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REVIEW

Garlic and Its Bioactive Derivatives as Host-Directed Therapies in Sepsis

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Abstract: Sepsis, a life-threatening dysregulated host response to infection, urgently requires novel adjunctive therapies due to the limitations of antibiotics and rising multidrug resistance. Garlic and its bioactive organosulfur compounds, such as allicin and diallyl sulfides, demonstrate significant therapeutic potential for sepsis management through diverse mechanisms. Their efficacy primarily stems from simultaneous immunomodulation and antioxidant activity. Garlic derivatives suppress the NF-κB pathway to curtail excessive pro-inflammatory cytokine release and activate the Nrf2/HO-1 pathway to mitigate oxidative stress. Emerging research highlights that they help mitigate mitochondrial dysfunction by enhancing the PINK1/Parkin- mediated mitophagy pathway, thereby preserving cellular integrity. Beyond these host-directed effects, they exert direct, broad-spectrum antimicrobial activity against critical pathogens, including *Pseudomonas aeruginosa, Escherichia coli*, and *Plasmodium* species. Notably, they act synergistically with antibiotics and are effective against multidrug-resistant (MDR) strains. The pleiotropic actions of garlic compounds also confer protection against sepsis-induced multi-organ injury in major organs such as the lung, kidney, and liver. This combination of direct antimicrobial effects, immunomodulation, and organ protection positions garlic derivatives as a promising integrative therapeutic strategy. Given this broad therapeutic potential, further efforts will be required to translate these pleiotropic benefits into clinical practice and establish their efficacy through rigorous clinical trials for sepsis adjunctive therapy ultimately. Notably, current evidence predominantly relies on preclinical data, while critical clinical insights, such as the pharmacokinetics of allicin in humans, remain lacking, posing potential translational challenges.

Keywords: sepsis, garlic, nuclear factor kappa B, NF-κB, diallyl disulfide, DADS, S-allyl cysteine, SAC

Introduction

Sepsis, a life-threatening organ dysfunction induced by a dysregulated host response to infection, remains a leading cause of mortality in intensive care units (ICU) worldwide.[1–3] Its pathophysiology is complex and multidimensional, involving concurrent hyperinflammation, immune suppression, and metabolic reprogramming, which collectively contribute to high mortality and long-term morbidity.[2,4] While antibiotics are cornerstone therapies, the rising threat of antimicrobial resistance and the considerable economic burden of sepsis underscore the urgent need for novel therapeutic strategies.[5–7] Notably, sepsis etiology is not confined to bacteria but also include other pathogens encompasses fungi and viruses. Viral pathogens, including dengue, Ebola, and COVID-19 (SARS-CoV-2), are responsible for a significant proportion, estimated at around 30%, of all sepsis cases.[8] Given that sepsis is fundamentally characterized by a dysregulated host response,[9,10] therapeutic strategies have consequently evolved beyond pathogen-targeted approaches to include modulation of the host's aberrant immune activity. This shift has established host-directed therapies as a central and expanding frontier in sepsis management.[11–14]

Phytochemicals, with their pleiotropic mechanisms, have emerged as promising host-directed candidates for modulating the dysregulated immune response in sepsis. Beyond their primary pharmacological roles, compounds such as glycyrrhizin, silymarin, and curcumin have shown efficacy in attenuating inflammation and organ injury in preclinical models, largely through pathways involving HMGB1, nuclear factor kappa B (NF-κB), and Nrf2.[15–18] Among these,

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garlic (*Allium sativum* L.) and its bioactive derivatives present a particularly compelling case, given their documented anti-inflammatory, antimicrobial, and antioxidant properties relevant to sepsis pathology.[19–22] Garlic's therapeutic potential is exemplified by bioactive compounds including allicin, S-allyl cysteine (SAC), and sucrose methyl 3-formyl-4-methylpentanoate (SMFM). Experimental studies indicate these agents modulate key signaling cascades-such as NF-κB, JAK-STAT, PI3K-Akt, and p38-MAPK-thereby reducing pro-inflammatory cytokines (eg, TNF-α, IL-6, IL-1β) and mitigating oxidative stress and organ damage in models of sepsis.[15,23–27]

Despite the promising preclinical evidence supporting the therapeutic potential of garlic and its bioactive derivatives, in mitigating sepsis-induced organ injuries through anti-inflammatory, antioxidant, and autophagy-modulating mechanisms, a significant translational gap persists. Given that the current evidence is predominantly derived from animal models, key translational barriers remain. These include a lack of human pharmacokinetic and safety data, undefined optimal dosing, and insufficient clinical efficacy validation. Furthermore, challenges related to the compound's bioavailability, stability, and the absence of specific regulatory frameworks for its therapeutic application must be resolved to assess its true translational relevance. The preclinical and clinical data was extracted into Table 1.

