Natural Bioactive Compounds in Sepsis: A Systematic Review of the Effects of Propolis and Curcumin on Inflammatory Cytokines

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Abstract. Sepsis is a life-threatening condition caused by a dysregulated host response to infection, in which excessive production of inflammatory cytokines drives tissue injury and multiple organ dysfunction. Natural bioactive compounds such as propolis and curcumin have attracted attention for their anti-inflammatory, antioxidant and immunomodulatory properties. This systematic review followed the PRISMA 2020 guidelines; the protocol was defined a priori but was not eligible for prospective registration in PROSPERO, which accepts only reviews reporting direct human health outcomes. PubMed, Scopus, ScienceDirect, SpringerLink, Wiley Online Library, Taylor & Francis Online and Google Scholar were searched for studies pub-lished between 2020 and 2026 that evaluated propolis, curcumin or their combination on inflammatory cytokines. Risk of bias was appraised inde-pendently by two reviewers using SYRCLE's tool for animal experiments, Cochrane RoB 2 for randomised trials and modified OHAT criteria for in vitro work. Of 218 records identified, 18 studies met the eligibility criteria and were synthesised qualitatively. Tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1 beta (IL-1β) and interleukin-10 (IL-10) were the most frequently evaluated cytokines. Both compounds consistent-ly reduced TNF-α, IL-6 and IL-1β, whereas several studies reported en-hancement or preservation of IL-10, through inhibition of NF-κB, TLR4 and MAPK signalling and suppression of oxidative stress. Most appraised components were at unclear risk of bias, only one study used a sepsis mod-el, no trial has been conducted in septic patients and no study tested for-mally for synergy. The findings are therefore hypothesis-generating: propo-lis and curcumin plausibly regulate key cytokines of the inflammatory re-sponse, but their clinical value in sepsis remains un proven and requires adequately powered trials.

Keywords: Curcumin, Cytokines, Inflammation, Propolis, Sepsis.

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1 Introduction

Sepsis is a life-threatening syndrome caused by a dysregulated host response to infection that triggers excessive inflammation, immune dysfunction, tissue injury and ultimately multiple organ failure, and it remains a leading cause of morbidity and mortality worldwide [1]. Global estimates indicate millions of cases annually, with marked regional variation attributable to differences in health infrastructure, socioeco-nomic status and the prevalence of infectious disease [2, 3], and severe sepsis and septic shock carry a particularly poor prognosis [4]. Prolonged hospitalisation, inten-sive care use and rehabilitation add to the burden, while delayed diagnosis, patient heterogeneity and antimicrobial resistance continue to complicate management [1, 5].

Inflammatory cytokines are central to the pathogenesis of sepsis and largely responsible for progression from localised infection to systemic inflammation and organ dysfunction. A hallmark of the syndrome is the cytokine storm, in which uncontrolled release of pro-inflammatory mediators disrupts immune homeostasis and pro-motes widespread tissue injury [6, 7]. Tumour necrosis factor-alpha (TNF-α) is among the earliest cytokines released after pathogen recognition and initiates a cascade that stimulates further cytokine and chemokine production [6, 8], while interleukin-1 beta (IL-1β) and interleukin-6 (IL-6) amplify the response by enhancing leukocyte recruitment, vascular permeability, endothelial dysfunction and acute-phase activation [9, 10]. Severity depends on the balance between pro- and anti-inflammatory cytokines, since excessive inflammation destroys tissue whereas profound immunosuppression increases susceptibility to secondary infection [8, 10]; comparable pathogenic roles have been described in other inflammatory disorders [11].

Current management focuses on rapid infection control through antimicrobial therapy, source control, haemodynamic stabilisation and organ support [12, 13], yet mortality remains high because of the complexity and heterogeneity of the host inflammatory response [14]. Therapies directed against individual cytokines have largely failed in clinical trials, owing to variability in patient characteristics, disease stage and immune phenotype [15, 16], and broad suppression of inflammation risks secondary infection and delayed pathogen clearance; the dynamic transition between hyperinflammatory and immunosuppressive phases makes it difficult to attenuate harmful responses without compromising host defence [13, 15, 16]. Attention has therefore shifted towards approaches that modulate inflammation, oxidative stress and immune dysfunction simultaneously and in a more balanced manner [12, 14].

