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REVIEW

Andrographolide in Sepsis: Mechanistic Basis, New Drug States, and Advanced Delivery Systems

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Abstract: Sepsis is a leading cause of preventable mortality, and effective adjunct therapies that recalibrate the host response remain scarce. Andrographolide, a diterpenoid lactone from Andrographis paniculata, shows anti-inflammatory, antioxidant, endothelial-protective, and immunomodulatory activity in experimental sepsis and related inflammatory models. This narrative review examines both the mechanistic basis and the translational constraints of andrographolide in sepsis, with emphasis on modulation of Toll-like receptor 4 signaling and downstream NF-κB/MAPK activation, restraint of NLRP3 inflammasome activity, mitigation of mitochondrial stress and danger-signal amplification, and preservation of endothelial barrier function while partially maintaining bacterial clearance. We also discuss the major pharmaceutical liabilities of andrographolide, including extremely low aqueous solubility and limited systemic exposure, and distinguish exposure-enabling solid-state strategies from delivery platforms with potential relevance to acute sepsis care. Because the direct evidence base remains largely preclinical and the available human data derive mainly from non-sepsis conditions, current findings support hypothesis generation and translational exploration rather than clinical positioning in sepsis. Future priorities include septic PK/PD definition, route-appropriate formulation development, entity-specific safety evaluation, and rigorous validation in clinically relevant models and trials.

Keywords: andrographolide, sepsis, inflammation, drug delivery systems, cocrystals, solid dispersions

Introduction

Sepsis is a life-threatening syndrome caused by a dysregulated host response to infection, and it remains a major global health burden. In 2017, an estimated 48.9 million cases of sepsis occurred worldwide, with 11 million sepsis-related deaths, accounting for roughly 19.7% of all global deaths.[1] Clinically, sepsis is highly heterogeneous and pathophysiologically complex. It often begins with an overwhelming inflammatory reaction to infection, commonly described as a cytokine storm, that can precipitate shock, disseminated tissue injury, and multi-organ failure, yet many patients later progress toward immunosuppression and immune exhaustion.[2] This shifting balance between hyperinflammation and impaired host defense underlies the difficulty of defining broadly effective host-directed therapies.

Current management of sepsis focuses on prompt antimicrobial therapy and organ-supportive care, but specific pharmacologic interventions aimed at modulating the host response have largely proven ineffective.[3,4] Despite decades of research and numerous clinical trials, no targeted anti-sepsis drug has demonstrated a definitive survival benefit.[5,6] Evidence-based treatment therefore remains centered on infection control, hemodynamic resuscitation, vasopressor support, and other supportive measures.[7] Mortality also remains high: pooled estimates suggest 30-day mortality of 24.4% for sepsis and 34.7% for septic shock, rising to 32.2% and 38.5% at 90 days, respectively.[8] This difficult translational record provides an important backdrop for evaluating any candidate immunomodulator in sepsis.[9,10]

Andrographolide (AG) has emerged as a candidate of interest in this context. AG is a bioactive diterpenoid lactone isolated from the medicinal herb Andrographis paniculata, which has long been used in traditional medicine for treating infections, fever, and inflammatory disorders.[11,12] Pharmacologically, andrographolide exhibits broad anti-inflammatory and immunomodulatory properties, primarily through inhibition of signaling pathways such as NF-κB, with consequent

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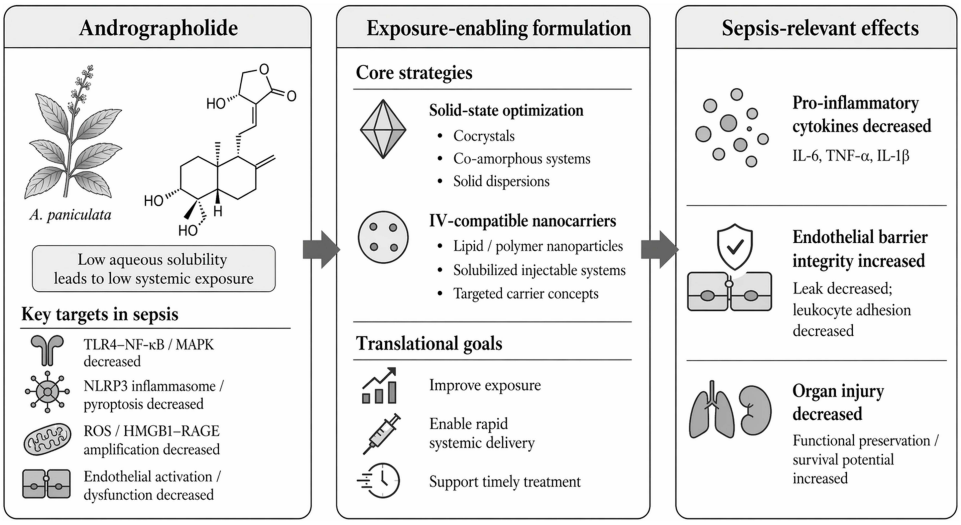
Graphical Abstract



