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Review Article

Reprogramming the Macrophage Inflammasome: Palm-Derived γ-Tocotrienol, NLRP3 Signalling, and the Balance Between Host Defence and Immunopathology—A Critical Review

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Abstract

Macrophage NLRP3 inflammasomes are essential sentinels of microbial danger but can also amplify tissue injury. Palm-derived gamma-tocotrienol has been associated with attenuation of inflammatory signalling and remodelling of macrophage lipid mediators in selected experimental systems. Whether these responses improve infection outcomes remains unknown. This critical qualitative literature review integrates primarily 2020–2026 peer-reviewed studies and one foundational 2018 experiment addressing tocotrienol chemistry, pharmacokinetics, immunometabolism, canonical and noncanonical inflammasome signalling, pathogen-specific host defence, and therapeutic translation. Its interpretive synthesis separates purified gamma-tocotrienol from tocotrienol-rich fractions, sterile endotoxin/lipotoxicity experiments from live-pathogen models, and inflammatory biomarkers from antimicrobial efficacy. Five findings emerge: lipid and mitochondrial states condition inflammasome activity; different pathogen contexts assign protective and injurious roles to pyroptosis; isomer identity and tissue exposure constrain inference; human infection-specific gamma-tocotrienol evidence is absent; and credible translation requires concurrent measurements of microbial burden and tissue damage. A dual-outcome conceptual model and stage-gated research roadmap are proposed. Gamma-tocotrienol should therefore be considered a mechanistically interesting experimental immunomodulator, not a validated host-directed anti-infective treatment. Future studies should integrate chemically verified exposures, human macrophage systems, viable-pathogen killing assays, and organism-level safety and efficacy endpoints.

Keywords: Gamma-Tocotrienol, Palm Oil Bioactives, NLRP3 Inflammasome, Macrophage Immunometabolism, Innate Immunity, Pyroptosis, Gasdermin D, Host-Directed Therapy, Pathogen Clearance, Immunopathology

JEL Classification: I12, I18, L65, O33, Q16.

Introduction

The immune-defence problem

Macrophages occupy a strategic interface between tissue maintenance and antimicrobial defence. They remove debris, engulf microorganisms, sense microbial and endogenous danger, recruit leukocytes, and help coordinate adaptive immunity. Their inflammatory programs are costly and therefore must be calibrated to the nature and location of the threat. A macrophage response that contains microbes in one tissue may destabilise another tissue through protease release, inflammatory cell death, vascular leakage, or prolonged cytokine production. Current work on tissue-specific immunometabolism demonstrates that metabolic inputs are not uniform across intestinal, lung, and other resident macrophage populations. Consequently, reducing a single soluble inflammatory mediator cannot be regarded as equivalent to improving immune competence (Ben-Arosh and Avraham, 2023, Gauthier and Chen, 2022, Rosenberg et al., 2022).

Recent synthesis of tissue-resident macrophage biology makes this heterogeneity more concrete. Tissue-resident populations develop and coordinate organ-specific protective functions, while inducible antibacterial programmes recruit oxidative, lysosomal, metabolic and nutrient-restriction mechanisms that vary across organisms. Consequently, an anti-inflammatory intervention must be tested against the relevant macrophage compartment and its direct antimicrobial capacities, not only against a generalised cytokine profile (Mass et al., 2023, Sweet et al., 2025).

The NLRP3 inflammasome provides a prominent molecular example of this tension. Primed macrophages assemble a multiprotein platform that recruits the adaptor ASC and caspase-1 after particular disturbances of intracellular homeostasis. Caspase-1 then processes pro-interleukin-1beta and pro-interleukin-18 and cleaves gasdermin D, allowing cytokine release and potentially pyroptotic cell death. These processes mobilise immunity, yet persistent or misplaced activation can fuel injury. High-resolution structures now distinguish inactive NLRP3 arrangements from activated oligomers and show that molecular licensing is more elaborate than a simple on/off switch. Both the functional benefit and the danger of this machinery depend on the infected cell, organism, compartment, and phase of disease (Xu and Nunez, 2023, Fu and Wu, 2023, Fu et al., 2024).

Infection-associated inflammation poses a different optimisation problem from sterile inflammatory disease. Therapeutic restraint may be desirable when excess IL-1 signalling destroys tissue, but the same restraint could preserve the intracellular niche of a replicating microbe or postpone the recruitment of effective effector cells. The literature documents strikingly divergent consequences of manipulating inflammasome-associated pathways

in viral, bacterial, and parasitic infections. Host-directed therapy thus requires evidence of what happens to the pathogen as well as what happens to the host inflammatory response. Where these two dimensions are not reported together, efficacy claims are inherently incomplete (Wallis et al., 2023, Booty and Bryant, 2022, Li et al., 2024).

Why palm-derived gamma-tocotrienol merits critical study

Tocotrienols are unsaturated members of the vitamin E family found in palm and several other botanical materials. Their chemical diversity matters: alpha-, beta-, gamma-, and delta-tocotrienols are not interchangeable with one another, nor are they equivalent to the corresponding tocopherols. Palm-derived tocotrienol-rich fractions contain multiple isomers and may contain tocopherols, commercial preparations also differ in extraction, formulation, and purity. The label 'palm vitamin E' therefore does not describe a single molecular intervention. This review focuses on γ-tocotrienol as the candidate compound while considering mixed products only as relevant comparators, not as conclusive proxies for isolated γ-tocotrienol (Szewczyk et al., 2021, Wong et al., 2020, Zainal et al., 2022).

