inflammatory cytokines.[18] Additionally, curcumin may also mitigate oxidative stress-induced cell damage through its antioxidant effects, further inhibiting pyroptosis.[18,29]

Pyroptosis plays an important role in the pathogenesis of sepsis. Curcumin, as a natural compound with multiple biological activities, may exert therapeutic effects by regulating the process of pyroptosis. In the future, further in-depth research on the specific mechanisms of curcumin in sepsis-induced pyroptosis can provide new effective strategies for the treatment of sepsis and other infectious diseases.

Protection of Vascular Endothelium

Sepsis, as a systemic inflammatory response syndrome caused by infection, often leads to impaired vascular endothelial function.[55,56] The vascular endothelium plays a crucial role in maintaining vascular permeability, blood flow, and regulating the inflammatory response.[57] Therefore, protecting vascular endothelial function is of great importance in the treatment of sepsis.

As a natural active compound, curcumin has garnered extensive attention in recent years for its protective effects on vascular endothelium in sepsis. Studies have shown that curcumin can significantly improve vascular endothelial function in sepsis patients (Figure 3). Curcumin can reduce the permeability of endothelial cells and decrease the exudation of inflammatory mediators, thereby mitigating inflammation-induced damage to the vascular endothelium.[58] Additionally, curcumin can inhibit the adhesion of leukocytes to endothelial cells, reduce leukocyte infiltration into the vasculature, and lower the inflammatory response of the vascular walls.[34]

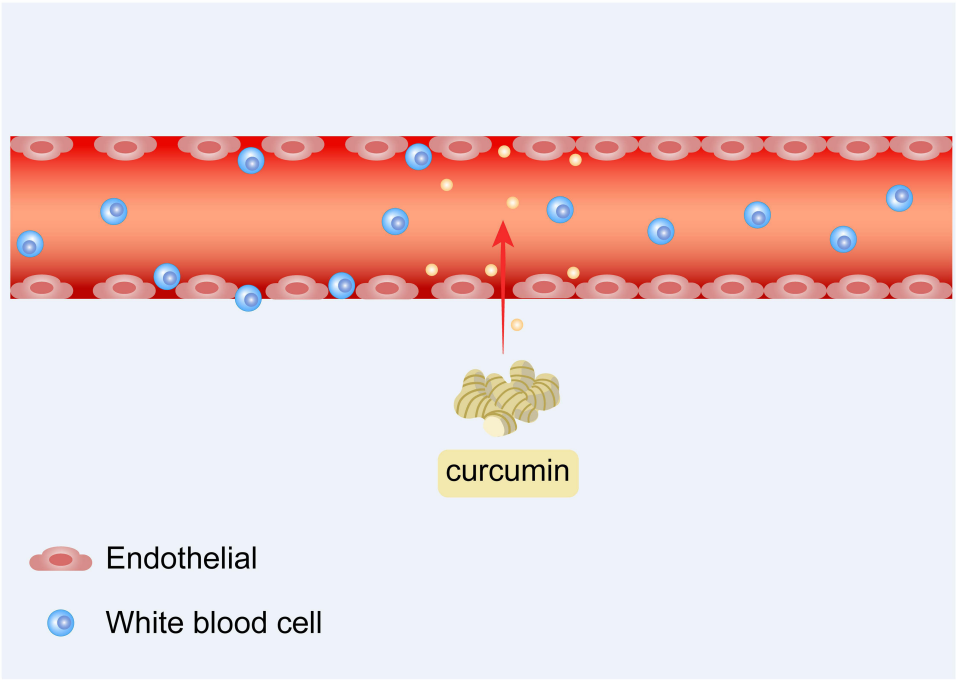

Figure 3 Curcumin Protects Vascular Endothelial Function.

Clinically, sepsis patients often exhibit vascular endothelial dysfunction, characterized by increased vascular permeability, coagulation system disorders, and microcirculation disturbances.[55] Therefore, the application of curcumin and other drugs with endothelial protective effects is expected to improve vascular endothelial function in sepsis patients and enhance treatment outcomes.

Protection of Mitochondrial Integrity

Mitochondria, being the primary site of intracellular energy production, are crucial for normal cellular physiological activities. When mitochondrial function is impaired, it can lead to cellular dysfunction and subsequently various diseases.[59,60] In the context of sepsis, the mitochondrial electron transport chain complexes experience dysfunction, and these malfunctioning mitochondria further promote inflammation.[61,62] Additionally, dysfunctional mitochondria increase oxidative stress, which in turn damages the mitochondrial membrane, increases mitochondrial permeability, and leads to mitochondrial DNA leaking into the circulation. This perpetuates systemic inflammation, damages cells, and can result in cell death, ultimately affecting organ function.[63,64]