Given the broad-spectrum biological activities of garlic and its derivatives, including anti-infection, antioxidant, and immunomodulatory effects, they represent a promising therapeutic avenue for sepsis. This review compiles and evaluates evidence from preclinical and clinical, in vitro, and in vivo studies to delineate their efficacy in sepsis management.

The Mechanism of Garlic and Its Derivatives on Sepsis

NF-κB Pathway

The NF-κB signaling pathway is mediated through two distinct mechanisms: the canonical and non-canonical pathways.[48–50] TRAF6 serving as a crucial regulatory node in the canonical pathway activation. The canonical NF-κB activation pathway is regulated by the IκB kinase (IKK) complex, comprising catalytic subunits IKKα/IKKβ and regulatory subunit NEMO. IKK activation triggers IκBα phosphorylation, leading to polyubiquitination and proteasomal degradation. This releases NF-κB dimers for nuclear translocation and target gene regulation. IKKβ is the principal catalytic subunit phosphorylating IκBα. TNF receptor-associated factor 6 (TRAF6), an E3 ubiquitin ligase, undergoes K63-linked autopolyubiquitination, hence activating its signaling activity. K63-polyubiquitinated TRAF6, as well as presumably TRAF6-modified NEMO, serves as scaffolds for recruiting the TAK1-TAB2 kinase complex. Activated TAK1 then phosphorylates and activates IKKβ.

Evidence indicates that allicin protects against sepsis-induced lung injury by inhibiting the TLR4/MyD88/NF-κB pathway. Allicin dose-dependently suppressed TRAF6, thereby inhibiting NF-κB activation and the subsequent production of inflammatory and apoptotic mediators.[41] In psoriatic models, allicin has been shown to directly inhibit the TRAF6/MAPK/NF-κB and STAT3/NF-κB cascades in IL-17-stimulated keratinocytes, thereby disrupting the inflammatory positive feedback loop. Consequently, allicin reduces the release of multiple inflammatory factors (eg, IL-17A/F, IL-22, IL-12, IL-20), chemokines (CXCL2, CXCL5, CCL20), and antimicrobial peptides (S100A1/9).[33] Similarly, in studies on bovine mammary epithelial cells, allicin mitigates lipopolysaccharide (LPS)-induced inflammation by suppressing the TLR4/NF-κB pathway and NLRP3 inflammasome activation, leading to decreased levels of TNF-α, IL-1β, IL-6, and IL-8. Consistent with these findings, allicin also alleviated LPS-induced mastitis in a mouse model.[32]

In vitro research[40] demonstrated that aged black garlic extract (BG10) potently inhibited the production of nitric oxide (NO) and IL-6. This anti-inflammatory effect was achieved by suppressing the nuclear translocation of NF-κB, thereby downregulating the expression of its downstream targets, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), while concurrently increasing the intracellular levels of IκBα. Moreover, SAC, as an active component of garlic, showed multiple therapeutic benefits, including anti-inflammatory and antioxidant properties.[51–53] SAC has been demonstrated to ameliorate acute kidney injury by preserving mitochondrial integrity and attenuating oxidative stress, inflammation, and apoptosis. In 2019, MR et al found that pretreatment with SAC (100 mg/kg) in an LPS-induced AKI model led to a significant reduction in renal function markers (BUN and creatinine) and a concurrent increase in inflammatory mediators (NF-κB, TLR4, IL-1β, and IL-6), suggesting dose-dependent efficacy.[39]