reduction in pro-inflammatory mediator production.[13,14] Preclinical studies suggest that AG can modulate the host response in sepsis, including lowering TNF-α and IL-6, increasing IL-10, limiting tissue injury, and improving bacterial clearance in selected models.[15] At the same time, AG has extremely low aqueous solubility and limited systemic exposure, and the acute hemodynamic instability of septic shock raises concern that oral absorption may be unreliable during early resuscitation. For this reason, mechanistic promise and route-appropriate pharmaceutical feasibility need to be considered together when assessing the relevance of AG to sepsis.

In this review, we first outline the inflammatory and endothelial context of sepsis, then evaluate the mechanistic evidence for AG with explicit distinction between direct sepsis-related observations and supportive findings from broader inflammatory models. We next discuss the physicochemical liabilities and formulation strategies relevant to translation, with particular attention to platforms that may be more plausible in acute sepsis care, and finally summarize safety considerations, indirect human data, and research priorities. The major sepsis-related mechanisms discussed in this review are summarized in Figure 1.

Literature Search and Scope

This article is a narrative review. Literature was identified through searches of major biomedical databases, including PubMed, Web of Science, and Scopus, using combinations of the terms “andrographolide,” “sepsis,” “endotoxemia,” “cecal ligation and puncture,” “inflammation,” “formulation,” and “drug delivery,” together with manual screening of relevant reference lists. Direct evidence from sepsis-related models was prioritized in the mechanistic interpretation, whereas data from broader inflammatory, endothelial, and formulation studies were used as supportive evidence when direct sepsis data were limited. Human studies were interpreted as indirect translational signals unless they specifically involved sepsis.

Sepsis and Inflammation

The pathogenesis of sepsis centers on an aberrant inflammatory cascade triggered by the host’s innate immune recognition of infection.[16] When microbial components known as pathogen-associated molecular patterns (PAMPs), such as endotoxin lipopolysaccharide from Gram-negative bacteria, are detected by pattern-recognition receptors including Toll-like receptor 4 (TLR4) on monocytes and macrophages, a vigorous inflammatory signaling response is initiated.[17] TLR4 engagement activates MyD88-dependent and MyD88-independent pathways that converge on NF-κB,

