

The Effect of Propolis (Bee Glue) on Sepsis: A Systematic Review

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ABSTRACT

Background: With pathogenic resistance and risk of dysbiosis, antimicrobial therapy for sepsis becomes less effective. Therefore, there is a need for an additional therapy, such as immunomodulation, either directly or through modulation of the gut microbiota. Propolis, or bee glue, has immunomodulatory properties and positive effects on the gut microbiota. This systematic review aims to assess the potential of propolis as an adjunctive therapy in alleviating sepsis through pathways associated with gut microbiota, such as inflammation and oxidative stress.

Methods: This study was made in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The keywords for the literature search and study relevance were determined with the Population, Intervention, Comparison, and Outcome (PICO) formula: Population (P): Septic human or animal; Intervention (I): Propolis administration; Comparison (C): Septic human or animal without propolis administration; Outcome (O): Gut microbiota and inflammatory as well as oxidative stress biomarkers. A literature search was conducted in PubMed, ScienceDirect, and Google Scholar to obtain relevant studies with a download period from January 2015 to March 2025.

Results: The literature search yielded 3,189 articles, with four articles eligible for inclusion in this literature review. The four studies were animal studies and reported that propolis administration improved sepsis by reducing inflammatory and oxidative stress biomarkers and mitigating organ damage. None of the studies reported the outcome on gut microbiota in sepsis.

Conclusion: Propolis showed potential as an adjunctive therapy for sepsis through its anti-inflammatory and antioxidative effects, but there is no evidence from human studies.

INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by an inappropriate immune response to infection [1]. The Global Burden of Diseases report states that there are 50 million cases of sepsis per year globally. The incidence and mortality of sepsis vary across regions, with the greatest burden found in Sub-Saharan Africa, Oceania, East Asia, South Asia, and Southeast Asia [2]. The proinflammatory cytokines released in sepsis can affect the balance between host



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immunity and the gut microbiota. Furthermore, inflammation-induced reactive oxygen species (ROS) can worsen gut dysbiosis [3,4].

Gut dysbiosis can affect physiological functions and lead to inflammatory diseases through various mechanisms, such as intestinal barrier damage and leaky gut. A damaged intestinal barrier allows gut microbiota, toxins, and proinflammatory factors to enter the circulation, migrate to various tissues, and cause inflammation at multiple sites. Dysbiosis and sepsis are interconnected, as sepsis can cause dysbiosis and dysbiosis can worsen sepsis [3,5].

The 2021 Surviving Sepsis Campaign (SSC) recommended empiric broad-spectrum therapy with one or more antimicrobials for patients with sepsis [6]. However, broad-spectrum antimicrobial therapy is becoming less effective due to the continuous shift in the distribution of causative pathogens and the emergence of pathogen resistance. Furthermore, prolonged antibiotic therapy can worsen sepsis by causing dysbiosis through decreasing the colonization of short-chain fatty acid (SCFA)-producing commensal bacteria. Therefore, additional therapies are needed to alleviate the severity of sepsis. One of them is immunomodulation, either directly or through improving the balance of the gut microbiota [3,7,8].

Propolis, or bee glue, has been the focus of research in recent decades due to its pharmacological value. Since ancient times, propolis has been used in many parts of the world, such as Egypt, Greece, and Rome, as a food supplement and traditional medicine. The immunomodulatory effects of propolis have been considered complementary or alternative treatments for many immune disorders, including acute and chronic inflammation [9,10,11]. Studies have also shown positive effects of propolis on the gut microbiota and SCFA production, both of which play a role in maintaining gut barrier integrity and regulating inflammatory responses and oxidative stress [4,12,13]. Therefore, this systematic review aims to analyze the potential of propolis as an adjunctive therapy to reduce the severity of sepsis through pathways associated with the gut microbiota, such as inflammation and oxidative stress, by reviewing studies examining the use of propolis in sepsis.

