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Potential Role of *Castanopsis costata* Leaf Extract in Sepsis: A Systematic Review of Indirect Evidence and Mechanistic Insights

Potensi Peran Ekstrak Daun *Castanopsis costata* pada Sepsis: Tinjauan Sistematis terhadap Bukti Tidak Langsung dan Wawasan Mekanistik

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Abstract

Sepsis is a life-threatening systemic inflammatory condition characterized by dysregulated immune responses, excessive cytokine release, oxidative stress, and progressive multi-organ dysfunction. Natural products with anti-inflammatory and antioxidant properties are increasingly investigated as adjunctive therapeutic candidates. *Castanopsis costata*, a Southeast Asian medicinal plant, has shown pharmacological potential in experimental studies, but its role in sepsis has not been systematically evaluated. This review assessed available evidence on the effects of *C. costata* leaf extract on sepsis-related outcomes in rat models. A literature search was conducted in Scopus and Google Scholar. A total of 388 records were identified, including 132 from Scopus and 256 from Google Scholar. After removing 122 duplicates, 266 records were screened against predefined eligibility criteria for animal model, sepsis induction, intervention, control, and reported outcomes. Five studies were included in the qualitative synthesis. No study directly evaluated *C. costata* leaf extract in experimental sepsis. However, studies using chemical organ injury models showed that C. costata leaf extract at 100–400 mg/kg significantly reduced TNF-α and IFN-γ levels, enhanced hepatic antioxidant enzyme activity, and protected liver and kidney tissues from paracetamol- and gentamicin-induced injury. Leaf fractions also demonstrated anti-inflammatory activity comparable to diclofenac sodium, strong antioxidant capacity, and no toxicity up to 5000 mg/kg/day. Although direct evidence of sepsis is unavailable, the anti-inflammatory and antioxidant effects of *C. costata* suggest potential relevance to sepsis pathophysiology. Further in vivo studies using established sepsis models are required.

Keywords*: *Castanopsis costata; sepsis; anti-inflammatory; cytokines; literature review.

Abstrak

Sepsis merupakan kondisi inflamasi sistemik yang mengancam jiwa, ditandai dengan disregulasi respons imun, pelepasan sitokin berlebihan, stres oksidatif, serta disfungsi multiorgan yang progresif. Produk alam dengan sifat antiinflamasi dan antioksidan semakin banyak diteliti sebagai kandidat terapi tambahan. *Castanopsis costata*, tanaman obat asal Asia Tenggara, telah menunjukkan potensi farmakologis dalam berbagai studi eksperimental, tetapi perannya dalam sepsis belum dievaluasi secara sistematis. Tinjauan ini menilai bukti yang tersedia mengenai efek ekstrak daun *C. costata* terhadap luaran terkait sepsis pada model tikus. Pencarian literatur dilakukan pada basis data Scopus dan Google Scholar. Sebanyak 388 artikel diidentifikasi, terdiri atas 132 artikel dari Scopus dan 256 artikel dari Google Scholar. Setelah penghapusan 122 duplikasi, 266 artikel disaring berdasarkan kriteria kelayakan yang telah ditetapkan, meliputi model hewan, induksi sepsis, intervensi, kelompok kontrol, dan luaran yang dilaporkan. Lima studi dimasukkan dalam sintesis kualitatif. Tidak ada studi yang secara langsung mengevaluasi ekstrak daun *C. costata* pada model sepsis eksperimental. Namun, studi yang menggunakan model cedera organ akibat bahan kimia menunjukkan bahwa ekstrak daun *C. costata* pada dosis 100–400 mg/kg secara signifikan menurunkan TNF-α dan IFN-γ, meningkatkan aktivitas enzim antioksidan pada hati, serta melindungi jaringan hati dan ginjal dari cedera yang diinduksi parasetamol dan gentamisin. Fraksi daun juga menunjukkan aktivitas antiinflamasi yang sebanding dengan natrium diklofenak, kapasitas antioksidan yang kuat, serta tidak menunjukkan toksisitas hingga dosis 5000 mg/kg/hari. Meskipun bukti langsung pada sepsis belum tersedia, efek antiinflamasi dan antioksidan *C. costata* menunjukkan potensi relevansinya terhadap patofisiologi sepsis. Penelitian in vivo lebih lanjut menggunakan model sepsis yang telah tervalidasi diperlukan untuk mengevaluasi potensi terapinya pada sepsis.

Kata Kunci: Castanopsis costata; sepsis; antiinflamasi; sitokin; tinjauan literatur.

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Introduction

Sepsis is defined as a life-threatening clinical syndrome caused by a dysregulated host immune response to infection, resulting in systemic inflammation, oxidative stress, cellular injury, and progressive multiple organ dysfunction [1,2]. This condition is among the most complex and severe complications of infection because the host response, initially intended to eliminate invading pathogens, becomes excessive and harmful to the body. During sepsis, the interaction between infectious agents and the immune system triggers a cascade of inflammatory and metabolic disturbances that may rapidly progress to septic shock, tissue hypoperfusion, and organ failure. Despite substantial advances in antimicrobial therapy, resuscitation strategies, organ support, and intensive care management, sepsis remains a major global health problem associated with high morbidity, prolonged hospitalization, increased healthcare costs, and considerable mortality [3]. The burden of sepsis is particularly important in low- and middle-income countries, where delayed diagnosis, limited access to intensive care facilities, antimicrobial resistance, and comorbid conditions may worsen clinical outcomes.

The pathophysiology of sepsis is highly complex and involves interactions among pathogens, immune cells, inflammatory mediators, endothelial cells, coagulation pathways, and oxidative stress responses. In the early phase of sepsis, pathogen-associated molecular patterns and damage-associated molecular patterns activate innate immune receptors, leading to the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interferon-gamma (IFN-γ) [4]. Although these mediators play important roles in pathogen clearance, their excessive production may amplify systemic inflammation and cause widespread tissue damage. At the same time, anti-inflammatory responses may occur, leading to immune dysregulation and impaired host defense. This imbalance contributes to persistent inflammation, immunosuppression, and catabolism, which are important features of severe sepsis.

Inflammatory mediators released during sepsis affect the vascular endothelium, microcirculation, and cellular metabolism. Endothelial dysfunction increases vascular permeability, promotes leukocyte adhesion, activates coagulation, and impairs tissue oxygen delivery. These changes may lead to microvascular thrombosis, mitochondrial dysfunction, and reduced cellular energy production. As a result, major organs such as the kidney, liver, lung, heart, and brain become vulnerable to progressive injury [5]. Acute kidney injury, hepatic dysfunction, acute respiratory distress syndrome, myocardial depression, and encephalopathy are frequent complications of sepsis and contribute significantly to mortality. Oxidative stress also plays a central role in sepsis-related organ dysfunction. Excessive production of reactive oxygen species (ROS) and reactive nitrogen species can damage lipids, proteins, DNA, and cellular membranes. Therefore, therapeutic approaches targeting inflammatory cascades, oxidative stress, endothelial dysfunction, and organ injury have become important areas of investigation in sepsis management.