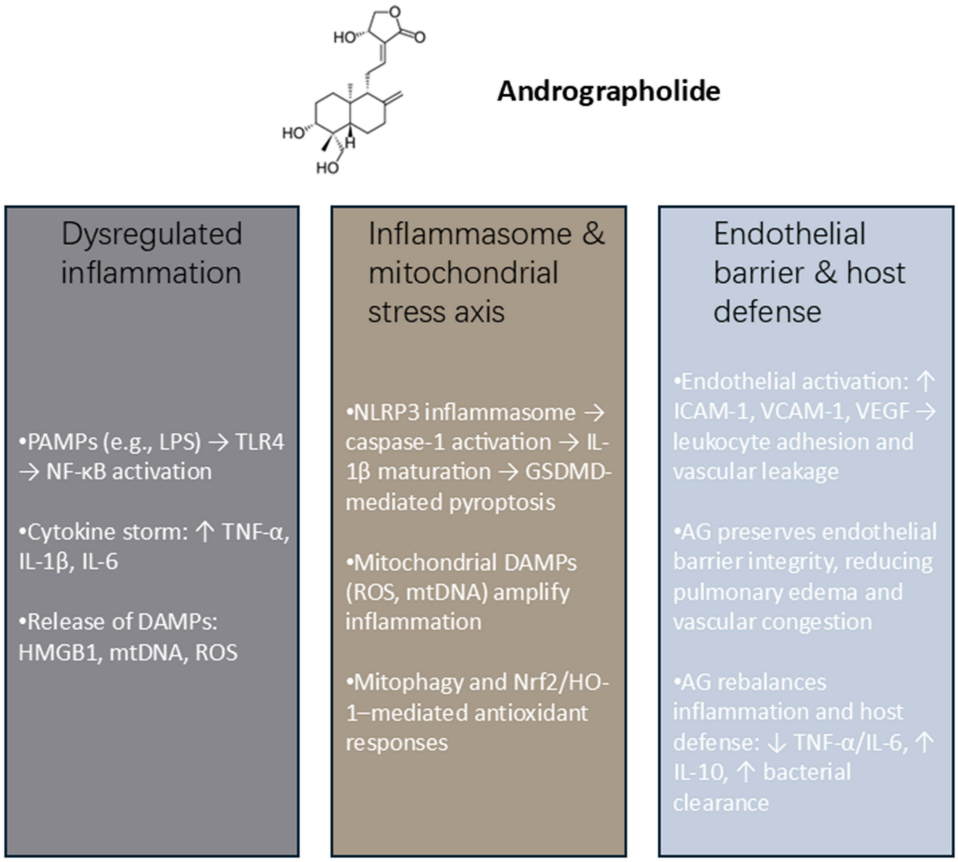


Figure 1 Mechanistic framework of andrographolide in sepsis. The figure summarizes principal sepsis-related processes and andrographolide-associated protective effects discussed in this review, including dysregulated inflammation driven by PAMP-TLR4-NF-κB signaling, cytokine storm and DAMP release; inflammasome activation, mitochondrial DAMP amplification, mitophagy and Nrf2/HO-1-mediated antioxidant responses; and endothelial barrier protection with partial maintenance of host defense. ↑ indicates increase or activation; ↓ indicates decrease or inhibition; → indicates pathway progression or signaling direction.

leading to rapid expression of pro-inflammatory genes and cytokines.[18] This results in release of mediators such as tumor necrosis factor-α, interleukin-1β, and IL-6, which drive systemic inflammation. As this response escalates, host-cell injury and death generate damage-associated molecular patterns such as HMGB1 and mitochondrial DNA, further amplifying inflammation through feed-forward signaling.[19,20] In parallel, cytosolic sensors assemble inflammasomes including NLRP3, leading to caspase-1 activation, maturation of IL-1β and IL-18, and pyroptotic cell death.[21]

A key downstream consequence of this dysregulated response is profound endothelial dysfunction. Circulating cytokines and DAMPs activate vascular endothelial cells, degrade barrier integrity, and upregulate adhesion molecules and pro-coagulant programs.[19] Endothelial leakiness and dysregulated vasomotor tone promote extravasation of fluid and leukocytes, contributing to hypotension, edema, impaired organ perfusion, and disruption of the alveolar–capillary interface in acute respiratory distress syndrome.[22] Systemic inflammation also drives coagulopathy through tissue-factor induction and loss of endogenous anticoagulant function, thereby favoring microvascular thrombosis and worsening ischemic injury.[23,24] As sepsis progresses, early hyperinflammation may coexist with or transition toward immune dysfunction, including lymphocyte apoptosis, impaired antigen presentation, and vulnerability to secondary infection.[25] This dynamic and heterogeneous pathobiology means that any host-directed therapy must be judged not only by its anti-inflammatory effects, but also by whether it preserves endothelial integrity and avoids compromising pathogen clearance.[10,16]

This framework also clarifies how the mechanistic evidence for AG should be read. Because sepsis models vary substantially in infectious burden, hemodynamic disturbance, organ involvement, and time course, evidence from CLP, endotoxemia, and organ-focused inflammatory systems should not be assumed to be interchangeable. The following

sections therefore distinguish, where possible, between direct sepsis-related observations and supportive findings derived from broader inflammatory models.

The preclinical evidence base for AG in sepsis is mechanistically interesting but not uniform in evidentiary weight. In the sections below, direct observations from sepsis-related models are considered separately from supportive non-sepsis studies, and native AG is distinguished from water-soluble derivatives when formulation-specific differences may influence interpretation.

Andrographolide in Sepsis

Inflammasome and Pyroptosis Axis

Direct evidence for modulation of the inflammasome–pyroptosis axis in sepsis-related settings is suggestive but still limited. In a murine cecal ligation and puncture sepsis model, AG promoted autophagy in alveolar macrophages, suppressed NLRP3 activity, reduced downstream IL-1β release, and attenuated pyroptosis-associated lung injury.[26] By contrast, several mechanistic details often cited for this pathway come from non-sepsis systems. Suppression of NLRP3 overactivation, caspase-1 cleavage, IL-1β release, and gasdermin D activation has been shown in LPS-primed macrophage or other inflammatory cell models, and Parkin-mediated mitophagy–linked restraint of inflammasome activation was demonstrated in an LPS-driven microglial Parkinson disease model rather than in sepsis itself.[27,28] Together, these data support biological plausibility for AG-mediated inflammasome restraint, but they do not yet establish that all steps of this pathway have been validated in clinically relevant sepsis settings.