Natural bioactive compounds are attractive candidates because they act on several molecular pathways at once. Propolis, a resin produced by honeybees from plant exudates, contains flavonoids, phenolic acids, terpenoids and caffeic acid phenethyl ester (CAPE), constituents associated with anti-inflammatory, antioxidant and immunomodulatory activity [17, 18]. Curcumin, the principal polyphenol of Curcuma longa, suppresses inflammatory signalling through inhibition of NF-κB, TLR4, MAPK and reactive oxygen species-mediated pathways [19], while propolis regulates TNF-α, IL-1β, IL-6 and IL-10 and thereby helps restore immune balance [20, 21]. Interest in these compounds has nevertheless produced a fragmented literature: findings are dispersed across cell culture systems, animal models and clinical investigations [18, 20], available

reviews generally address propolis or curcumin in isolation [17, 18], and it remains unclear which cytokines are most consistently affected and which mecha-nisms mediate their action [19, 21]. This review therefore synthesises current evidence on the effects of propolis and curcumin on TNF-α, IL-6, IL-1β and IL-10, appraises its methodological reliability and clarifies what can and cannot yet be inferred for sepsis-associated inflammation.

2 Methods

2.1 Study Design and Search Strategy

This systematic literature review synthesised the available evidence on the anti-inflammatory effects of propolis, curcumin and their combinations in sepsis and relat-ed inflammatory conditions, focusing on TNF-α, IL-6, IL-1β and IL-10 and on the mechanisms underlying their immunomodulatory activity. It was performed in ac-cordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines and proceeded through identification, screening, eligibility assessment, data extraction, risk-of-bias appraisal and qualitative synthesis. Because the eligible evidence was expected to be heterogeneous and predominantly preclinical, narrative synthesis rather than meta-analysis was planned from the outset.

A written protocol specifying the research question, search strategy, eligibility criteria, data-extraction fields, risk-of-bias instruments and synthesis plan was agreed by all authors before the search began and followed without amendment. It was not registered prospectively, since PROSPERO accepts only reviews reporting direct health-related outcomes in humans whereas this review was designed to include in vitro and animal evidence; no equivalent preclinical registry was used. The protocol is available from the corresponding author, and the absence of registration is acknowledged as a limitation.

A comprehensive search was carried out in PubMed, Scopus, ScienceDirect, SpringerLink, Wiley Online Library, Taylor & Francis Online and Google Scholar, covering publications issued from 2020 onwards; searches were run between January and May 2026 and combined Medical Subject Headings (MeSH) terms with free-text keywords. The primary search string was (“propolis” OR “bee propolis”) AND (“cur-cumin” OR “Curcuma longa”) AND (“inflammatory cytokines” OR “TNF-alpha” OR “IL-6” OR “IL-1β” OR “IL-10”) AND (“inflammation” OR “oxidative stress” OR “immunomodulation” OR “sepsis”), with database-specific modifications applied where indexing systems required them.

2.2 Eligibility Criteria and Study Selection

All records retrieved were exported to a reference management system for duplicate removal and screening. Selection proceeded in two stages: titles and abstracts were screened first, after which the full texts of potentially relevant articles were assessed against predefined criteria. Studies were eligible if they investigated propolis, curcumin

or their combination and reported measurable outcomes related to inflammatory cytokines, immunomodulation, oxidative stress or sepsis-associated inflammatory responses. Both experimental and clinical studies were considered. The full criteria are presented in Table 1.

Table 1. Inclusion and exclusion criteria applied in the review.