Interest in γ-tocotrienol is biologically plausible because the compound can affect redox balance, inflammatory gene expression, and lipid mediator pathways. Influential experiments before the review period reported attenuation of NLRP3-related responses and remodelling of arachidonic-acid and sphingolipid metabolism in LPS-primed, saturated-fat-exposed murine macrophages. Contemporary reviews discuss these findings and broaden the account of tocotrienol pharmacology. Nonetheless, the experiments are not live-microbial challenge tests and do not establish pathogen control, tissue benefit during infection, or clinical efficacy. The present paper therefore treats the reported response as a mechanistic lead rather than as a demonstrated anti-infective property (Ranasinghe et al., 2022, Zainal et al., 2022, Khor et al., 2021).

The problem of compound exposure is equally fundamental. Tocotrienols are lipophilic, their oral absorption can be variable, and isomer-specific systemic distribution depends on formulation and physiology. Concentrations added to cultured cells cannot simply be equated with achievable unbound concentrations in macrophages after oral intake. Even a well-controlled change in macrophage signalling at a nominal culture concentration has limited translational meaning without measurements of the actual free and intracellular dose. Reviews of vitamin E nanoformulations and human pharmacokinetics reinforce this caution, while advances in oral delivery systems suggest testable strategies rather than proven solutions (Mohd Zaffarin et al., 2020, Sharif et al., 2023, Ooi et al., 2026).

Research gap, questions and contribution

The gap is not an absence of NLRP3 biology or antioxidant studies. Rather, it is the absence of a bridge that connects precisely characterised γ-tocotrienol exposure with causal inflammasome target engagement, microbial killing, host tissue integrity, and outcome after authentic infection. Reviews of tocotrienol supplementation have evaluated chronic-disease endpoints or general inflammatory biomarkers, whereas infection biology reveals that inflammasome activity may be either protective or damaging. The tension between these two bodies of literature provides the rationale for a qualified host-directed immunology model (Looi et al., 2025, Coll and Schroder, 2025, Vande Walle and Lamkanfi, 2024).

This article asks what mechanisms are plausible, what observations actually support them, when inflammasome down-modulation might be protective or hazardous, and what evidence should precede application. Its objectives are to consolidate a critical conceptual basis, organize contemporary studies into coherent themes, distinguish experimental models from clinical indications, and propose falsifiable translational criteria. The central proposition is deliberately conditional: carefully timed modulation of macrophage inflammatory signalling might be useful in selected contexts if antimicrobial control is preserved, but there is currently no basis for describing palm-derived γ-tocotrienol as an established intervention for sepsis, pneumonia, tuberculosis, or fungal infection. This qualification is an analytical outcome, not a lack of enthusiasm for molecular discovery (Li et al., 2024, Wallis et al., 2023).

Literature Review: Conceptual and Theoretical Foundations

Compound identity and pharmacological inference

Vitamin E nomenclature can conceal important differences in molecule, source, and mixture composition. Tocotrienols possess an unsaturated isoprenoid side chain, whereas tocopherols have a saturated side chain, methylation of the chromanol ring generates the alpha, beta, gamma, and delta isoforms. An observed effect of a heterogeneous tocotrienol-rich fraction cannot be attributed to γ-tocotrienol unless the mixture is analytically characterised and appropriate isomer controls are included. Similarly, an effect of annatto-derived delta-tocotrienol or a vitamin E long-chain metabolite does not, by itself, establish an effect of palm-derived γ-tocotrienol. These distinctions are necessary for valid chemical attribution and reproducibility (Szewczyk et al., 2021, Wong et al., 2020, Ranasinghe et al., 2022).

The source distinction matters in practice because palm tocotrienol-rich fractions can be biologically heterogeneous even when supplied at the same total vitamin E dose. Human clinical trial syntheses support investigation of palm TRF in selected metabolic and inflammatory conditions but do not provide a validated infection indication. A meta-analysis of tocotrienol supplementation found that an apparent reduction in C-reactive protein was substantially attributable to one delta-tocotrienol study, while pooled effects on several other systemic inflammatory markers were not significant. This pattern warns against generalizing a result to all tocotrienols or interpreting a biochemical change as broad immunoprotective efficacy (Looi et al., 2025, Khor et al., 2021, Zainal et al., 2022).

Macrophage heterogeneity and immunometabolism

Macrophages do not constitute a uniform population with a fixed pro-inflammatory or anti-inflammatory identity. Their origins, differentiation histories, local nutrients, oxygen tension, cytokines, and microbial exposures create diverse states. Classifications such as M1 and M2 remain useful shorthand for some laboratory perturbations but inadequately represent continuous and tissue-specific cell programs. Studies of macrophage metabolism during infections show that glycolysis, mitochondrial respiration, glutamine utilization, and the tricarboxylic acid cycle can be redirected in stimulus- and pathogen-specific ways. A compound capable of altering one metabolic node may have different effects in an alveolar macrophage, an intestinal resident macrophage, or an inflammatory monocyte (He et al., 2021, Ben-Arosh and Avraham, 2023, Galli and Saleh, 2020).

Metabolic reprogramming is not merely an adaptation to energy expenditure. Citrate, succinate, itaconate, and alpha-ketoglutarate participate in signalling, chromatin regulation, oxidant production, and cytokine expression. Bacterial pathogens may respond directly to the altered availability of host metabolites and use these signals to tune virulence, creating a metabolic dialogue rather than a one-way host response. Methodological guidance also emphasizes measuring flux and function rather than assuming that

expression of a single metabolic enzyme reveals pathway activity. These insights undermine overly linear antioxidant explanations of macrophage signalling and motivate multimodal assays in γ-tocotrienol experiments (Ryan and O'Neill, 2020, Rosenberg et al., 2022, Voss et al., 2021).