Current sepsis treatment primarily relies on early recognition, source control, appropriate antimicrobial therapy, fluid resuscitation, vasopressor support, and management of organ dysfunction. However, these interventions do not always fully prevent excessive inflammation and oxidative tissue damage. For this reason, adjunctive therapies that can modulate the host response have attracted increasing attention. Among these, natural products derived from medicinal plants are widely studied for their diverse bioactive compounds, which have potential anti-inflammatory, antioxidant, antimicrobial, immunomodulatory, and organ-protective activities [6]. Plant-derived compounds may offer complementary benefits by attenuating inflammatory signaling, reducing oxidative stress, preserving tissue structure, and improving biochemical

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markers of organ function. Although natural products should not replace standard sepsis therapy, they may provide useful leads for developing adjunctive strategies.

Several classes of phytochemicals have been reported to modulate biological pathways involved in inflammation and oxidative stress. Flavonoids, phenolic acids, tannins, alkaloids, saponins, and terpenoids are among the major compounds associated with antioxidant and anti-inflammatory activities in medicinal plants. Experimental studies have shown that these compounds may regulate nuclear factor-kappa B (NF-κB), inducible nitric oxide synthase (iNOS), cyclooxygenase pathways, cytokine production, nitric oxide formation, and ROS signaling [7]. In sepsis, activation of NF-κB promotes transcription of inflammatory mediators, while iNOS-derived nitric oxide and ROS contribute to vascular dysfunction and tissue injury. Therefore, phytochemicals that modulate these pathways may theoretically reduce the severity of sepsis-induced inflammation and organ damage. This biological rationale supports the exploration of medicinal plants as potential sources of adjunctive therapeutic agents.

Castanopsis costata, a member of the Fagaceae family, is distributed in several Southeast Asian regions, including Indonesia. Species within the genus *Castanopsis* have gained scientific interest because they contain secondary metabolites that may contribute to various pharmacological activities. Traditionally and experimentally, members of this genus have been associated with anti-inflammatory, antioxidant, antimicrobial, antipyretic, analgesic, and organ-protective effects. Recent studies indicate that *C. costata* leaf extract and its fractions contain bioactive constituents that may support these activities [8,9,10]. This pharmacological profile is relevant to sepsis because inflammation and oxidative stress are central mechanisms in its pathogenesis. However, whether findings from non-sepsis experimental models can be translated into sepsis-related outcomes remains uncertain.

Experimental studies have shown that *C. costata* leaf extract may reduce pro-inflammatory cytokines, improve antioxidant enzyme activity, and protect hepatic and renal tissues in chemically induced injury models [11]. These findings suggest a potential role of the extract in limiting inflammatory and oxidative organ damage. In hepatotoxicity and nephrotoxicity models, improvements in biochemical parameters and tissue architecture indicate that *C. costata* may help preserve organ function under toxic stress conditions. This is relevant because liver and kidney dysfunction commonly occur during sepsis-associated systemic inflammation and oxidative injury. Nevertheless, chemical organ-injury models differ from infection-induced sepsis, which involves pathogen recognition, immune dysregulation, microbial toxins, endothelial activation, coagulation disturbances, and systemic metabolic alterations that are not fully represented in toxic injury models.

Another important consideration is that evidence from related *Castanopsis* species or in vitro inflammatory models may provide mechanistic support but cannot directly establish therapeutic efficacy in sepsis. Cell-based studies using lipopolysaccharide-stimulated macrophages may help explain how plant extracts influence inflammatory mediators, nitric oxide production, and oxidative stress pathways. However, in vivo sepsis is more complex because it involves interactions among multiple organs, circulating immune cells, vascular responses, microbial burden, and survival outcomes. Therefore, while the anti-inflammatory and antioxidant properties of *C. costata* are promising, direct evaluation in established sepsis models is required before stronger conclusions can be made.

The increasing interest in plant-derived therapeutics and the limited evidence regarding *C. costata* in sepsis highlight the need for a structured review of the available literature. To date, the potential role of *C. costata* leaf extract in sepsis management has not been systematically clarified. It remains uncertain whether the pharmacological effects observed in organ injury, inflammation, antioxidant, or related experimental models are sufficiently relevant to the pathophysiology of sepsis. Therefore, this literature review aims to assess available evidence on the effects of *Castanopsis costata* leaf extract and related *Castanopsis*-derived interventions on sepsis-related outcomes, particularly inflammation, oxidative stress, cytokine regulation, organ protection, and safety in experimental models. This review also seeks to identify knowledge gaps and provide a scientific basis for future in vivo studies using established sepsis models.

Methods

Literature Search Strategy

This review was conducted to identify studies evaluating the potential effects of *Castanopsis costata* leaf extract on sepsis outcomes in rat models. A comprehensive literature search was performed using two

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electronic databases: Scopus and Google Scholar [12]. A comprehensive literature search was conducted to identify available direct and indirect preclinical evidence regarding the potential role of *Castanopsis costata* leaf extract in sepsis-related mechanisms. The search was performed in four electronic databases: Scopus, PubMed, Web of Science, and Google Scholar. The final search was conducted on 3 March 2026. These databases were selected to provide broad coverage of biomedical, pharmacological, and multidisciplinary literature. Scopus and Web of Science were used because they index peer-reviewed scientific publications across multiple disciplines, PubMed was included because of its relevance to biomedical and preclinical research, and Google Scholar was used to capture additional articles that might not be indexed in conventional bibliographic databases.

The search strategy combined terms related to the plant species, disease condition, experimental model, and sepsis-related mechanisms. The search terms included: ("Castanopsis costata" OR "Castanopsis" OR "Castanopsis leaf" OR "Castanopsis extract") AND ("sepsis" OR "septic shock" OR "endotoxemia" OR "lipopolysaccharide" OR "LPS" OR "inflammation" OR "oxidative stress" OR "organ injury" OR "hepatoprotective" OR "nephroprotective") AND ("rat" OR "rats" OR "animal model" OR "in vivo" OR "mouse" OR "mice"). In Scopus, searches were performed using title, abstract, and keyword fields. In Google Scholar, keyword combinations were searched manually. Search fields were adjusted according to the database format, including title, abstract, and keywords where available. No restriction was applied to the publication year. Articles written in English and Indonesian were considered eligible. Review articles were used only for citation tracking and background information, but they were not included in the qualitative synthesis.

All identified records were imported into a reference management system, and duplicates were removed before screening. Titles and abstracts were screened according to predefined eligibility criteria. Full-text articles were then assessed for inclusion. Studies were included if they investigated *C. costata* or related *Castanopsis* species in experimental models relevant to sepsis-related mechanisms, including inflammation, oxidative stress, cytokine regulation, organ injury, or safety. Studies directly evaluating sepsis models were prioritized; however, because no direct experimental sepsis study using *C. costata* was identified, indirect mechanistic and preclinical evidence were included and interpreted with caution.