Inclusion criteria	Exclusion criteria
Studies of propolis, curcumin or their combination	Reviews, meta-analyses, editorials and abstracts
Studies of TNF-α, IL-6, IL-1β or IL-10	No inflammatory cytokine or inflammatory outcome
In vitro, in vivo, translational and clinical studies	Purely chemical characterisation, no biological assay
Anti-inflammatory or immunomodulatory effects	Unrelated to inflammation or sepsis conditions
Peer-reviewed original articles in English, 2020–2026	Duplicates, overlapping datasets, non-English
Full-text articles available for review	Inaccessible full text or insufficient data

2.3 Data Extraction, Risk-of-Bias Assessment and Synthesis

Data were extracted independently by two reviewers using a predefined form covering author and publication year, country, research design, inflammatory model, intervention, cytokines measured, anti-inflammatory effects and proposed mechanisms, with particular attention to TNF-α, IL-6, IL-1β and IL-10; discrepancies were resolved by a third reviewer. Findings were synthesised qualitatively through narrative analysis and thematic grouping by study characteristics, inflammatory model, cytokine outcome and underlying mechanism.

Because the eligible evidence spanned several designs, risk of bias was appraised with the instrument appropriate to each design component rather than a single generic checklist. Animal experiments were assessed with SYRCLE's Risk of Bias tool across its ten domains (sequence generation, baseline characteristics, allocation concealment, random housing, blinding of caregivers and investigators, random outcome assessment, blinding of outcome assessors, incomplete outcome data, selective reporting and other bias), and randomised clinical trials with the Cochrane Risk of Bias 2 tool across its five domains. For in vitro and ex vivo experiments, for which no consensus instrument exists, criteria adapted from the OHAT/NTP approach were applied: characterisation of the cell or tissue model, reporting of exposure concentration and duration, use of vehicle and positive controls, randomisation or blinding of assay conditions, number of independent biological replicates and completeness of outcome reporting. Each domain was rated low, unclear or high risk, two reviewers appraised every study independently and disagreements were settled by consensus. No study was excluded on the basis of its appraisal; the ratings were used instead to weight the certainty attached to each finding.

3 Results

3.1 Study Identification and Selection

The initial search yielded 218 records. After duplicate removal, 176 articles were screened by title and abstract, at which stage 124 were excluded as unrelated to propolis or curcumin, not evaluating inflammatory cytokines, addressing chemical characterisation without biological assessment, or being reviews, conference papers or editorials. The remaining 52 articles underwent full-text assessment, of which 34 were excluded for absence of cytokine-related outcomes (n = 12), non-relevant intervention or disease model (n = 9), insufficient data (n = 6), duplicate datasets (n = 4) and inaccessible full text (n = 3). Eighteen studies met all inclusion criteria and entered the final qualitative synthesis, as summarised in Fig. 1.