Evidence for broader immune rebalancing is somewhat stronger in sepsis-related models. In CLP-induced intra-abdominal sepsis, AG decreased TNF-α and IL-6, increased peritoneal IL-10, improved bacterial clearance, enhanced macrophage recruitment and phagocytic activity, and improved 7-day survival.[15] A water-soluble andrographolide derivative likewise improved survival and reduced inflammatory injury in endotoxemia.[29] These findings are encouraging because they suggest that AG-related interventions may dampen injurious inflammation while preserving antibacterial host defense, and key preclinical evidence is summarized in Table 1.

At the same time, these results should not be interpreted as interchangeable evidence for native AG and derivative molecules, because solubility, route of administration, and systemic exposure may differ materially between studies.[15,29] More broadly, the published literature remains dominated by positive preclinical reports, while dose levels, treatment timing, and pharmacokinetic exposure are variably described. Accordingly, current evidence supports a possible immune-balancing effect of AG in sepsis, but not yet a fully resolved exposure–response framework.

Table 1 Selected Preclinical Evidence for Andrographolide (AG) in Sepsis and Systemic Inflammation

Model/System	Intervention	Key Targets/Axis	Main Outcomes	Reference
Murine CLP polymicrobial sepsis	AG (route/dose NR)	Cytokine rebalancing; macrophage recruitment and phagocytosis	↓TNF-α/IL-6, ↑IL-10; improved bacterial clearance; ↑7-day survival	[15]
Murine CLP septic lung injury (alveolar macrophages)	AG (route/dose NR)	Autophagy-dependent NLRP3 restraint and pyroptosis inhibition	↓NLRP3/caspase-1/IL-1β; reduced pyroptosis; ameliorated lung injury	[26]
Endotoxemia (LPS challenge, mouse)	AG derivative (water-soluble; NR)	Suppression of pro-inflammatory cytokines	↑Survival; ↓TNF-α/IL-1β; reduced organ injury	[29]
D-galactosamine/LPS-induced acute liver injury	AG (NR)	Antioxidant defense activation (Nrf2/HO-1)	↓ROS/lipid peroxidation; attenuated inflammatory injury	[30]
CLP/LPS models; endothelial hyperpermeability	AG (post-treatment; NR)	HMGB1 pathway attenuation; barrier stabilization	↓HMGB1 release; reduced capillary leak and leukocyte migration	[31]
Human endothelial cells (TNF-α stimulation)	AG (NR)	NF-κB inhibition; adhesion molecule suppression	↓ICAM-1; reduced leukocyte adhesion	[32]
LPS-induced acute lung injury (animal model)	AG (NR)	Endothelial activation and permeability mediators	↓VCAM-1/VEGF; ↓neutrophil infiltration and edema	[33]

Notes: ↑ indicates increase; ↓ indicates decrease.
Abbreviation: NR, not reported.

Mitochondrial Stress and DAMP Signaling

Direct sepsis-related evidence for this domain centers mainly on DAMP signaling rather than on fully mapped mitochondrial pharmacology. In polymicrobial sepsis, AG suppressed HMGB1-driven inflammatory responses, reduced capillary leakage, and limited leukocyte migration, supporting attenuation of a clinically relevant late inflammatory amplifier.[31] In a septic lung injury model, AG also engaged RAGE/PI3K/AKT/mTOR-linked autophagy signaling in alveolar macrophages.[26] However, much of the mechanistic detail regarding mitophagy, mitochondrial ROS control, ATP preservation, and Nrf2/HO-1–linked antioxidant defense derives from non-sepsis models, including LPS-driven microglial injury and acute endotoxin-induced liver injury.[28,30] These studies support the concept that AG may restrain mitochondrial stress and DAMP amplification, but they remain indirect with respect to sepsis and do not yet define whether native AG reaches the relevant tissue compartments at therapeutically meaningful exposures during critical illness.