PRISMA Flow Diagram

The study selection process was summarized using a PRISMA flow diagram to improve transparency in reporting the identification, screening, eligibility assessment, and inclusion stages [13,14]. A total of 388 records were identified from Scopus and Google Scholar. After removal of 122 duplicates, 266 records were screened based on titles and abstracts. Of these, 261 records were excluded because they did not meet the eligibility criteria. Five full-text articles were assessed and included in the final synthesis. Importantly, no study directly evaluated *Castanopsis costata* leaf extract in an established in vivo sepsis model. Therefore, the included studies were categorized into two groups: indirect evidence from non-sepsis in vivo models (n = 2) and mechanistic evidence from in vitro studies or related *Castanopsis* species (n = 3).

Study Selection and Eligibility Criteria

The study selection process was initially based on predefined eligibility criteria. Direct evidence was defined as in vivo experimental studies using established sepsis or septic shock models, such as lipopolysaccharide-induced endotoxemia or cecal ligation and puncture, and evaluating *Castanopsis costata* leaf extract as the intervention. Eligible direct studies were expected to include an appropriate control group and report at least one sepsis-related outcome, including survival rate, clinical severity score, inflammatory cytokines, bacterial burden, organ dysfunction markers, oxidative stress indicators, or histopathological findings. However, after screening the available literature, no direct experimental study evaluating *C. costata* leaf extract in sepsis or septic shock models was identified. Therefore, the eligibility criteria were modified to include indirect preclinical evidence that was mechanistically relevant to sepsis pathophysiology [15].

Modified Eligibility Criteria for Indirect Evidence

Because no direct sepsis study was available, secondary eligibility criteria were applied. Studies were considered eligible as indirect evidence if they evaluated *C. costata* leaf extract or its fractions in experimental models of major biological mechanisms of sepsis, including inflammation, oxidative stress, cytokine regulation, organ injury, hepatoprotection, nephroprotection, or toxicity. In addition, studies involving related *Castanopsis* species were considered only as supporting mechanistic evidence when they assessed

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inflammatory responses in lipopolysaccharide-stimulated macrophage models or other inflammation-related experimental systems.

Studies were excluded if they were review articles, case reports, conference abstracts without sufficient data, studies unrelated to *Castanopsis* species, studies without relevant inflammatory or oxidative stress outcomes, or studies that did not provide adequate methodological information. In vitro studies were not interpreted as direct evidence of sepsis efficacy but were included only to support mechanistic discussion regarding inflammatory mediator regulation, nitric oxide production, and macrophage activation. This modified approach was applied to avoid overstating the evidence while still allowing synthesis of available pharmacological findings relevant to sepsis-related mechanisms. Therefore, the included studies were categorized as either direct evidence of sepsis or indirect mechanistic evidence.

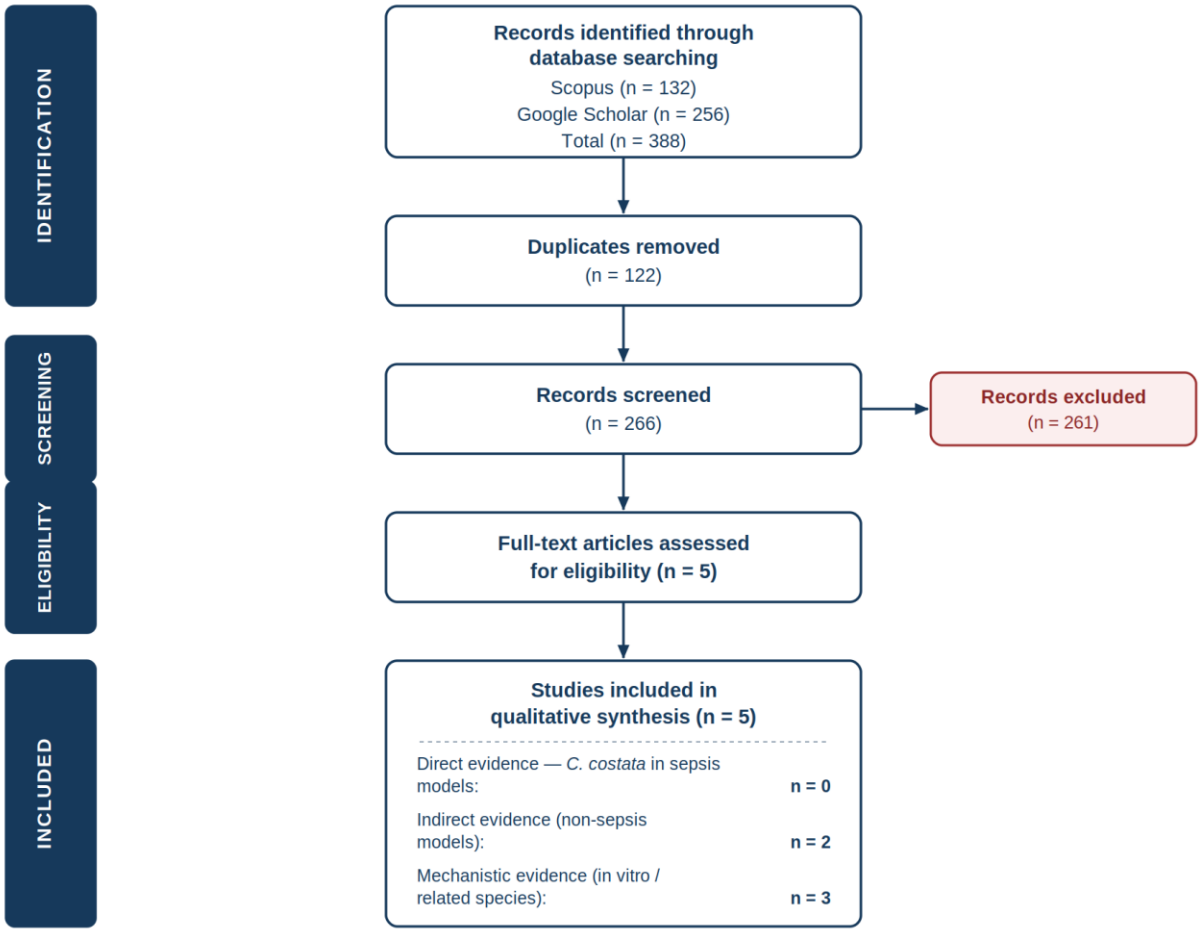

Figure 1. Prima flow diagram

Data Extraction

Data extraction was conducted using a structured framework to ensure consistency across the included studies. Information collected from each article included the study design (type of experiment, number of treatment and control groups, sample size per group, study duration, and any reported randomization or blinding procedures) [16]. Details regarding *Castanopsis costata* leaf extract were also extracted, including the extraction method, extract standardization or concentration, tested doses (mg/kg), route of administration, treatment duration, and vehicle used. Information on the sepsis model was recorded, including the induction method (e.g., lipopolysaccharide injection or cecal ligation and puncture), dose, and route of the inducing agent, and the timing of induction relative to treatment. In addition, characteristics of the experimental animals were collected, including rat strain, sex, age, body weight, housing conditions, and reported inclusion or exclusion criteria. Outcome measures extracted from the studies included inflammatory biomarkers (e.g., TNF-α, IL-6, and NF-κB), oxidative stress markers, organ function parameters (liver, kidney, lung, and heart), survival or mortality rates, clinical severity scores, and histopathological findings. Finally, information regarding treatment effects and mechanistic insights was recorded, including the direction and magnitude of

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effects, statistical significance (p-values), dose–response relationships, comparisons with positive controls, reported adverse effects, proposed biological mechanisms, molecular pathways, and potential bioactive compounds associated with the extract.