Table 1 Summary of Preclinical and Clinical Data

Author/Year/[Reference]	Types of Animal/Participants	Types of Model Inducer	Intervention Group	Laboratory Data	Clinical Data	Effect (Conclusion)
Li XJ et al /2024/[28]	c57BL/6 mice/ HK2 cells	CLP/LPS	Allicin	Y		Positive
Zhou S et al /2024/[29]	BALB/c female mice	*S. aureu*	GELNs	Y		Positive
Chen Y et al /2024/[30]	Male C57BL/6J mice	LPS	SPRC	Y		Positive
Avendaño-Ortiz J et al /2023/[31]	Healthy volunteers and patients with sepsis	LPS	TASE		Y	Positive
Che HY et al /2023/[32]	Pregnant ICR mice/ MAC-T cell line	LPS	Allicin	Y		Positive
Zhang L et al /2023/[33]	Male and female BALB/c mice	IMQ	Allicin	Y		Positive
Tong YC et al /2023/[22]	Cats	-	Garlic oil	Y		Positive
Chang Z et al /2022/[34]	Sprague–Dawley female rats	*Escherichia coli*	Allicin	Y		Positive
Liu M et al /2022/[35]	C57BL/6J male mice/ THP-1 cells	LPS	Alliin (CAS: 556–27-4)	Y		Positive
Redondo-Calvo FJ et al /2022/[36]	Male Sprague–Dawley® rats	*Escherichia coli* ATCC 25922	TASE/ BGE	Y		Positive
Zhu L et al /2022/[37]	Female C57BL/6 strain mice	C. *rodentium*	PTS, PTSO	Y		Positive
Torres KAM et al /2021/[38]	*Streptococcus agalactiae*	-	CGE	Y		Positive
Zhang Y et al /2021/Uncited	Male SPF DBA/1 mice	Chicken collagen type II	Allicin	Y		Positive
Khajevand-Khazaei MR et al /2019/[39]	Male C57BL/6 mice	LPS	SAC	Y		Positive
You BR et al /2019/[40]	RAW264.7 cells	LPS	BG10	Y		Positive
Shen N et al /2019/[41]	Male SD rats	LPS	Allicin	Y		Positive
Shi L et al /2017/ Uncited	RAW264.7 cell/Male ICR mice	LPS/DSS	Alliin	Y		Positive
Anandasadagopan SK et al /2017/[42]	Male Wistar albino rats	Cr (VI)	SAC	Y		Positive
Percival SS et al / 2016/[43]	Healthy human participants / RCT	-	AGE		Y	
Lee SK et al /2015/[26]	Male wild type ICR mice	CLP	SMFM	Y		Positive
Bayraktar O et al /2015/[27]	Male Wistar rats	LPS	SAC	Y		Positive
Salama AA et al /2014/[44]	*Babesia parasites, B. bovis and B. caballi*	BALB/c mice /In vitro	Allicin	Y		Positive
Kim MJ et al /2014/ Uncited	Male C57BL/6 mice /RAW 264.7	LPS	AGE/RGE	Y		Positive

(*Continued*)

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Table 1 (Continued).

Author/Year/[Reference]	Types of Animal/Participants	Types of Model Inducer	Intervention Group	Laboratory Data	Clinical Data	Effect (Conclusion)
Watson CJ et al /2014/Uncited	Asymptomatic women who were culture-positive for Candida species (n=63)/RCT	-	Garlic		Y	Positive
Feng Y et al /2012/[45]	Female BALB/c mice	*Plasmodium yoelii* 17XL	Allicin	Y		Positive
Park HJ et al /2012/Uncited	RAW 264.7 macrophages	LPS	ARGE	Y		Positive
Kuo CH et al /2011/Uncited	Male Wistar rats	Endotoxin	Garlic oil	Y		Positive
Yalindag-Ozturk N et al /2011/[46]	A critically ill infant	-	Garlic extract		Y	Positive
Smyth AR et al /2010/Uncited	Patients (n=26)/RCT	-	Garlic		Y	Positive
Cutler RR et al /2009/[21]	Clinical isolates of Lancefield GBS	In vitro	Allicin extract and topical gel formulation	Y		Positive
Yu J et al /2007/ Uncited	Patients (n=30)	SGD	Garlicin		Y	Negative
Coppi A et al /2006/[47]	Female Swiss Webster mice	*Plasmodium berghei* and *yoelii*	Allicin	Y		Positive
Stjernberg L et al /2000/Uncited	Military personnel /PRDBIS	-	Garlic		Y	Positive

