Received: 1 March 2019 | Revised: 28 May 2019 | Accepted: 12 July 2019

DOI: 10.1002/ptr.6467

REVIEW

WILEY

Therapeutic effects of curcumin on sepsis and mechanisms of action: A systematic review of preclinical studies

Arash Karimi[1,2] | Ramin Ghodsi[1,2] | Fateme Kooshki[1,2] | Mozhdeh Karimi[3] | Vahid Asghariazar[1,4] | Ali Tarighat-Esfanjani[2]

[1] Student Research Committee, Faculty of Nutrition and Food Sciences, Tabriz University of Medical Sciences, Tabriz, Iran

[2] Nutrition Research Center, Faculty of Nutrition and Food Sciences, Tabriz University of Medical Sciences, Tabriz, Iran

[3] Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

[4] Department of Medical Genetics, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

Correspondence
Ali Tarighat-Esfanjani, Department of Clinical Nutrition, Faculty of Nutrition and Food Sciences, Tabriz University of Medical Sciences, PO Box 14711, Attar Nishabouri St., Tabriz 5166614711, Iran.
Email: tarighata@tbzmed.ac.ir; tarighat45@gmail.com

Sepsis is a complex disease that begins with an infectious disorder and causes excessive immune responses. Curcumin is considered as an active component of turmeric that can improve the condition in sepsis due to its anti-inflammatory and antioxidant properties. PubMed, Embase, Google Scholar, Web of Science, and Scopus databases were searched. Searching was not limited to a specific publication period. Only English-language original articles, which had examined the effect of curcumin on sepsis, were included. At first, 1,098 articles were totally found, and 209 articles were selected after excluding duplicated data; 46 articles were remained due to the curcumin effects on sepsis. These included 23 in vitro studies and 23 animal studies. Our results showed that curcumin and various analogs of curcumin can have an inhibitory effect on sepsis-induced complications. Curcumin has the ability to inhibit the inflammatory, oxidative coagulation factors, and regulation of immune responses in sepsis. Despite the promising evidence of the therapeutic effects of curcumin on the sepsis complication, further studies seem necessary to investigate its effect and possible mechanisms of action in human studies.

KEYWORDS

curcumin, immune response, inflammatory response, oxidative stress, sepsis

1 | INTRODUCTION

Sepsis is one of the most important medical problems associated with severe complications and increased mortality in critically ill patient. Sepsis is defined as a life-threatening condition caused by an impairment of host immune response (both innate and acquired) to infection (Al-Hasan & Justo, 2018; Moon et al., 2018). This dysregulation of the immune response during sepsis results in an overreaction of the immune system to eliminate pathogens, which can be accompanied by tissue damage, organ failure, and death (Al-Hasan & Justo, 2018). Infection can be attributed to many pathogens (fungi, virus, and parasite), but it is usually due to gram-positive or gram-negative bacteria (Saeedi, Halabian, & Fooladi, 2019). Sepsis is an important reason for morbidity and mortality in hospital. According to the global statistics, there are 31.5 million sepsis and 19.4 million severe sepsis cases, with potentially 5.3 million deaths annually worldwide (Yin, Tao, Wei, Zhang, & Ma, 2016). Innate immune system and hemostasis process (coagulation factors and platelets) are a major contributor of sepsis pathogenesis (McDonald et al., 2017). When the body is exposed to pathogen, the first line of defense is innate immune response (Jin, Batra, & Jeyaseelan, 2017; Taner et al., 2014). Innate immune includes monocyte–macrophage cells (Dominguez-Andres & Netea, 2019) and leukocyte and dendritic cells (DCs; Lee, Park, Van Kaer, Hong, & Hong, 2018) that play an important role against pathogens (Chen, Peng, Zhou, & Zhuang, 2017). Because the phagocytic cells are encountered with pathogens, dysregulated immune response (Bangsgaard, Hjorth, Olufsen, Mehlsen, & Ottesen, 2017) cause to the release of products such as chemokines, cytokine, lipid mediators, nitric oxide (NO), and oxygen radicals (Arango Duque & Descoteaux, 2014; Markose, Kirkland, Ramachandran, & Henderson, 2018). On the other hand, the

activation of neutrophils increases the bacteria clearance and causes inflammation and tissue damage (Park et al., 2017) through respiratory burst (Bae et al., 2016), myeloperoxidases (MPOs; Schrijver, Kemperman, Roest, Kesecioglu, & de Lange, 2017), proteases, and releasing several cytokine mediators (Bosmann & Ward, 2013; Park et al., 2017). Neutrophils also release neutrophil extracellular traps that lead to increase vascular inflammation and coagulation (Martinod et al., 2013; McDonald et al., 2017).

Oxidative stress is the serious cause of organ disability in critically ill patients (Ghashut et al., 2017). Reducing the antioxidant capacity (Rogobete et al., 2017) in these patients due to inefficient oxidative phosphorylation (Lorente et al., 2018) leads to an increase in free radicals (Oliveira, Pontes-de-Carvalho, Couto, & Noronha-Dutra, 2017), which is actually a possible mechanism for damage caused by the sepsis (Kumar et al., 2018). Some natural compounds and herbal derivatives have anti-inflammatory and antioxidant effects that can improve sepsis symptoms, such as zinc (Ganatra et al., 2017), magnesium (Esen et al., 2004), Q10 (Abitagaoglu et al., 2015), and curcumin (Chen, Lu, et al., 2018). Turmeric is a medicinal plant that belongs to the ginger species (Zingiberaceae), distributed throughout subtropical and tropical regions of the world, and broadly growing in Asian countries such as India and China (Yadav, Yadav, Khar, Mujeeb, & Akhtar, 2013). This plant contains mainly fats (5.1%), protein (6.3%), carbohydrates (69.4%), minerals (3.5%), and moisture content (Kocaadam & Şanlier, 2017) and also includes three curcuminoids (curcumin, 60% up to 70%; demethoxycurcumin, 20% up to 27%; and bisdemethoxycurcumin, 10% up to 15%; Hajialilo et al., 2019; Imran et al., 2018). Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) or diferuloylmethane is an important bioactive constituent and hydrophobic polyphenol that isolated from the rhizome of the turmeric plant (*Curcuma longa*; Fereydouni et al., 2019; Ghazimoradi et al., 2017). Curcumin is widely used in medicine due to medicinal properties, cost-effectiveness, and simple extraction from a turmeric plant that grows in different regions in the world. Recent evidences have shown that curcumin possesses multiple biological activities and pharmacological properties including anti-inflammation (Dhir, 2018), antioxidation (Khanji et al., 2018), anticancer and antiproliferation (Barati, Momtazi-Borojeni, Majeed, & Sahebkar, 2019; Pan, Chen, Baek, & Zhong, 2018), antimicrobial (Marini et al., 2018), and free radical scavenger (Vaughn et al., 2017; Zhong et al., 2016). Some studies have suggested protective effects of curcumin against numerous diseases such as metabolic syndrome (due to improving insulin sensitivity, suppressing adipogenesis, reducing elevated blood pressure and decrease inflammation) (Ghazimoradi et al., 2017), inflammatory bowel disease (inhibit nuclear factor kappa-light-chain-enhancer of activated B [NF-κB], 5-lipoxygenase, and Toll-like receptor 4 (TLR-4)) (Singla et al., 2014), rheumatoid arthritis (due to regulating immune response and decrease the expression of cytokines and chemokine, (such as monocyte chemoattractant protein1 (MCP-1)) (Khayyal et al., 2018), cardiovascular disease (due to adjustment of the enzyme related to the metabolism of lipoproteins, decrease inflammation, and oxidative stress) (Li et al., 2019), and sepsis (due to modulate immune responses) (Chen, Lu, et al., 2018). Furthermore, several studies have shown the role of curcumin in regulating immune response to infection, through targeting multiple molecular pathways, including NF-κB cell and activator protein 1 (AP-1) (Tabrizi et al., 2019) and activation of nuclear factor erythroid 2-related factor 2 (Nrf-2), which are respectively led to inhibiting inflammation and oxidative factor (Xie et al., 2017). However, several researches have been performed on the therapeutic effects of curcumin in sepsis, but there is not any systematic review to show the effect of curcumin in sepsis; thus, the study objective was to conduct a systematic review of both animal and in vitro studies, to describe the effect of curcumin supplementation on sepsis and possible mechanisms.

2 | METHODS

2.1 | Study protocol

This systematic review was performed based on the Preferred Reporting Items Systematic Meta-Analyses Checklist (Moher, Liberati, Tetzlaff, & Altman, 2009), and all published and unpublished English-language studies were related to curcumin effects on sepsis. All the relevant articles were initially transferred to Endnote software, and duplicated references were separated.

2.2 | Selection criteria

2.2.1 | Inclusion criteria

Population, Intervention, Comparison, and Outcome approach was used for the inclusion criteria of this systematic review. Population, Intervention, Comparison, and Outcome questions included the following: (a) in vitro, in vivo, or human were as population, (b) the intervention was curcumin supplementation or curcumin analogs and its dosage, (c) it was compared without treatment with curcumin or curcumin analogs or other drugs, and (d) the result was the effect of curcumin on inflammation, oxidative stress, and innate immune response.

2.2.2 | Exclusion criteria

Studies were being excluded if (a) the intervention was not curcumin or the combination of curcumin with other compounds or curcumin was used as a treatment for other conditions, (b) the articles were from reviews, books, editorials, reports, comments, or presentations, and (c) a language other than English was used in abstracts.

2.3 | Search strategy

An electronic search of PubMed, Scopus, Google Scholar (in title), Embase, and Web of Science databases has been conducted by two separate investigators (A. K. and R. G.) by the end of April 2019 with no time limit. The key words were as follows: "curcumin and sepsis," "curcumin and oxidative stress and sepsis" and "curcumin and

inflammatory response and sepsis" and "curcumin and immune response and sepsis," "curcumin and septic shock," "curcumin and oxidative stress and septic shock" and "curcumin and inflammatory response and septic shock" and "curcumin and immune response and septic shock," and "curcumin and endotoxin shock," "curcumin and oxidative stress and endotoxin shock" and "curcumin and inflammatory response and endotoxin shock" and "curcumin and immune response and endotoxin shock" in title or abstract. In addition, the search strategy used for PubMed was as MeSH terms. The full text of the articles, including the correct range for this review, was evaluated for further investigation and independent review of the articles (summaries, results, figures, and tables) for data extraction.

2.4 | Study selection

A. K. and R. G. independently reviewed titles and abstracts of all sources identified in the electronic database, and selected articles were in accordance with the inclusion criteria. The same authors (A. K. and R. G.) independently analyzed the full text of all selected articles in last phase and excluded the studies that did not meet the inclusion criteria. A third author (F. K.) was consulted if the contradiction between the two primary reviewers was not solved by consensus.

3 | RESULTS

A total of 1,098 articles were initially identified from databases (66 from PubMed, 288 from Scopus, 553 from Embase, 23 from Google Scholars, and 168 from Web of Science). After removing duplicated studies, 209 articles remained for analysis of title and abstract. After an initial screening, 82 articles, 58 reviews, 5 comments, 4 notes, 4 editorials, and 11 conference abstracts were excluded due to the type of studies. Finally, 128 studies were excluded after critical analysis of title, abstracts, and full texts. The remaining 46 articles were included in this overview (Figure 1).

3.1 | Characteristics of the included studies

Characteristics of the included studies for this systematic review have been summarized in Table 1. There was no human study in the field of curcumin effects on sepsis; therefore, the remaining articles were categorized into two groups: in vitro (n = 23) and animal (n = 23) studies.