Endothelial Barrier Protection

Evidence for endothelial protection is mechanistically consistent but heterogeneous in model context. In direct sepsis-related settings, AG inhibited HMGB1-induced endothelial inflammatory responses and reduced vascular leak and leukocyte migration in murine polymicrobial sepsis.[31] Supportive evidence from non-sepsis inflammatory models shows that AG suppresses endothelial NF-κB activation, attenuates TNF-α-induced ICAM-1 expression, and lowers VCAM-1 and VEGF in LPS-induced acute lung injury, findings that are concordant with reduced leukocyte adhesion, neutrophil infiltration, and edema.[32,33] Together, these data suggest that AG can modulate endothelial activation and barrier dysfunction, but the evidence base remains focused mainly on adhesion molecules, permeability-related mediators, and histologic injury.

Important gaps remain. Whether AG preserves VE-cadherin, claudins, occludin, ZO-1, or endothelial glycocalyx components in sepsis has not been defined systematically, and endothelial responses may differ substantially across lung, kidney, gut, and other vascular beds.[19,22] In addition, dose feasibility and route-dependent translational relevance remain insufficiently characterized, particularly when comparing native AG with more soluble derivative formulations.

Study on the New Drug States of Andrographolide

Because sepsis is an acute, time-critical syndrome, formulation discussion must be interpreted through a translational lens. Strategies that improve dissolution or oral exposure are mechanistically informative, but they are not equally relevant to early sepsis management. In the discussion below, solid-state approaches are considered primarily as exposure-enabling tools, whereas delivery platforms are prioritized according to their potential compatibility with rapid systemic administration.

Physical and Chemical Properties of Andrographolide

AG is a highly lipophilic labdane diterpene (MW 350.45) with extremely poor aqueous solubility. Its octanol/water partition coefficient is commonly reported around logP ≈ 2.63, and its equilibrium water solubility at 25 °C has been measured as 3.29 ± 0.73 μg/mL, underscoring its poorly soluble nature.[34,35] Temperature-elevation studies across 288–323 K likewise show very low water solubility with only modest temperature dependence.[36] By contrast, AG dissolves more readily in organic solvents such as ethanol, DMSO, and DMF, and it remains only sparingly soluble in aqueous buffers.[37] Crystalline AG has a high melting point of about 243 °C, and only a single anhydrous polymorph has been structurally characterized to date.[38] Collectively, these properties place AG in the low-solubility range of the Biopharmaceutics Classification System, most often discussed as dissolution-limited despite occasional class II/class III ambiguity.[39,40] Available pharmacokinetic work further suggests that poor exposure reflects not only slow dissolution but also transporter- and metabolism-related barriers. In intestinal permeability models, AG shows efflux behavior consistent with P-glycoprotein involvement, and metabolic studies have identified hydroxylation together with glucuronide, sulfate, and sulfonic acid-related metabolites after systemic handling.[41–44] These features are especially relevant in sepsis, where unpredictable gastrointestinal absorption and the need for timely systemic exposure make route selection more consequential than in routine oral therapy.

The chemical stability of andrographolide is also a practical concern in formulation. In aqueous solution AG is comparatively stable in moderately acidic media but undergoes hydrolysis at neutral to alkaline pH.[45] Degradation kinetics studies indicate that AG has optimal stability around pH 2.0–4.0, whereas at pH ≥6 significant lactone cleavage occurs, yielding products with reduced biological activity.[45] Thermally, pure crystalline AG remains intact until near its melting point, but amorphous or co-amorphous forms may recrystallize at substantially lower temperature; for example, a co-amorphous AG–lysine phase crystallized at about 100 °C.[46] Accelerated storage studies in powdered Andrographis herb also indicate time- and temperature-dependent degradation of AG content during storage.[47] By contrast, photostability, humidity tolerance, and long-term formulation-specific storage robustness remain less consistently characterized in the AG literature. Accordingly, formulation design should be understood as a balance among dissolution enhancement, metabolic liability, and physical stability rather than as a simple solubility-maximization exercise. For sepsis translation in particular, improvements in oral dissolution alone do not necessarily resolve the need for rapid and reliable systemic exposure.