Abbreviations: AGE, aged black garlic; BG10, black garlic extract BG10; BGE, ceftriaxone plus black garlic extract; CGE, crude garlic extract; CLP, cecal ligation and puncture; LPS, lipopolysaccharide; Cr (VI), hexavalent chromium; DAT, Diallyl trisulfide; DSS, dextran sulfate sodium; GBS, group B streptococci; GELNs, garlic- derived exosome-like nanovesicles; IMQ, imiquimod; MAC-T cell line, immortalized dairy cow mammary epithelial cell line; PTS, propyl propane thiosulfinate; PTSO, propyl propane thiosulfonate; RGE, raw garlic extract; SMFM, sucrose methyl 3-formyl-4-methylpentanoate; SAC, S-allyl cysteine; ARGE, aged red garlic extract; SGD, selected gut decontamination; TPA, 12- *O*-tetradecanoylphorbol- 13- acetate; TASE, thiosulfinate-enriched *Allium sativum* extract; *S. aureus*, Staphylococcus aureus.

Nrf2/HO-1 Pathway

Nrf2 is a key transcription factor that regulates cellular redox homeostasis by controlling antioxidant and cytoprotective gene expression. By binding to antioxidant response elements (AREs), Nrf2 activates a suite of Phase II detoxifying enzymes, thereby maintaining redox equilibrium and enhancing cellular defense mechanisms in pathological circumstances.[54] Studies have demonstrated that Nrf2 activation mitigates sepsis-induced organ dysfunction by attenuating excessive inflammatory responses and oxidative damage.[55] Notably, these protective effects are particularly evident in the amelioration of complications such as acute lung injury, acute kidney injury, and sepsis-associated myocardial depression.[28,56,57]

Furthermore, evidence indicates that Nrf2 activation stimulates mitochondrial biogenesis, reduces apoptosis, and enhances tissue regeneration, underscoring its vital role in preserving organ integrity during sepsis.[58–60] Activation of the Nrf2 signaling pathway has been shown to mitigate sepsis-induced inflammatory responses, oxidative stress, and organ dysfunction, thereby contributing to improved clinical outcomes. These findings highlight the therapeutic potential of targeting Nrf2 for developing novel strategies to reduce complications and enhance prognosis in sepsis. In a mouse model of sepsis-induced acute kidney injury (S-AKI), allicin was found to downregulate levels of serum creatinine, blood urea nitrogen, UALB, KIM-1, and NGAL, indicating improved renal function. Allicin also inhibited inflammatory and apoptotic processes, as reflected by reduced levels of inflammatory cytokines and apoptosis-related proteins.[28]

PINK1/Parkin Pathway

Sepsis can lead to irreversible tissue damage and organ dysfunction, significantly contributing to the pathogenesis of type 5 cardiorenal syndrome (CRS-5).[61] Studies have confirmed that activation of PINK1/Parkin-mediated mitophagy protects against sepsis-associated acute kidney injury by reducing inflammatory cytokine levels and restoring renal function.[62] S-propargyl-cysteine (SPRC), a garlic-derived chemical, is a hydrogen sulfide (H_2S) donor that reduces macrophage inflammation and reactive oxygen species (ROS) production during sepsis and promotes an M1-to-M2 transition. This protective effect is mediated through the PINK1/Parkin pathway, which triggers adaptive autophagy in response to LPS challenge, thereby attenuating immune dysregulation.[30] Furthermore, alliin has been shown to mitigate LPS-induced macrophage pyroptosis by enhancing PINK1/Parkin-dependent mitophagy, leading to reduced mitochondrial ROS and suppression of NLRP3 inflammasome activation.[35]

Other

The above mechanism is shown as Figure 1. Garlic and its derivatives have been shown can ameliorate clinical symptoms in diverse pathogen infections.[29,63,64] However, their precise roles and underlying mechanisms in sepsis remain incompletely understood and necessitate further investigation.