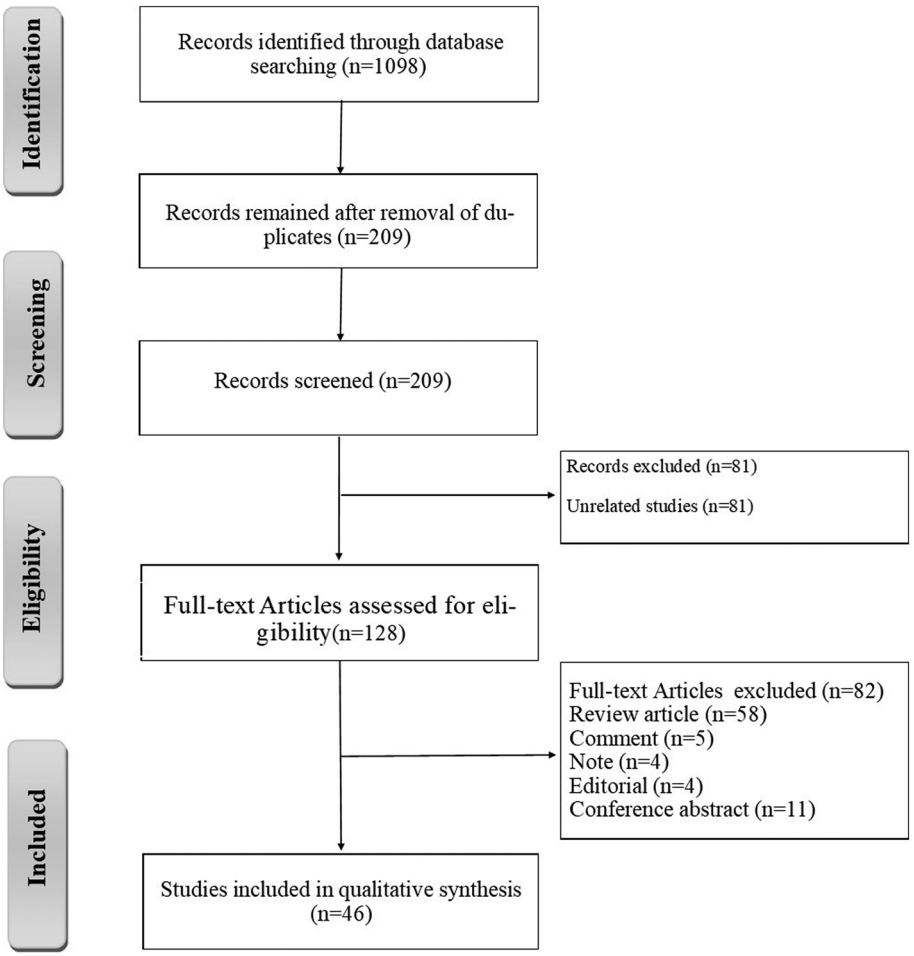

FIGURE 1 Flowchart of study selection

TABLE 1 Studies of the relation between curcumin and sepsis

Reference	Study design	Number and type of subjects	Dosage and type of administration	Assay	Study duration	Results	Main conclusion
Hu et al. (2018)	In vitro	RAW 264.7 macrophages	1 to 10 μM/ml curcumin analog	ELISA	Single dose 2 hr before treatment by LPS	Analogs of curcumin showed inhibition of the TNF-α and IL-6 by dosage.	The β-ionone-derived curcumin analogs can act as anti-inflammatory therapeutic agents.
Zhang et al. (2018)	In vivo and in vitro	Human umbilical vein endothelial cells, RAW 264.7, mice (*N* = 32) and rats (*N* = 14)	1- to 10-μM curcumin analog for cells and 10 mg/kg for mice, i.v., 20 mg/kg/day for rats, orally	ELISA, Western blot, real-time quantitative PCR, EMSA, NF-κB-luciferase reporter assay, BALF analysis, myeloperoxidase activity	Single dose	Curcumin analogs identified as potential MD2 inhibitors and showed anti-inflammatory activity and protected against LPS-induced acute lung injury and sepsis.	Curcumin analogs can be used as a therapeutic drugs in inflammatory diseases.
Wu et al. (2018)	In vitro	Mouse macrophages RAW 264.7	10-, 20-, or 40-μM curcumin analog	ELISA, cell viability assay, Western blotting	Single dose	Pretreatment of curcumin analog (FM0807) inhibited the inflammatory factors, the production of ROS and apoptosis. In addition, the activation of the inflammation signaling pathway was inhibited by FM0807.	FM0807 has anti-inflammatory activity in vitro, which proposes a potential clinical used in sepsis.
W. Liu et al. (2018)	In vivo and in vitro	Human THP-1 and mice (*N* = 30)	1, 3, or 10 mg/kg curcumin analog for mice 0.25 to 4 μM for cell	ELISA, immunofluorescence histochemistry and cytochemistry, Western blot, biotin pull-down assay, cellular thermal shift assay	Single dose	AI-44 inhibited LPS-induced endotoxemia via suppressing NLRP3 inflammasome activation that decreased the activation of caspase-1.	I-44 as a promising candidate compound for the treatment of sepsis or other NLRP3 inflammasome-driven diseases.
Ahn et al. (2017)	In vivo and in vitro	RAW 264.7 macrophages and mice (*N* = 6)	50 mg/kg CLEN for mice and 5-μM CLEN for cell	MTT assay, Western blot, real-time PCR	Single dose	*Curcuma longa* suppressing NO signaling and decrease the release of the proinflammatory cytokine HMGB1	*C. longa* can prevent HMGB1 production, and/or activity may help the treatment of endotoxemia.
Ma et al. (2017)	In vivo and in vitro	RAW 264.7 macrophages and mice (*N* = 6)	5, 10, and 15 μM, 2 hr for cells and 20 mg/kg for mice	qPCR, Western blot, automatic biochemical analyzer, flow cytometric analysis	3 days for mice	Curcumin efficiently inhibited LPS-induced cytokines (TNF-α, IL-6) and microRNA-155 expression in cells and mice. Curcumin reduced AST, blood urea nitrogen, and levels and the proportion of macrophages in spleen.	Curcumin has the ability to suppress LPS-induced inflammatory response.
Zhong et al. (2016)	In vivo and in vitro	Hepatic stellate cells and mice (*N* = 30)	20,40, and 80 mg/kg, orally, for mice and 0.5 to 2 μM for cell	Immunofluorescence, electron microscopy, biochemical assay, ROS measurement, ELISA,	4 weeks for mice and 24 hr for cell	Curcumin decrease serum cytokines, liver NO, and accelerated liver antioxidant enzymes. Curcumin decrease	Curcumin in clinical practice may be used for treatment of inflammatory conditions such as sepsis.

(Continues)

TABLE 1 (Continued)

Reference	Study design	Number and type of subjects	Dosage and type of administration	Assay	Study duration	Results	Main conclusion
				histological analysis, RT-PCR, Western blot		inflammatory signaling pathways in the livers of LPS-induced rats.	
Rana et al. (2016)	In vivo and in vitro	THP-1 cells, HL-60 cells, MCF-7, and MDA-MB-231 and mice (*N* = 18)	30, 100, and 300 mg/kg and 1 or 10 μM/m for THP-1 cells and 1-100 μM/m for other cells	ELISA, real-time RT-PCR, Western blot, coimmunoprecipitation	10 day and 14 hr followed by LPS stimulation for cells	*C. longa* L. extract in both in vitro and in vivo molecular inhibition of the IRAK pathway and regulated inflammation and cytotoxicity	Curcumin can be effective in treating sepsis due to the regulation of immune response.
Wang, Shan, et al. (2015)	In vitro	Human PBMCs	1- to 10-μM curcumin analog	Protein expression, ELISA, Western blot, coimmunoprecipitation assay, LPS binding assay, fluorescence measurements, surface plasmon resonance analysis, RT-qPCR, NF-κB p-65 translocation analysis	2 hr followed by incubation with LPS	Curcumin analog (L48H37) inhibited the contact and signaling transduction of LPS-TLR4/MD2 and suppressed mitogen-activated protein kinase phosphorylation and NF-κB activation.	Curcumin as a new MD2-specific inhibitor is a candidate in the treatment of sepsis.
Zhang et al. (2015)	In vivo and in vitro	Human pulmonary epithelial cells and mice (*N* = 12)	20 mg/kg/day for mice and 1-, 5-, and 10-μM curcumin analog for cells	ELISA, UV assay and Western blot, histological analysis, pulmonary histopathology analysis, immunohistochemistry analysis	24 hr for cell and 7 days for mice	Curcumin analog significantly reduces LPS-induced pulmonary edema, inflammatory cell infiltration, inflammatory cytokines in the serum and BALF, expression of cytokine mRNA inflammation, and ERK phosphorylation.	Curcumin analog (c26) has remarkable protective effects on LPS-induced ALI in septic mice.
Gong et al. (2015)	In vivo and in vitro	The murine macrophage cell line J774A and mice (*N* = 8)	2 mg for mice and 50 μM for cell	ELISA, Western blot, fluorospectrophotometry, apoptosis assay, ICP-OES assay, ROS measurement	Single dose 6 hr after i.p. injection of LPS	Curcumin dramatically prevented the production of mature IL-1 and cleaved caspase-1 in LPS-primed macrophages. Also, it inhibited K+ efflux, the common trigger for NLRP3 inflammasome activation, lysosomes disruption, and intracellular ROS formation.	Curcumin inhibits the activation of NLRP3 inflammasome and could be therapeutic potential for septic shock.
Zhao et al. (2015)	In vivo and in vitro	Mouse primary, peritoneal macrophage, and mice (*N* = 10)	10 mg/kg, intravenously, for mice and 2.5 to 20 μg/ml for cell	ELISA, Western blot	Single dose	Curcumin analogs demonstrated potent preventive and therapeutic effects on LPS-induced sepsis.	Analog of curcumin may be developed as a potential mediator for treatment of sepsis.
				ELISA, real-time PCR			

(Continues)

TABLE 1 (Continued)

Reference	Study design	Number and type of subjects	Dosage and type of administration	Assay	Study duration	Results	Main conclusion
Shukla, Verma, Dewangan, Rath, and Mishra (2015)	In vitro and in vivo	J774 macrophages, HepG2, and mice (*N* = 36)	Different ratios of Chi-CUR-NC-4b (0 to 3 mg/L) for cell and 10 and 20 mg/kg for mice		Single dose (0.25, 0.5, 1, 2, 4, 8, and 12 hr postdosing)	Curcumin upregulation of Nrf-2 as well as via downregulation of NF-κB leading to reduced cytokine secretion in the murine model of sepsis	Curcumin could be one of the appropriate methods of intervention for the treatment of sepsis and associated hyper-inflammatory disorders
Shukla, Dwivedi, Gupta, and Mishra (2014)	In vitro and in vivo	RAW 264.7 macrophages, HepG2 and embryonic kidney cell line HEK-2936, and rats (*N* = 6)	10 mg/kg, intravenously, and 1.5 and 3 mg/L for cells	ELISA, MPO activity, lipid peroxides and carbonylated proteins analysis, and histopathological analysis	Single dose at different time	Nanoemulsion of curcumin decreased LPS-induced lung and liver injury by decreasing less neutrophil migration, reduce oxidative stress and TNF-α levels.	Curcumin could reduce oxidative damage in tissues.
Zhang et al. (2014)	In vitro	Mouse macrophages	1- to 5-μM curcumin analog	ELISA, Western blot, methyl thiazolyl tetrazolium assay	Single dose for 2 hr after LPS	Analogs of curcumin effectively inhibited the LPS-induced production of TNF-α and IL-6, and it could be an antisepsis compound.	Analogs of curcumin have therapeutic properties in inflammatory diseases.
Wu et al. (2013)	In vivo and in vitro	RAW 264.7 and mice (*N* = 10)	1 to 10 μM for cell and 20 mg/kg, i.v., for animals	ELISA, Western blot	7 days for mice	Some analogs of curcumin dose dependently inhibited LPS-induced NF-κB and ERK activation.	Analogs of curcumin are anti-inflammatory agents.
Yuan et al. (2012)	In vivo and in vitro	Myeloid cells and mice (*N* = 3 to 5)	200 mg/kg, i.p., for mice and 10 μM/L for cells	Myeloperoxidase assay, histological analysis, ELISA, q-RT PCR, Western blot, ChIP assay, immunofluorescence and flow cytometry, reactive oxygen species production assays	Single dose	Curcumin inhibits the binding of p65 to TREM-1 promoter in response to LPS. Curcumin suppressed p300 activity in the TREM-1 promoter region leading to hypoacetylation of histone 3 and 4 in the lysine residues.	Curcumin inhibits inflammatory conditions such as septic lung injury.
Sun et al. (2010)	In vitro and in vivo	RAW 264.7 and mice (*N* = 10)	100 mg/kg of b.w. for mice and 20 μmol for cell	Western blot, ELISA, apoptosis assays	Single dose 0.5, 1, 2, 4, 8, and 12 hr for mice and 1 hr for cells	Exosomal curcumin can inhibit IL-6 and TNF-α secretion in LPS-stimulated mice; also, it decreased the CD11b+Gr-1+ cell population in the lungs	Curcumin is an effective treatment for many inflammatory diseases
Poylin et al. (2008)	In vitro and in vivo	Muscles cells and rats (*N* = 4 to 16)	600 mg/kg, intraperitoneally, for rats and 100 μM for muscles cells	Real-time PCR, proteolytic activity, calpain and cathepsin L activity, Western blot, EZ-Detect	1 hr before and 8 and 15 hr after sham operation or CLP and 16 hr after CLP or sham for cells	Curcumin reduced calpain, proteasome, and cathepsin L-dependent protein breakdown rates and nuclear NF-KB/p65 expression and activity and phosphorylated (activated) p38	Curcumin can reduce sepsis-induced changes.

(Continues)

TABLE 1 (Continued)

Reference	Study design	Number and type of subjects	Dosage and type of administration	Assay	Study duration	Results	Main conclusion
						in muscle. Curcumin upregulated expression of the ubiquitin ligases atrogin-1, and MuRFl was not influenced by curcumin	
Olszanecki, Gebska, and Korbut (2007)	In vitro and in vivo	EA.hy926 and mice (*N* = 4)	30 mg/kg, i.p., and 10 and 30 μM for cells	Assay of myeloperoxidase activity	2 hr prior to LPS injection. 15 min/day for cell	Curcumin in both in vitro and in vivo induced heme oxygenase 1 and inhibition ICAM-1 expression, and also, curcumin significantly inhibited pulmonary sequestration of leucocytes in response to lipopolysaccharide.	Curcumin and its derivatives may be a useful treatment for sepsis-induced lung injury.
Gradišar, Keber, Pristovšek, and Jerala (2007)	In vivo	Human embryonic kidney-293	0 to 20 μM	Fluorescence measurements, ELISA, luciferase reporter assay	1 hr prior to stimulation with LPS	Curcumin inhibition of MyD88-dependent and -independent signaling pathways of LPS signaling through TLR4, indicating that MD2 is one of the important targets of curcumin in its suppression of the innate immune response to bacterial infection.	Curcumin as a new MD2-specific inhibitor is a candidate in the treatment of bacterial infection.
Siddiqui et al. (2006)	In vivo and in vitro	RAW 264.76 and rats (*N* = 6)	0.2 and 0.24 μM/kg b.w. intravenously for rats and 0 to 100 μM	Transaminases, lactate, and albumin determination, ELISA, immunohistochemistry, MTT assay	3 days	Administration of curcumin before and after the onset of sepsis attenuated tissue injury, reduced mortality, and decreased the expression of TNF-α.	Curcumin or its analogs are novel therapies for sepsis.
Hu et al. (2005)	In vivo	Human peripheral neutrophils	10 to 50 μM	Apoptosis assessment, neutrophil migration assay, MPO analysis, Western blot, LDH analysis, fluorospectrophotometry, superoxide analysis	—	Curcumin increased constitutive neutrophil apoptosis and abolished the transbilayer migration-induced interruption in neutrophil apoptosis, neutrophil, migration, and MPO release. An increase in p38 phosphorylation and caspase-3 activity was observed.	Curcumin is a potential candidate for the treatment of lung injury due to increased neutrophil activity in sepsis.
Chen, Lu, et al. (2018)	In vivo	Mice (*N* = 24)		RT-PCR analysis, ELISA, Western blot,	1, 3, 5, and 7 days	Curcumin significantly decreased inflammatory injury of the	

(Continues)

TABLE 1 (Continued)

Reference	Study design	Number and type of subjects	Dosage and type of administration	Assay	Study duration	Results	Main conclusion
			50, 100, and 200 mg/kg, intragastric administration	histopathological examination, flow cytometry, proliferation assay		kidney and lung by inhibition of IL-6 and TNF-α.	Curcumin could be used as a novel therapeutic drug in sepsis.
Vasanthkumar, Hanumanthappa, and Prabhakar (2018)	In vivo	Mice (*N* = 12)	10 and 20 mg/kg b. w., oral administration	LPO analysis, SOD activity, histological analysis	7 days	Curcumin and its combination with capsaicin had shown significant improve of nonspecific serum enzymes, antioxidant enzymes, and attenuated inflammatory cells infiltration thereby preventing tissue/organ damage in mice.	Curcumin and capsaicin were effective in reducing the oxidant stress.
Kumari, Dash, and Singh (2017)	In vivo	Mice (*N* = 20)	20 mg/kg, i.p., and 10 mg/kg, i.n.	ROS measurement, nitrite measurement, ELISA, MPO activity, hydroxyproline measurement, RT-PCR, histopathological determination	Single dose, 1, 6, 24, and 72 hr	Curcumin pretreatment significantly reduced endotoxin-induced mortality. Also, curcumin lowered mRNA expression of MPO activity, TNF-α, TGF-β1, inducible nitric oxide synthase, and inflammatory cell count, ROS, and collagen deposition in lungs.	Curcumin can be used as additional intervention at early phase of endotoxemia
Liu, Yang, Liu, Sui, and Li (2017)	In vivo	Rats (*N* = 12)	50 and 100 mg/kg b. w., orally	Myeloperoxidase activity, MDA determination, antioxidant enzyme activities, inflammatory cytokines determination, histopathological analysis, protein content determination, total cell count determination	45 days	Curcumin significantly reduced inflammation and pulmonary edema, MPO activity, and the expression of IL-A, TNF-α, MDA, SOD, and W/D ratio in the lung tissues	Curcumin can react as a therapeutic drug against CLP-induced CLI.
Silva et al. (2017)	In vivo	Rats (*N* = 3 to 11)	100 mg/kg, p.o.	HPLC, hematocrit and blood glucose determination, ELISA, Western blot, nitrate determination	7 days prior to CLP and at 2 hr after surgery	Curcumin decreased proinflammatory cytokines (IL-1β and IL-6) and HSP70 production and peritoneal lavage fluid. Also, curcumin temporarily increased the survival rate of the septic rats.	Curcumin dispersion dose decreased complication of sepsis.