The canonical NLRP3 axis

The canonical inflammasome is conventionally described in two functionally connected stages. Priming through pattern-recognition or cytokine receptors can increase NLRP3 and pro-IL-1β expression, while also inducing post-translational modifications that prepare the complex for assembly. Activation then follows a compatible cellular perturbation such as potassium efflux, membrane injury, organelle dysfunction, or specific metabolic stress. NLRP3 interacts with regulatory proteins including NEK7, promotes ASC polymerization, and recruits caspase-1. Precise details vary across cell types and stimuli, the model should not be reduced to the claim that all oxidative signals directly activate the sensor (Xu and Nunez, 2023, Niu et al., 2021, Yu et al., 2024). Cryo-electron microscopy and biochemical work have refined this view of NLRP3 activation. Inactive oligomeric cages, intermediate conformations, and assembly-competent structural states constrain the plausible loci of small-molecule regulation. A reduction in released IL-1β does not show that a compound directly binds NLRP3: it might instead inhibit priming, diminish cell viability, interfere with cytokine synthesis, alter potassium flux, or change secretion. Consequently, an assignment of direct NLRP3 inhibition requires more than a cytokine assay, orthogonal readouts and genetic or biochemical confirmation are necessary. This inferential discipline is central to the proposed appraisal (Fu and Wu, 2023, Fu et al., 2024, Yu et al., 2024).

An updated account of NLRP3 molecular regulation distinguishes priming, post-translational licensing, spatial organisation and assembly as experimentally separable processes. This additional resolution is important when interpreting lipophilic natural products: reduced mature IL-1β could arise from changes at several upstream or downstream checkpoints. It also reinforces the need for genetic dependency controls before describing γ-tocotrienol as a direct NLRP3-binding inhibitor (Paik et al., 2025).

Noncanonical inflammasomes, gasdermins and cell fate

Noncanonical inflammasome signalling further complicates attribution. In human cells, inflammatory caspases-4 and -5, and in mice caspase-11, can respond to cytosolic bacterial lipopolysaccharide and engage gasdermin-dependent membrane changes. The resulting ionic disturbances may secondarily promote NLRP3 activation, but the upstream sensor, microbial context, and order of events differ from canonical priming-plus-ATP assays. Live bacterial viability signals can also participate in this interface, strengthening the argument that purified LPS exposure is not a complete substitute for an actual infection (Moretti et al., 2022, Gangopadhyay et al., 2022).

Gasdermin D cleavage releases a pore-forming N-terminal fragment, permitting cytokine export and changes in membrane permeability. Full cellular rupture can involve additional components including NINJ1, while cells may sometimes release cytokines without immediate lysis. These distinctions matter because enzyme activation, pore formation, cytokine secretion, and terminal pyroptosis are related but nonidentical endpoints. An intervention that reduces lactate dehydrogenase release might preserve viable phagocytes without necessarily preventing all inflammatory signalling, conversely, delayed lysis might prolong pathogen replication. Cellular fate therefore requires direct imaging and time-resolved analysis, not a single terminal viability measurement (Broz et al., 2020, Liu et al., 2021, Kayagaki et al., 2021, Xia et al., 2021).

Immunological resistance, tolerance and host-directed treatment

Host resistance refers broadly to mechanisms that prevent microbial expansion or accelerate clearance, whereas disease tolerance denotes maintenance of host function despite a given pathogen burden. These dimensions can dissociate. A host-directed anti-inflammatory intervention might improve organ function while leaving microbial burden unchanged, but may also inadvertently increase pathogen load. During infection, inflammasome-mediated removal of an intracellular niche can protect the host, while excessive pyroptosis can facilitate extracellular spread or fuel destructive systemic inflammation. This creates a need to report both antimicrobial and host injury outcomes, rather than presenting their combination as a single undifferentiated measure of health (Booty and Bryant, 2022, Churchill et al., 2022, Wallis et al., 2023).

This duality also makes intervention timing an essential variable. In an early containment phase, IL-1 family signals and inflammatory cell death may help recruit effective defenses, once the pathogen is adequately controlled, persistent inflammatory amplification may become dispensable or harmful. Infection phenotypes arise from pathogen-specific tactics, tissue architecture, host genetics, and associated therapies, so a fixed universal direction of benefit should not be expected. Selective inflammasome drugs illustrate that pathway modulation is pharmacologically plausible, but their development does not validate an uncharacterised plant-derived molecule for an infectious indication (Vande Walle and Lamkanfi, 2024, Coll and Schroder, 2025, Li et al., 2024).

Method: Critical Qualitative Literature Review

Review orientation and interpretive scope

This study employs a critical qualitative literature review, not a systematic literature review or meta-analysis. Its purpose is conceptual integration: to compare experimentally observed biological events, evaluate whether mechanistic explanations survive changes in model context, and identify what must be demonstrated before moving from molecular plausibility to infectious-disease application. The cited scholarship is predominantly from 2020–2026, one foundational 2018 primary macrophage experiment is retained transparently because it provides the most directly relevant compound-specific lipidomics evidence. The earlier experiment is explicitly identified by its original publication year and is not misrepresented as a recent clinical or infection study. The approach is appropriate because literature on tocotrienols is dispersed across nutrition, pharmacology, lipid biology, immunology, and infection research, and because numerical pooling would merge endpoints that answer fundamentally different causal questions (Ranasinghe et al., 2022, Zainal et al., 2022, Xu and Nunez, 2023).

Literature identification and source appraisal

Relevant concepts were explored across biomedical scholarly literature using combinations of γ-tocotrienol, tocotrienol-rich fraction, macrophage, NLRP3, caspase-1, gasdermin D, pyroptosis, lipid metabolism, immunometabolism, bacterial killing, fungal infection, viral infection, and host-directed therapy. Particular attention was given to mechanistic articles and substantial reviews in established journals, with DOI-resolvable publication records used to anchor the final bibliography. As a qualitative synthesis, this review does not claim exhaustive retrieval, prespecified inclusion counts, blinded screening, formal risk-of-bias scoring, or a PRISMA flow diagram. It also does not use the number of

publications in an area as a substitute for the quality or relevance of direct evidence (Olona et al., 2022, Coll and Schroder, 2025).