METHODS

The writing method is a Systematic Review and is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [14]. The extracted data were as follows: septic animal model or patient, propolis origin, propolis dose and administration route, biomarker characteristics, gut microbiota characteristics, and organ damage characteristics. Literature search keywords and study relevance were determined based on the Population, Intervention, Comparison, and Outcome (PICO) formula, namely: Population (P): Septic human or animal; Intervention (I): Propolis administration; Comparison (C): Septic human

or animal without propolis administration; Outcome (O): Gut microbiota and inflammatory as well as oxidative stress biomarkers.

A literature search was conducted in PubMed, ScienceDirect, and Google Scholar using the keywords “propolis AND sepsis AND (inflammation OR oxidative stress OR gut microbiota)”. The study period was from 2015 to 2025, with the download period from January 2015 to March 2025. Observational, pilot, cohort, case-control, prospective, retrospective, cross-sectional, randomized controlled trials, and clinical trials with gut microbiota data and/or biomarkers of inflammation and/or oxidative stress were included. The exclusion criteria were based on information from case reports, reviews, books, commentaries, abstracts, correspondence, encyclopedias, and editorials.

Two independent reviewers performed article screening. Study quality and risk of bias were assessed using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) tool for animal studies and the Cochrane Risk of Bias (RoB) 2.0 tool for human studies [15,16]. Any disagreements were resolved via a discussion between the reviewers, and the final decision was made by mutual agreement.

RESULTS

The literature search in PubMed, ScienceDirect, and Google Scholar yielded 3,189 articles. Automation tools were used to exclude the 38 articles that were downloaded more than once and the 45 articles without full access. A screening of 3,106 articles was conducted using inclusion and exclusion criteria to identify relevant articles. Of the 30 articles that were not excluded, 22 were downloaded and assessed for eligibility. Four articles met the criteria and were subsequently analyzed for this systematic review (Figure 1).

The methodological quality assessment using the SYRCLE risk of bias tool revealed a variable level of bias across the four included studies (Table 1). While all studies demonstrated low risk with respect to baseline characteristics and incomplete outcome data, critical domains such as sequence generation, allocation concealment, and blinding predominantly rated as unclear. Notably, Abd-Elzarek et al. [17] exhibited the highest uncertainty, with six unclear domains, whereas Esmat et al. [18] showed greater robustness, with five low-risk ratings. The persistent unclear risks in randomization and blinding procedures across most studies suggest potential limitations in internal validity, warranting cautious interpretation of the collective evidence.