(Continues)

TABLE 1 (Continued)

Reference	Study design	Number and type of subjects	Dosage and type of administration	Assay	Study duration	Results	Main conclusion
Yin et al. (2016)	In vivo	Rats (*N* = 60)	50, 100, and 150 mg/kg, i.p.	Histological evaluation, ELISA, Western blot, PCR	Single dose, 8, 16, and 24 hr post-CLP	Curcumin significantly decreased inflammation indicators, regulated cytokines, and had protective effect on CLP-induced liver dysfunction.	Curcumin can protect against CLP-induced liver dysfunction.
Zhao et al. (2016)	In vivo	Mice (*N* = 60)	100 mg/kg, i.p.	TUNEL staining, Western blot, MMP measurement, ROS production detection, mitochondrial complex I activity measurement	Single dose, 3, 12, and 24 hr after surgery	Curcumin improved survival rate, attenuates brain edema, enhanced BBB integrity, decreased apoptosis, and attenuated mitochondrial dysfunction in septic mice.	Curcumin could be a potential drug for the treatment of sepsis.
Kumari, Tyagi, Dash, and Singh (2015)	In vivo	Mice (*N* = 5)	10 mg/kg, intranasally	Evans blue capillary leakage assay, bronchoalveolar lavage protein content determination, nitrite measurement, SOD activity, catalase activity, lipid peroxidation evaluation, ELISA, MPO activity, histopathological determination	Single dose After 24 hr of intranasal LPS	Curcumin ameliorated neutrophil recruitment and MPO activity, oxidative stress markers MDA and like NO level and inflammatory cytokine. Curcumin increase levels of antioxidative enzymes such as SOD and catalase	Intranasal curcumin might be a novel therapeutic towards the treatment of ALI.
Lu, Jiang, Hu, Wang, and Zheng (2015)	In vivo	Rats (*N* = 24)	5 to 20 mg/kg, i.p.	ELISA, immunohistochemistry and histology	Single dose	Curcumin prevented the vasoconstrictive dysfunction induced the serum level of E-selectin and the expression levels of thrombospondin 1 and TGF-β1 by LPS.	Curcumin alleviates LPS-induced vasoconstrictive dysfunction.
Wang, Wang, et al. (2015)	In vivo	Mice (*N* = 6)	30 mg/kg free	Western blot, ELISA, histopathological analysis	Single dose	Curcumin-loaded solid lipid nanoparticles significantly decreased the expression of serum proinflammatory cytokines.	Curcumin-loaded solid lipid nanoparticles may be used as an effective and safe therapeutic agent in treating sepsis.
Savcun et al. (2013)	In vivo	Rats (*N* = 8)	200 mg/kg, i.p.	ELISA, spectrophotometry, myeloperoxidase activity, Na+/K+-ATPase activity, histopathological examination	After perforation and 12 hr postperforation	Curcumin decreased IL-1β and TNF-α, and tissue MDA and MPO. Also, curcumin increased tissue GSH and Na+/K+-ATPase	Curcumin has the strong antioxidant and anti-inflammatory effects in sepsis.
Xu et al. (2013)	In vivo	Rats (*N* = 25)	200 mg/kg/day, i.p.	Transmission electron microscopy, RNA isolation and analysis, real-time	24 hr after	Curcumin significantly decreased expression of TGF-β1 and	Curcumin played a protective role in sepsis-induced ALI.

(Continues)

TABLE 1 (Continued)

Reference	Study design	Number and type of subjects	Dosage and type of administration	Assay	Study duration	Results	Main conclusion
				PCR, ELISA, histopathological examination, protein determination, Western blot		SMAD3-dependent signaling pathway.	
Yang, Wu, Li, and You (2013)	In vivo	Rats (*N* = 10)	200 mg/kg/day, i.p.	Cardiac ultrasound, histological analysis, microplate reader	3 days	Curcumin significantly decreased elevated levels of *cardiac troponin I*I and MDA in plasma and increased the levels of SOD.	Curcumin has the protective effects on cardiac function in sepsis.
Xiao, Yang, Sun, and Sun (2012)	In vivo	Rats (*N* = 40)	50 or 200 mg/kg, i.p.	Cell count, protein content, histopathologic examination, MPO activity, oxidative stress measurement, ELISA	At 2 hr post-CLP	Curcumin significantly attenuated the CLP-induced inflammation and pulmonary edema. Curcumin significantly increased SOD activity and significantly decreased inflammatory cytokines TNF-α, IL-8, and MDA content and MIF levels in the lung.	Curcumin can protect against CLP-induced ALI.
Tham et al. (2011)	In vivo	Mice (*N* = 72)	BHMC (0.5, 1, 2, and 10 mg/kg) and curcumin (1 and 10 mg/kg), intraperitoneally	Immunoprecipitation and kinase activity assays, EMSA	Single dose, 1 hr prior to CLP	BHMC as a curcumin analog exhibited dose-dependent inhibitory effects on p38, JNK, and ERK 1/2 activity by inhibition of phosphorylation of transcription factors ATF-2, c-Jun, and Elk-1.	Curcumin analog BHMC is effective in preventing death following lethal sepsis, and this is possibly due to its increase potency to p38 inhibition.
Vachharajani et al. (2010)	In vivo	Mice (*N* = 5 to 7)	100 mg/kg, intraperitoneally	Intravital fluorescent video microscopy, Evans blue leakage method, dual radiolabeling technique	24, 48, and 72 hr of pretreatment	Curcumin significantly attenuated platelet adhesion and leukocyte in cerebral microcirculation in the brain tissue, P-selectin expression, and improved survival in mice with CLP.	Curcumin modulates immune system dysfunction in CLP.
Yun, Kim, Kang, and Nam (2010)	In vivo	Mice (*N* = 9)	100 mg/kg, i.p.	ELISA, histological analysis	3 hr before LPS/GalN	Curcumin protects hepatic injury through inhibiting the expression level of TNF-α in septic mice	Curcumin alleviates LPS-induced hepatic injury.
Sompamit, Kukongviriyapan, Nakmareong,	In vivo	Mice (*N* = 16 to 20)	50 or 100 mg/kg, i.p.	ELISA, assay of glutathione, malondialdehyde, protein	15 hr	Curcumin decreased oxidative stress by reducing superoxide production, suppression of	Curcumin can be effective in the treatment of vascular

(Continues)

TABLE 1 (Continued)

Reference	Study design	Number and type of subjects	Dosage and type of administration	Assay	Study duration	Results	Main conclusion
Pannangpetch, and Kukongviriyapan (2009)				carbonyl, and O2- production		protein oxidation, lipid peroxidation, and a decrease in urinary nitric oxide metabolites with protection of the ratio of glutathione/glutathione disulfide	dysfunction in mice with endotoxemia elicited by LPS.
Memis et al. (2008)	In vivo	Rats (*N* = 10)	1.2 g/kg, orogastric tube	Histopathological analysis	7 days	Curcumin lead to no hydropic degeneration of hepatocytes and no portal inflammation, inflammation and hyperemia in the lamina propria, and restricted tubular necrosis.	Curcumin may be beneficial in the treatment of organ dysfunction in sepsis.
Chen, Kuo, Chai, Ou, and Yang (2007)	In vivo	Rats (*N* = 12)	60 mg/kg, b.w. i.p.	ELISA, histopathological examination	Single dose, 3 hr before LPS infusion	Curcumin reduced circulating TNF-α levels, the plasma fibrinogen, and consumption of peripheral platelets.	The results expose the therapeutic use of curcumin in infection.
Wu et al. (2006)	In vivo	Rats (*N* = 6)	1-mM injection	Gene expression, ELISA	7 days	Curcumin decreased levels of TNF-α·and IL-1β post-CLP, by inhibition of proinflammatory cytokines.	Proinflammatory cytokines inhibition by curcumin may offer a new method to modulate the hepatic CYP in sepsis.
Carter, Liu, Yang, Fier, and Mendez (2003)	In vivo	Rats (*N* = 10)	42 mg/kg, i.p.	Western blot, ELISA, histological evaluation, MPO analysis	Single dose, 4 to 12 hr	Curcumin significantly reversed survival after CLP. Also, curcumin significantly inhibited MAPK activity.	Curcumin can attenuate acute lung injury and improves survival.
Madan and Ghosh (2003)	In vivo	Mice (*N* = 20)	20–60 mg/kg b.w. oral administration	Western blot, histological analysis	Different time	Diferuloylmethane (curcumin) inhibits the induced expression of ICAM-1 and VCAM-1 in liver and lungs and inhibits the migration and infiltration of neutrophils from blood vessels to the liver tissue	Diferuloylmethane may be useful in reducing multiple organ injury in pathological conditions caused by excessive penetration of neutrophils into the tissues

Abbreviations: ALI, acute lung injury; AST, aspartate aminotransferase; BBB, blood brain barrier; b.w., body weight; CLP, cecal ligation and puncture; ERK, extracellular signal-regulated kinase; GalN, D-galactosamine; GSH, reduced glutathione; HEK-293, human embryonic kidney 293 cells; HepG2, hepatocellular cancer cell lines; HMGB1, high mobility group box 1; i.p., intraperitoneally; ICAM-1, intercellular adhesion molecule 1; IL-1β, interleukin-1β; IL-6, interleukin 6; IRAK1, interleukin-1 receptor-associated kinase 1; LPS, lipopolysaccharides; MAPK, mitogen-activated protein kinases; MCF-7, Michigan Cancer Foundation-7; MD2, myeloid differentiation factor-2; MDA-MB-231, triple negative breast cancer cell line; MPO, myeloperoxidase; MuRF1, muscle-specific RING finger protein 1; MyD88, myeloid differentiation primary response 88; NLRP3, Nod-like receptor pyrin domain-containing protein 3; NO, nitric oxide; Nrf-2, the nuclear factor erythroid 2-related factor 2; PBMCs, peripheral blood mononuclear cells; PCR, polymerase chain reaction; PI3K/AKT, phosphatidylinositol 3-kinase/protein kinase B; ROS, reactive oxygen species; SMAD3, mothers against decapentaplegic homolog 3; TGF-β1, transforming growth factor β1; THP-1, human monocytic cell line; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor-α; TREM-1, triggering receptor expressed on myeloid cells 1; VCAM-1, vascular cell adhesion molecule 1.

3.2 | In vitro studies

Yali Zhang et al. (2018) have investigated the effects of analog of curcumin on improved anti-inflammatory activity and myeloid differentiation protein 2 (MD2) in human umbilical vein endothelial cells and RAW 264.7 macrophages. The authors have reported that curcumin inhibited the Toll-like receptor 4 (TLR4) and MD2 signaling complex by competition with lipopolysaccharides (LPSs) forbidding on MD2.

Wu et al. (2013) found that the amount of 1 up to 5 μM of curcumin analog can play an important role in the effective prevention LPS-induced production of interleukin 6 (IL-6) and tumor necrosis factor-α (TNF-α), and it could be an antisepsis compound.

Zhong et al. (2016) showed that 0.5 up to 2 μM curcumin has the ability to decrease in serum cytokines and liver NO and enhance the production of liver antioxidant enzymes.

Ma et al. (2017) showed that various concentrations of curcumin efficiently inhibited the LPS-induced microRNA-155 expression and cytokines by blockade of phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signaling pathways without affecting the normal growth of RAW 264.7.

Shukla et al. (2015) have investigated the effects of curcumin on inflammatory pathways and Nrf-2 expression in hepatocellular cancer cell lines (HepG2), RAW 264.7 macrophages, and human embryonic kidney 293 cells. They have reported curcumin increased expression level of Nrf2 and inhibits cytokine secretion through down regulation of NF-κB pathwayp.

In another study, Hu, Du, et al. (2005) showed that 10 up to 50 μM of curcumin lead to decrease in migration and MPO release by increasing neutrophil apoptosis and decreasing neutrophil activation. There was also an increase in the phosphorylation of p38 and caspase-3 activity.

Ahn et al. (2017) found that curcumin has the ability to suppress NO signaling and reduce the release of the proinflammatory cytokine.

Yuan et al. (2012) have investigated the effects of curcumin on triggering receptor expressed on myeloid cells 1 (TREM-1) expression in response to LPS. The authors found that curcumin inhibited the binding of p65 to TREM-1 promoter in response to LPS. In addition, curcumin inhibited p300 activity in the TREM-1 promoter region leading to hypoacetylation of histone 3 and histone 4 in the lysine residues.

3.3 | Animal studies

Savcun et al. (2013) have investigated the antioxidant and anti-inflammatory effects of curcumin on oxidative and inflammatory injury in septic rat. In this study, septic rats were intraperitoneally (i.p.) given curcumin 200 mg/kg, 12 hr after surgery. Curcumin treatment significantly decreased the oxidative enzymes and level of inflammatory in septic rats.

In other study conducted by Yang et al. (2013), the administration of 200 mg/kg/day curcumin for 3 days significantly decreased the oxidative factor, myocardial inflammation, and structure damage of myocardial cells and enhanced the levels of superoxide dismutase (SOD) in sepsis.

Xiao et al. (2012) investigated the effects of curcumin on sepsis-induced acute lung infection in rats. In this study, animals were divided in two experimental groups and administered 50 mg/kg (low-dose curcumin (or 200 mg/kg (high-dose curcumin) i.p., for three times (6, 12, and 24 hr). The authors reported that treatment with curcumin in both quantities significantly decreased the oxidative factor malondialdehyde (MDA), cytokine production, and pulmonary MPO activity significantly. Curcumin also decreased the inflammatory cells in the blood and bronchoalveolar lavage fluid.

In other study conducted by Silva et al. (2017), 100 mg/kg/day curcumin in the form of oral gavage were reduced for 7 days by the proinflammatory cytokines and heat shock protein (HSP70) production and temporarily increased their survival rate.

Liu et al. (2017) investigated the effects of curcumin on sepsis-induced chronic lung injury in rats. Septic rats were orally treated by curcumin at 100 or 200 mg/kg of body weight dose for 45 days. Curcumin treatment significantly decreased the MPO activity, MDA, SOD, and wet and dry (W/D) ratio in the lung tissues. Furthermore, curcumin decreased the expression of IL-1, TNF-α, macrophage inhibitory factor, total cell counts, lymphocytes, and neutrophils.

Xu, Yang, and Liu (2011) investigated the protective effect of curcumin on mice with acute lung injury induced by sepsis. Experimental septic rats received the injection of curcumin (200 mg/kg) for 48 hr. Septic rats had significant overexpression of TNF-α and intercellular adhesion molecule 1 (ICAM-1) in lung tissues, whereas curcumin significantly reduced the expression level of TNF-α and ICAM-1.

Tao, Yin, and Ma (2014) showed that oral supplementation of curcumin reduced the intracellular calcium concentration, caspase-3 activation, Bax gene, and elevation of antiapoptotic B-cell lymphoma 2 (Bcl-2) gene expression for 7 days.

Kumari et al. (2017) investigated the effects of curcumin on LPS-induced endotoxemia and airway inflammation in septic mice. The authors have shown that injection treatment with curcumin significantly decreases MPO activity, inflammatory cell count, reactive oxygen species (ROS), and nitrite levels in septic mice.

Madan and Ghosh (2003) demonstrated that oral curcumin supplementation for 7 days decreases the expression of ICAM-1 and vascular cell adhesion molecule 1 (VCAM-1) in liver and lungs and suppresses the migration and infiltration of neutrophils from blood vessels to the liver tissue. Some other studies, which are mentioned in Table 1, have also shown the effect of curcumin on sepsis.

4 | DISCUSSION

4.1 | Possible mechanisms of curcumin action on sepsis

The proposed multiple mechanisms are shown in Figures 2 and 3 and are also presented as follows.