Characteristics of Included Studies

The analysis of the included studies demonstrates that direct experimental evidence evaluating the effect of *Castanopsis costata* leaf extract in sepsis models is currently unavailable. Among the five studies identified through the literature search, none directly investigated *C. costata* in experimentally induced sepsis or septic shock in rats. Therefore, the available evidence should be interpreted as indirect evidence rather than definitive proof of therapeutic efficacy in sepsis. The included studies provide relevant information through several experimental contexts, including chemical organ injury, acute inflammation, pyrexia, pain models, oxidative stress assays, and macrophage-based inflammatory models. Although these models do not fully capture the complexity of sepsis, they offer important mechanistic insights, as inflammation, oxidative stress, cytokine activation, and organ dysfunction are central components of sepsis pathophysiology.

Two studies specifically evaluated *C. costata* in non-sepsis animal models. Alkandahri et al. [17] investigated the hepatoprotective and nephroprotective effects of *C. costata* extract in rats using paracetamol-induced liver injury and gentamicin-induced kidney injury models. The extract was prepared by 70% ethanol maceration and administered orally at doses of 100, 200, and 400 mg/kg. The study used male Wistar rats aged 8–12 weeks with body weights ranging from 150 to 250 g. Although this model did not involve infection, endotoxin exposure, or experimentally induced sepsis, it was relevant to the present review because sepsis frequently leads to liver and kidney dysfunction through inflammatory and oxidative mechanisms. The findings showed that *C. costata* extract improved several biochemical markers associated with hepatic and renal injury, suggesting potential antioxidant and organ-protective properties [17].

The second study by Alkandahri et al. [18] evaluated the pharmacological activities of *C. costata* leaf fractions using models of inflammation, pyrexia, pain, and antioxidant activity. The study tested water, ethyl acetate, and n-hexane fractions at doses of 50 and 100 mg/kg. The experimental models included carrageenan-induced paw edema, brewer's yeast-induced pyrexia, and pain models. Although these models were not sepsis models, they were useful for evaluating the anti-inflammatory and antioxidant potential of *C. costata*. These biological activities are relevant because excessive inflammatory responses and oxidative stress contribute to tissue injury and multiple organ dysfunction in sepsis. The study demonstrated that *C. costata* fractions exhibited anti-inflammatory, antipyretic, analgesic, and antioxidant effects, supporting the potential pharmacological relevance of this plant for inflammation-related conditions [18].

In addition to the two *C. costata* animal studies, three other studies provided supporting mechanistic evidence from related *Castanopsis* species or plant-derived preparations. Gao et al. [19] investigated the effects of *Castanopsis lamontii* water extract on lipopolysaccharide-induced inflammatory responses in RAW 264.7 macrophage cells. This model is commonly used to study inflammatory signaling because lipopolysaccharide activates macrophages and induces the production of inflammatory mediators. The study reported that the extract suppressed inflammatory responses by inhibiting inflammatory mediators and modulating key signaling pathways [19]. Although the study was conducted in vitro and used a different *Castanopsis* species, the findings are relevant because macrophage activation and the release of inflammatory mediators are important events in sepsis.

Kim et al. [20] evaluated an ethanol extract of *Castanopsis sieboldii* leaves in an LPS-induced model of macrophage inflammation and pyroptosis. The study showed that the extract reduced nitric oxide production and downregulated inducible nitric oxide synthase expression in LPS-stimulated macrophages [20]. This finding is mechanistically important because excessive nitric oxide production and iNOS activation contribute to vascular dysfunction, hypotension, and inflammatory tissue damage during sepsis. However, because the study was limited to a cell-based model, it cannot be directly extrapolated to in vivo sepsis outcomes. Nevertheless, it supports the broader concept that bioactive compounds from the genus *Castanopsis* may regulate inflammatory pathways relevant to systemic inflammation.

Another related study by Park et al. [21] evaluated the anti-inflammatory effect of *Castanopsis cuspidata* extract on inflammatory mediators in macrophage cells. The study reported that the extract reduced the production of inflammatory mediators, indicating potential anti-inflammatory activity [21]. Although this study did not use *C. costata* and did not involve animal models or sepsis induction, it provides mechanistic support for the possibility that *Castanopsis*-derived compounds may influence inflammation-related pathways. Taken together, these three studies suggest that species within the genus *Castanopsis* may contain

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bioactive compounds capable of suppressing macrophage-mediated inflammation, oxidative stress, and nitric oxide-related pathways [19–21].

Table 1. Characteristics of Included Studies

Study	Study Type	Intervention	Disease/Experimental Model	Model	Relevance to Research Question
Alkandahri et al. [17]	Controlled experiment with randomization and blinding	*C. costata* extract prepared by 70% ethanol maceration; 100, 200, and 400 mg/kg orally	Paracetamol-induced hepatotoxicity and gentamicin-induced nephrotoxicity	Male Wistar rats, 8–12 weeks, 150–250 g	Indirect evidence; evaluated organ-protective effects of *C. costata*, but not in a sepsis model
Alkandahri et al. [18]	Controlled experimental study	*C. costata* leaf fractions: water, ethyl acetate, and n-hexane fractions; 50 and 100 mg/kg	Carrageenan-induced inflammation, brewer's yeast-induced pyrexia, and pain models	Rats; strain, sex, and body weight not clearly specified	Indirect evidence; evaluated anti-inflammatory and antioxidant activities of *C. costata*, but not in sepsis
Gao et al. [19]	In vitro experimental study	Water extract of *Castanopsis lamontii* buds	LPS-induced inflammatory response	RAW 264.7 macrophage cells	Supporting mechanistic evidence: suppressed LPS-induced inflammation through modulation of inflammatory mediators.
Kim et al. [20]	In vitro mechanistic study	Ethanol extract of *Castanopsis sieboldii* leaves	LPS-induced inflammation and pyroptosis	Macrophage cell model	Supporting evidence: reduced nitric oxide production and downregulated iNOS expression in LPS-stimulated macrophages.
Yu et al. [21]	Cell-based anti-inflammatory and antioxidant study	Polyphenol-rich extract of *Castanopsis* honey	LPS-induced inflammatory response	RAW 264.7 macrophage cells	Supporting mechanistic evidence; reduced inflammatory mediator production, including NO and TNF-α, and modulated NF-κB-related inflammatory responses, but not using *C. costata* or an in vivo sepsis model.