Evidence was interpreted across five deliberately separate levels: analytically verified compound identity, intracellular pathway engagement, changes in macrophage survival and microbial killing, benefits or harms in infected animals, and validated clinical outcomes. A study was assigned greater weight for an infection claim only when it investigated an actual infection system with a meaningful endpoint. LPS stimulation, palmitate challenge, or cytokine suppression are informative for pathway biology but cannot establish improved microbial control. Conversely, results from live-pathogen systems using other inflammasome inhibitors inform possible risks and experimental designs, not the demonstrated efficacy of γ-tocotrienol itself (Sefik et al., 2022, Beckwith et al., 2020, de Sa et al., 2023).

Comparative analysis and limits

Themes were developed by repeatedly examining convergences and tensions in the literature: priming versus assembly, sterile inflammation versus infection, antimicrobial resistance versus tolerance, purified isomers versus mixtures, and target engagement versus human pharmacokinetic feasibility. An apparently contradictory finding was retained when it could be explained by differences in organism, route of infection, cell type, or timing, discordance was considered scientifically informative rather than an inconvenience to be averaged away. This is a narrative critical synthesis and not a causal demonstration. Selective citation, publication bias, differences in model nomenclature, and incomplete access to unpublished negative studies remain limitations, as does the changing publication landscape through 2026 (Jiang et al., 2022, Vande Walle and Lamkanfi, 2024).

Results: Thematic Findings

Theme I: The identity-to-exposure problem

The first thematic finding is a chemical attribution problem. Palm-derived tocotrienol-rich fractions are not interchangeable with purified γ-tocotrienol, and their biological profiles cannot be inferred from the nominal percentage of total vitamin E alone. Tocopherol content, relative alpha-, gamma-, and delta-tocotrienol abundance, oxidation products, excipients, extraction processes, and batch stability are plausible sources of between-study variation. Comparative mechanistic claims therefore require chromatographically verified composition and matched concentrations of the relevant isomers. A response to an annatto-rich delta-tocotrienol preparation can generate a hypothesis about shared tocotrienol pharmacology but does not identify a palm gamma-isomer effect (Wong et al., 2020, Szewczyk et al., 2021, Looi et al., 2025).

The second part of this finding is exposure mismatch. Culture experiments commonly deliver hydrophobic compounds in solvents or carrier systems that produce a highly uncertain relationship between nominal media concentration and free compound at the plasma membrane or intracellular site of action. Oral administration adds gastrointestinal incorporation into mixed micelles, lymphatic transport, serum lipoprotein carriage, hepatic metabolism, and tissue-specific delivery. Inflammatory macrophages might accumulate a lipophilic agent differently from uninflamed cells, however, this possibility should be measured rather than presumed. Formulation improvements can raise delivery plausibility without establishing that a particular intracellular dose is achievable or safe in infection (Mohd Zaffarin et al., 2020, Sharif et al., 2023, Ooi et al., 2026).

Clinical studies of palm tocotrienol-rich fractions also reveal an endpoint mismatch. Such studies may evaluate lipids, metabolic or inflammatory biomarkers, or chronic disease outcomes, but clinical infection protection is a distinct outcome requiring a distinct evidentiary program. Even a reproducible decline in C-reactive protein cannot determine whether phagocytosis, phagolysosomal maturation, intracellular killing, or microbe-specific T-cell responses are improved. Accordingly, the most defensible label at present is experimental immunomodulatory candidate, not antimicrobial therapeutic or clinically validated host-defense enhancer (Khor et al., 2021, Looi et al., 2025, Ranasinghe et al., 2022).

Theme II: Multiple checkpoints precede the inflammasome readout

The literature identifies several separable checkpoints between microbial or metabolic stimulation and observed inflammatory outcomes. NF-κB-mediated priming changes availability of pro-IL-1β and inflammasome machinery, while assembly depends on appropriately configured NLRP3, NEK7-associated activation steps, ASC recruitment, and caspase-1 processing. Downstream gasdermin cleavage can permit cytokine release, membrane permeability, and variable degrees of lysis. A single change in IL-1β concentration does not show which checkpoint has been altered. This matters acutely when a candidate compound also affects cellular lipid pathways or viability, both of which can secondarily affect cytokine production (Fu and Wu, 2023, Fu et al., 2024, Yu et al., 2024).

Recent structural insights make simple linear interpretations even less defensible. Activation entails conformational and organizational transitions rather than an invariant switch flipped by one reactive oxygen species signal. NLRP3 sensing and assembly interact with post-translational changes, ion fluxes, and organelle state. Moreover, human and murine inflammasome systems are not molecularly identical. Human NLRP11 has been implicated in human macrophage NLRP3 responses, providing a specific example of the danger of translating a murine observation directly into a universal account of human target engagement (Niu et al., 2021, Wang, Y. et al., 2022, Xu and Nunez, 2023).

The first visualisation formalises the evidence hierarchy and prevents a consequential logical shortcut. Figure 1 traces four specific evidentiary stages: established inflammasome biology, compound-associated mechanisms observed in sterile macrophage experiments, untested live-pathogen challenge, and unproven clinical infection benefit. Each transition requires experiments addressing a different causal question, so evidence at an earlier stage must not be presented as confirmation of the next (Coll and Schroder, 2025, Vande Walle and Lamkanfi, 2024).