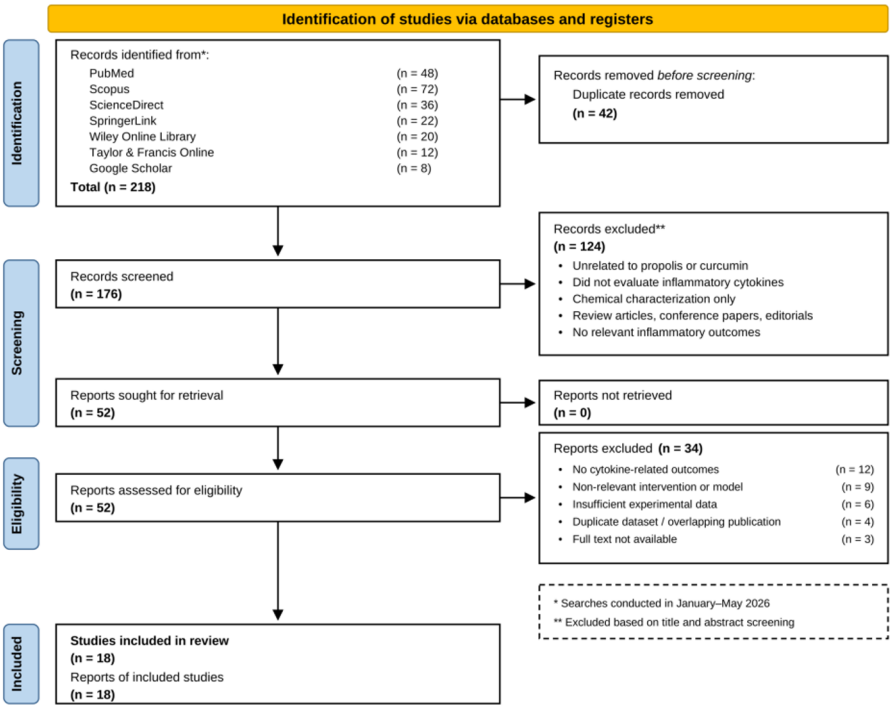


Fig. 1. PRISMA 2020 flow diagram of the study identification, screening, eligibility assessment and inclusion process.

3.2 Characteristics of the Included Studies

The 18 included studies were published between 2020 and 2026 and originated from twelve countries or country groups. Seven evaluated propolis alone, eight curcumin alone and three combined propolis–curcumin formulations, across in vitro experiments,

in vivo animal studies, combined and translational designs and two randomised clinical trials. Characteristics are presented in Table 2.

Table 2. Characteristics of the 18 included studies. TNF-α, tumour necrosis factor-alpha; IL, interleukin; LPS, lipopolysaccharide; PBMC, peripheral blood mononuclear cell; CAPE, caffeic acid phenethyl ester.

Code	Author (year), country	Design and model	Intervention	Cytokines measured and main findings
A1	Zamarrenho et al. (2023), Brazil	In vitro; LPS-stimulated bone marrow-derived macrophages	Polar fraction, dry and microencapsulated extracts, artepillin C, baccharin	TNF-α, IL-6, IL-10. Microencapsulated extract raised IL-10 and baccharin lowered IL-6; high dry-extract doses raised TNF-α, lowered IL-10
A2	Kurek-Górecka et al. (2023), Poland	In vitro; LPS/IFN-α-stimulated gingival fibroblasts (HGF-1)	Ethanolic extract of Polish propolis (EEP) and CAPE	TNF-α, IL-6, IL-8. CAPE lowered TNF-α, IL-6 and IL-8 more than EEP, which alone raised IL-6 and IL-8
A3	Steintún et al. (2026), multinational	In vitro; LPS- and PHA-stimulated human PBMCs	Ethanolic propolis extracts and polyphenols	TNF-α, IL-1β, IL-4, IL-6, IL-10, IFN-γ. IL-1β fell 13–41%; IL-4, IL-6 and TNF-α rose; chrysin best
A4	Franchin et al. (2025), Brazil	In vitro/in vivo; THP-1 macrophages and DSS colitis in mice	Alginate microcapsules with green propolis extract	TNF-α, IL-6, IL-1β. All three and reactive oxygen species fell and colonic lesions decreased by 86.1%
A5	Song et al. (2020), South Korea	In vitro; Helicobacter pylori-infected gastric epithelial cells	Korean propolis	TNF-α, IL-1β, IL-8, IL-12. All fell significantly in a dose-dependent manner
A6	Le et al. (2025), South Korea	In vitro; LPS-stimulated RAW264.7 macrophages	Propolis-derived vesicle-like nanoparticles	TNF-α, IL-1β, IL-6, IL-10, IL-12. All fell significantly, with lower nitric oxide and PGE2 production
A7	Gupta et al. (2022), India	In vivo; rat excisional wound model	5% propolis extract–Passiflora edulis seed oil emulgel	TNF-α, IL-1β, IL-6. All fell significantly while wound contraction and antioxidant activity improved
A8	Abd-Elrazek et al. (2020), Egypt	In vivo; endotoxemia-induced sepsis in adult male rats	Curcumin and propolis pretreatment	IL-1β, PGE2. Both markedly reduced renal IL-1β and PGE2; curcumin was more effective against NF-κB
A9	Britto et al. (2025), Brazil	Randomised double-blind; haemodialysis with CKD (n = 38)	C. longa 137 mg/day + green propolis 500 mg/day, 8 wk	CRP, MIP-1. Both fell versus baseline ($p = 0.026$ and 0.019); uraemic toxins unchanged
A10	Yagci et al. (2025), Turkey	In vitro; beclomethasone-induced oxidative stress in fibroblasts	Anatolian propolis, curcumin and their combination	IL-25, IL-10. Beclomethasone raised both; both agents attenuated the changes, the combination most
A11	Alsulaim et al. (2024), Saudi Arabia	In vivo; streptozotocin-induced type 2 diabetes in rats	Curcumin 50 mg/kg body weight	TNF-α, IL-6. Both, elevated in diabetic rats, fell significantly after curcumin treatment
A12	Asanga et al. (2024), Nigeria	In vivo, in vitro, in silico; inflammation, analgesia, antioxidant assays, docking	C. longa rhizome extract and constituents (curcumin, ar-turmerone)	Cytokines not quantified. Anti-inflammatory activity exceeded aspirin and antioxidant activity vitamin C; 20 bioactive compounds identified
A13	Bisht et al. (2020), New Zealand	In vitro; LPS-stimulated human THP-1 macrophages	Curcumin, chlorogenic acid and their 1:1 combination	TNF-α, IL-6. Curcumin lowered TNF-α dose-dependently; the combination cut TNF-α ~88% and IL-6 ~99%