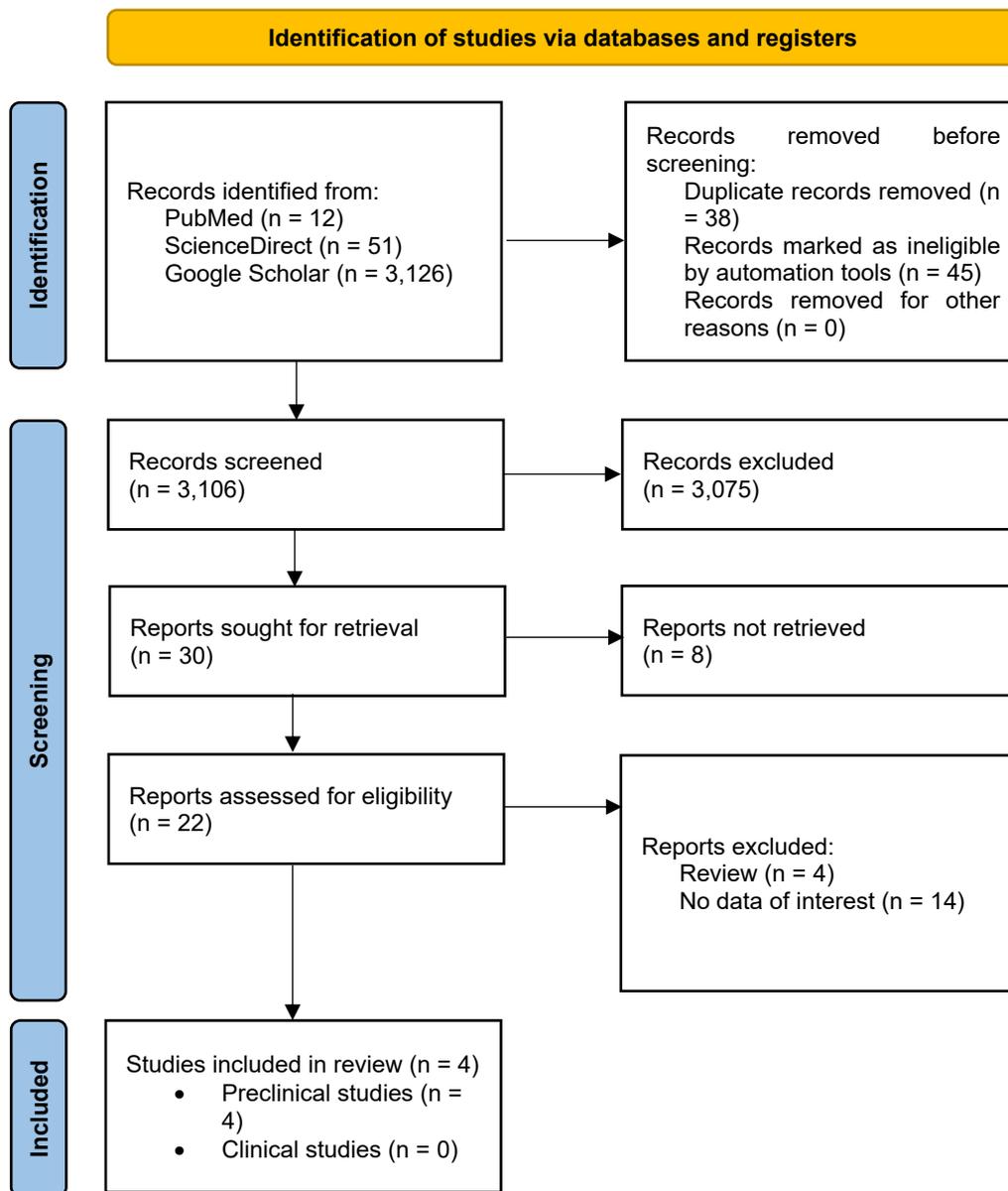


Figure 1. Study Selection Flowchart

Table 1. Study Quality Assessment with SYRCLE Tool

Bias Type	Domain	Study			
		Abd-Elzarek et al., 2020 [17]	Esmat et al., 2019 [18]	Silveira et al., 2021 [19]	Wang et al., 2015 [20]
Selection	Sequence generation	?	?	?	?
Selection	Baseline characteristics	+	+	+	+
Selection	Allocation concealment	?	?	?	?
Performance	Random housing	?	+	+	+
Performance	Blinding	?	?	?	?

Detection	Random outcome assessment	?	+	+	+
Detection	Blinding	?	?	?	?
Attrition	Incomplete outcome data	+	+	+	+
Reporting	Selective outcome reporting	+	+	+	+
Other	Other sources of bias	+	?	+	-

Explanation:

+: Low risk

-: High risk

?: Unclear risk

All included studies were animal studies, with rats as the model in three of the four studies [17,18,19,20]. Propolis was administered orally at a dose of 250 mg/kgBW/day in two of the three studies mentioned above [17,18].

Table 2. Summary of Studies

Number	1	
Reference	Abd-Elzarek et al., 2020 [17]	
Septic Animal Model or Patient	Rat, cecal slurry	
Propolis Origin	Egypt	
Propolis Dose and Administration Route	250 mg/kgBW/day of propolis extract for 14 days before sepsis induction, oral	
Biomarker Characteristics	<ul style="list-style-type: none"> • Significantly increased glutathione (GSH) levels and glutathione peroxidase (GPx), glutathione reductase (GR), superoxide dismutase (SOD), and catalase (CAT) activity in kidney tissue homogenate compared to the septic rat group without propolis extract administration • Significantly decreased lipid peroxidation and nitric oxide (NO) levels in kidney tissue homogenate compared to the septic rat group without propolis extract administration • Significantly decreased interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and prostaglandin E2 (PGE2) in kidney tissue homogenate compared to the septic rat group without propolis extract administration 	
Gut Microbiota Characteristics	Not determined	
Organ Damage Characteristics	The septic rat group given propolis extract shows improvements in kidney tissue, but with mild cognition and interstitial hemorrhage	
Number	2	
Reference	Esmat et al., 2019 [18]	