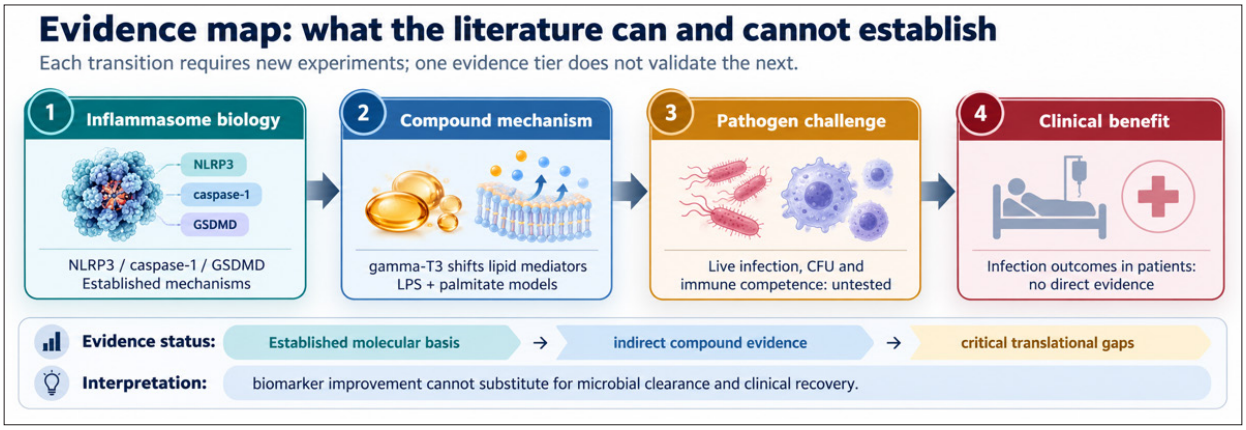


Figure 1: Evidence map separating established inflammasome biology, indirect γ-tocotrienol mechanisms, untested pathogen challenge and absent clinical evidence.

Figure 1 differentiates accepted molecular pathways from compound-level experimental evidence and explicitly marks the absence of validated infection outcomes. The macrophage lipid-mediator observations concern noninfectious LPS-plus-palmitate challenges and cannot establish microbial clearance or recovery after infection. This distinction also clarifies why analytically verified γ-tocotrienol, live-pathogen experiments and prospective clinical evaluation represent necessary, separate stages (Kim et al., 2018, Sweet et al., 2025).

Theme III: Immunometabolic rewiring can alter both immunity and pathogen opportunity

Macrophage metabolic regulation offers several plausible routes for γ-tocotrienol-associated signalling changes. Lipid remodeling may affect arachidonic-acid-derived mediators, ceramide generation, membrane microdomains, and mitochondrial behavior. Redox balance can modify inflammatory transcription and downstream injury, while oxidants can also contribute to antimicrobial processes. The direction of benefit consequently depends on which metabolic signal is altered and the physiological location of that alteration. A reduction in a lipid inflammatory mediator may preserve a tissue barrier yet simultaneously diminish recruitment signals or phagocyte activation in an infection requiring vigorous local defense (Ryan and O'Neill, 2020, Galli and Saleh, 2020, Olona et al., 2022).

The most direct γ-tocotrienol-specific experimental anchor is the earlier macrophage lipidomics study of Kim et al. (2018), which deserves explicit attribution despite falling outside the principal 2020–2026 review period. Using murine bone-marrow-derived macrophages exposed to lipopolysaccharide and palmitate, that study reported changes in arachidonic-acid mobilisation, cyclooxygenase-2-associated prostaglandin E2 production, ceramide synthesis and energy-related measurements. These observations support a lipid-immunometabolic hypothesis but do not constitute direct evidence of pathogen killing, improved survival or clinical infection protection, the older study is cited solely as foundational primary evidence (Kim et al., 2018, Ranasinghe et al., 2022).

The relationship between macrophage energy metabolism and microbes is reciprocal. Intracellular bacteria sense host nutritional status, and host metabolites can influence both innate signalling and microbial behavior. In turn, pathogens deploy effectors that redirect cellular metabolism for their own replication or persistence. This means that suppressing mitochondrial reactive oxygen species or changing fatty-acid metabolism cannot be assessed solely through the host cytokine transcriptome. Investigators should quantify oxygen consumption, extracellular acidification, targeted lipids, carbon-source flux where possible, and the viability of the invading organism in parallel (Rosenberg et al., 2022, Voss et al., 2021, Ben-Arosh and Avraham, 2023).

Itaconate illustrates both the promise and ambiguity of metabolic control. This macrophage-associated metabolite can change inflammatory signalling and exert antimicrobial effects in some settings, but exogenous derivatives may not faithfully reproduce endogenous mechanisms. The broader lesson is transferable to tocotrienol research: a molecule that modulates immunometabolic networks cannot automatically be treated as a selective inhibitor of one inflammasome protein. Chemical specificity, concentrations, subcellular localization, and cell type must be established before pathway attribution can be credible (Olona et al., 2022, Zito et al., 2020, Gauthier and Chen, 2022).

Figure 2 summarizes plausible points of influence without depicting a verified direct binding interaction between γ-tocotrienol and NLRP3. The schematic links compound exposure and lipid/redox pathways to priming, activation, execution, and host-defense outcomes. Its arrows indicate testable hypotheses and established relationships within general macrophage biology, they must not be read as demonstrations that the compound affects every depicted step (Fu et al., 2024, Ranasinghe et al., 2022).