Overall, the included studies demonstrate that *C. costata* has been evaluated mainly in models of organ injury, inflammation, pyrexia, pain, and oxidative stress, but not in direct sepsis models. This distinction is important because sepsis is a systemic, infection-related condition involving complex interactions among pathogens, immune responses, endothelial dysfunction, coagulation abnormalities, mitochondrial impairment, and multiple organ injury. Chemical hepatotoxicity or nephrotoxicity models can provide useful information about organ protection, but they cannot reproduce all major features of sepsis. Similarly, carrageenan-induced inflammation and macrophage-based LPS models can demonstrate anti-inflammatory activity but do not provide information on survival, bacterial clearance, septic shock, or multi-organ dysfunction.

Nevertheless, the available findings remain biologically relevant. The ability of *C. costata* extract to reduce pro-inflammatory cytokines, improve antioxidant enzyme activity, and protect liver and kidney tissues may be important, as these mechanisms are closely related to sepsis-induced organ damage [17]. The anti-inflammatory and antioxidant activities reported for *C. costata* fractions also support the possibility that this plant may reduce excessive inflammatory responses under pathological conditions [18]. In addition, findings from related *Castanopsis* species suggest that this genus may modulate macrophage activation, nitric oxide production, iNOS expression, and the release of inflammatory mediators [19–21]. These pathways are closely associated with the progression of systemic inflammation and tissue injury during sepsis.

However, the evidence must be interpreted cautiously. None of the included studies measured sepsis-specific outcomes such as survival rate, clinical severity score, bacterial burden, endotoxin-induced shock, cecal ligation and puncture outcomes, serum lactate, or sepsis-associated organ dysfunction scores. Furthermore, the included studies differed in plant species, extraction methods, experimental models, doses, and outcome parameters. These differences limit the ability to compare results across studies or draw firm

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conclusions regarding the efficacy of *C. costata* in sepsis. Therefore, the current evidence supports only a hypothesis-generating conclusion: *C. costata* may be relevant to sepsis-related inflammation and oxidative organ injury, but direct confirmation is still required.

Indirect Evidence from *Castanopsis costata* Studies

Although no included study directly evaluated *Castanopsis costata* leaf extract in an experimental sepsis model, the available evidence provides mechanistically relevant information related to sepsis-associated inflammation, oxidative stress, and organ injury. Two studies specifically investigated *C. costata* in non-sepsis experimental models and reported pharmacological effects that may be relevant to the biological pathways involved in sepsis. These studies should be interpreted as indirect evidence because their experimental designs did not involve systemic infection, endotoxin-induced shock, cecal ligation and puncture, or other established sepsis models. Nevertheless, their findings remain important because sepsis progression is strongly associated with excessive cytokine production, oxidative damage, endothelial dysfunction, and multiple organ injury.

Alkandahri et al. [17] evaluated the hepatoprotective and nephroprotective activities of *C. costata* leaf extract in rats using paracetamol-induced hepatotoxicity and gentamicin-induced nephrotoxicity models. The extract was administered orally at doses of 100, 200, and 400 mg/kg. The study demonstrated that *C. costata* extract significantly reduced inflammatory cytokines, particularly TNF-α and IFN-γ, compared with pathological control groups. In addition, the extract improved antioxidant enzyme activity and restored biochemical markers related to liver and kidney function. These findings suggest that *C. costata* may exert anti-inflammatory, antioxidant, and organ-protective effects. Although chemical organ injury differs from sepsis, the observed effects are relevant because sepsis commonly causes liver and kidney dysfunction through inflammatory and oxidative mechanisms.

Improvements in hepatic and renal biochemical parameters supported the organ-protective effect reported by Alkandahri et al. [17]. The extract reduced liver injury markers, including AST, ALT, ALP, total bilirubin, and total cholesterol, while increasing total albumin and total protein. In the kidney injury model, *C. costata* extract reduced serum levels of creatinine, urea, and uric acid. These outcomes indicate that the extract may help maintain liver and kidney function under toxic injury conditions. Histopathological evaluation also confirmed improvement in liver and kidney tissue architecture after treatment. In the context of sepsis, preservation of organ structure and function is highly relevant because multiple organ dysfunction is a major determinant of disease severity and mortality.

Another study by Alkandahri et al. [18] investigated the pharmacological activities of *C. costata* leaf fractions, including water, ethyl acetate, and n-hexane. The study used experimental models of inflammation, pyrexia, pain, antioxidant activity, and acute toxicity. The findings showed that *C. costata* fractions significantly inhibited carrageenan-induced paw edema, indicating anti-inflammatory activity. In addition, the fractions demonstrated strong antioxidant activity across tested concentrations. These results support the possibility that *C. costata* contains bioactive compounds that can reduce inflammatory responses and oxidative stress. Both mechanisms are closely related to sepsis pathophysiology, although the study itself did not involve sepsis induction.

The safety findings from Alkandahri et al. [18] also provide useful information for future experimental development. The study reported no adverse histopathological findings in the liver, stomach, and kidney at high acute toxicity doses up to 5000 mg/kg/day. This suggests a favorable preliminary safety profile of *C. costata* fractions. Safety data are important because any potential adjunctive therapy for sepsis should not worsen organ injury or systemic toxicity. However, acute toxicity findings in healthy or non-septic animals cannot fully predict safety in sepsis, where altered metabolism, immune dysfunction, vascular leakage, and organ impairment may influence drug response.

Taken together, the two *C. costata* studies suggest that this plant has pharmacological properties relevant to sepsis-related mechanisms. The strongest indirect evidence includes reductions in pro-inflammatory cytokines, enhanced antioxidant defense, improvements in liver and kidney biochemical markers, and histopathological protection. However, these findings cannot be interpreted as direct evidence of efficacy in sepsis. The main limitation is that the models used were chemical injury and acute inflammation models rather than systemic infection models. Therefore, the potential role of *C. costata* in sepsis remains hypothetical and requires direct validation using established in vivo sepsis models.