Septic Animal Model or Patient	Rat, cecal slurry
Propolis Origin	Egypt
Propolis Dose and Administration Route	250 mg/kgBW/day of propolis extract for 14 days before sepsis induction, oral
Biomarker Characteristics	<ul style="list-style-type: none"> • Significantly decreased liver nitrite, nitrate, glutathione disulfide (GSSG), and malondialdehyde (MDA) levels compared to the septic rat group without propolis extract administration • Significantly increased liver GSH levels and CAT and SOD activity compared to the septic rat group without propolis extract administration • Significantly decreased serum and liver TNF-α and PGE2 compared to the septic rat group without propolis extract administration
Gut Microbiota Characteristics	Not determined
Organ Damage Characteristics	<ul style="list-style-type: none"> • The septic rat group given propolis extract showed decreased cellular changes, cell infiltration, and tissue fibrosis in the liver • The septic rat group given propolis extract showed a mild decrease in blood vessel dilatation and congestion in the liver tissue
Number	3
Reference	Silveira et al., 2021 [19]
Septic Animal Model or Patient	Rat, cecal ligation puncture (CLP)
Propolis Origin	Brazil
Propolis Dose and Administration Route	500 mg/kgBW/day of Brazilian green propolis extract 6 hours after sepsis induction, intraperitoneal
Biomarker Characteristics	<ul style="list-style-type: none"> • Significantly increased whole blood GSH levels compared to septic rat group without propolis extract administration • Significantly decreased IL-17a, IL-12p70, IL-1β, TNF-α, and interferon (IFN)-γ levels in kidney tissue compared to the septic rat group without propolis extract administration
Gut Microbiota Characteristics	Not determined
Organ Damage Characteristics	<ul style="list-style-type: none"> • The septic rat group given propolis extract showed an improvement in kidney tubulus and a reduction in kidney tissue apoptosis • The septic rat group given propolis extract showed a reduction in lung tissue apoptosis
Number	4
Reference	Wang et al., 2015 [20]
Septic Animal Model or Patient	Mouse, lipopolysaccharide (LPS)
Propolis Origin	China and Brazil

Propolis Dose and Administration Route	<ul style="list-style-type: none"> • 25 mg/kgBW/day (low dose) and 100 mg/kgBW/day (high dose) of polyphenol-rich propolis extract from China (CPPE) for three days before LPS injection, oral • 25 mg/kgBW/day (low dose) and 100 mg/kgBW/day (high dose) of polyphenol-rich propolis extract from Brazil (BPPE) for three days before LPS injection, oral
Biomarker Characteristics	<ul style="list-style-type: none"> • Significantly decreased serum IL-6, <i>monocyte chemoattractant protein</i> (MCP)-1, IFN-γ, TNF-α, and IL-12p70 levels in the septic mouse group given low dose CPPE compared to the septic mouse group without treatment • Significantly decreased serum IL-6, MCP-1, IFN-γ, TNF-α, and IL-12p70 levels in the septic mouse group given high dose CPPE compared to the septic mouse group without treatment • Significantly increased serum IL-10 levels in the septic mouse group given low dose CPPE compared to the septic mouse group without treatment • Significantly decreased serum IL-6, MCP-1, and IL-12p70 levels in the septic mouse group given low dose BPPE compared to the septic mouse group without treatment • Significantly decreased serum IL-6, MCP-1, TNF-α, and IL-12p70 levels in the septic mouse group given high dose BPPE compared to the septic mouse group without treatment • Significantly decreased serum IL-10 levels in the septic mouse group given high dose BPPE compared to the septic mouse group without treatment
Gut Microbiota Characteristics	Not determined
Organ Damage Characteristics	Not determined