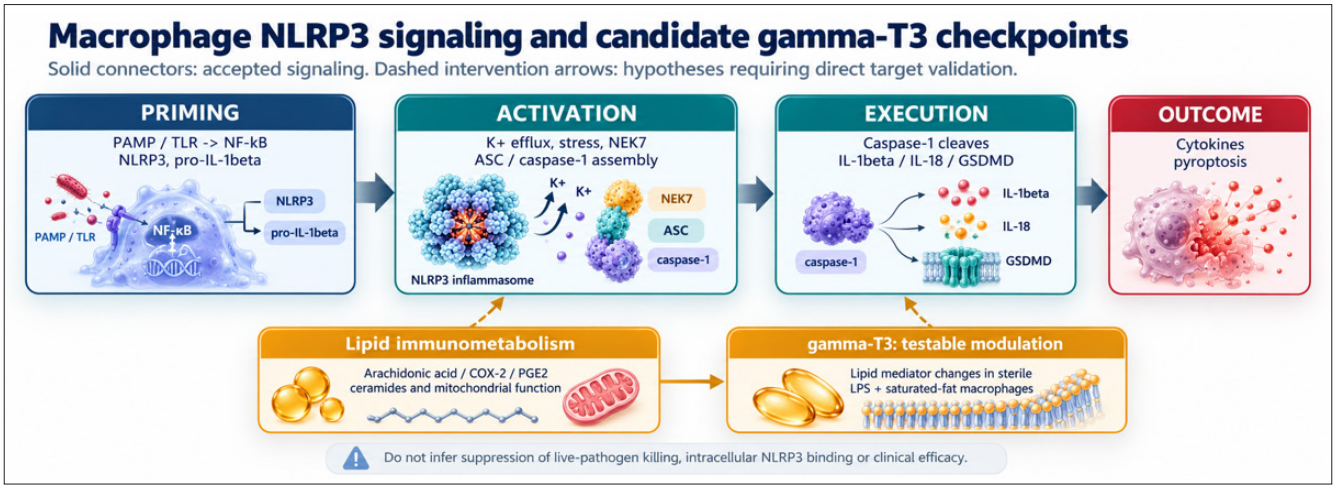


Figure 2: Macrophage NLRP3 priming, activation, execution and outcome, with hypothesised γ-tocotrienol-associated immunometabolic checkpoints.

The central message of Figure 2 is that pathway-level observations require disaggregation. If an experiment reports decreased IL-1β, the researcher must still determine whether altered NF-κB priming, caspase processing, inflammasome assembly, cytokine export, or cell viability accounts for the change. Measurements of cell-associated pro-IL-1β, ASC specks, cleaved caspase-1, cleaved gasdermin D, and viable microbial load supply complementary evidence and cannot be replaced by a single multiplex cytokine panel.

Theme IV: Authentic infections reveal opposing directions of inflammasome benefit

Inflammasome outcomes diverge sharply across pathogen systems. During Mycobacterium tuberculosis infection, plasma-membrane damage can activate NLRP3 and pyroptosis, and this process has been associated with pathogenic consequences in experimental models. In a model of pyogenic bacterial infection, TREM2 signalling promoted bacterial clearance by limiting excessive inflammasome activation and pyroptotic death, illustrating a scenario in which preservation of viable phagocytes could be beneficial. These results make it plausible that carefully moderated pyroptosis may improve certain forms of host defense, they do not show that γ-tocotrienol achieves this result (Beckwith et al., 2020, Wang, Y. et al., 2022).

Opposing examples are equally important. In experimental Leishmania infection, gasdermin-D-related inflammasome activity has been linked to host resistance, indicating that indiscriminate suppression of that axis could weaken protection. In respiratory viral studies, infected macrophage inflammasome activation can drive harmful inflammation while also influencing the capacity to contain infection, creating a context-dependent trade-off. Moreover, inflammatory cell death of epithelial or neutrophil populations may contribute to infection outcomes through mechanisms not attributable to macrophages alone. A conclusion drawn from an isolated cell culture may therefore reverse when the organism and tissue environment are considered (de Sa et al., 2023, Sefik et al., 2022, Churchill et al., 2022, Minns et al., 2023).

Regulated cell-death research provides an additional reason to avoid treating decreased pyroptosis as a universally beneficial endpoint. Pyroptosis, apoptosis and other death programmes may eliminate infected cellular niches, but their activation can also amplify pathology depending on the microorganism and tissue. Thus, any future γ-tocotrienol intervention should be evaluated alongside microbial burden, phagocyte survival and organ function rather than alongside death markers alone (Lee et al., 2023, Sweet et al., 2025).

Inflammasome regulation is also intertwined with pathogen viability and microbial molecular products. Cytosolic LPS detection, interferon-dependent pathways, and the distinction between living and dead bacteria can alter both canonical and noncanonical inflammatory programs. Gasdermin pore generation may accelerate the release of inflammatory mediators, eliminate a replication niche, or expose microbes to extracellular defense, depending on pathogen strategy and timing. This variability provides a strong mechanistic reason why LPS-challenged uninfected macrophages cannot substitute for assays involving replicating bacteria, protozoa, or fungi (Gangopadhyay et al., 2022, Moretti et al., 2022, Booty and Bryant, 2022).

The net host response also depends on regulated termination. IL-1 family cytokines and pyroptosis may help initiate protective responses, yet continued amplification can disrupt endothelial barriers, damage lung tissue, or sustain systemic inflammatory dysfunction. Conversely, cell death pathways cannot simply be disabled without considering antimicrobial consequences. This bifunctional character has encouraged interest in selective inflammasome-targeting compounds, but the therapeutic rationale is narrower than the claim that lower inflammatory signalling is universally beneficial (Shao, 2021, Coll and Schroder, 2025, Li et al., 2024).

Early sepsis illustrates a more granular relationship between membrane lipids and inflammasome responses than the general terms oxidative stress and inflammation imply. Lysophosphatidylcholine-associated GITR signalling was shown to exacerbate macrophage pyroptosis through post-translational regulation of NLRP3, supporting investigation of discrete lipid-sensing checkpoints rather than assuming all lipids converge on a single mitochondrial route. In another sepsis-relevant study, CARD9 protection was linked to RIPK2-regulated NLRP3 activity, highlighting the importance of upstream signalling architecture. Both studies inform potential experimental checkpoints, neither tests tocotrienol treatment and neither can be used as direct evidence of a palm-derived intervention (Liang et al., 2024, Xu, Z. et al., 2022).