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Table 2. Indirect Evidence from *Castanopsis costata* Studies

Outcome Domain	Alkandahri et al. [17]	Alkandahri et al. [18]
Anti-inflammatory activity	Reduced TNF-α and IFN-γ compared with pathological controls, with significant differences reported from $p < 0.05$ to $p < 0.0001$.	Significantly inhibited carrageenan-induced paw edema, indicating anti-inflammatory activity.
Antioxidant activity	Increased hepatic antioxidant enzyme activity compared with the pathological group.	Demonstrated strong antioxidant activity across tested concentrations of 25–200 μg/mL.
Organ protection	Reduced AST, ALT, ALP, total bilirubin, total cholesterol, serum creatinine, serum urea, and uric acid; increased total albumin and total protein.	Histopathological examination of the liver, stomach, and kidney showed no toxic effects at doses up to 5000 mg/kg/day.
Dose-response relationship	Significant effects were observed at 100, 200, and 400 mg/kg; however, silymarin, as the positive control, showed stronger effects on some hepatic parameters.	Tested at 50 and 100 mg/kg; the ethyl acetate fraction at 100 mg/kg showed antipyretic activity comparable to paracetamol.
Histopathological findings	Improved liver and kidney tissue architecture was confirmed histopathologically.	No adverse histopathological findings were observed at the acute toxicity dose limit.
Proposed mechanisms	Antioxidant and anti-inflammatory effects through reduction of TNF-α and IFN-γ and improvement of antioxidant defense.	Anti-inflammatory, antipyretic, analgesic, and antioxidant mechanisms were suggested, although specific molecular pathways were not fully described.

Synthesis

Overall, the available evidence suggests that Castanopsis costata exhibits pharmacological properties relevant to inflammatory and oxidative mechanisms associated with sepsis. As summarized in **Table 3**, the strongest findings from *studies on C. costata* include anti-inflammatory activity, antioxidant effects, and protection against liver and kidney injury [17,18]. These mechanisms are relevant because sepsis is characterized by excessive cytokine release, oxidative stress, and progressive organ dysfunction. However, none of the included studies directly evaluated *C. costata* leaf extract in experimental sepsis models. As a result, the current evidence cannot establish whether *C. costata* improves survival, reduces the severity of septic shock, decreases bacterial burden, or prevents sepsis-induced multiple organ failure.

The proposed relationship between *C. costata* and sepsis-related injury is illustrated in **Figure 2**. This figure presents a conceptual mechanism in which the anti-inflammatory, antioxidant, and organ-protective effects of *C. costata* may modulate sepsis-related pathological pathways. However, this mechanism should be interpreted with caution because the evidence is largely indirect. The effects reported for *C. costata* were derived from chemical organ injury, inflammation, pyrexia, pain, antioxidant, and toxicity models rather than from validated sepsis models [17,18]. Meanwhile, mechanistic evidence for macrophage activation, nitric oxide production, iNOS expression, and regulation of inflammatory mediators was primarily derived from in vitro studies or from studies involving related *Castanopsis* species [19–21].

As shown in **Table 3**, the included studies differed substantially in terms of experimental model, intervention type, dose, route or system of administration, and measured outcomes. The two studies on *C. costata* provided indirect evidence from non-sepsis models. In contrast, the remaining three studies provided supporting mechanistic evidence from related *Castanopsis* species or cell-based inflammatory models [17–21]. Although the findings generally suggest anti-inflammatory and antioxidant potential, these differences limit the strength of inference and prevent direct comparison across studies.

Therefore, the current evidence should be considered hypothesis-generating rather than confirmatory. *C. costata* may have potential as a source of bioactive compounds targeting inflammatory and oxidative pathways, but direct in vivo studies using validated sepsis models are required. Future studies should use lipopolysaccharide-induced endotoxemia or cecal ligation and puncture models to evaluate survival, clinical severity, cytokine levels, oxidative stress markers, liver and kidney function, histopathological injury, bacterial clearance, and safety. Standardization of extract preparation, phytochemical characterization, dose optimization, and comparison with standard therapy are also necessary to determine whether the indirect pharmacological effects of *C. costata* can be translated into meaningful therapeutic benefits in sepsis.

Phytochemical Considerations and Biological Activity

The phytochemical evidence for *C. costata* remains limited and should be interpreted cautiously. Available studies suggest that *C. costata* leaf extract and fractions may contain bioactive constituents associated with anti-inflammatory, antioxidant, and organ-protective activities [17,18]. However, detailed phytochemical

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standardization, quantitative marker analysis, and chromatographic profiling have not been fully established. The use of 70% ethanol may extract relatively polar and semi-polar compounds, including phenolic and flavonoid-related constituents. Fractionation into water, ethyl acetate, and n-hexane fractions may further separate compounds by polarity, potentially influencing biological activity [18]. The ethyl acetate fraction may be relevant because semi-polar compounds are often associated with antioxidant and anti-inflammatory effects. However, the specific compounds responsible for these activities in *C. costata* remain unclear. Therefore, future studies should include phytochemical profiling, identification of marker compounds, and standardization of extracts to improve reproducibility. Such information is needed to clarify whether the observed anti-inflammatory and antioxidant activities are specific to *C. costata* or represent general effects of polyphenol-rich medicinal plants.