The Effect of Garlic and Its Derivatives on Pathogens

Anti-Protozoal Potential

Malaria

As early as 2006, allicin, a cysteine protease inhibitor present in garlic extracts, has been proven to possess ability to inhibit malaria infection. Malaria parasite proteases are essential for completing the parasite's life cycle and represent promising targets for novel antimalarial drugs. Allicin has been shown to inhibit the processing of the circumsporozoite protein (CSP) and block sporozoite invasion of host cells in both in vitro and in vivo models.[47] In 2012, a study further demonstrated that allicin confers protection against *Plasmodium yoelii* 17XL infection by enhancing both innate and adaptive immune responses.[45] The protective mechanism is primarily mediated through the upregulation of pro-inflammatory mediators-including IFN-γ, TNF, IL-12p70, and NO, as well as the activation of $CD4^+$ T cells, dendritic cells (DCs), and macrophages. Additionally, allicin promotes the maturation of $CD11c^+$ DCs, thereby strengthening the host's overall anti-malarial immunity.

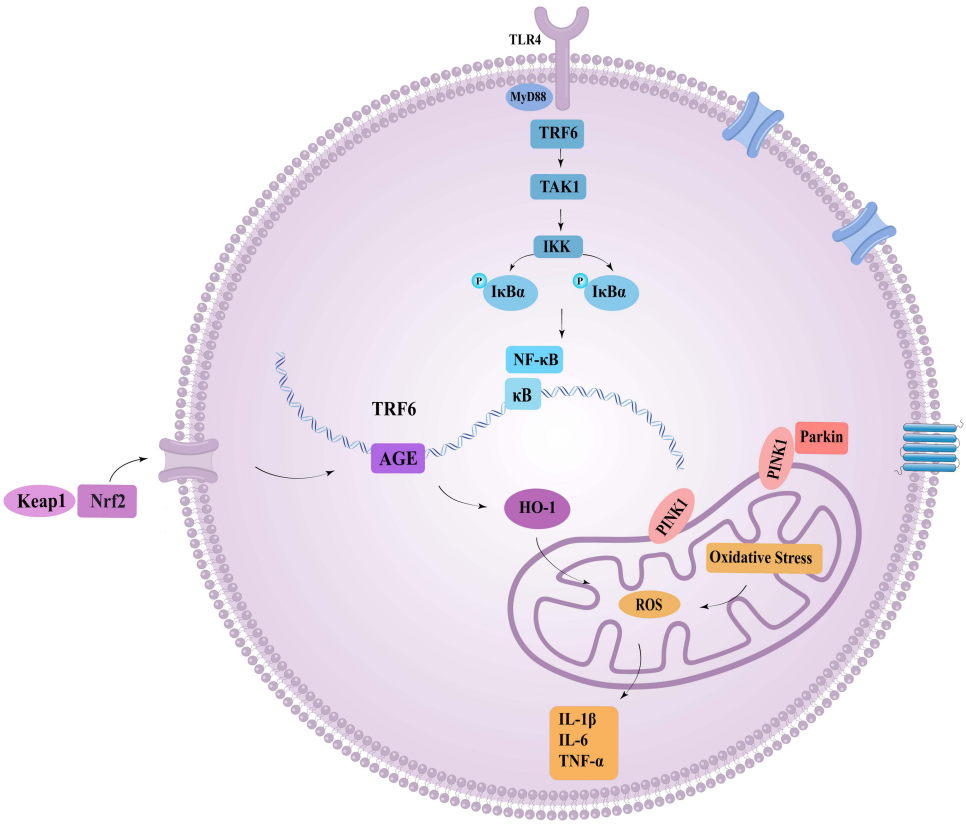

Figure 1 The role of garlic and its derivatives in the signaling pathway during sepsis development.

Babesia and Theileria equi Parasites

Further evidence suggests allicin demonstrated dose-dependent (30 mg/kg for 5 days) in vitro growth inhibition against several *Babesia* and *Theileria parasite* species.[44] Importantly, it significantly inhibited merozoite invasion into erythrocytes. In a mouse model of *Babesia microti* infection, allicin treatment significantly reduced parasitemia. Notably, combining allicin with the common antibabesial drug diminazene aceturate produced a synergistic inhibitory effect both in vitro and in vivo, suggesting its potential as a beneficial combination therapy for babesiosis.