The infection evidence also spans organism compartments outside macrophages. SARS-CoV-2 infection of monocytes can trigger Fc receptor-associated inflammatory responses, whereas

pathogen-induced neutrophil NLRP3 activation can affect corneal pathology. These findings identify important cellular sources of inflammasome activity but do not establish that a macrophage-targeted treatment controls a multicellular tissue response. Meanwhile, mitochondrial damage induced by bacterial outer membrane vesicles offers a noninfected-cell mechanism of host injury that could coexist with bona fide pathogen replication, complicating the interpretation of circulating inflammatory biomarkers (Junqueira et al., 2022, Minns et al., 2023, Deo et al., 2020).

Theme V: Host resistance and tissue tolerance must be measured independently

An infection experiment requires two distinct outcome families. The first represents resistance or pathogen control: colony-forming units, viral infectious titers, intracellular replication, pathogen viability, and microbial burden in organs. The second represents host injury or tolerance: barrier integrity, histopathology, physiological function, inflammatory damage, and survival conditional on pathogen burden. Cytokine concentrations, macrophage numbers, and pyroptosis are mechanistic intermediates rather than sufficient surrogates for either family. A compound could lower tissue injury while failing to control a growing pathogen population, or could accelerate clearance while provoking inflammatory organ damage (Churchill et al., 2022, Wallis et al., 2023, Sefik et al., 2022).

Figure 3 provides a four-quadrant decision matrix that places pathogen control on one axis and tissue harm on the other. The desirable quadrant is improved clearance with reduced damage, improved pathology without preserved pathogen control is ambiguous, and worsening both endpoints is clearly unfavorable. This representation is particularly useful for assessing putative anti-inflammasome substances because it prevents the reduced-IL-1β phenotype from being automatically assigned to a beneficial outcome category (Wang, Y. et al., 2022, de Sa et al., 2023).

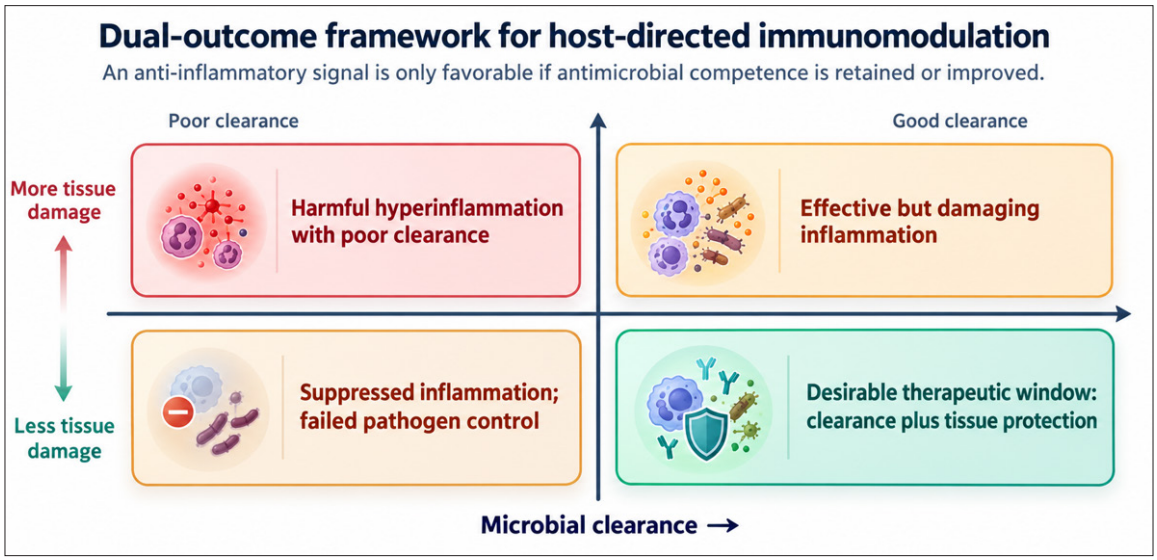


Figure 3: Dual-outcome matrix integrating microbial clearance and host tissue damage following immunomodulation

The matrix also clarifies how a treatment may change classification over time. Early down-modulation may impair containment while late down-modulation may limit residual injury after microbes have been controlled by appropriate therapy. Therefore, identical treatment doses may fall in different outcome quadrants depending on treatment initiation, antimicrobial co-therapy, tissue compartment, or pathogen burden. Sequential measurement is necessary to distinguish a true mechanistic benefit from a temporary reduction in inflammatory signals.

Theme VI: Stage of infection, macrophage phenotype and experimental context

Macrophage populations respond differently because organ location is immunologically formative. Resident alveolar macrophages encounter inhaled pathogens in a surfactant-rich environment, whereas blood-derived inflammatory macrophages in sepsis experience a highly dynamic cytokine and metabolic milieu. Macrophages recruited to granulomas, wounds, or mucosal tissues confront additional constraints of oxygen availability and cell-to-cell signalling. An effect seen in a murine bone-marrow-derived macrophage assay may therefore be absent, attenuated, or even reversed in a differentiated human monocyte-derived macrophage or a tissue-resident population (He et al., 2021, Ben-Arosh and Avraham, 2023, Minns et al., 2023).

Temporal design is as important as cell identity. Pretreating macrophages before LPS exposure largely tests prophylactic pathway conditioning. Introducing γ-tocotrienol after microbial uptake instead asks whether the compound modifies an established infection response, while treatment after microbial control evaluates repair-phase inflammation. These settings should not be described under a single therapeutic label because their clinical counterparts differ substantially. Longitudinal microscopy and parallel measurement of pathogen viability could reveal whether a surviving macrophage remains effective, exhausted, or an expanded intracellular niche (Huston et al., 2023, Ramachandran et al., 2024, Shi and Cai, 2022).