Code	Author (year), country	Design and model	Intervention	Cytokines measured and main findings
A14	Valizadeh et al. (2020), Iran	Randomised placebo-controlled trial; COVID-19 (n = 40)	Nano-curcumin therapy	TNF-α, IL-1β, IL-6, IL-18. IL-1β and IL-6 expression and secretion fell; TNF-α and IL-18 unaffected
A15	Saied et al. (2021), Egypt	In vivo; ovariectomised rat neuroinflammation model	Curcumin 100 mg/kg/day orally vs fluoxetine, estradiol	TNF-α, IL-1β, IL-6. All attenuated, with lower corticosterone and nitric oxide and improved behaviour
A16	Asadi et al. (2020), Iran	In vitro; TGF-β-stimulated human vascular smooth muscle cells	Curcumin 5, 10, 20 μM vs DPI and N-acetylcysteine	TNF-α, IL-6. TGF-β-induced expression of both fell dose-dependently, with fewer reactive oxygen species
A17	Salah et al. (2022), France	In vitro/ex vivo; Caco-2 cells and colonic explants from mice	Curcumin-loaded crosslinked starch nanoparticles	IL-1β, IL-6, IL-8, IL-10. The first three fell, IL-10 rose; nanoformulation beat free curcumin
A18	Hatipoglu and Keskin (2022), Turkey	In vivo; aflatoxin B1-induced chronic hepatotoxicity in rats	Curcumin 300 mg/kg/day orally with aflatoxin B1	TNF-α, IL-1β, IL-6. Aflatoxin B1 raised all three and curcumin normalised them

3.3 Distribution of the Included Studies

Publication activity was sustained across the review period (five studies in 2020, four in 2021–2022, four in 2023–2024 and five in 2025–2026): earlier work concentrated on individual compounds, whereas more recent studies increasingly examined delivery systems, nanoformulations and combinations intended to improve bioavailability. Brazil was the largest single contributor (3 studies, 16.7%), followed by Turkey, Egypt, Iran and South Korea (2 each, 11.1%). By design, eight studies (44.4%) were in vitro, five (27.8%) in vivo, three (16.7%) combined or translational and two (11.1%) randomised clinical trials; by compound, seven (38.9%) evaluated propolis alone (A1–A7), eight (44.4%) curcumin alone (A11–A18) and three (16.7%) their combination (A8–A10).

In vitro and in vivo work therefore accounted for more than 70% of the evidence, so current knowledge derives principally from preclinical investigation, and neither of the two randomised trials enrolled patients with sepsis.

3.4 Inflammatory Cytokines and Anti-Inflammatory Effects

The most frequently evaluated biomarkers were TNF-α and IL-6 (13 studies each, 72.2%), followed by IL-1β (10 studies, 55.6%) and IL-10 (5 studies, 27.8%), reflecting the central role of the first three in initiating and amplifying inflammation and the use of IL-10 as an index of immunoregulatory activity. The distribution of cytokines and the direction of the reported effects are presented in Table 3.