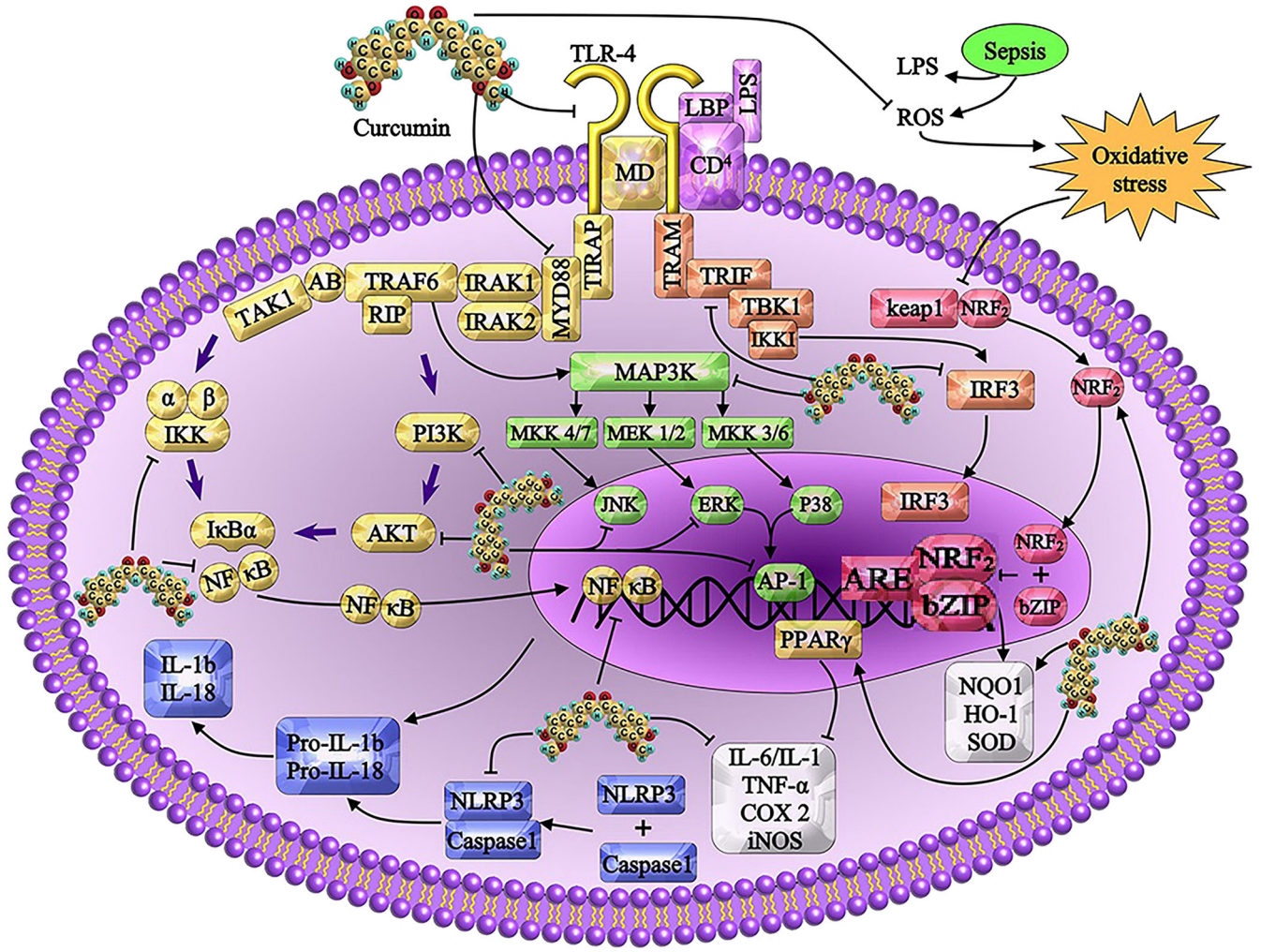

FIGURE 2 Effects of curcumin on inflammatory and oxidative pathways. IRAK1, interleukin-1 receptor-associated kinase 1; RIP, interacting protein; TBK1, TANK-binding kinase 1; TRAF, TNF receptor-associated factor; TRAM, TRIF-related adaptor molecule; TRIF, TIR-domain-containing adapter-inducing interferon-β [Colour figure can be viewed at wileyonlinelibrary.com]

4.2 | The effects of curcumin on cytokine production and inflammatory mediators

Previous studies have shown that excessive immune responses (dysregulated immune response) to counteract pathogens produce a wide range of inflammatory and anti-inflammatory mediators to deal with pathogenic agents that lead to tissue damage, organ failure, and death during sepsis (Kakihana, Ito, Nakahara, Yamaguchi, & Yasuda, 2016). Curcumin has strong inhibitory effects on proinflammatory cytokines such as TNF-α, IL-6, and IL-1 (Arshad, Haque, Abbas Bukhari, & Jantan, 2017), and moreover, curcumin decreases the expression of cyclooxygenase (COX-2), inducible NO synthase, the activation of p38 mitogen-activated protein kinases (Camacho-Barquero et al., 2007), NF-κB (Xu & Liu, 2017), and AP-1 (Gupta et al., 2011). NF-κB plays a main role in modulation of innate and adaptive immune response by controlling the transcription of cytokines such as IL-2, IL-1, and interferon-γ (IFN-γ) (Okunieff et al., 2006; Park et al., 2007). The curcumin can suppress activity of NF-κB through inhibition of IκB kinase-α (IKK-α) phosphorylation (such as inhibition of IL-1), nuclear translocation, and activation of the NF-κB p65 subunit (Huang, Zhao, Kim, Lee, & Hwang, 2008; Marquardt et al., 2015). Curcumin inhibits IKK which leads to activation of nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IκBα). Activation of IκBα leads to inhibition in NF-κB signaling pathway. (Jobin et al., 1999).

Moreover, Zhong et al. (2016) have studied effects of dietary curcumin on LPS-induced mice, and hepatic stellate cells showed that curcumin caused to suppressing PI3K/AKT signaling pathway and inhibited activation of the mitogen-activated protein kinases/c-Jun NH2-terminal kinase (P38/JNK) cascade in the livers of rat.

H.-W. Chen et al. (2007) evaluated the effects of curcumin on inflammatory and coagulation factor in rats suffering from sepsis. Results showed that curcumin reduced the circulating TNF-α levels, plasma fibrinogen, and peripheral platelets and the mortality rate in rats.

Furthermore, curcumin through increasing expression of peroxisome proliferator-activated receptor gamma (PPARγ) (Jacob, Wu, Zhou, & Wang, 2007; Liu, Zhang, et al., 2018), which leads to suppression of

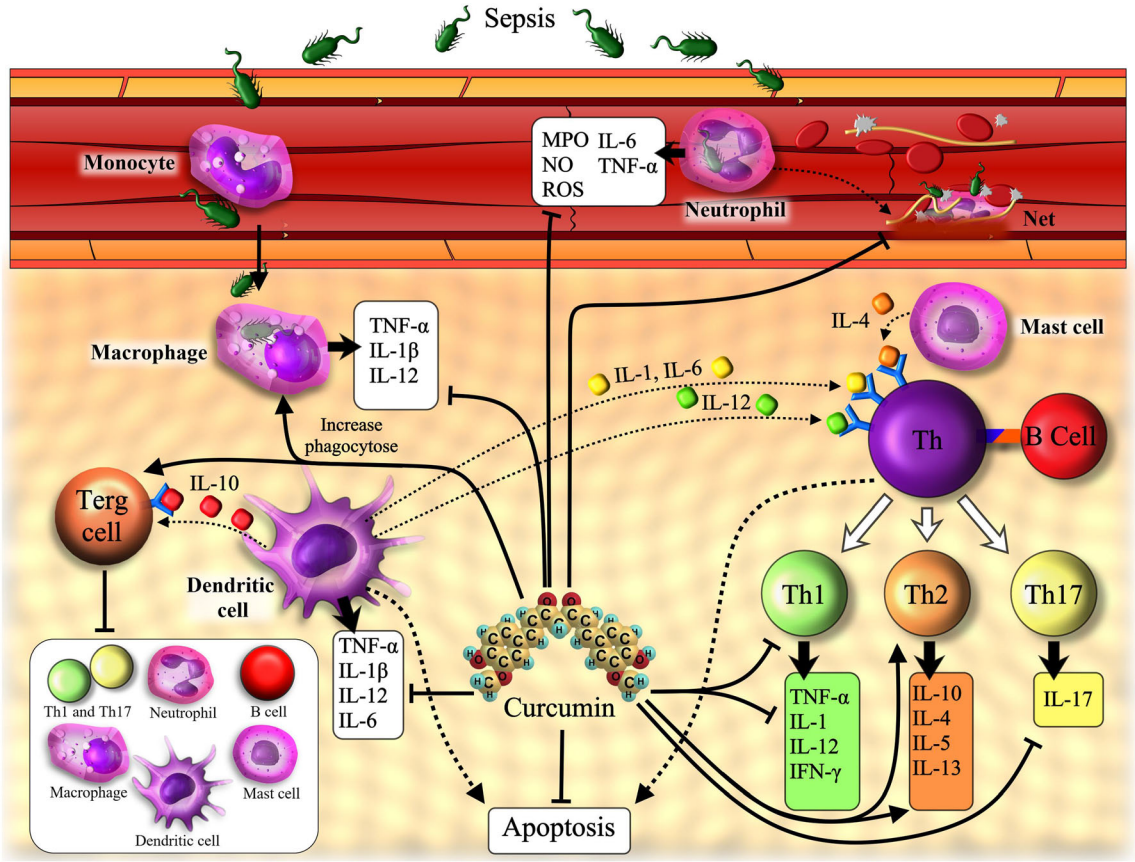

FIGURE 3 Effect of curcumin on the immune response to sepsis [Colour figure can be viewed at wileyonlinelibrary.com]

NF-κB pathway and increase the release of anti-inflammatory cytokines (Liu, Zhang, et al., 2018; Siddiqui et al., 2006).

4.3 | Inflammasome pathways

4.3.1 | Inhibition of Nod-like receptor pyrin domain-containing protein 3 inflammasome

Inflammasome such as Nod-like receptor pyrin domain-containing protein 3 (NLRP3) is a cytoplasmic multiportion complex of the innate immune system (Hao et al., 2017) that leads to maturation and production of cytokines such as IL-18, IL-1β, and pyroptosis (lytic host cell death; Liu, Jing, et al., 2018; Luo et al., 2014).

Gong et al. (2015) have studied the effect of curcumin on treated murine macrophage cell line J774A with septic shock and reported that curcumin inhibited the Nod-like receptor pyrin domain-containing protein 3 inflammasome activators significantly, consequently decreased the level of activated caspase-1, which leads to a decrease in IL-1 β secretion as well as improves the condition of illness caused by endotoxic shock.

4.4 | Effect of curcumin on Toll-like receptors

Toll-like receptor (TLR) is a type of receptor recognition pattern (RRP) that plays an important role in innate immune system response (Claushuis et al., 2019). TLRs are the most important triggers for the exceed immune response, especially in sepsis and other inflammatory diseases (Vilahur & Badimon, 2014). Curcumin has several drug activities that can affect signaling pathways and biological targets. Several studies have proposed that curcumin can directly bind to MD2 (extracellular protein that is related with the extracellular area of TLR4 and plays a main role in LPS cluster of differentiation 14 (CD14)) complex recognition and inhibits the recognition of LPS by blocking TLR4 singling pathway. Therefore, it can inhibit the production of inflammatory mediators in sepsis (Wang, Shan, et al., 2015; Zhang et al., 2018). Curcumin also prevents the LPS-induced activation of both myeloid differentiation primary response 88 (MyD88) and TIR-domain-containing adapter-inducing interferon-β-(TRIF) dependent pathways of TLR4 and consequently inhibits the activation of interferon regulatory factor 3 (IRF3) and NF-κB pathways (Youn, Saitoh, Miyake, & Hwang, 2006).

4.5 | The effects of curcumin on oxidative stress

Dysregulated immune response in sepsis causes oxidative stress due to pathogen phagocytosis by immune cells (such as neutrophils and macrophages) that lead to endothelial cell injuries and mitochondrial inhibition by the formation of ROS and reactive nitrogen species (RNS), which has an important role in the sepsis pathogenesis.

Oxidative stress leads to endothelial cell injuries through formation of ROS and RNS which is important in the sepsis pathogenesis (Mantzarlis, Tsolaki, & Zakynthinos, 2017). Curcumin contains high levels of antioxidant compounds, including the carbon–carbon double bonds, phenyl rings, and β-diketo group (Nimse & Pal, 2015). It has been shown that curcumin can protect cell membrane by eliminating lipid peroxidation due to its lipid-soluble property and antioxidant activity (Priyadarsini et al., 2003). Furthermore, curcumin has ability to suppress lipid peroxidation (MDA; Indira Priyadarsini, 2013) through induced quinine reductase and glutathione-S-transferase and neutralizes hydroxyl radicals (HO), ROS (superoxide [O^{2-}] and hydrogen peroxide [H_2O_2]; Park, Amin, Chen, & Shin, 2013), and RNS (peroxynitrite and NO).

Yang et al. (2013) have reported the effect of injectable curcumin on oxidative stress in cardiac dysfunction mice with sepsis and found that curcumin protects oxidative stress and elevated SOD levels in these mice.

Nrf-2 is a transcription factor that eliminates ROS (7) products by increasing the antioxidant enzymes (DeNicola et al., 2011). As a result, curcumin activates the expression of Nrf-2, thus protecting the cells against oxidative stress damage and by regulating the genes that contain antioxidant enzymes (Peng, Dai, Liu, Li, & Qiu, 2018) heme oxygenase (HO)-1 and NAD(P)H:quinone oxidoreductase 1 (NQO1) (Shehzad & Lee, 2013) and prevents lipid peroxidation (Deogade & Ghate, 2015), thereby reducing the damage caused by oxidative stress in sepsis

4.6 | Effect of curcumin on immune response

4.6.1 | Immunomodulatory effect of curcumin on monocytes and macrophages

Several studies have shown that curcumin has ability to regulate macrophage activation (Jagetia & Aggarwal, 2007) and increase phagocytic activity (Khajehdehi, 2012). Curcumin decreases oxidation reaction products and lipid peroxidation damages in macrophages (Brouet & Ohshima, 1995; Sou, Inenaga, Takeoka, & Tsuchida, 2008). It also prevents the production of IL-8, macrophage inflammatory protein (MIP)-1α, (MCP-1), and TNF-α) by downregulating NF-κB signaling pathway) by monocytes and macrophages (ABE, Hashimoto, & HORIE, 1999). Furthermore, curcumin significantly suppressed IL-12 generation by decreasing the expression of NF-κB in LPS-stimulated macrophages (Kim et al., 2016) that inhibited Th-1 cytokine profile (increased IL-4 production and decreased IFN-γ) in CD4+ T cells (Yadav, Mishra, Singh, Mehrotra, & Singh, 2005).

4.6.2 | Immunomodulatory effect of curcumin on polymorphonuclear neutrophil cells

In humans, polymorphonuclear neutrophils (PMNs) are the most common circulating leukocytes and vital components of the innate immune against invading, during sepsis (Tak, Tesselaar, Pillay, Borghans, & Koenderman, 2013). PMN releases important regulatory chemokines, leukotrienes, and cytokines; it also attacks to the pathogens, antimicrobial peptides, and oxidative products (Alves-Filho, Spiller, & Cunha, 2010). Neutrophil function during an uncontrolled sepsis leads to tissue damage or multiple fractures due to their accumulation in vital organs (Alves-Filho et al., 2010; Cohen, 2002). Direct effect of curcumin on neutrophilic chemical activity and chemical activity reduces infiltration of neutrophils into inflammatory tissues (Larmonier et al., 2010; Takahashi et al., 2007). Curcumin also prevented PMN chemotaxis through downregulation of PI3K activity, AKT phosphorylation, superoxide, and IL-8 that plays chemotaxis mediator role in human neutrophils (Ezekiel & Heuertz, 2015; Larmonier et al., 2010).