New Crystal form of Andrographolide

Systematic crystal engineering of AG has so far revealed only limited polymorphism. Database curation indicates a single anhydrous AG polymorph deposited since the original small-molecule structure report, underscoring how sparse the polymorph landscape appears for this diterpenoid lactone.[46] By contrast, multiple pharmaceutical cocrystals have been generated through targeted hydrogen-bonding with small GRAS coformers. Liquid-assisted grinding of AG with phenols and benzoic-acid derivatives yielded a family of 1:1 isostructural cocrystals with vanillin, vanillic acid, salicylic acid, resorcinol, and guaiacol.[48] These systems illustrate how donor–acceptor pairing and crystal-packing reorganization can modify dissolution behavior and, in some cases, metabolic susceptibility. Notably, the AG–salicylic acid cocrystal slowed conversion to an inactive sulfate metabolite and showed about threefold faster dissolution with roughly twofold higher total release than crystalline AG under matched conditions.[48] Drug–drug cocrystallization with bosentan further demonstrates that AG can participate in API–API lattices, although the translational rationale in sepsis would depend less on chronic dual therapy than on manufacturability, stability, and compatible systemic administration.[49] Overall, cocrystals are best viewed here as exposure-enabling solid-state tools. Their relevance to acute sepsis remains indirect unless future work also defines humidity tolerance, dissociation during dissolution, and scalable manufacturing performance.

Amorphous conversions complement cocrystal strategies when higher drug loading or carrier flexibility is required. Polymeric solid dispersions of AG, often prepared by spray- or vacuum-drying, consistently depress crystallinity and accelerate release. In water, raw AG dissolves only about 22% at 120 min, whereas optimized PEG-based or graft-PEG dispersions reach 85–92% in the same window, with dissolution gains tracking reductions in PXRD crystallinity and melting transitions.[50] A spray-dried PVP K30 solid dispersion likewise improved saturation solubility, accelerated early release, and enhanced oral performance in rats.[51] More recently, low-molecular-weight coformers enabled a 1:1 AG–L-lysine co-amorph with about 70 wt% drug loading and markedly higher aqueous solubility, whereas an AG–tryptophan co-amorph conferred little benefit.[46] These findings are useful because they define controllable solid-state levers for AG exposure, but they should be interpreted mainly as preformulation and exposure-optimization data rather than as sepsis-specific delivery solutions. Physical stability during storage and recrystallization control remain central translational hurdles.

Delivery Strategies with Potential Translational Relevance to Acute Sepsis

Most published AG delivery studies were not developed specifically for sepsis and instead sought to improve oral bioavailability or tissue-targeted delivery in other disease settings. As proof of principle, these studies show that cyclodextrin or phospholipid complexation, nanoscale dispersion, and lipid incorporation can materially increase apparent solubility, dissolution, or systemic exposure.[39,52–58] However, for acute sepsis their relevance is uneven. Platforms optimized for oral absorption, soft-capsule administration, or local delivery do not directly solve the central clinical problem of achieving immediate and predictable systemic exposure during hemodynamic instability and possible gastrointestinal absorption failure. Representative exposure-enabling solid-state approaches and carrier platforms for AG are summarized in Table 2.

Table 2 Exposure-Enabling New Drug States and Carrier Platforms for Andrographolide (AG): Representative Examples with Potential Translational Relevance

Category	Principle	Main Findings	Reference
Cocrystal	1:1 AG–salicylic acid and phenolic/benzoic-acid cocrystals prepared by liquid-assisted grinding	~3× faster dissolution and ~2× total release vs crystalline AG; reduced formation of inactive sulfate metabolite	[48]
	API–API cocrystal of AG with bosentan, followed by nano-size reduction into rod-shaped nanococrystals	Enhanced pulmonary-endothelium targeting and improved efficacy in pulmonary hypertension models	[49]
Dosage form	Co-amorphous 1:1 AG–L-lysine prepared by neat ball milling	≈70 wt% drug loading and markedly higher aqueous solubility; AG–Trp co-amorph showed little benefit	[46]
	Solid dispersions of AG with various polymer carriers (eg., PEG) by spray/vacuum drying	Optimised PEG-based SDs reached ≥85–92% dissolution at 120 min vs ~22% for raw AG	[50]
	Spray-dried amorphous AG–PVP K30 solid dispersion	Increased saturation solubility, faster initial release, and improved oral performance in rats	[51]
	AG-loaded solid lipid nanoparticles prepared by high-pressure homogenisation	Sustained release and ~2-fold higher oral bioavailability (~241% relative) vs suspension	[53]
	Lymphatic-targeting AG SLNs with optimised lipid and Poloxamer surfactant (~200 nm)	Prolonged release up to 24 h, higher systemic exposure, and enhanced spleen/thymus uptake vs free AG	[54]
	Mannosylated chitosan-coated AG nanoliposomes for hepatitis therapy	AUC ↑ ~1.56-fold and MRT ↑ ~2.25-fold with improved anti-hepatitis efficacy	[57]

Notes: ↑ indicates increase. Low-value local, mucosal, depot, and slow-release routes were omitted from the main table to maintain relevance to acute sepsis translation.