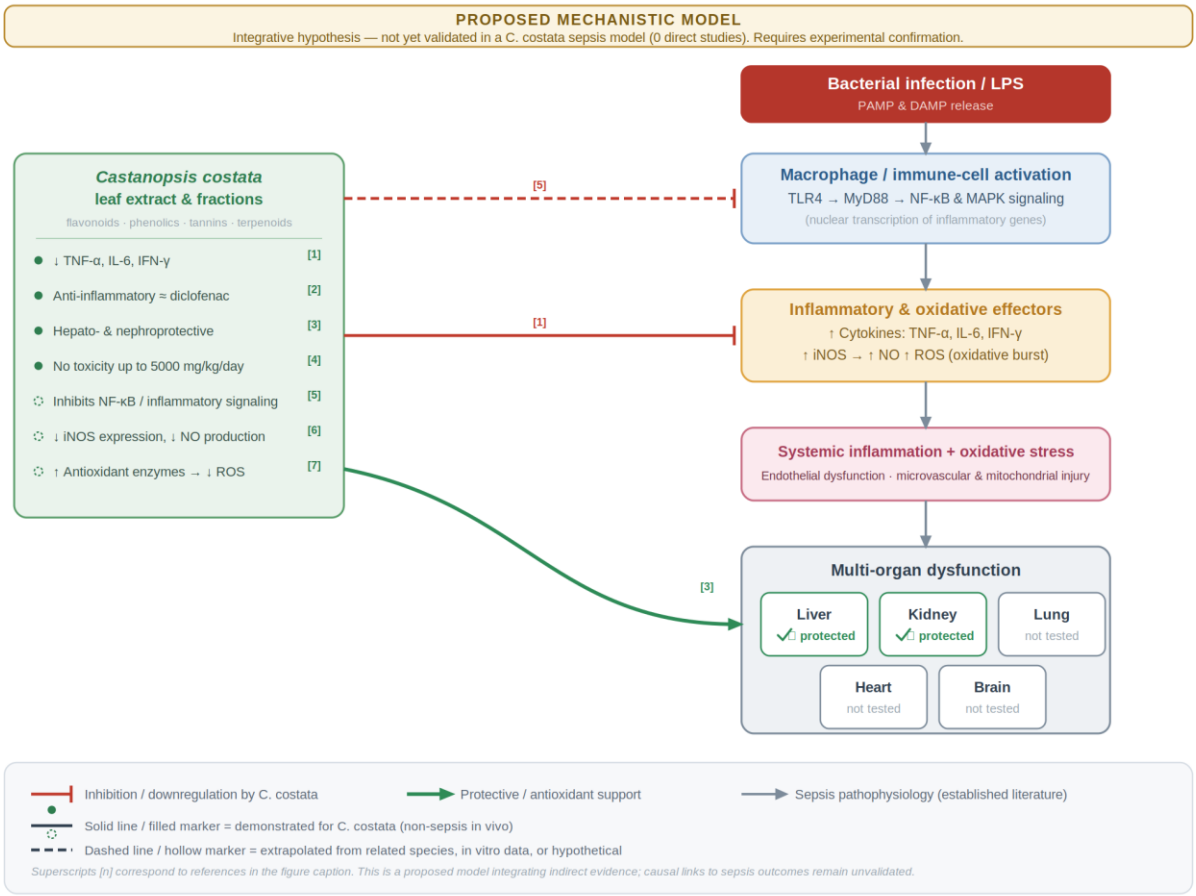

Figure 2. Proposed Mechanism of Action in Sepsis-Related Injury of *Castanopsis costata* Leaf Extract

Comparison with Other Anti-inflammatory Natural Products in Sepsis

Compared with other natural anti-inflammatory products evaluated in experimental sepsis models, evidence for Castanopsis costata remains in its early stages. Compounds derived from *Curcuma longa*, particularly curcumin, have been investigated in experimental sepsis models and have been reported to modulate inflammatory cytokines, oxidative stress, and organ injury. Similarly, bioactive compounds from *Zingiber officinale*, such as 6-gingerol, have been studied in sepsis-related models and are associated with improved inflammatory balance, reduced oxidative injury, and improved survival outcomes. In addition, ginsenosides from *Panax ginseng*, including the rare ginsenoside Rg4, have been tested in cecal ligation and puncture models and reported to reduce inflammatory cytokines and improve survival [22–24].

In contrast, *C. costata* has not yet been evaluated in validated sepsis models. The available evidence is limited to non-sepsis models, including chemical liver and kidney injury, acute inflammation, pyrexia, pain, antioxidant assays, and toxicity assessment [17,18]. Therefore, while *C. Costata exhibits anti-inflammatory, antioxidant, and organ-protective activities; its evidence base is weaker than that of natural products already* tested in LPS-induced endotoxemia or CLP-induced polymicrobial sepsis models. This comparison indicates that *C. costata* should currently be considered a candidate for further preclinical investigation rather than an established adjunctive anti-sepsis agent.

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Table 3. Critical Synthesis and Comparative Summary of the Included Studies

Study	Evidence Type	Model / Subject	Intervention and Dose	Control / Comparator	Main Findings	Critical Appraisal / Limitation	Relevance to Sepsis
Alkandahri et al. [17]	Indirect in vivo evidence	Paracetamol-induced hepatotoxicity and gentamicin-induced nephrotoxicity in rats	*C. costata* leaf extract; 100, 200, and 400 mg/kg; oral administration	Pathological control; positive control including silymarin	Reduced TNF-α and IFN-γ; improved liver and kidney markers; histopathological protection	Non-sepsis chemical injury model; no bacterial challenge; no survival, lactate, bacterial burden, or sepsis severity score	Relevant to inflammation, oxidative stress, and organ protection, but there is no direct evidence of sepsis efficacy
Alkandahri et al. [18]	Indirect pharmacological evidence	Carrageenan-induced inflammation, pyrexia, pain, antioxidant assay, and acute toxicity model	Water, ethyl acetate, and n-hexane fractions; 50 and 100 mg/kg; antioxidant assay 25–200 µg/mL	Diclofenac sodium, paracetamol, and assay-specific controls	Anti-inflammatory, antipyretic, analgesic, antioxidant effects; no major toxicity at high dose	Not a sepsis model; limited cytokine and molecular pathway assessment; no sepsis-specific outcomes	Supports anti-inflammatory, antioxidant, and preliminary safety relevance
Gao et al. [19]	Supporting mechanistic evidence	LPS-induced inflammation in RAW 264.7 macrophages	*Castanopsis lamontii* water extract	LPS-stimulated control	Suppressed inflammatory responses and oxidative stress-related injury	In vitro model; different *Castanopsis* species; no animal or sepsis model	Mechanistic support only; cannot confirm activity of *C. costata* in sepsis
Kim et al. [20]	Supporting mechanistic evidence	LPS-induced macrophage inflammation and pyroptosis model	*Castanopsis sieboldii* leaf extract	LPS-stimulated control	Reduced NO production and downregulated iNOS expression	Different species; cell-based model; no direct evaluation of *C. costata*	Supports possible NO/iNOS-related anti-inflammatory mechanism
Yu et al. [21]	Supporting mechanistic evidence	Macrophage-related inflammatory model	Polyphenol-rich *Castanopsis* honey extract	Inflammatory control	Reduced inflammatory mediators and oxidative stress-related responses	Not *C. costata* leaf extract; not in vivo; not a sepsis model	General mechanistic support for *Castanopsis*-derived bioactive compounds

External Validity of the Included Experimental Models

The external validity of the available *C. costata* studies is limited because the models used do not fully reproduce the biological complexity of sepsis. Paracetamol-induced hepatotoxicity is primarily driven by toxic metabolite formation, oxidative stress, mitochondrial injury, and direct hepatocellular damage. These mechanisms overlap partially with sepsis-associated liver injury, particularly in relation to oxidative stress and inflammation. However, sepsis-associated liver dysfunction also involves pathogen recognition, endotoxin exposure, systemic immune dysregulation, endothelial dysfunction, coagulation abnormalities, hypoperfusion, and metabolic reprogramming. Therefore, the hepatoprotective effect of *C. costata* in paracetamol-induced injury cannot be directly generalized to septic liver injury [17].

A similar limitation applies to gentamicin-induced nephrotoxicity. Gentamicin kidney injury is mainly associated with direct tubular toxicity, oxidative stress, and renal cellular damage. In contrast, sepsis-

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associated acute kidney injury is more complex and involves renal hypoperfusion, endothelial activation, inflammatory mediator release, microcirculatory dysfunction, mitochondrial impairment, and systemic hemodynamic instability. Thus, the nephroprotective effects observed in gentamicin-induced injury provide useful information on renal protection but do not confirm efficacy in sepsis-associated kidney injury [17].

Carrageenan-induced paw edema, pyrexia, and pain models also have limited relevance to sepsis. These models are useful for evaluating local acute inflammation, antipyretic activity, analgesic effects, and general anti-inflammatory potential. However, sepsis is a systemic and infection-driven condition involving pathogen-associated molecular patterns, circulating immune cells, bacterial burden, endothelial injury, coagulation disturbances, and multiple organ dysfunction. Therefore, the anti-inflammatory activity of *C. costata* fractions in carrageenan-induced inflammation should be interpreted as supportive pharmacological evidence rather than proof of anti-sepsis activity [18].