DISCUSSION

Propolis Effect on Inflammation

The dose of propolis used in rat models varies by disease, with 50-250 mg/kg BW/day being the common dose. Propolis starts to be toxic to animal models at doses of 200 and 300 mg/kgBW/day [21,22]. It should be noted that the effective dose may vary due to the chemical composition of propolis, which depends on bee species, season, weather, environmental factors, and plant ecology [23,24]. For example, 70% of the total flavonoids in New Zealand propolis are hydroflavonoids, while the hydroflavonoid content in propolis from Uruguay and China is less than 10%. On the other hand, Brazilian propolis contains up to 50% hydroflavonoids [25]. Meanwhile, terpenoids are the dominant compounds in propolis produced by stingless bees from tropical regions [26]. This variation was demonstrated in a study by Wang et al. [20], which showed that administering CPPE at both low and high doses significantly decreased serum levels

of IL-6, MCP-1, IFN- γ , TNF- α , and IL-12p70 in a septic rat model. In contrast, even at high doses, BPPE administration did not significantly decrease serum IFN- γ levels [20].

There are studies on intraperitoneal propolis administration in murine models of various diseases, and propolis has been shown to reduce levels of inflammatory cytokines such as TNF- α and IL-1 β in gastric ulcers, regardless of the administration route [23,27]. In line with this, all studies reported that propolis administration reduced TNF- α levels in murine models of sepsis, with studies by Abd-Elzarek et al. [17] and Silveira et al. [19] also reporting reduced IL-1 β levels. In the early phase of sepsis, pathogen-associated molecular patterns (PAMPs), such as bacterial components, and damage-associated molecular patterns (DAMPs), such as mitochondrial fragments from injured tissues, bind to Toll-like receptor (TLR)-4. It activates nuclear factor kappa beta (NF- κ B), a transcription factor that regulates the expression of proinflammatory cytokines such as TNF- α , IL-1 β , IL-6, IL-8, and IFN- γ [8,28,29]. Propolis constituents, namely caffeic acid phenethyl ester (CAPE), p-coumaric acid, ferulic acid, and artemillin C, are known to inhibit NF- κ B and thus suppress the expression of proinflammatory cytokines [24,30,31].

Propolis Effect on Oxidative Stress

NF- κ B activation occurs in response to PAMPs, proinflammatory cytokines, growth factors, and oxidative stress [32]. Oxidative stress is defined by four categories of biological changes: the formation of ROS and reactive nitrogen species (RNS); a change, usually a decrease, in cellular antioxidant defense capacity, including a decrease in the antioxidant activities or levels such as GSH and antioxidant enzymes such as SOD, CAT, and GPx; the presence of oxidative stress biomarkers, most commonly lipid peroxidation markers such as MDA; and disturbances in cellular redox status [33]. Two studies in Egypt and one study in Brazil reported that propolis ameliorated oxidative stress through various pathways [17,18,19]. In contrast, the study in China did not assess the effect of propolis on oxidative stress [20]. All three studies reported significant increases in GSH levels [17,18,19]. In comparison, the two studies in Egypt also reported significant increases in CAT and SOD activity and significant decreases in lipid peroxidation markers [17,18].

The general composition of propolis is 50% resin, 30% wax, 10% essential oil, 5% pollen, 2% mineral salts, and other compounds such as vitamins, minerals, and polyphenols [10]. With their ability to bind ROS such as superoxide, hydroxyl radicals, and hydrogen peroxide, polyphenols are best known for their antioxidant activity. Polyphenols also inhibit free radical-generating enzymes, such as reduced nicotinamide adenine dinucleotide phosphate (NADPH) and xanthine oxidase, or increase the expression of antioxidant enzymes such as CAT and SOD [30,34], which is in line with the studies by Abd-Elzarek et al. [17] and Esmat et al. [18].