From a sepsis-translation perspective, the more relevant question is which systems could support rapid systemic administration and acceptable intravascular behavior. Lipid and polymeric nanocarriers, nanosuspensions, and other IV-compatible formulations are conceptually attractive because they may improve dispersion, protect the payload, and alter organ distribution; broader nanocrystal strategies also support dissolution and dispersion enhancement for poorly soluble drugs, although their relevance to AG in sepsis remains indirect.[59] The current AG literature nevertheless provides only partial support for this goal. Some nanoparticle systems improved exposure or tissue uptake, and injectable concepts such as PLGA microspheres or long-acting nanosuspensions demonstrate technical feasibility for non-oral delivery.[53,54,56,57,60,61] Yet most were evaluated in non-sepsis models, and comparative data on infusion feasibility, plasma compatibility, sepsis-specific pharmacokinetics, and organ distribution under critical illness are still lacking.

Accordingly, inhaled powders, intranasal liposomes, intra-articular hydrogels, oral depot systems, and other local or slow-release platforms should be interpreted in this review as indirect formulation evidence rather than frontline sepsis solutions.[58,60,62–67] Their value is to demonstrate how modifiable AG physicochemical behavior can be, not to imply equal clinical relevance across all routes. For acute sepsis, formulation priorities should remain centered on rapid exposure, systemic deployability, and safety under conditions of vascular instability.

Toxicological and Safety Studies of Andrographolide

Safety evidence in the AG literature should be interpreted by entity and route rather than pooled across all preparations. Native andrographolide, AG-containing botanical extracts, and sulfonated injectable derivatives differ in composition, exposure profile, excipients, and clinical use context; therefore, their toxicological findings are not interchangeable.

For native or formulation-defined AG products, available animal data suggest a relatively broad oral safety window, but the evidence base remains limited and formulation dependent. An andrographolide–2-hydroxypropyl-β-cyclodextrin inclusion complex showed LD50 > 2000 mg/kg and a 28-day oral NOAEL of 666 mg/kg·d in rats.[68] However, increased exposure can alter the acute toxicity profile: an AG self-nanoemulsifying system yielded an estimated oral LD50 of about 833 mg/kg and early hepatic/renal histologic changes at high single doses.[69] These observations support caution against extrapolating safety from one AG formulation to another, particularly when excipients or delivery systems materially change bioavailability.

By contrast, much of the apparently reassuring repeated-dose and genotoxicity evidence comes from AG-containing botanical preparations rather than purified AG itself. Standardized A. paniculata extract preparations showed high acute oral tolerability and no major treatment-related abnormalities in subacute or 90-day studies, and another standardized

extract was negative in Ames, chromosomal aberration, and in-vivo micronucleus assays.[70–72] These data are useful for contextualizing the safety of extract-based oral products, but they should not be treated as direct proof of safety for native AG, high-exposure nanoformulations, or injectable derivatives.

Sulfonated injectable derivatives require separate consideration because their formulation and route create a distinct risk profile. At suprapharmacological doses in mice, intravenous andrographolide sodium bisulfite increased renal oxidative-stress markers and produced tubular injury.[73] In humans, the main concern with andrographolide sodium bisulfite injection, commercially known as Xiyanping, and related injectable derivatives is immediate hypersensitivity rather than dose-limiting oral-type intolerance. Pharmacovigilance and post-marketing datasets consistently identify allergic reactions, including anaphylactic shock, as the dominant serious adverse events, even when overall ADR incidence under monitored use appears low.[74–79]

Several safety gaps remain directly relevant for translation into sepsis care. Human hepatotoxicity case reports, reproductive toxicity, chronic toxicity, CYP/transporter-mediated drug–drug interactions, and nanoformulation-specific toxicology are not yet sufficiently defined in the AG literature. In addition, sepsis itself may alter vascular permeability, organ perfusion, and concomitant medication exposure, so safety data generated in non-septic oral-use settings cannot be assumed to predict risk during critical illness.