Anti-Bacterial Potential

Pseudomonas aeruginosa

Pseudomonas aeruginosa (PA) is a prevalent opportunistic pathogen in healthcare-associated settings, particularly in ICU, where it is a leading cause of bloodstream and respiratory infections. This pathogen exhibits intrinsic resistance to multiple antibiotic classes and a demonstrated capacity to develop further resistance to novel agents.[65] The potential of garlic-based compounds as adjuvant therapy was initially reported in 2011, when a critically ill infant with severe multidrug-resistant PA pneumonia and bacteremia showed gradual clinical improvement following treatment with garlic and antibiotics.[46] A growing body of evidence now points to the underlying mechanisms. Emerging evidence indicates that diallyl disulfide (DADS), a key component of garlic oil, interferes with the quorum-sensing (QS) networks of *P. aeruginosa* PAO1. It suppresses the major genes (las, rhl, pqs) across all three QS systems, consequently reducing the production of associated virulence factors such as LasA/LasB proteases, LecA/LecB lectins, pyocyanin, and biofilm.[66] Similarly, diallyl sulfide (DAS), another garlic-derived compound, inhibits PA QS systems. This inhibition attenuates the production of host-damaging virulence factors and may enhance the synthesis of certain host-beneficial nutritional factors.[67]

Group B Streptococcus

Group B *streptococcus* (GBS) remains a leading cause of invasive neonatal disease and associated morbidity. Maternal GBS colonization represents the primary risk factor for neonatal sepsis.[68] To mitigate the incidence of early-onset GBS disease, current clinical guidelines recommend universal culture-based screening during late gestation and intrapartum antibiotic prophylaxis (IAP).[69] Nevertheless, the widespread use of antibiotics contributes to the selection and dissemination of antimicrobial- resistant strains, highlighting the urgent need for alternative therapeutic strategies. In this context, recent investigations have identified specific garlic- derived compounds that exhibit inhibitory effects against clinical isolates of GBS, including γ- glutamyl-S- allyl- cysteine (fraction 18), γ- glutamyl- phenylalanine (fraction 20), and E- and Z-stereoisomers of ajoene (fraction 42).[38]

Escherichia coli

Allicin has been demonstrated to significantly suppress the upregulation of the MALT1 and AKT/NF- κB pathways and the expression of cytokines such as IL- 6 and IL- 1β in *Escherichia coli*- induced urinary tract infections (UTI).[34] Separately, an evaluation of thirty clinical *E. coli* isolates revealed that the antibacterial activity of garlic extract (AGE) and manuka honey against extended- spectrum beta- lactamase (ESBL)- producing strains, as well as their interactive effects, are concentration- dependent.[70]

Furthermore, extensive studies have demonstrated that garlic and its extracts exhibit broad-spectrum antimicrobial, antibiofilm, alongside selective cytotoxic properties.[37,71–75] These bioactive compounds demonstrate efficacy against various pathogens including *Klebsiella pneumoniae, Clostridioides difficile strains, Bacillus anthracis, Citrobacter spp*., and *diverse fungi*, particularly drug-resistant strains.

Anti-Viral Potential

Clinical and preclinical evidence supports the antiviral properties of garlic and its bioactive compounds.[76] A randomized controlled trial (RCT) demonstrated that supplementation with AGE significantly enhanced the proliferation of γδ-T cells and natural killer (NK) cells in healthy subjects.[77] Although the incidence of colds and flu was unchanged, AGE consumption led to a marked reduction in illness severity, including fewer symptoms and days of impairment. A subsequent RCT confirmed these immunomodulatory findings, further positing that the improved cellular function with AGE may be associated with more efficient immune activity and potentially reduced inflammation.[43] Similarly, a long-acting garlic tablet formulation markedly decreased the incidence of acute respiratory infections in children compared to placebo.[78] Beyond these common viral illnesses, research indicates a broader antiviral potential. Organosulfur compounds from garlic show inhibitory activity against human immunodeficiency virus type 1 (HIV-1).[79] Furthermore, a selenium-enriched garlic powder demonstrated the ability to inhibit SARS-CoV-2 replication in vitro, potentially through mechanisms involving antioxidant activity and downregulation of host proteins crucial for viral entry.[80] These effects are attributed to multiple mechanisms, including direct inhibition of viral replication, blocking viral entry into host cells, and modulation of immune responses, positioning garlic as a promising candidate for non-specific prophylaxis against viral infections.