Propolis Effect on Gut Microbiota

None of the included studies examined outcomes in the gut microbiota. However, the effects of propolis on the gut microbiota have been extensively studied in conditions other than sepsis. The study by Fonseca et. al in hemodialysis patients reported that two months of propolis supplementation improved the uniformity and richness of the gut microbiota. However, the effect was not significant [13]. The study by Lesmana et al. showed that propolis restored gut microbiota homeostasis and improved the histological structure of the ileum in rats fed a high-fat diet compared to rats fed a normal diet [35]. The polyphenols in propolis also influence the composition of the gut microbiota by inhibiting the growth of pathogenic bacteria and promoting the growth of probiotics. These beneficial bacteria will increase polyphenol metabolism, thereby increasing their bioavailability and producing metabolites that further modulate the gut microbiota. In addition, polyphenols increase the expression of tight junction genes and improve intestinal barrier function [13,36,37].

The gut microbiota also produces enzymes that ferment non-digestible carbohydrates into SCFAs, which regulate the immune system and inflammatory responses in various ways. For example, butyrate significantly reduces mucosal inflammation by inhibiting neutrophil extracellular trap formation and the release of proinflammatory cytokines, chemokines, and calprotectin in a mouse model of colitis [7,38]. In addition, SCFAs maintain intestinal epithelial barrier function by increasing goblet cell mucin expression and mucus production, thereby preventing LPS translocation and providing protection against inflammation [39]. SCFAs also modulate oxidative stress through the Keap1-Nrf2 defense pathway, and Nrf2 is known to inhibit NF- κ B activation by decreasing intracellular ROS levels, preventing the proteasomal degradation of I κ B- α , and inhibiting the nuclear translocation of NF- κ B [4,32,40,41].

On the other hand, an imbalance in the gut microbiota, known as gut dysbiosis, induces excessive ROS production, which then leads to inflammation, forming a cycle of oxidative stress-inflammation-oxidative stress [41]. In sepsis-induced dysbiosis, highly virulent gut organisms can become abundant because they possess factors that help them survive the harsh environment. In contrast, most of the normal microbiota lack these factors. Dysbiosis decreases SCFA production, which intestinal epithelial cells use as an energy source and also affects their proliferation and differentiation. In addition, proinflammatory cytokines such as TNF- α , IL-1 β , and IL-6 modulate intestinal barrier function and increase intestinal permeability. Intestinal hyperpermeability, combined with intestinal hypoperfusion due to systemic vasodilation, leads to intestinal barrier breakdown and the translocation of microbial molecules into the bloodstream [3,7,42].

Propolis Effect on Organ Damage

Three of the four studies examined the effects of propolis on organ damage, with two focusing on the kidneys [17,18,19]. Decreased kidney function is common in sepsis, and acute renal failure affects up to 60% of patients with sepsis [43,44]. Endothelial cell activation by proinflammatory cytokines leads to adhesion molecule expression and the production of vasoactive compounds, inflammatory cytokines, and chemoattractants, thus shifting the cells from an anticoagulant to a procoagulant state. Systemic activation of endothelial cells can lead to tissue damage via microvascular thrombosis, increased capillary permeability, hypotension, and tissue hypoxia [45,46]. The three studies reported that propolis ameliorated organ damage, which may be associated with improvements in inflammatory and oxidative stress biomarkers [17,18,19].

Limitations and Suggestions

Limitations of this study include the small number of studies and the absence of clinical studies, which may be due to the focus solely on inflammation, oxidative stress, and gut microbiota. For future studies, it is recommended to adopt a broader focus on the pathophysiology of sepsis, including coagulopathy and tissue perfusion.

CONCLUSION

Preclinical studies have shown the potential of propolis as an adjunctive therapy for sepsis through its anti-inflammatory and antioxidant effects. However, there is no evidence from human studies, and further studies are needed before clinical application in humans.

DECLARATIONS

Ethics approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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