Clinical Research and Application Prospects

Direct randomized trials of andrographolide itself in sepsis are not yet available. Human data come primarily from infection-related and immune-inflammatory indications, which provide translational signals but do not substitute for sepsis RCTs. In acute respiratory tract infections (ARTIs), a meta-analysis of 33 RCTs (n = 7,175) found that Andrographis paniculata improved cough and sore throat and shortened symptom duration vs. placebo/usual care, while cautioning about heterogeneity and overall trial quality.[80] In COVID-19, a 2025 systematic review/meta-analysis of 6 RCTs (n = 660) concluded that single-herb AP products (typically delivering andrographolide for 4–5 days) did not significantly improve fever or cough resolution or reduce CRP/IL-6 compared with antivirals/supportive care; adverse events were generally mild (eg., transient liver enzyme elevations).[81]

Evidence for clinically relevant immunomodulation also exists outside respiratory infections. In ulcerative colitis, a double-blind, placebo-controlled RCT (n = 224) of ethanol extract HMPL-004 (1,200–1,800 mg/day, 8 weeks) improved clinical response vs. placebo, supporting anti-inflammatory activity in humans.[82] Additional randomized trials of andrographis-standardized extracts report symptom improvement in knee osteoarthritis over 12–14 weeks, indicating broader anti-inflammatory effects, though these results are not specific to infection or critical illness.[83]

Discussion

Preclinical data present a compelling rationale for andrographolide in sepsis. Mechanistically, andrographolide inhibits multiple inflammatory pathways (NF-κB, STAT3, MAPKs) and reduces cytokine release, endothelial injury and organ damage in septic models. Importantly, recent studies suggest it does not simply suppress immunity, instead, andrographolide may enhance host defense. For example, in intra-abdominal sepsis models it improved bacterial clearance and increased macrophage phagocytosis and bactericidal activity.[84] Thus, andrographolide seems to dampen the damaging "cytokine storm" while preserving innate immune function, where a balanced immunomodulation that is desirable in sepsis.

However, there are significant translational bottlenecks. Andrographolide itself has poor water solubility and bioavailability, necessitating high oral doses or injectable prodrugs. Water-soluble andrographolide sulfonates improve solubility but may introduce formulation- and route-specific safety concerns and require IV administration. Novel formulations or chemical modifications will be needed to enhance delivery and reduce side effects. Inspired by sulfonation-based solubility improvement, chemical strategies to improve andrographolide's solubility (eg. prodrugs, liposomes, nanoparticles) could broaden administration options (oral, inhaled, IV).[85] Additionally, virtually no human PK/PD data exist in septic patients: the appropriate dose, timing and exposure-response relationships remain unknown. Without this information, it is difficult to design effective dosing regimens or understand tissue drug levels in critical illness.

Clinically, the evidence so far is too limited to draw firm conclusions. The human studies reviewed involved relatively healthy outpatients or patients with non-sepsis inflammatory conditions rather than true septic shock or multi-organ

failure. In sepsis, any anti-inflammatory strategy must also avoid impairing microbial clearance. Although AG has shown potentially favorable immune-balancing effects in selected preclinical models, these signals remain indirect and insufficient for clinical extrapolation.

Future research should therefore proceed along several lines. First, pharmaceutical development should prioritize route-appropriate formulations and derivatives that improve exposure while remaining realistic for acute sepsis care. Second, PK/PD investigations are needed in relevant sepsis models, and eventually in human infection settings, to define dosing, distribution, and exposure-response relationships. Third, mechanistic work should continue to test whether AG can modulate inflammatory injury without compromising pathogen clearance. Fourth, any future clinical studies must be rigorously designed and should focus on clearly defined patient populations and clinically meaningful endpoints.

Taken together, the present literature provides a rationale for continued mechanistic and translational investigation, but it does not yet justify therapeutic claims for sepsis care.

Conclusion

Andrographolide has a mechanistically interesting preclinical profile in sepsis, with reported effects on inflammatory signaling, inflammasome activity, mitochondrial stress, endothelial dysfunction, and selected host-defense readouts. However, the direct evidence base remains limited, heterogeneous, and overwhelmingly preclinical, while the available human data come largely from non-sepsis settings. Poor solubility and exposure, the need for route-appropriate formulations, unresolved PK/PD questions in sepsis, and entity-specific safety issues further constrain interpretation. At present, the literature supports hypothesis generation and translational exploration rather than clinical positioning of AG in sepsis care.

Data Sharing Statement

All data supporting this article are included in the manuscript. Additional data can be requested from the corresponding author.

Ethics Approval

This is a review article and does not involve studies with human participants or animals; therefore, ethical approval was not required.

Informed Consent

Not applicable. This article is a literature review and does not include research involving human participants.

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

The authors declare no conflicts of interest in this work.

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