In summary, emerging evidence collectively supports the potential of garlic- derived bioactive compounds and their formulated extracts as promising plant-based candidates for adjunctive sepsis therapy. Their utility is attributed to multifaceted immunomodulatory, antioxidant, and antimicrobial effects against resistant pathogens.

Pleiotropic Effects of Garlic and Its Derivatives as Sepsis Adjunctive Therapy

Synergistic Effects in Enhancing Antibiotic Efficacy

Emerging evidence indicates that garlic and its bioactive constituents can enhance the efficacy of conventional antibiotics- such as gentamicin, ciprofloxacin, and ceftriaxone- through synergistic interactions.[36,81,82] This synergy not only enhances bactericidal outcomes but may also allow for dose reduction, thereby potentially mitigating side effects and delaying the development of resistance. The underlying mechanisms involve multiple pathways that compromise

bacterial defenses, including inhibition of efflux pumps, impairment of biofilm formation, and increased membrane permeability, collectively promoting antibiotic penetration and intracellular accumulation. Notably, ajoene, a sulfur- rich compound derived from garlic, exhibits promising antitubercular properties.[82] When combined with first- line anti-*Mycobacterium tuberculosis* (TB) drugs such as isoniazid and rifampicin, it significantly enhances anti- biofilm activity. The direct bactericidal activity of ajoene is mediated through the efflux pumps inhibition and subsequent augmentation of ROS.

Potential as a Novel Anti-Resistance Strategy

The global escalation of antimicrobial resistance (AMR) underscores the critical need for alternative therapeutic agents. *Allium sativum* (garlic) and its organosulfur compounds have re- emerged as promising candidates due to their broad-spectrum antimicrobial activity against multidrug-resistant (MDR) pathogens. Evidence indicates that garlic and its derivatives can effectively inhibit key virulence traits, including biofilm formation and QS systems, in diverse bacteria.[83–86] As evidenced by studies on AGE exhibits strong efficacy against drug-resistant C. *albicans* and its associated polymicrobial biofilms, highlighting its potential as a safe and effective option for developing synergistic adjuvant therapies.[83]

The mechanism of garlic and its derivatives demonstrates potential as a novel strategy to combat antimicrobial resistance. Research has identified garlic as a source of natural quorum-sensing inhibitors (QSIs), which can suppress fungal growth, prevent biofilm formation, and potentially augment host immune responses. These properties suggest its utility as a complementary therapeutic approach, particularly for infections in immunocompromised patients and those caused by drug- resistant fungal pathogens.[86]

Immunomodulatory Role in Sepsis

The pathophysiology of sepsis is defined by a simultaneous and dysregulated host response, featuring concurrent hyperinflammation and profound immunosuppression.[87] This immunopathology typically evolves in a biphasic manner: an initial phase of systemic inflammatory response syndrome (SIRS), often manifesting as a "cytokine storm", is frequently followed by a compensatory anti-inflammatory response syndrome (CARS). The CARS phase leads to protracted immunosuppression, characterized by features such as neutrophilia, an increase in regulatory T cell numbers, a monocytic endotoxin tolerance phenotype, elevated levels of IL-10 and TGF-β, and significant lymphocyte apoptosis. Consequently, an effective therapeutic regimen requires a dual-pronged strategy: mitigating the early cytokine storm and reversing the subsequent state of immune paralysis.[88–90]

Immunomodulation has emerged as a pivotal therapeutic strategy for sepsis, shifting the paradigm from a sole focus on pathogen eradication to the active restoration of the host's dysregulated immune response. The dual immunomodulatory effect of thiosulfinate-enriched garlic extract (TASE) on LPS-stimulated monocytes, dependent on inflammatory status, has been demonstrated. TASE was shown to enhance cytokine production in low-inflammatory states while suppressing it in hyperinflammatory contexts, primarily through inhibition of the HIF-1α pathway and downregulation of IRAK-M, VEGFA and PD-L1.[31] Additionally, NaSH and SPRC significantly attenuated the inflammatory response by suppressing the secretion of pro-inflammatory cytokines, reducing ROS generation.[30] This potential was linked to a phenotypic shift in macrophages from pro-inflammatory M1 to anti-inflammatory M2, coupled with the induction of PINK1/Parkin- mediated mitophagy, which improved mitochondrial function and dampened the inflammatory cascade. Earlier-cited studies also have substantially deepened our understanding of the immunomodulatory mechanisms of garlic and its extracts in sepsis.[48,91] Together, this evolving body of evidence underscores the potential of garlic and its bioactive derivatives as a multi-target agent for re-establishing immune homeostasis in sepsis.