4.6.3 | Immunomodulatory effect of curcumin on T cell

CD4+ T helper (Th) lymphocytes are separated to a number of subclasses cells including Th1, Th2, Th17, and T regulatory cells (Tregs; Saito, Nakashima, Shima, & Ito, 2010). These subsets are identified to have several profiles of transcription factors and cytokines expression. It has been investigated that curcumin has the ability to decrease the expression of Th1 cytokines (TNF-α, IL-12, IL-1, and IFN-γ) in CD4+ T cells through suppressing IL-12 production in macrophages and arise the Th2 cytokines expression (IL-10 and IL-4; Kang et al., 1999). Curcumin blocks expansion and differentiation of Th17 cells by inhibiting the expression of IL-17, IL-6, IL-21, and related orphan receptor gamma t (RORγt) signaling and signal transducers and activators of transcription 3 (STAT3) phosphorylation (Bakır et al., 2016; Kanakasabai et al., 2012).

$CD4^+$ $CD25^+$ Tregs are modulator of adaptive and innate immune responses (Bakır et al., 2016; Kanakasabai et al., 2012). Some cytokines prevent the immune system, for example, transforming growth factor-beta (TGF-β) and IL-10 produced by Tregs, which play an important role in tolerating the immune system in sepsis (Chen, Zhou, Shan, Li, & Lin, 2015; Sharma, Yang, Matsuo, & Wang, 2015).

Forkhead/winged helix transcription factor p3 (FOXP3) is a protein participant in the immune response that is especially expressed by $CD25^+$ $CD4^+$ Tregs and regulates their development and also activity (Bakır et al., 2016; Fontenot, Gavin, & Rudensky, 2003). As it is mentioned in a lot of studies, curcumin has the ability to modulate the activation and the proliferation of T cells (Ranjan, Chen, Johnston, Jeon, & Nagabhushan, 2004). Chen, Lu, et al. (2018) have shown that curcumin can upregulate the $CD4^+$ $CD25^+$ $Foxp3^+$ Treg cells and increase the production of TGF-β and IL-10 that leads to downregulated proliferation activity of $CD4^+$ $CD25^-$ T cells in the spleen of the septic mice.

4.6.4 | Immunomodulatory effect of curcumin on DCs

DCs are part of the proprietary antigenic prescribing cells that initiate primary immune responses (Rogers, Kireta, & Coates, 2010) and have the ability to both innate and adaptive immune (Steinman, Turley, Mellman, & Inaba, 2000). Kim et al. (2005) found that curcumin

inhibited the maturation of DCs and suppressed the expression of CD80, major histocompatibility complex class II, CD40, and CD86 on the surfaces of DCs. It also prevents the LPS induced, IL-6, IL-1β, IL-12, TNF-α, the phosphorylation of mitogen-activated protein kinases, and NF-κB nuclear translocation.

4.7 | Effect of curcumin on organ function and mortality in sepsis

Sepsis and septic shock are the main causes of mortality in critically ill patients. Mortality due to sepsis and septic shock is directly linked to the disruption of the major organs such as the kidney, lung, cardiac, liver, and brain (Vachharajani et al., 2010).

4.7.1 | Cardiac dysfunction

Previous studies have shown that cardiovascular dysfunction due to sepsis is a major cause of death in patients with sepsis (Yang et al., 2013). TNF-α and NF-κB can cause excessive E-selectin protein stimulation by vascular endothelial cells. E-selectin molecules on the cell membrane surface may be separated or dissolved (Roldán, Marín, Lip, & Blann, 2003). Serum soluble E-selectin is an important factor of vascular endothelial cell injury (Leeuwenberg et al., 1992). Curcumin, by regulating the immune response, and improves vascular endothelial through decrease serum E-selectin levels, may lead to a decrease in cardiovascular dysfunction sepsis (Lu et al., 2015). Another role of curcumin in prevention of vascular damage is associated to Thrombospondin-1 (TSP1). TSP-1 is a matrix glycoprotein with different roles in diverse cellular and physiological processes (Esemuede, Lee, Pierre-Paul, Sumpio, & Gahtan, 2004). Sources of TSP-1 include activated leukocytes, platelets, vascular smooth muscle cells, endothelial cells, and fibroblasts (Chen, Herndon, & Lawler, 2000). TSP-1 is also an important activator of TGF-β1 (Brunner & Blakytny, 2004). TSP-1 expression may affect the prognosis of patients with sepsis by preventing innate immune function (McMaken et al., 2011). Lu et al. (2015) have shown that curcumin decreases LPS-induced vasoconstrictive dysfunction in thoracic aortas. In addition, curcumin may be involved in this protective effect by inhibiting the expression of TGF-β1 and TSP-1.

4.7.2 | Kidney injury

Disseminated intravascular coagulation (DIC) is one of the major complications of sepsis (Yadav, Mishra, et al., 2005). DIC with systemic intravascular activation of coagulation cascade causes the fibrin deposition and formation of thrombosis deposition in the microvasculature (Zeerleder, Hack, & Wuillemin, 2005). Glomerular fibrin deposition (GFD) is a serious pathophysiological process that is associated with renal damage (Aslan et al., 2018). The anti-inflammatory effects of curcumin may be one of the vital mechanisms to reduce coagulation disturbances related to DIC that prevents intravascular formation of fibrin sedimentation in the kidney by reducing the amount of platelets and the level of fibrinogen (Yadav, Mishra, et al., 2005). Curcumin also suppressed the release of cytokines and mediators of inflammation through blocking c-Jun/AP-1, IKK/I-κB, and the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathways. Therefore, curcumin reduced the risk of kidney damage and mortality due to organ dysfunction (Chen, Kuo, et al., 2007).

4.7.3 | Brain injury

Evidence suggests that brain dysfunction (known as septic encephalopathy) is one of the leading causes of mortality in critically ill patients (Gofton & Young, 2012). Sepsis causes oxidative stress, mitochondrial dysfunction, inflammation, and death of brain cells (Vachharajani et al., 2010). Zhao et al. (2016) have shown that curcumin enhanced blood brain barrier (BBB) integrity and alleviate brain edema after sepsis. Moreover, curcumin relieved neuronal apoptosis induced by sepsis as supported by the decrease expression of Bax, reduced number of dUTP nick-end labeling (TUNEL) positive neurons and increased expression of B-cell lymphoma 2 (Bcl-2). Also, Vachharajani et al. (2010) showed that curcumin decreased leukocyte adhesion and platelet adhesion and blood brain barrier dysfunction in septic mice via modulation of P-selectin expression and improved survival in septic mice.

4.7.4 | Liver injury

Patients with sepsis have remarkable levels of inflammatory mediators and oxidative stress (oxygen free radicals) due to dysregulated immune response, which cause damage to the mitochondrial membranes, liver cell structures, and increased membrane permeability (Yin et al., 2016). Sodium pump dysfunction leads to sodium hold, hepatocyte edema, and eventually, hepatocyte apoptosis (Sakaguchi & Furusawa, 2006). Also, this dysfunction inhibits total cytochromes (CYPs), exacerbates inflammatory responses, and increases mortality in sepsis (Albuszies et al., 2005). Curcumin can inhibit the production of inflammatory cytokines (such as IL-1β and TNF from macrophages). This reduction in IL-1β and TNF-α is accompanied with increased expression of aryl hydrocarbon receptor, aryl hydrocarbon receptor (AhR) nuclear translocator (Arnt), and CYP1A2 in the liver, which reduces liver injury and mortality due to sepsis (Wu et al., 2006; Yin et al., 2017).

4.7.5 | Lung injury

In sepsis, lung disorder is one of the main reasons for the development of multiple organ failure, acute respiratory distress syndrome (ARDS), and acute lung injury (ALI), which significantly increases mortality rates in ICU (Xu et al., 2013). Curcumin can reduce pulmonary edema by decreasing the inflammatory cell infiltration (neutrophils and macrophages) and lung W/D ratio (Xiao et al., 2012). Furthermore, the protective effect of curcumin play an important role in suppression of ROS generation and, PMN infiltration. Curcumin also increases the antioxidant status, and regulates inflammatory cytokines production such as TNF-α and IL-8. (Xiao et al., 2012). Also, Yuan et al. (2012)

have shown that curcumin, through the TREM-1 (one of the families of immunoglobulins is expressed by macrophages and neutrophils and is an amplifier of TLR) suppression, leads to increased anti-inflammatory cytokines and inflammatory cytokines and reduces lung damage and improves survival in septic animals.

As a result, most studies have shown that curcumin reduces damage to various organs and reduces mortality by improving the immune response, reducing oxidative stress, inflammatory mediators, and increasing anti-inflammatory factors.

4.8 | Side effects of curcumin

As a final note, curcumin has been confirmed by the U.S. Food and Drug Administration (FDA) as Generally Recognized as Safe (GRAS), and safety profiles and good tolerability have been shown by clinical trials, even at doses between 4 and 8 g/day (Hewlings & Kalman, 2017). Despite curcumin has a good safety profile, some negative side effects have been reported including mainly gastrointestinal (nausea and diarrhea), headache, rash, and increase in lactate dehydrogenase contents and serum alkaline phosphatase (Asher & Spelman, 2013; Hewlings & Kalman, 2017).

4.9 | Study strengths and weaknesses

Our study is the first systematic review study on the therapeutic effects of curcumin on sepsis. In the context of the effect of curcumin on sepsis, sufficient animal and cell studies have been available, which, due to physiological control of the conditions, can provide a better result in this regard. Some of these studies have evaluated the therapeutic effects of curcumin on sepsis in both the animal models and the cell lines. Other strengths of these studies included the enough sample size in animal studies and the use of different cell classes. Furthermore, different doses of curcumin and its analogs were used in these studies, and most of the pathways were investigated for inflammatory, oxidative, coagulation, and immune responses.

Lack of human study was considered as the most important limitation of studies on the therapeutic effect of curcumin on sepsis. Also, the short duration of interventions was one of the limitations of other studies.

5 | CONCLUSION

All studies have shown that curcumin and its various analogs can inhibit inflammatory, oxidative stress, and coagulation factors through modulation of immune responses by different mechanisms. The effective role of curcumin in regulating the immune response has been shown in human interventions in other diseases (such as inflammatory bowel disease, metabolic syndrome, and rheumatoid arthritis; Ghazimoradi et al., 2017; Khayyal et al., 2018; Singla et al., 2014). Therefore, these effects may also be seen in sepsis. Despite the promising evidence of the therapeutic effects of curcumin on the sepsis complication, further studies seem necessary to investigate its effect and possible mechanisms of action in human studies.

ACKNOWLEDGEMENTS

There is no acknowledgment.

AUTHOR CONTRIBUTIONS

Authors conducted the search and participated in manuscript writing. Authors read and approved the final manuscript.

CONFLICT OF INTERESTS

The authors declare that they have no financial or nonfinancial conflict of interests.

ORCID

Arash Karimi https://orcid.org/0000-0001-6407-8286
Ramin Ghodsi https://orcid.org/0000-0002-2355-6349
Fateme Kooshki https://orcid.org/0000-0002-2247-9097
Mozhdeh Karimi https://orcid.org/0000-0002-9280-3737
Vahid Asghariazar https://orcid.org/0000-0002-9809-6711
Ali Tarighat-Esfanjani https://orcid.org/0000-0003-0481-3685

REFERENCES

Abe, Y., Hashimoto, S., & Horie, T. (1999). Curcumin inhibition of inflammatory cytokine production by human peripheral blood monocytes and alveolar macrophages. *Pharmacological Research*, *39*(1), 41–47. https://doi.org/10.1006/phrs.1998.0404

Abitagaoglu, S., Akinci, S., Saricaoglu, F., Akinci, M., Zeybek, N., Muftuoglu, S., & Aypar, U. (2015). Effect of coenzyme Q10 on organ damage in sepsis. *Bratislavské Lekárske Listy*, *116*(7), 433–439.

Ahn, M. Y., Hwang, J. S., Lee, S. B., Ham, S. A., Hur, J., Kim, J. T., & Seo, H. G. (2017). Curcumin longa extract-loaded nanoemulsion improves the survival of endotoxemic mice by inhibiting nitric oxide-dependent HMGB1 release. *PeerJ*, *5*, e3808. https://doi.org/10.7717/peerj.3808

Albuszies, G., Radermacher, P., Vogt, J., Wachter, U., Weber, S., Schoaff, M., … Barth, E. (2005). Effect of increased cardiac output on hepatic and intestinal microcirculatory blood flow, oxygenation, and metabolism in hyperdynamic marine septic shock. *Critical Care Medicine*, *33*(10), 2332–2338. https://doi.org/10.1097/01.ccm.0000182817.20977.e9

Al-Hasan, M. N., & Justo, J. A. (2018). Ignoring the elephant: Does the Infectious Diseases Society of America support Sepsis-3 or Pre-sepsis criteria? *Clinical Infectious Diseases*, *68*(8), 1431.

Alves-Filho, J. C., Spiller, F., & Cunha, F. Q. (2010). Neutrophil paralysis in sepsis. *Shock*, *34*(7), 15–21. https://doi.org/10.1097/SHK.0b013e3181e7e61b

Arango Duque, G., & Descoteaux, A. (2014). Macrophage cytokines: Involvement in immunity and infectious diseases. *Frontiers in Immunology*, *5*, 491.

Arshad, L., Haque, M. A., Abbas Bukhari, S. N., & Jantan, I. (2017). An overview of structure–activity relationship studies of curcumin analogs as antioxidant and anti-inflammatory agents. *Future Medicinal Chemistry*, *9*(6), 605–626. https://doi.org/10.4155/fmc-2016-0223

Asher, G. N., & Spelman, K. (2013). Clinical utility of curcumin extract. *Alternative Therapies in Health and Medicine*, *19*(2), 20–22.