Table 3. Inflammatory cytokines evaluated across the included studies and direction of the reported effects.

Cytokine	n (%)	Article codes	Direction of effect and main observation
TNF-α	13 (72.2)	A1–A7, A11, A13–A16, A18	Reduced in most studies; unchanged in COVID-19 (A14) and raised at high extract doses (A1) or by whole propolis extract in PBMCs (A3)
IL-6	13 (72.2)	A1–A4, A6, A7, A11, A13–A18	Consistently suppressed, except in gingival fibroblasts (A2) and PBMCs (A3) exposed to whole ethanolic propolis extract
IL-1β	10 (55.6)	A3–A8, A14, A15, A17, A18	Consistently reduced, indicating inhibition of inflammasome-associated inflammatory responses
IL-10	5 (27.8)	A1, A3, A6, A10, A17	Increased or preserved after microencapsulated propolis (A1), combination (A10) and curcumin nanoparticles (A17); reduced in A3 and A6
IL-8	3 (16.7)	A2, A5, A17	Reduced by CAPE (A2), Korean propolis (A5) and curcumin-loaded starch nanoparticles (A17)
IL-12	2 (11.1)	A5, A6	Reduced in gastric epithelial cells and in LPS-stimulated macrophages
Other mediators	6 (33.3)	A3, A6, A8, A9, A10, A14	IL-4, IL-18, IL-25, IFN-γ, CRP, MIP-1, PGE2; modulation was model-dependent, CRP and MIP-1 falling in haemodialysis patients (A9) and PGE2 in endotoxemic rats (A8) and macrophages (A6)

Most studies reported significant reductions in TNF-α, IL-6 and IL-1β after treatment, while IL-10 was generally increased or preserved. The pattern was not uniform: whole ethanolic propolis extract increased IL-6 and TNF-α while lowering IL-1β and IL-10 in peripheral blood mononuclear cells (A3) and increased IL-6 and IL-8 in gingival fibroblasts although its isolated constituent CAPE suppressed them (A2), and high concentrations of a soluble propolis dry extract raised TNF-α and lowered IL-10 (A1). The cytokine response to propolis therefore depends on formulation, concentration and the specific bioactive constituent, whereas curcumin produced more uniformly suppressive effects. Combined propolis–curcumin formulations outperformed either compound alone (A8–A10), and a curcumin–chlorogenic acid combination was described as synergistic in LPS-stimulated macrophages (A13), although none of these studies applied a formal test of interaction.

3.5 Biological Mechanisms Underlying the Anti-Inflammatory Effects

A consistent pattern of interconnected mechanisms emerged across the different models, summarised in Table 4. The most frequently reported were reduction of oxidative stress (10 studies), enhancement of endogenous antioxidant defences (7 studies) and inhibition of NF-κB signalling (4 studies), with additional suppression of TLR4, MAPK and Smad pathways and of cyclooxygenase-dependent mediator synthesis. Curcumin was more often associated with direct suppression of oxidative stress and intracellular signalling, propolis with broader immunomodulatory actions affecting both pro- and anti-inflammatory cytokines. Six studies used nanoformulation or microencapsulation

and reported improved bioavailability, indicating that the delivery system is an important determinant of efficacy.

Table 4. Biological mechanisms underlying the anti-inflammatory effects of propolis and curcumin.