Research has found that during sepsis treatment, curcumin can inhibit mitochondrial membrane permeability transition, reduce mitochondrial swelling, and improve cell viability. This mechanism may be related to the reduction of intracellular calcium ion concentration, promotion of anti-apoptotic Bcl-2 gene expression, inhibition of caspase-3 activation, and Bax gene expression.[65] Furthermore, curcumin can enhance mitochondrial quality and regulate mitochondrial function by reducing the translocation of dynamin-related protein 1 from the cytoplasm to mitochondria, decreasing excessive mitochondrial fission, and restoring mitochondrial quality, ultimately normalizing mitochondrial morphology and function.[20] At the same time, curcumin can target macrophage immunometabolism by inhibiting mitochondrial STAT3 activity, which might be a significant breakthrough in treating sepsis.[28]

Mitochondria are the "powerhouses" of the cell, responsible for converting nutrients into usable energy. In sepsis, mitochondrial energy metabolism can be disrupted, leading to insufficient cellular energy supply. Curcumin might alleviate the impact of sepsis on cellular energy metabolism by improving mitochondrial function integrity and influencing mitochondrial biogenesis, thereby enhancing organ function.

Regulation of Immune Cells

The quantity and activity of immune cells are crucial for maintaining overall health, as dysfunction or insufficient numbers of immune cells can lead to immune system imbalance. The immunoregulation of sepsis is a complex and multifaceted process involving various immune cells. Effective regulation of these immune cells can significantly reduce inflammatory responses and tissue damage.

Curcumin can modulate the polarization state of macrophages, promoting their polarization towards an anti-inflammatory type and reducing the number and function of pro-inflammatory macrophages.[30] In sepsis mice treated with curcumin, the suppressive function of Treg cells is enhanced, plasma IL-10 levels increase, and the secretion of plasma TNF-α and IL-6 is significantly inhibited, alleviating acute organ dysfunction caused by an overactive immune response.[66] Curcumin reduces the expression of TNF-α, IL-6, and IL-8 in LPS-stimulated neutrophils and the phosphorylation levels of p38 and JNK, but it does not affect the phosphorylation level of ERK1/2. Additionally, curcumin can restore delayed apoptosis in LPS-stimulated neutrophils.[33]

Changes in immune function play a critical role in the occurrence and development of sepsis.[67] By comprehensively monitoring the immune function status of patients and dynamically adjusting immune cell functions, it is expected to reduce the mortality rate of sepsis and improve patient prognosis.

Curcumin in Clinical Research on Sepsis

At present, the clinical research on curcumin in the treatment of sepsis is still in its early stages. A few small-scale human studies have shown that, compared with placebo, curcumin significantly reduces levels of leukocytes, neutrophils, erythrocyte sedimentation rate (ESR), and interleukin-8 (IL-8).[68] In addition, curcumin has been found to significantly lower the Sequential Organ Failure Assessment (SOFA) score and the duration of mechanical ventilation,[69] suggesting its potential therapeutic effect in sepsis. Moreover, oral administration of curcumin at a dose of 160 mg twice daily for 10 days did not cause any adverse effects, indicating good safety.[68,69] However, these findings are limited to small-sample studies, and large-scale, multicenter, randomized controlled trials are still lacking. Furthermore, data on safety remain insufficient, and effective curcumin formulations are yet to be developed. Therefore, well-designed multicenter, double-blind, randomized controlled clinical trials are needed in the future to clearly determine the safety, efficacy, optimal dosage, and administration regimen of curcumin in patients with sepsis.

Summary

Sepsis is a systemic inflammatory response syndrome caused by infection, with a complex pathogenesis involving various cytokines and chemical mediators. During sepsis, endotoxins and other stimuli activate inflammatory cells, producing large amounts of inflammatory mediators and lipid metabolites. This promotes the recruitment and activation of inflammatory response cells in target organs, further inducing the production of cytokines, chemokines, reactive oxygen species, and proteases. This cascade reaction leads to tissue damage and organ dysfunction.

In recent years, research on the therapeutic potential of curcumin in sepsis has been steadily increasing. As a natural compound with multiple biological properties, curcumin has demonstrated promising potential in the treatment of sepsis. Curcumin can inhibit the cytokine storm and alleviate sepsis-induced organ damage through various mechanisms, including anti-inflammatory and antioxidant effects, inhibition of inflammatory cell death, protection of vascular endothelial cells, maintenance of mitochondrial function, and modulation of immune cells. However, discrepancies in preclinical studies have been observed due to differences in sepsis models, curcumin dosage, routes of administration, as well as species and strains of experimental animals. These variations have led to inconsistent experimental outcomes.[70] In addition, the low oral bioavailability of curcumin, the lack of standardized dosing regimens, and the small sample sizes of clinical trials have resulted in insufficient clinical evidence to fully support its efficacy in sepsis treatment.[71] Therefore, the specific mechanisms of curcumin in sepsis remain to be further investigated and elucidated by researchers.

In the future, with a deeper understanding of curcumin's mechanisms of action and the continuous advancement of clinical research, curcumin is expected to become an important drug in the treatment of sepsis.

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The authors have declared no conflicts of interest in this work.

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