Aslan, A., van den Heuvel, M. C., Stegeman, C. A., Popa, E. R., Leliveld, A. M., Molema, G., … van Meurs, M. (2018). Kidney histopathology in lethal human sepsis. *Critical Care*, *22*(1), 359. https://doi.org/10.1186/s13054-018-2287-3

Bae, M. H., Park, S. H., Park, C. J., Cho, E. J., Lee, B. R., Kim, Y. J., … Song, D. K. (2016). Flow cytometric measurement of respiratory burst activity and surface expression of neutrophils for septic patient prognosis. *Cytometry Part B: Clinical Cytometry*, *90*(4), 368–375. https://doi.org/10.1002/cyto.b.21274

Bakır, B., Yetkin Ay, Z., Büyükbayram, H. İ., Kumbul Doğuç, D., Bayram, D., Candan, İ. A., & Uskun, E. (2016). Effect of curcumin on systemic T helper 17 cell response; gingival expressions of Interleukin-17 and retinoic acid receptor-related orphan receptor γt; and alveolar bone loss in experimental periodontitis. *Journal of Periodontology*, *87*(11), e183–e191. https://doi.org/10.1902/jop.2016.150722

Bangsgaard, E. O., Hjorth, P. G., Olufsen, M. S., Mehlsen, J., & Ottesen, J. T. (2017). Integrated inflammatory stress (ITIS) model. *Bulletin of Mathematical Biology*, *79*(7), 1487–1509. https://doi.org/10.1007/s11538-017-0293-2

Barati, N., Momtazi-Borojeni, A. A., Majeed, M., & Sahebkar, A. (2019). Potential therapeutic effects of curcumin in gastric cancer. *Journal of Cellular Physiology*, *234*(3), 2317–2328. https://doi.org/10.1002/jcp.27229

Bosmann, M., & Ward, P. A. (2013). The inflammatory response in sepsis. *Trends in Immunology*, *34*(3), 129–136. https://doi.org/10.1016/j.it.2012.09.004

Brouet, I., & Ohshima, H. (1995). Curcumin, an anti-tumor promoter and anti-inflammatory agent, inhibits induction of nitric oxide synthase in activated macrophages. *Biochemical and Biophysical Research Communications*, *206*(2), 533–540. https://doi.org/10.1006/bbrc.1995.1076

Brunner, G., & Blakytny, R. (2004). Extracellular regulation of TGF-β activity in wound repair: Growth factor latency as a sensor mechanism for injury. *Thrombosis and Haemostasis*, *92*(2), 253–261. https://doi.org/10.1160/th04-05-0324

Camacho-Barquero, L., Villegas, I., Sánchez-Calvo, J. M., Talero, E., Sánchez-Fidalgo, S., Motilva, V., & de la Lastra, C. A. (2007). Curcumin, a *Curcuma longa* constituent, acts on MAPK p38 pathway modulating COX-2 and iNOS expression in chronic experimental colitis. *International Immunopharmacology*, *7*(3), 333–342. https://doi.org/10.1016/j.intimp.2006.11.006

Carter, Y., Liu, G., Yang, J., Fier, A., & Mendez, C. (2003). Sublethal hemorrhage induces tolerance in animals exposed to cecal ligation and puncture by altering p38, p44/42, and SAPK/JNK MAP kinase activation. *Surgical Infections*, *4*(1), 17–27. https://doi.org/10.1089/109629603764655245

Chen, H., Herndon, M. E., & Lawler, J. (2000). The cell biology of thrombospondin-1. *Matrix Biology*, *19*(7), 597–614. https://doi.org/10.1016/S0945-053X(00)00107-4

Chen, H. W., Kuo, H. T., Chai, C. Y., Ou, J. L., & Yang, R. C. (2007). Pretreatment of curcumin attenuates coagulopathy and renal injury in LPS-induced endotoxemia. *Journal of Endotoxin Research*, *13*(1), 15–23. https://doi.org/10.1177/0968051907078605

Chen, K., Zhou, Q.-X., Shan, H.-W., Li, W.-F., & Lin, Z.-F. (2015). Prognostic value of CD4+ CD25+ Tregs as a valuable biomarker for patients with sepsis in ICU. *World Journal of Emergency Medicine*, *6*(1), 40. https://doi.org/10.5847/wjem.j.1920-8642.2015.01.007

Chen, L., Lu, Y., Zhao, L., Hu, L., Qiu, Q., Zhang, Z., … Lu, Z. (2018). Curcumin attenuates sepsis-induced acute organ dysfunction by preventing inflammation and enhancing the suppressive function of Tregs. *International Immunopharmacology*, *61*, 1–7. https://doi.org/10.1016/j.intimp.2018.04.041

Chen, Y., Peng, H., Zhou, S., & Zhuang, Y. (2017). ADAR1 is targeted by miR-143 to regulate IL-1β-induced endothelial activation through the NFκB pathway. *The International Journal of Biochemistry & Cell Biology*, *89*, 25–33. https://doi.org/10.1016/j.biocel.2017.05.021

Claushuis, T. A. M., Van Der Veen, A. I. P., Horn, J., Schultz, M. J., Houtkooper, R. H., Van'T Veer, C., & Van Der Poll, T. (2019). Platelet Toll-like receptor expression and activation induced by lipopolysaccharide and sepsis. *Platelets*, *30*(3), 296–304. https://doi.org/10.1080/09537104.2018.1445841

Cohen, J. (2002). The immunopathogenesis of sepsis. *Nature*, *420*(6917), 885–891. https://doi.org/10.1038/nature01326

DeNicola, G. M., Karreth, F. A., Humpton, T. J., Gopinathan, A., Wei, C., Frese, K., … Scrimieri, F. (2011). Oncogene-induced Nrf2 transcription promotes ROS detoxification and tumorigenesis. *Nature*, *475*(7354), 106–109. https://doi.org/10.1038/nature10189

Deogade, S. C., & Ghate, S. (2015). Curcumin: Therapeutic applications in systemic and oral health. *International Journal of Biological & Pharmaceutical Research*, *6*(4), 281–290.

Dhir, A. (2018). Curcumin in epilepsy disorders. *Phytotherapy Research*, *32*(10), 1865–1875. https://doi.org/10.1002/ptr.6125

Dominguez-Andres, J., & Netea, M. G. (2019). Long-term reprogramming of the innate immune system. *Journal of Leukocyte Biology*, *105*(2), 329–338. https://doi.org/10.1002/JLB.MR0318-104R

Esemuede, N., Lee, T., Pierre-Paul, D., Sumpio, B. E., & Gahtan, V. (2004). The role of thrombospondin-1 in human disease1. *Journal of Surgical Research*, *122*(1), 135–142. https://doi.org/10.1016/j.jss.2004.05.015

Esen, F., Erdem, T., Aktan, D., Orhan, M., Kaya, M., Eraksoy, H., … Telci, L. (2004). Effect of magnesium sulfate administration on blood–brain barrier in a rat model of intraperitoneal sepsis: A randomized controlled experimental study. *Critical Care*, *9*(1), R18.

Ezekiel, U. R., & Heuertz, R. M. (2015). Preliminary screening of anti-inflammatory effect of phytochemicals on chemotaxis of human neutrophils. *Journal of Pharmacognosy and Phytotherapy*, *7*(8), 183–188.

Fereydouni, N., Darroudi, M., Movaffagh, J., Shahroodi, A., Butler, A. E., Ganjali, S., & Sahebkar, A. (2019). Curcumin nanofibers for the purpose of wound healing. *Journal of Cellular Physiology*, *234*(5), 5537–5554. https://doi.org/10.1002/jcp.27362

Fontenot, J. D., Gavin, M. A., & Rudensky, A. Y. (2003). Foxp3 programs the development and function of CD4+ CD25+ regulatory T cells. *Nature Immunology*, *4*(4), 330–336. https://doi.org/10.1038/ni904

Ganatra, H. A., Varisco, B. M., Harmon, K., Lahni, P., Opoka, A., & Wong, H. R. (2017). Zinc supplementation leads to immune modulation and improved survival in a juvenile model of murine sepsis. *Innate Immunity*, *23*(1), 67–76. https://doi.org/10.1177/1753425916677073

Ghashut, R. A., Blackwell, S., Ryan, S., Willox, L., McMillan, D. C., Kinsella, J., & Talwar, D. (2017). Assessment of asymmetrical dimethylarginine metabolism in patients with critical illness. *European Journal of Clinical Investigation*, *47*(4), 279–288. https://doi.org/10.1111/eci.12710

Ghazimoradi, M., Saberi-Karimian, M., Mohammadi, F., Sahebkar, A., Tavallaie, S., Safarian, H., … Ahmadinejad, M. (2017). The effects of curcumin and curcumin–phospholipid complex on the serum pro-oxidant–antioxidant balance in subjects with metabolic syndrome. *Phytotherapy Research*, *31*(11), 1715–1721. https://doi.org/10.1002/ptr.5899

Gofton, T. E., & Young, G. B. (2012). Sepsis-associated encephalopathy. *Nature Reviews Neurology*, *8*(10), 557–566. https://doi.org/10.1038/nrneurol.2012.183

Gong, Z., Zhou, J., Li, H., Gao, Y., Xu, C., Zhao, S., … Wu, J. (2015). Curcumin suppresses NLRP3 inflammasome activation and protects

against LPS-induced septic shock. *Molecular Nutrition & Food Research*, *59*(11), 2132–2142. https://doi.org/10.1002/mnfr.201500316

Gradišar, H., Keber, M. M., Pristovšek, P., & Jerala, R. (2007). MD-2 as the target of curcumin in the inhibition of response to LPS. *Journal of Leukocyte Biology*, *82*(4), 968–974. https://doi.org/10.1189/jlb.1206727

Gupta, S. C., Prasad, S., Kim, J. H., Patchva, S., Webb, L. J., Priyadarsini, I. K., & Aggarwal, B. B. (2011). Multitargeting by curcumin as revealed by molecular interaction studies. *Natural Product Reports*, *28*(12), 1937–1955. https://doi.org/10.1039/c1np00051a

Hajialilo, M., Dolati, S., Abdolmohammadi-Vahid, S., Ahmadi, M., Kamrani, A., Eghbal-Fard, S., … Yousefi, M. (2019). Nanocurcumin: A novel strategy in treating ankylosing spondylitis by modulating Th17 cells frequency and function. *Journal of Cellular Biochemistry*, *120*(7), 12027–12038. https://doi.org/10.1002/jcb.28488

Hao, H., Cao, L., Jiang, C., Che, Y., Zhang, S., Takahashi, S., … Gonzalez, F. J. (2017). Farnesoid X receptor regulation of the NLRP3 inflammasome underlies cholestasis-associated sepsis. *Cell Metabolism*, *25*(4), 856–867. e855. https://doi.org/10.1016/j.cmet.2017.03.007

Hewlings, S. J., & Kalman, D. S. (2017). Curcumin: A review of its' effects on human health. *Foods*, *6*(10), 92. https://doi.org/10.3390/foods6100092

Hu, M., Du, Q., Vancurova, I., Lin, X., Miller, E. J., Simms, H. H., & Wang, P. (2005). Proapoptotic effect of curcumin on human neutrophils: Activation of the p38 mitogen-activated protein kinase pathway. *Critical Care Medicine*, *33*(11), 2571–2578. https://doi.org/10.1097/01.CCM.0000186760.20502.C7

Hu, W., Cai, M., Qi, D., Ying, X., Huang, C., & Xing, C. (2018). β-Ionone-derived curcumin analogs as potent anti-inflammatory agents. *Pharmaceutical Chemistry Journal*, *51*(10), 902–906. https://doi.org/10.1007/s11094-018-1713-9

Huang, S., Zhao, L., Kim, K., Lee, D. S., & Hwang, D. H. (2008). Inhibition of Nod2 signaling and target gene expression by curcumin. *Molecular Pharmacology*, *74*(1), 274–281. https://doi.org/10.1124/mol.108.046169

Imran, M., Ullah, A., Saeed, F., Nadeem, M., Arshad, M. U., & Suleria, H. A. R. (2018). Cucurmin, anticancer, & antitumor perspectives: A comprehensive review. *Critical Reviews in Food Science and Nutrition*, *58*(8), 1271–1293. https://doi.org/10.1080/10408398.2016.1252711

Indira Priyadarsini, K. (2013). Chemical and structural features influencing the biological activity of curcumin. *Current Pharmaceutical Design*, *19*(11), 2093–2100.

Jacob, A., Wu, R., Zhou, M., & Wang, P. (2007). Mechanism of the anti-inflammatory effect of curcumin: PPAR-γ activation. *PPAR Research*, *2007*, 5. https://doi.org/10.1155/2007/89369

Jagetia, G. C., & Aggarwal, B. B. (2007). "Spicing up" of the immune system by curcumin. *Journal of Clinical Immunology*, *27*(1), 19–35. https://doi.org/10.1007/s10875-006-9066-7

Jin, L., Batra, S., & Jeyaseelan, S. (2017). Diminished neutrophil extracellular trap (NET) formation is a novel innate immune deficiency induced by acute ethanol exposure in polymicrobial sepsis, which can be rescued by CXCL1. *PLoS Pathogens*, *13*(9), e1006637. https://doi.org/10.1371/journal.ppat.1006637

Jobin, C., Bradham, C. A., Russo, M. P., Juma, B., Narula, A. S., Brenner, D. A., & Sartor, R. B. (1999). Curcumin blocks cytokine-mediated NF-κB activation and proinflammatory gene expression by inhibiting inhibitory factor I-κB kinase activity. *The Journal of Immunology*, *163*(6), 3474–3483.

Kakihana, Y., Ito, T., Nakahara, M., Yamaguchi, K., & Yasuda, T. (2016). Sepsis-induced myocardial dysfunction: Pathophysiology and management. *Journal of Intensive Care*, *4*(1), 22. https://doi.org/10.1186/s40560-016-0148-1

Kanakasabai, S., Casalini, E., Walline, C. C., Mo, C., Chearwae, W., & Bright, J. J. (2012). Differential regulation of CD4+ T helper cell responses by curcumin in experimental autoimmune encephalomyelitis. *The Journal of Nutritional Biochemistry*, *23*(11), 1498–1507. https://doi.org/10.1016/j.jnutbio.2011.10.002

Kang, B., Song, Y., Kim, K. M., Choe, Y., Hwang, S., & Kim, T. S. (1999). Curcumin inhibits Th1 cytokine profile in CD4+ T cells by suppressing interleukin-12 production in macrophages. *British Journal of Pharmacology*, *128*(2), 380–384. https://doi.org/10.1038/sj.bjp.0702803

Khajehdehi, P. (2012). Turmeric: Reemerging of a neglected Asian traditional remedy. *Journal of Nephropathology*, *1*(1), 17–22. https://doi.org/10.5812/jnp.5

Khanji, A. N., Michaux, F., Petit, J., Salameh, D., Rizk, T., Jasniewski, J., & Banon, S. (2018). Structure, gelation, and antioxidant properties of curcumin-doped casein micelle powder produced by spray-drying. *Food & Function*, *9*(2), 971–981. https://doi.org/10.1039/C7FO01923H

Khayyal, M. T., El-Hazek, R. M., El-Sabbagh, W. A., Frank, J., Behnam, D., & Abdel-Tawab, M. (2018). Micellar solubilisation enhances the antiinflammatory activities of curcumin and boswellic acids in rats with adjuvant-induced arthritis. *Nutrition*, *54*, 189–196. https://doi.org/10.1016/j.nut.2018.03.055

Kim, G.-Y., Kim, K.-H., Lee, S.-H., Yoon, M.-S., Lee, H.-J., Moon, D.-O., … Park, Y.-M. (2005). Curcumin inhibits immunostimulatory function of dendritic cells: MAPKs and translocation of NF-κB as potential targets. *The Journal of Immunology*, *174*(12), 8116–8124. https://doi.org/10.4049/jimmunol.174.12.8116

Kim, J., Jeong, S.-W., Quan, H., Jeong, C.-W., Choi, J.-I., & Bae, H.-B. (2016). Effect of curcumin (*Curcuma longa* extract) on LPS-induced acute lung injury is mediated by the activation of AMPK. *Journal of Anesthesia*, *30*(1), 100–108. https://doi.org/10.1007/s00540-015-2073-1

Kocaadam, B., & Şanlier, N. (2017). Curcumin, an active component of turmeric (*Curcuma longa*), and its effects on health. *Critical Reviews in Food Science and Nutrition*, *57*(13), 2889–2895. https://doi.org/10.1080/10408398.2015.1077195

Kumar, S., Gupta, E., Kaushik, S., Kumar Srivastava, V., Mehta, S. K., & Jyoti, A. (2018). Evaluation of oxidative stress and antioxidant status: Correlation with the severity of sepsis. *Scandinavian Journal of Immunology*, *87*(4), e12653. https://doi.org/10.1111/sji.12653

Kumari, A., Dash, D., & Singh, R. (2017). Curcumin inhibits lipopolysaccharide (LPS)-induced endotoxemia and airway inflammation through modulation of sequential release of inflammatory mediators (TNF-α and TGF-β1) in murine model. *Inflammopharmacology*, *25*(3), 329–341. https://doi.org/10.1007/s10787-017-0334-3

Kumari, A., Tyagi, N., Dash, D., & Singh, R. (2015). Intranasal curcumin ameliorates lipopolysaccharide-induced acute lung injury in mice. *Inflammation*, *38*(3), 1103–1112. https://doi.org/10.1007/s10753-014-0076-y

Larmonier, C., Midura-Kiela, M., Ramalingam, R., Laubitz, D., Janikashvili, N., Larmonier, N., … Kiela, P. (2010). Modulation of neutrophil motility by curcumin: Implications for inflammatory bowel disease. *Inflammatory Bowel Diseases*, *17*(2), 503–515.