Mechanism	n	Article codes	Key findings
Reduction of oxidative stress	10	A4, A5, A6, A8, A10, A11, A12, A15, A16, A18	Decreased reactive oxygen species, nitric oxide and lipid peroxidation, with improved redox status
Enhancement of endogenous antioxidant defences	7	A5, A7, A8, A11, A12, A15, A18	Increased superoxide dismutase, catalase, glutathione peroxidase and glutathione
Inhibition of NF-κB signalling	4	A5, A6, A8, A13	Reduced transcription of TNF-α, IL-1β, IL-6 and other pro-inflammatory mediators
Inhibition of COX and prostaglandin synthesis	4	A6, A8, A12, A13	Reduced COX-2 expression and PGE2 production
Nanoformulation or microencapsulation	6	A1, A4, A6, A9, A14, A17	Enhanced delivery, producing greater cytokine modulation than free compounds
Regulation of Th1/Th2 and cytokine balance	4	A1, A2, A3, A10	Modulation of IL-4, IL-10, IL-25 and IFN-γ and of the pro-/anti-inflammatory balance
Suppression of TLR4 signalling	2	A6, A13	Reduced cytokine production and macrophage activation
Modulation of MAPK and Smad signalling	2	A5, A16	Suppression of pathways driving inflammatory gene expression
Regulation of apoptotic signalling	2	A8, A12	Decreased Bax/Bcl-2 ratio and apoptosis-associated tissue damage
Promotion of tissue repair and regeneration	2	A7, A10	Enhanced collagen synthesis, remodelling and growth factor signalling

3.6 Risk of Bias in the Included Studies

The 18 studies yielded 21 separately appraised design components. No animal experiment satisfied every SYRCLE domain, sequence generation, allocation concealment and blinding being rarely reported, so six components were rated unclear and one (A11) high risk for incomplete outcome data. Of the randomised trials, A14 was judged low risk overall whereas A9 raised some concerns given its small sample (n = 38), eight-week exposure and limited description of randomisation. Among the in vitro and ex vivo components, three were rated low risk and eight unclear, most often because blinding, replicate number or the use of vehicle and positive controls was not stated; the in-silico component of A12 was not appraised, no validated instrument being available (Table 5).

Table 5. Risk-of-bias appraisal by design component. Studies contributing more than one design were appraised separately for each, so the total (21) exceeds the 18 studies. SYRCLE, Systematic Review Centre for Laboratory animal Experimentation; OHAT, Office of Health Assessment and Translation.

Design component (appraisal tool)	n	Overall judgement	Domains most often unclear or at risk
In vivo animal experiments (SYRCLE RoB)	7	6 unclear, 1 high	Sequence generation, allocation concealment, random housing, blinding of caregivers and outcome assessors; incomplete outcome data (A11)
Randomised clinical trials (Cochrane RoB 2)	2	1 low, 1 some concerns	Randomisation process; small sample and short exposure (A9). Outcome measurement was otherwise adequately reported
In vitro and ex vivo experiments (modified OHAT criteria)	11	3 low, 8 unclear	Blinding of outcome assessment, number of independent biological replicates, reporting of vehicle and positive controls
In silico component (A12)	1	Not appraised	No validated instrument available; treated as supportive evidence only

Most evidence was therefore at unclear rather than high risk of bias, reflecting incomplete reporting rather than demonstrably flawed conduct; because no component was free of concern across all domains, consistency between studies should not by itself be read as confirmation of validity.

4 Discussion

The evidence reviewed here indicates that propolis and curcumin modulate the cytokines most closely implicated in sepsis. Propolis reduced pro-inflammatory cytokine production in macrophages, peripheral blood mononuclear cells, gingival and gastric epithelial cells and healing wound tissue [22–28], while curcumin showed comparable activity in endotoxemia-induced sepsis, diabetes, neuroinflammation, hepatotoxicity, intestinal and vascular inflammation and COVID-19 [29, 30, 31–39]. This is consistent with the view that excessive cytokine production drives inflammatory disease progression and that compounds acting on several pathways at once merit further investigation.

TNF-α, IL-6 and IL-1β emerge as the most plausible targets. TNF-α initiates the inflammatory cascade, promoting downstream cytokine production, leukocyte recruitment and vascular injury, and was consistently reduced across experimental settings [23, 25, 27, 34, 39]. Similar patterns were observed for IL-6 and IL-1β, cytokines closely associated with cytokine storm development and organ dysfunction: nano-curcumin significantly lowered both in patients with COVID-19 [35], while propolis-derived nanoparticles and microencapsulated formulations suppressed them in cellular and animal models [25, 27].