Interpretation of Evidence from Related *Castanopsis* Species

The findings from related *Castanopsis* species provide mechanistic support but also introduce uncertainty. Studies using *Castanopsis lamontii*, *Castanopsis sieboldii*, and *Castanopsis* honey suggest that bioactive compounds in this genus may suppress macrophage activation, nitric oxide production, iNOS expression, and the release of inflammatory mediators [19–21]. These pathways are relevant to sepsis because macrophage activation, NO overproduction, and cytokine release contribute to systemic inflammation and organ injury. However, these studies did not use *C. costata* leaf extract and were mostly conducted in cell-based models. Differences in plant species, plant parts, extraction methods, phytochemical composition, and experimental systems limit the extent to which these findings can be extrapolated to *C. costata*. Therefore, these studies strengthen the biological plausibility of the hypothesis but do not confirm the specific therapeutic activity of *C. costata* in sepsis.

Research Gaps and Future Directions

The main contribution of this review is not to establish the efficacy of *C. costata* in sepsis, but to clarify the current evidence gap and propose a structured framework for future investigation. Based on the available evidence, several specific research gaps can be identified.

Gap 1: Absence of direct sepsis studies.

No study has directly evaluated *C. costata* leaf extract in validated experimental sepsis models. The available evidence comes from chemical organ-injury models, acute inflammation models, antioxidant assays, toxicity studies, and mechanistic studies involving related *Castanopsis* species [17–21]. Future studies should evaluate *C. costata* in lipopolysaccharide-induced endotoxemia as an initial inflammatory screening model and in cecal ligation and puncture as a confirmatory polymicrobial sepsis model. Key outcomes should include survival rate, clinical severity score, body temperature, serum lactate, bacterial burden, TNF-α, IL-6, IL-1β, oxidative stress markers, liver and kidney function, and histopathological injury.

Gap 2: Lack of extract standardization.

The available studies show pharmacological activity of *C. costata* extract and its fractions, but the extract has not been standardized using defined marker compounds [17,18]. This limits reproducibility and makes comparison across studies difficult. Future studies should include phytochemical profiling, quantification of marker compounds, and quality control parameters for extract preparation. Standardization is essential before *C. costata* can be tested consistently in sepsis models.

Gap 3: Absence of pharmacokinetic evidence.

No study has evaluated the absorption, distribution, metabolism, and excretion profiles of bioactive compounds from C. costata. Without pharmacokinetic data, it remains unclear whether the active constituents reach biologically relevant concentrations in blood or target organs during systemic inflammation. Future studies should assess oral bioavailability, plasma concentration, tissue distribution, metabolic stability, and half-life of major compounds or standardized extract fractions.

Gap 4: Limited molecular mechanism studies.

The proposed anti-inflammatory and antioxidant mechanisms are based mainly on reductions in cytokine levels and antioxidant activity, along with supporting evidence from related *Castanopsis* species [17–21]. However, the specific molecular targets of *C. costata* remain unclear. Future studies should investigate NF-κB, iNOS, NLRP3 inflammasome, HMGB1, oxidative stress signaling, mitochondrial dysfunction, and endothelial injury pathways. Omics-based approaches, including transcriptomics, proteomics, and metabolomics, may help identify the molecular networks affected by *C. costata* in sepsis-related injury.

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Gap 5: No comparison with standard therapy.

The available studies have not compared *C. costata* with standard sepsis therapy or evaluated its potential as an adjunctive treatment. Future studies should compare *C. costata* with appropriate controls, including antibiotics, corticosteroids, or established anti-inflammatory and antioxidant comparators. Combination studies are also needed to determine whether *C. costata* produces synergistic, additive, or antagonistic effects when combined with standard therapy. Based on the available dose range, crude *C. costata* leaf extract at 100, 200, and 400 mg/kg may be considered for initial in vivo sepsis studies, while fraction-based studies may begin with 50 and 100 mg/kg [17,18]. However, these doses should be validated through toxicity, pharmacokinetic, and dose-response studies before efficacy testing in sepsis models.

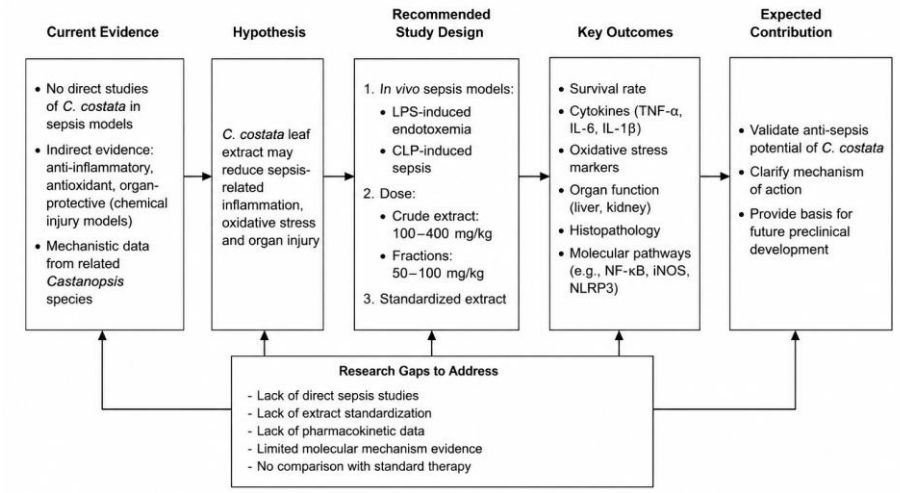

Figure 3. Conceptual Framework for Future Research

Take-Home Messages

First, no direct experimental evidence currently supports the efficacy of *C. costata* in sepsis models. Second, available indirect evidence suggests that *C. costata* has anti-inflammatory, antioxidant, organ-protective, and preliminary safety properties that are biologically relevant to sepsis-related mechanisms. Third, these findings are hypothesis-generating and should not be interpreted as proof of therapeutic efficacy. Fourth, future studies should use standardized extracts, validated sepsis models, sepsis-specific outcomes, pharmacokinetic assessments, analyses of molecular mechanisms, and comparisons with standard therapy.

Conclusions

This systematic review found no direct experimental evidence evaluating the effect of *Castanopsis costata* leaf extract on sepsis outcomes in rat models. However, indirect evidence indicates that *C. costata* possesses anti-inflammatory, antioxidant, and organ-protective properties relevant to sepsis pathophysiology. These findings suggest that *C. costata* may be a source of bioactive compounds for modulating inflammatory responses, oxidative stress, and organ injury associated with sepsis. Nevertheless, the current evidence remains preliminary because available studies were conducted in non-sepsis models or related inflammatory systems.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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