Lee, S. W., Park, H. J., Van Kaer, L., Hong, S., & Hong, S. (2018). Graphene oxide polarizes iNKT cells for production of TGFβ and attenuates inflammation in an iNKT cell-mediated sepsis model. *Scientific Reports*, *8*(1), 10081. https://doi.org/10.1038/s41598-018-28396-9

Leeuwenberg, J., Smeets, E., Neefjes, J., Shaffer, M., Cinek, T., Jeunhomme, T., … Buurman, W. (1992). E-selectin and intercellular adhesion molecule-1 are released by activated human endothelial cells in vitro. *Immunology*, *77*(4), 543–549.

Li, C., Miao, X., Li, F., Adhikari, B. K., Liu, Y., Sun, J., … Wang, Y. (2019). Curcuminoids: Implication for inflammation and oxidative stress in cardiovascular diseases. *Phytotherapy Research*, *33*(5), 1302–1317. https://doi.org/10.1002/ptr.6324

Liu, W., Guo, W., Zhu, Y., Peng, S., Zheng, W., Zhang, C., … Meng, X. (2018). Targeting peroxiredoxin 1 by a curcumin analogue, AI-44, inhibits NLRP3 inflammasome activation and attenuates lipopolysaccharide-induced sepsis in mice. *The Journal of Immunology*, *201*(8), 2403–2413. https://doi.org/10.4049/jimmunol.1700796

Liu, Y., Jing, Y.-Y., Zeng, C.-Y., Li, C.-G., Xu, L.-H., Yan, L., … He, X.-H. (2018). Scutellarin suppresses NLRP3 inflammasome activation in macrophages and protects mice against bacterial sepsis. *Frontiers in Pharmacology*, *8*, 975. https://doi.org/10.3389/fphar.2017.00975

Liu, Y., Zhang, W., Cheng, Y., Miao, C., Gong, J., & Wang, M. (2018). Activation of PPARγ by curcumin protects mice from ischemia/reperfusion injury induced by orthotopic liver transplantation via modulating polarization of Kupffer cells. *International Immunopharmacology*, *62*, 270–276. https://doi.org/10.1016/j.intimp.2018.07.013

Liu, Y.-F., Yang, C.-W., Liu, H., Sui, S.-G., & Li, X.-D. (2017). Efficacy and therapeutic potential of curcumin against sepsis-induced chronic lung injury in male albino rats. *The Journal of Nutrition, Health & Aging*, *21*(3), 307–313. https://doi.org/10.1007/s12603-016-0722-1

Lorente, L., Martín, M. M., Pérez-Cejas, A., Abreu-González, P., López, R. O., Ferreres, J., … Jiménez, A. (2018). Serum total antioxidant capacity during the first week of sepsis and mortality. *Journal of Critical Care*, *47*, 139–144. https://doi.org/10.1016/j.jcrc.2018.06.025

Lu, W., Jiang, J. P., Hu, J., Wang, J., & Zheng, M. Z. (2015). Curcumin protects against lipopolysaccharide-induced vasoconstriction dysfunction via inhibition of thrombospondin-1 and transforming growth factor-β1. *Experimental and Therapeutic Medicine*, *9*(2), 377–383. https://doi.org/10.3892/etm.2014.2105

Luo, Y.-P., Jiang, L., Kang, K., Fei, D.-S., Meng, X.-L., Nan, C.-C., … Zhao, M.-Y. (2014). Hemin inhibits NLRP3 inflammasome activation in sepsis-induced acute lung injury, involving heme oxygenase-1. *International Immunopharmacology*, *20*(1), 24–32.

Ma, F., Liu, F., Ding, L., You, M., Yue, H., Zhou, Y., & Hou, Y. (2017). Anti-inflammatory effects of curcumin are associated with down regulating microRNA-155 in LPS-treated macrophages and mice. *Pharmaceutical Biology*, *55*(1), 1263–1273. https://doi.org/10.1080/13880209.2017.1297838

Madan, B., & Ghosh, B. (2003). Diferuloylmethane inhibits neutrophil infiltration and improves survival of mice in high-dose endotoxin shock. *Shock*, *19*(1), 91–96. https://doi.org/10.1097/00024382-200301000-00017

Mantzarlis, K., Tsolaki, V., & Zakynthinos, E. (2017). Role of oxidative stress and mitochondrial dysfunction in sepsis and potential therapies. *Oxidative Medicine and Cellular Longevity*, *2017*, 10. https://doi.org/10.1155/2017/598520

Marini, E., Di Giulio, M., Magi, G., Di Lodovico, S., Cimarelli, M. E., Brenciani, A., … Facinelli, B. (2018). Curcumin, an antibiotic resistance breaker against a multiresistant clinical isolate of *Mycobacterium abscessus*. *Phytotherapy Research*, *32*(3), 488–495. https://doi.org/10.1002/ptr.5994

Markose, D., Kirkland, P., Ramachandran, P., & Henderson, N. (2018). Immune cell regulation of liver regeneration and repair. *Journal of Immunology and Regenerative Medicine*, *2*, 1–10. https://doi.org/10.1016/j.regen.2018.03.003

Marquardt, J. U., Gomez-Quiroz, L., Camacho, L. O. A., Pinna, F., Lee, Y.-H., Kitade, M., … Galle, P. R. (2015). Curcumin effectively inhibits oncogenic NF-κB signaling and restrains stemness features in liver cancer. *Journal of Hepatology*, *63*(3), 661–669. https://doi.org/10.1016/j.jhep.2015.04.018

Martinod, K., Demers, M., Fuchs, T. A., Wong, S. L., Brill, A., Gallant, M., … Wagner, D. D. (2013). Neutrophil histone modification by peptidylarginine deiminase 4 is critical for deep vein thrombosis in mice. *Proceedings of the National Academy of Sciences*, *110*(21), 8674–8679. https://doi.org/10.1073/pnas.1301059110

McDonald, B., Davis, R. P., Kim, S.-J., Tse, M., Esmon, C. T., Kolaczkowska, E., & Jenne, C. N. (2017). Platelets and neutrophil extracellular traps collaborate to promote intravascular coagulation during sepsis in mice. *Blood*, *129*(10), 1357–1367. https://doi.org/10.1182/blood-2016-09-741298

McMaken, S., Exline, M. C., Mehta, P., Piper, M., Wang, Y., Fischer, S. N., … Ali, N. A. (2011). Thrombospondin-1 contributes to mortality in murine sepsis through effects on innate immunity. *PLoS ONE*, *6*(5), e19654. https://doi.org/10.1371/journal.pone.0019654

Memis, D., Hekimoglu, S., Sezer, A., Altaner, S., Sut, N., & Usta, U. (2008). Curcumin attenuates the organ dysfunction caused by endotoxemia in the rat. *Nutrition*, *24*(11-12), 1133–1138. https://doi.org/10.1016/j.nut.2008.06.008

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Annals of Internal Medicine*, *151*(4), 264–269. https://doi.org/10.7326/0003-4819-151-4-200908180-00135

Moon, S. J., Kim, H. Y., Kim, Y. H., Kim, K. S., Noh, J. R., Kim, H. J., … Lee, C. H. (2018). GADD45β plays a protective role in acute lung injury by regulating apoptosis in experimental sepsis in vivo. *Journal of Cellular Physiology*, *233*(10), 7128–7138. https://doi.org/10.1002/jcp.26635

Nimse, S. B., & Pal, D. (2015). Free radicals, natural antioxidants, and their reaction mechanisms. *RSC Advances*, *5*(35), 27986–28006. https://doi.org/10.1039/C4RA13315C

Okunieff, P., Xu, J., Hu, D., Liu, W., Zhang, L., Morrow, G., … Ding, I. (2006). Curcumin protects against radiation-induced acute and chronic cutaneous toxicity in mice and decreases mRNA expression of inflammatory and fibrogenic cytokines. *International Journal of Radiation Oncology* Biology* Physics*, *65*(3), 890–898. https://doi.org/10.1016/j.ijrobp.2006.03.025

Oliveira, Y. P. A. d., Pontes-de-Carvalho, L. C., Couto, R. D., & Noronha-Dutra, A. A. (2017). Oxidative stress in sepsis. Possible production of free radicals through an erythrocyte-mediated positive feedback mechanism. *Brazilian Journal of Infectious Diseases*, *21*(1), 19–26.

Olszanecki, R., Gebska, A., & Korbut, R. (2007). The role of haem oxygenase-1 in the decrease of endothelial intercellular adhesion molecule-1 expression by curcumin. *Basic & Clinical Pharmacology & Toxicology*, *101*(6), 411–415. https://doi.org/10.1111/j.1742-7843.2007.00151.x

Pan, K., Chen, H., Baek, S. J., & Zhong, Q. (2018). Self-assembled curcumin-soluble soybean polysaccharide nanoparticles: Physicochemical properties and in vitro anti-proliferation activity against cancer cells. *Food Chemistry*, *246*, 82–89. https://doi.org/10.1016/j.foodchem.2017.11.002

Park, K.-R., Lee, J.-H., Choi, C., Liu, K.-H., Seog, D.-H., Kim, Y.-H., … Yea, S. S. (2007). Suppression of interleukin-2 gene expression by isoeugenol is mediated through down-regulation of NF-AT and NF-κB. *International Immunopharmacology*, *7*(9), 1251–1258. https://doi.org/10.1016/j.intimp.2007.05.015

Park, S. Y., Shrestha, S., Youn, Y.-J., Kim, J.-K., Kim, S.-Y., Kim, H. J., … Hong, C.-W. (2017). Autophagy primes neutrophils for neutrophil extracellular trap formation during sepsis. *American Journal of Respiratory and Critical Care Medicine*, *196*(5), 577–589. https://doi.org/10.1164/rccm.201603-0596OC

Park, W., Amin, A. R., Chen, Z. G., & Shin, D. M. (2013). New perspectives of curcumin in cancer prevention. *Cancer Prevention Research*, *6*(5), 387–400. https://doi.org/10.1158/1940-6207.CAPR-12-0410

Peng, X., Dai, C., Liu, Q., Li, J., & Qiu, J. (2018). Curcumin attenuates on carbon tetrachloride-induced acute liver injury in mice via modulation of the Nrf2/HO-1 and TGF-β1/Smad3 pathway. *Molecules*, *23*(1), 215. https://doi.org/10.3390/molecules23010215

Poylin, V., Fareed, M. U., O'Neal, P., Alamdari, N., Reilly, N., Menconi, M., & Hasselgren, P.-O. (2008). The NF-B inhibitor curcumin blocks sepsis-induced muscle proteolysis. *Mediators of Inflammation*, *2008*, 13–13. https://doi.org/10.1155/2008/317851

Priyadarsini, K. I., Maity, D. K., Naik, G., Kumar, M. S., Unnikrishnan, M., Satav, J., & Mohan, H. (2003). Role of phenolic OH and methylene hydrogen on the free radical reactions and antioxidant activity of curcumin. *Free Radical Biology and Medicine*, *35*(5), 475–484. https://doi.org/10.1016/S0891-5849(03)00325-3

Rana, M., Maurya, P., Reddy, S. S., Singh, V., Ahmad, H., Dwivedi, A. K., … Barthwal, M. K. (2016). A standardized chemically modified *Curcuma longa* extract modulates IRAK-MAPK signaling in inflammation and potentiates cytotoxicity. *Frontiers in Pharmacology*, *7*(223). https://doi.org/10.3389/fphar.2016.00223

Ranjan, D., Chen, C., Johnston, T. D., Jeon, H., & Nagabhushan, M. (2004). Curcumin inhibits mitogen stimulated lymphocyte proliferation, NFκB activation, and IL-2 signaling. *The Journal of Surgical Research*, *121*(2), 171–177. https://doi.org/10.1016/j.jss.2004.04.004

Rogers, N., Kireta, S., & Coates, P. (2010). Curcumin induces maturation-arrested dendritic cells that expand regulatory T cells in vitro and in vivo. *Clinical and Experimental Immunology*, *162*(3), 460–473. https://doi.org/10.1111/j.1365-2249.2010.04232.x

Rogobete, A. F., Sandesc, D., Papurica, M., Stoicescu, E. R., Popovici, S. E., Bratu, L. M., … Bedreag, O. H. (2017). The influence of metabolic imbalances and oxidative stress on the outcome of critically ill polytrauma patients: A review. *Burns & Trauma*, *5*(1), 8. https://doi.org/10.1186/s41038-017-0073-0

Roldán, V., Marín, F., Lip, G. Y., & Blann, A. D. (2003). Soluble E-selectin in cardiovascular disease and its risk factors. *Thrombosis and Haemostasis*, *90*(12), 1007–1020. https://doi.org/10.1160/TH02-09-0083

Saeedi, P., Halabian, R., & Fooladi, A. A. I. (2019). Antimicrobial effects of mesenchymal stem cells primed by modified LPS on bacterial clearance in sepsis. *Journal of Cellular Physiology*, *234*(4), 4970–4986. https://doi.org/10.1002/jcp.27298

Saito, S., Nakashima, A., Shima, T., & Ito, M. (2010). Th1/Th2/Th17 and regulatory T-cell paradigm in pregnancy. *American Journal of Reproductive Immunology*, *63*(6), 601–610. https://doi.org/10.1111/j.1600-0897.2010.00852.x

Sakaguchi, S., & Furusawa, S. (2006). Oxidative stress and septic shock: Metabolic aspects of oxygen-derived free radicals generated in the liver during endotoxemia. *FEMS Immunology and Medical Microbiology*, *47*(2), 167–177. https://doi.org/10.1111/J.574-695X.2006.00072.x

Savcun, G. Y., Özkan, E., Dulundu, E., Topaloğlu, Ü., Şehirli, A. Ö., Tok, O. E., … Şener, G. (2013). Antioxidant and anti-inflammatory effects of curcumin against hepatorenal oxidative injury in the experimental sepsis model created in rats. *Turkish Journal of Trauma and Emergency Surgery*, *19*(6), 507–515. https://doi.org/10.5505/tjtes.2013.76390

Schrijver, I. T., Kemperman, H., Roest, M., Kesecioglu, J., & de Lange, D. W. (2017). Myeloperoxidase can differentiate between sepsis and non-infectious SIRS and predicts mortality in intensive care patients with SIRS. *Intensive Care Medicine Experimental*, *5*(1), 43. https://doi.org/10.1186/s40635-017-0157-y

Sharma, A., Yang, W.-L., Matsuo, S., & Wang, P. (2015). Differential alterations of tissue T-cell subsets after sepsis. *Immunology Letters*, *168*(1), 41–50. https://doi.org/10.1016/j.imlet.2015.09.005

Shehzad, A., & Lee, Y. S. (2013). Molecular mechanisms of curcumin action: Signal transduction. *Biofactors*, *39*(1), 27–36. https://doi.org/10.1002/biof.1065

Shukla, P., Dwivedi, P., Gupta, P. K., & Mishra, P. R. (2014). Optimization of novel tocopheryl acetate nanoemulsions for parenteral delivery of curcumin for therapeutic intervention of sepsis. *Expert Opinion on Drug Delivery*, *11*(11), 1697–1712. https://doi.org/10.1517/17425247.2014.932769

Shukla, P., Verma, A. K., Dewangan, J., Rath, S. K., & Mishra, P. R. (2015). Chitosan coated curcumin nanocrystals augment pharmacotherapy via improved pharmacokinetics and interplay of NFκB, Keap1 and Nrf2 expression in Gram negative sepsis. *RSC Advances*, *5*(70), 57006–57020. https://doi.org/10.1039/C5RA06786C

Siddiqui, A. M., Cui, X., Wu, R., Dong, W., Zhou, M., Hu, M., … Wang, P. (2006). The anti-inflammatory effect of curcumin in an experimental model of sepsis is mediated by up-regulation of peroxisome proliferator-activated receptor-γ. *Critical Care Medicine*, *34*(7), 1874–1882. https://doi.org/10.1097/01.CCM.0000221921.71300.BF

Silva, L. S. d., Catalão, C. H. R., Felippotti, T. T., Oliveira-Pelegrin, G. R. d., Petenusci, S., de Freitas, L. A. P., & Rocha, M. J. A. (2017). Curcumin suppresses inflammatory cytokines and heat shock protein 70 release and improves metabolic parameters during experimental sepsis. *Pharmaceutical Biology*, *55*(1), 269–276.