Several studies also reported enhancement or preservation of IL-10, which matters because resolution of inflammation requires regulatory pathways as well as inhibition of inflammatory signalling. Microencapsulated propolis increased macrophage IL-10 secretion [22], curcumin-loaded starch nanoparticles raised IL-10 alongside reductions

in IL-1β, IL-6 and IL-8 [38], and combined treatment preserved IL-10 expression in fibroblasts under oxidative stress [31].

Mechanistically, both compounds inhibited NF-κB activation, suppressed TLR4-mediated signalling, reduced oxidative stress and downregulated COX-2 and iNOS [26, 27, 29, 33, 34]. Curcumin was particularly effective against oxidative stress through enhancement of endogenous antioxidant enzymes [29, 32, 39], whereas propolis showed broader immunomodulation attributable to its mixture of flavonoids, phenolic acids, CAPE, artepillin C and baccharin [18, 22, 25]. Combined formulations outperformed single agents in the three studies that tested them [29–31], which is compatible with complementary mechanisms; none, however, used isobolographic or combination-index analysis, a fixed-ratio dose matrix, or the concentration range needed to distinguish additivity from true synergy, so the interaction should at present be described as additive rather than synergistic.

Caution is nonetheless required before extending these observations to patients. Only one of the 18 studies used a sepsis model, and it was a rodent endotoxemia model reproducing early cytokine release rather than the immunoparalysis, microcirculatory failure and organ dysfunction of clinical sepsis; the two randomised trials enrolled patients with chronic kidney disease and COVID-19, used surrogate endpoints and included fewer than 40 participants each. No trial of propolis or curcumin in septic patients has been reported. Translation is further constrained by the low oral bioavailability of curcumin, by the chemical variability of propolis, whose composition depends on botanical and geographical origin, and by the absence of pharmacokinetic and safety data in critical illness. Because sepsis also involves an immunosuppressive phase in which further cytokine suppression could impair pathogen clearance, the timing of any such intervention would itself require evaluation.

Several limitations should be acknowledged. The included studies were heterogeneous in experimental model, disease condition, formulation, dosage and outcome measurement, and only one used a direct sepsis model, so most conclusions rest on surrogate inflammatory systems. Most appraised components were at unclear risk of bias, chiefly because randomisation, blinding and the number of independent replicates were incompletely reported, and the uniformly positive findings of small preclinical studies raise the possibility of publication bias, which could not be examined formally in the absence of a meta-analysis. Variation in cytokine assessment restricted direct comparison, and the concentration- and formulation-dependent effects of propolis caution against generalising from any single preparation. The review was also restricted to English-language publications, and its protocol was not prospectively registered.

5 Conclusion

This systematic review of 18 eligible studies indicates that propolis, curcumin and their combinations modulate the inflammatory mediators most relevant to sepsis. TNF-α, IL-6 and IL-1β were the most frequently investigated cytokines and were suppressed in most studies, while IL-10 was generally increased or preserved. Curcumin acted predominantly through suppression of NF-κB, TLR4, MAPK and oxidative stress-related

pathways, whereas propolis displayed broader immunomodulatory activity attributable to its diverse polyphenolic constituents. Combined formulations and nanoformulated or microencapsulated preparations reported greater efficacy than the free compounds, indicating that the delivery system is an important determinant of activity, although no study tested formally for synergy.

Taken together, propolis and curcumin are biologically plausible but as yet clinically unproven candidates as adjuncts for sepsis-associated inflammation, since they regulate cytokine production, oxidative stress and immune signalling simultaneously rather than targeting a single mediator. Because the evidence is predominantly preclinical, largely at unclear risk of bias and derived almost entirely from non-sepsis models, these findings should be regarded as hypothesis-generating and do not support clinical use. Confirmation requires adequately powered randomised trials in patients with sepsis, standardisation of bioactive composition, dosage, treatment duration and cytokine assessment, pharmacokinetic and safety evaluation in critical illness, and formal combination analyses to establish whether the apparent advantage of combined formulations reflects genuine synergy.

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