The Role in Sepsis-Induced Multi-Organ Dysfunction

Sepsis, a life-threatening condition arising from a dysregulated host response to infection, can progress to multi- organ dysfunction syndrome (MODS), a process driven by uncontrolled systemic inflammation, oxidative stress, and immune paralysis.[92–95] Given the limitations of conventional antibiotics and the lack of specific therapies targeting the host response, natural products with pleiotropic properties have garnered increasing attention. Garlic and its bioactive

constituents, particularly organosulfur compounds like allicin and SAC, have emerged as promising candidates for mitigating sepsis-associated organ injury via multiple interconnected mechanisms.

A prominent mechanism is the activation of the Nrf2 pathways. A 2024 study demonstrated that the combination of Selenomethionine (SeMet) and allicin synergistically attenuates oxidative stress and intestinal barrier injury in both cellular and murine models by activating the Nrf2- NQO1 axis and suppressing endoplasmic reticulum stress. This protective effect was abolished by an Nrf2 inhibitor, confirming the pathway's centrality.[96] Similarly, SAC has shown efficacy in reducing liver and lung injury in LPS- induced septic rats by lowering markers of oxidative stress and inhibiting DNA fragmentation.[27] The protective role of SAC against oxidative damage was also demonstrated in a model of chromium (VI)- induced hepatotoxicity, where it reduced NF- κB and TNF- α expression.[42] A 2024 study found that SPRC, protected against LPS-induced cardiorenal injury in mice.[30] These findings are consistent with reports on specialized pro-resolving mediators such as Resolvin D1, which protects against septic acute kidney injury by modulating inflammation and apoptosis,[97] underscoring a key therapeutic axis in sepsis management.

Limitations and Future Directions

Allicin is investigated as a potential adjunctive agent for sepsis management, primarily based on its multimodal mechanisms of action. Preclinical evidence suggests that its value stems not only from its direct anti-pathogen effect, but also from its ability to regulate host response dysregulation. A recent study (2023) found that garlic treatment in LPS-induced septic rats activates transient receptor potential vanilloid 1 (TRPV1) channels, upregulates calcitonin gene-related peptide (CGRP), and alleviates systemic oxidative stress and inflammatory damage.[24] Furthermore, garlic-derived exosome-like nanoparticles (GELNs) are shown to alleviate ulcerative colitis in mice. Orally administered GELNs ameliorate colitis symptoms, reduce proinflammatory cytokines, and protect the intestinal barrier. The mechanism involves the remodeling of gut microbiota, specifically through GELNs-enriched microRNAs that promote the growth of the beneficial bacterium *Bacteroides thetaiotaomicron*.[98]

However, the current evidence landscape possesses significant gaps that limit translational confidence. The promising data are almost exclusively derived from in vitro studies and animal experiments. Critical questions regarding optimal dosing, pharmacokinetics in critically ill patients, formulation stability, and safety profiles in human sepsis remain largely unaddressed. There is a notable absence of large-scale, rigorous randomized controlled trials to substantiate its clinical efficacy and safety. Consequently, while the consolidated mechanistic narrative supports allicin's biological plausibility, its definitive role in sepsis therapy await validation through targeted clinical research designed to bridge these translational gaps.

Conclusion

In conclusion, contemporary research provides compelling preclinical evidence that garlic and its extracts can attenuate the cascade of events leading to MODS in sepsis. Their ability to simultaneously target inflammation, oxidative stress, and apoptosis positions them as potential multi-target adjunctive therapies. However, translating these findings into clinical practice requires rigorous human trials to validate efficacy, determine optimal dosing, and standardize bioactive compound formulations for sepsis management.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work. There is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of the manuscript.

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