Singla, V., Pratap Mouli, V., Garg, S. K., Rai, T., Choudhury, B. N., Verma, P., … Ahuja, V. (2014). Induction with NCB-02 (curcumin) enema for mild-to-moderate distal ulcerative colitis—A randomized, placebo-controlled, pilot study. *Journal of Crohn's & Colitis*, *8*(3), 208–214. https://doi.org/10.1016/j.crohns.2013.08.006

Sompamit, K., Kukongviriyapan, U., Nakmareong, S., Pannangpetch, P., & Kukongviriyapan, V. (2009). Curcumin improves vascular function and alleviates oxidative stress in non-lethal lipopolysaccharide-induced endotoxaemia in mice. *European Journal of Pharmacology*, *616*(1-3), 192–199. https://doi.org/10.1016/j.ejphar.2009.06.014

Sou, K., Inenaga, S., Takeoka, S., & Tsuchida, E. (2008). Loading of curcumin into macrophages using lipid-based nanoparticles. *International Journal of Pharmaceutics*, *352*(1-2), 287–293. https://doi.org/10.1016/j.ijpharm.2007.10.033

Steinman, R. M., Turley, S., Mellman, I., & Inaba, K. (2000). The induction of tolerance by dendritic cells that have captured apoptotic cells. *The Journal of Experimental Medicine*, *191*(3), 411–416. https://doi.org/10.1084/jem.191.3.411

Sun, D., Zhuang, X., Xiang, X., Liu, Y., Zhang, S., Liu, C., … Zhang, H.-G. (2010). A novel nanoparticle drug delivery system: The anti-inflammatory activity of curcumin is enhanced when encapsulated in exosomes. *Molecular Therapy*, *18*(9), 1606–1614. https://doi.org/10.1038/mt.2010.105

Tabrizi, R., Vakili, S., Akbari, M., Mirhosseini, N., Lankarani, K. B., Rahimi, M., … Asemi, Z. (2019). The effects of curcumin-containing supplements on biomarkers of inflammation and oxidative stress: A systematic review and meta-analysis of randomized controlled trials. *Phytotherapy Research*, *33*(2), 253–262. https://doi.org/10.1002/ptr.6226

Tak, T., Tesselaar, K., Pillay, J., Borghans, J. A., & Koenderman, L. (2013). What's your age again? Determination of human neutrophil half-lives revisited. *Journal of Leukocyte Biology*, *94*(4), 595–601. https://doi.org/10.1189/jlb.1112571

Takahashi, M., Ishiko, T., Kamohara, H., Hidaka, H., Ikeda, O., Ogawa, M., & Baba, H. (2007). Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-

heptadiene-3,5-dione) blocks the chemotaxis of neutrophils by inhibiting signal transduction through IL-8 receptors. *Mediators of Inflammation*, *2007*, 11–11, 11. https://doi.org/10.1155/2007/10767

Taner, G., Aydın, S., Bacanlı, M., Sarıgöl, Z., Şahin, T., Başaran, A. A., & Başaran, N. (2014). Modulating effects of pycnogenol® on oxidative stress and DNA damage induced by sepsis in rats. *Phytotherapy Research*, *28*(11), 1692–1700. https://doi.org/10.1002/ptr.5184

Tao, P., Yin, H., & Ma, Y. (2014). Study of the mechanisms of curcumin on mitochondrial permeability transition of hepatocytes in rats with sepsis. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue*, *26*(9), 666–670. https://doi.org/10.3760/cma.j.issn.2095-4352.2014.09.012

Tham, C. L., Lam, K. W., Rajajendram, R., Cheah, Y. K., Sulaiman, M. R., Lajis, N. H., … Israf, D. A. (2011). The effects of a synthetic curcuminoid analogue, 2,6-bis-(4-hydroxyl-3-methoxybenzylidine)cyclohexanone on proinflammatory signaling pathways and CLP-induced lethal sepsis in mice. *European Journal of Pharmacology*, *652*(1-3), 136–144. https://doi.org/10.1016/j.ejphar.2010.10.092

Vachharajani, V., Wang, S. W., Mishra, N., El Gazzar, M., Yoza, B., & McCall, C. (2010). Curcumin modulates leukocyte and platelet adhesion in murine sepsis. *Microcirculation*, *17*(6), 407–416. https://doi.org/10.1111/j.1549-8719.2010.00039.x

Vasanthkumar, T., Hanumanthappa, M., & Prabhakar, B. (2018). Protective effect of dietary curcumin and capsaicin on LPS-induced inflammation in mice. *Pharmacognosy Journal*, *10*(4), 725–729. https://doi.org/10.5530/pj.2018.4.121

Vaughn, A. R., Haas, K. N., Burney, W., Andersen, E., Clark, A. K., Crawford, R., & Sivamani, R. K. (2017). Potential role of curcumin against biofilm-producing organisms on the skin: A review. *Phytotherapy Research*, *31*(12), 1807–1816. https://doi.org/10.1002/ptr.5912

Vilahur, G., & Badimon, L. (2014). Ischemia/reperfusion activates myocardial innate immune response: The key role of the toll-like receptor. *Frontiers in Physiology*, *5*, 64.

Wang, J., Wang, H., Zhu, R., Liu, Q., Fei, J., & Wang, S. (2015). Anti-inflammatory activity of curcumin-loaded solid lipid nanoparticles in IL-1β transgenic mice subjected to the lipopolysaccharide-induced sepsis. *Biomaterials*, *53*, 475–483. https://doi.org/10.1016/j.biomaterials.2015.02.116

Wang, Y., Shan, X., Dai, Y., Jiang, L., Chen, G., Zhang, Y., … Liang, G. (2015). Curcumin analog L48H37 prevents lipopolysaccharide-induced TLR4 signaling pathway activation and sepsis via targeting MD2. *The Journal of Pharmacology and Experimental Therapeutics*, *353*(3), 539–550. https://doi.org/10.1124/jpet.115.222570

Wu, J., Zhang, Y., Cai, Y., Wang, J., Weng, B., Tang, Q., … Yang, S. (2013). Discovery and evaluation of piperid-4-one-containing mono-carbonyl analogs of curcumin as anti-inflammatory agents. *Bioorganic & Medicinal Chemistry*, *21*(11), 3058–3065. https://doi.org/10.1016/j.bmc.2013.03.057

Wu, R., Cui, X., Dong, W., Zhou, M., Simms, H. H., & Wang, P. (2006). Suppression of hepatocyte CYP1A2 expression by Kupffer cells via AhR pathway: The central role of proinflammatory cytokines. *International Journal of Molecular Medicine*, *18*(2), 339–346.

Wu, Y., Liu, Z., Wu, W., Lin, S., Zhang, N., Wang, H., … Xu, J. (2018). Effects of FM0807, a novel curcumin derivative, on lipopolysaccharide-induced inflammatory factor release via the ROS/JNK/p53 pathway in RAW264.7 cells. *Bioscience Reports*, *38*(5), BSR20180849. https://doi.org/10.1042/BSR20180849

Xiao, X., Yang, M., Sun, D., & Sun, S. (2012). Curcumin protects against sepsis-induced acute lung injury in rats. *The Journal of Surgical Research*, *176*(1), e31–e39. https://doi.org/10.1016/j.jss.2011.11.1032

Xie, Y. L., Chu, J. G., Jian, X. M., Dong, J. Z., Wang, L. P., Li, G. X., & Yang, N. B. (2017). Curcumin attenuates lipopolysaccharide/D-galactosamine-induced acute liver injury by activating Nrf2 nuclear translocation and inhibiting NF-kB activation. *Biomedicine & Pharmacotherapy*, *91*, 70–77. https://doi.org/10.1016/j.biopha.2017.04.070

Xu, F., Lin, S.-H., Yang, Y.-Z., Guo, R., Cao, J., & Liu, Q. (2013). The effect of curcumin on sepsis-induced acute lung injury in a rat model through the inhibition of the TGF-β1/SMAD3 pathway. *International Immunopharmacology*, *16*(1), 1–6. https://doi.org/10.1016/j.intimp.2013.03.014

Xu, F., Yang, Y., & Liu, Q. (2011). Protective effect of curcumin on mice with acute lung injury induced by sepsis and its influence on expressions of intercellular adhesion molecule-1 and tumor necrosis factor-alpha. *Chinese Journal of Biologicals*, *24*(1), 75–78.

Xu, Y., & Liu, L. (2017). Curcumin alleviates macrophage activation and lung inflammation induced by influenza virus infection through inhibiting the NF-κB signaling pathway. *Influenza and Other Respiratory Viruses*, *11*(5), 457–463. https://doi.org/10.1111/irv.12459

Yadav, D., Yadav, S. K., Khar, R. K., Mujeeb, M., & Akhtar, M. (2013). Turmeric (*Curcuma longa* L.): A promising spice for phytochemical and pharmacological activities. *International Journal of Green Pharmacy (IJGP)*, *7*(2), 9–85.

Yadav, V. S., Mishra, K. P., Singh, D. P., Mehrotra, S., & Singh, V. K. (2005). Immunomodulatory effects of curcumin. *Immunopharmacology and Immunotoxicology*, *27*(3), 485–497. https://doi.org/10.1080/08923970500242244

Yang, C., Wu, K., Li, S.-H., & You, Q. (2013). Protective effect of curcumin against cardiac dysfunction in sepsis rats. *Pharmaceutical Biology*, *51*(4), 482–487. https://doi.org/10.3109/13880209.2012.742116

Yin, H., Qiu, M., He, D., Zhang, R., Tao, P., Liang, Y., … Ye, X. (2017). Protective effect of curcumin on hepatocytes in rats with sepsis. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue*, *29*(2), 162–166. https://doi.org/10.3760/cma.j.issn.2095-4352.2017.02.013

Yin, H.-Y., Tao, P., Wei, J.-R., Zhang, R., & Ma, Y.-H. (2016). Protective effects of curcumin on hepatocytes in cecal ligation and puncture-induced sepsis in rats. *International Journal of Clinical and Experimental Medicine*, *9*, 23072–23081.

Youn, H. S., Saitoh, S. I., Miyake, K., & Hwang, D. H. (2006). Inhibition of homodimerization of Toll-like receptor 4 by curcumin. *Biochemical Pharmacology*, *72*(1), 62–69. https://doi.org/10.1016/j.bcp.2006.03.022

Yuan, Z., Syed, M. A., Panchal, D., Rogers, D., Joo, M., & Sadikot, R. T. (2012). Curcumin mediated epigenetic modulation inhibits TREM-1 expression in response to lipopolysaccharide. *The International Journal of Biochemistry & Cell Biology*, *44*(11), 2032–2043. https://doi.org/10.1016/j.biocel.2012.08.001

Yun, S. S., Kim, S. P., Kang, M. Y., & Nam, S. H. (2010). Inhibitory effect of curcumin on liver injury in a murine model of endotoxemic shock. *Biotechnology Letters*, *32*(2), 209–214. https://doi.org/10.1007/s10529-009-0153-8

Zeerleder, S., Hack, C. E., & Wuillemin, W. A. (2005). Disseminated intravascular coagulation in sepsis. *Chest*, *128*(4), 2864–2875. https://doi.org/10.1378/chest.128.4.2864

Zhang, Y., Jiang, X., Peng, K., Chen, C., Fu, L., Wang, Z., … Pan, Z. (2014). Discovery and evaluation of novel anti-inflammatory derivatives of natural bioactive curcumin. *Drug Design, Development and Therapy*, *8*, 2161.

Zhang, Y., Liang, D., Dong, L., Ge, X., Xu, F., Chen, W., … Liang, G. (2015). Anti-inflammatory effects of novel curcumin analogs in experimental acute lung injury. *Respiratory Research*, *16*, 43. https://doi.org/10.1186/s12931-015-0199-1

Zhang, Y., Liu, Z., Wu, J., Bai, B., Chen, H., Xiao, Z., … Zhang, H. (2018). New MD2 inhibitors derived from curcumin with improved anti-

inflammatory activity. *European Journal of Medicinal Chemistry*, *148*, 291–305. https://doi.org/10.1016/j.ejmech.2018.02.008

Zhao, C., Zhang, Y., Zou, P., Wang, J., He, W., Shi, D., … Yang, S. (2015). Synthesis and biological evaluation of a novel class of curcumin analogs as anti-inflammatory agents for prevention and treatment of sepsis in mouse model. *Drug Design, Development and Therapy*, *9*, 1663.

Zhao, M., Wang, Y., Yue, Y., Zhang, R., Wang, S., Zhang, W., & Ma, S. (2016). Curcumin alleviates neuronal apoptosis and cerebral mitochondrial dysfunction in septic mice. *International Journal of Clinical and Experimental Medicine*, *9*(3), 6107–6113.

Zhong, W., Qian, K., Xiong, J., Ma, K., Wang, A., & Zou, Y. (2016). Curcumin alleviates lipopolysaccharide induced sepsis and liver failure by suppression of oxidative stress-related inflammation via PI3K/AKT and NF-κB related signaling. *Biomedicine & Pharmacotherapy*, *83*, 302–313. https://doi.org/10.1016/j.biopha.2016.06.036

How to cite this article: Karimi A, Ghodsi R, Kooshki F, Karimi M, Asghariazar V, Tarighat-Esfanjani A. Therapeutic effects of curcumin on sepsis and mechanisms of action: A systematic review of preclinical studies. *Phytotherapy Research*. 2019;1–23. https://doi.org/10.1002/ptr.6467