Host genetics and species differences add further limitations. Human monocytes and macrophages use pathways and regulatory proteins that may not be functionally identical to their mouse counterparts, while infections themselves recruit immune cells with different inflammasome capacities. Experiments should therefore progress from a reproducible murine mechanistic system to donor-diverse human primary macrophages, and subsequently to models that preserve tissue context. Investigators should record donor characteristics, cell maturity, bacterial multiplicity of infection, intracellular drug concentrations, and baseline inflammatory state before inferring a universal response (Wang, Y. et al., 2022, Hoyle et al., 2023, Xu and Nunez, 2023).

Theme VII: Biomarker quality and causal identification

A recurring methodological weakness in immunomodulation research is reliance on highly downstream measurements. ELISA detection of IL-1β can be influenced by its synthesis, processing, release, dilution, or degradation. Mitochondrial dye fluorescence may reflect redox chemistry and probe localization rather than a narrowly defined mitochondrial oxidative process. Likewise, bulk metabolic changes may arise from altered cell number or survival. Orthogonal assays are therefore crucial: quantitative ASC imaging, immunoblotting for cleaved caspase-1 and gasdermin D, live-cell permeability kinetics, gasdermin genetic controls, and direct bacterial viability measurement can resolve otherwise ambiguous interpretations (Yu et al., 2024, Gauthier and Chen, 2022, Olson et al., 2023).

Mechanistic inference also benefits from an explicit comparison against characterised NLRP3 inhibitors, antioxidant controls, and chemical vehicle controls. If γ-tocotrienol changes cytokines but not ASC assembly, an upstream or parallel mechanism is more plausible than direct inflammasome blockade. If the effect disappears with a change in lipid delivery vehicle, formulation is part of the causal story. Genetic deletion or selective chemical perturbation can test whether NLRP3 is required for the observed phenotype, but redundant pathways may necessitate additional controls. These principles extend broadly to natural-product immunology, where pleiotropy is common and high-concentration cytotoxicity can imitate anti-inflammatory activity (Coll and Schroder, 2025, Wang, T. et al., 2023, Fu et al., 2024).

Discussion and Critical Analysis

Answering the central mechanistic question

The contemporary literature supports a plausible but conditional mechanistic sequence: γ-tocotrienol can influence lipid and redox-associated inflammatory processes in selected experimental macrophage systems, these processes interface with NLRP3 priming and activation, altered inflammasome output could in turn change cell fate and the inflammatory environment during infection. The final step remains hypothetical for this specific compound because evidence of altered bacterial killing, pathogen load, and infected-host outcomes after verified palm-derived γ-tocotrienol exposure is not established by the cited contemporary literature. Scientific rigor requires preserving that boundary, even when adjacent evidence is mechanistically compelling (Ranasinghe et al., 2022, Zainal et al., 2022, Li et al., 2024).

The most productive hypothesis is not that γ-tocotrienol directly suppresses NLRP3 universally, but that its effect depends on macrophage lipid state and inflammatory history. Saturated-fat-associated sterile inflammatory priming changes the abundance of ceramides and related lipid products and may create conditions in which an altered lipid response produces a visible anti-inflammatory phenotype. A macrophage containing viable intracellular microorganisms operates under a different set of metabolic and antimicrobial demands. The proposed compound could be useful in one condition, ineffective in another, or hazardous in a third. Accordingly, a valid mechanistic study must test a range of activation contexts rather than relying on repeated measurements of the same priming protocol (Olona et al., 2022, Rosenberg et al., 2022, Galli and Saleh, 2020).

The issue of direct target engagement deserves separate emphasis. Because a γ-tocotrienol exposure may change lipid mediators, oxidative signalling, transcription, or plasma-membrane characteristics, inhibition of caspase-1 output would not prove binding to the NLRP3 sensor. A causal chain is stronger when purified compound identity, compound uptake, proximal pathway intermediates, and inflammasome dependencies are demonstrated separately. The structural sophistication of current NLRP3 research makes such distinctions feasible and increases the standard expected of new pharmacological claims (Fu and Wu, 2023, Fu et al., 2024, Niu et al., 2021).

Which infections might justify investigation, and which create concern?

Models characterised by excessive pyroptotic depletion of pathogen-controlling phagocytes may offer a reasonable entry point for experimental intervention. Studies of pyogenic bacteria and tuberculosis-associated inflammatory cell death suggest that the relationship between pyroptosis and infection can sometimes be pathogenic. Yet an observed reduction in macrophage death is only potentially useful if surviving cells retain or enhance microbial clearance. The experimental threshold is therefore straightforward: measure both the number of viable functional phagocytes and the number of viable pathogens, preferably with longitudinal imaging and burden measurements in infected tissue (Jiang et al., 2022, Beckwith et al., 2020, Booty and Bryant, 2022).

Other pathogens may depend more directly on inflammasome-associated defense. Where gasdermin activity contributes to parasite control, a broad anti-pyroptotic intervention would be mechanistically suspect. Viral infection provides additional complexity: an intervention could reduce pathological inflammation in a macrophage-rich tissue while permitting persistence of infectious material, changing replication niches or the kinetics of innate cell recruitment. These examples argue against a generic infection indication and for stratification by pathogen, microbial location, inflammatory stage, and host immune competence before any treatment hypothesis is advanced (de Sa et al., 2023, Sefik et al., 2022, Li et al., 2024).

Sepsis deserves special caution because it combines microbial infection with phases of inflammatory dysregulation and immunosuppression that differ across patients and time. Down-regulating IL-1β or pyroptosis in an LPS-only model does not reproduce the complex human course of source control, antibiotics, organ support, immunoparalysis, or secondary infection risk. Even if γ-tocotrienol reduces a sepsis-associated cytokine signature experimentally, that result would not establish a clinical benefit and could be misleading without infection severity, microbial burden, and survival endpoints. The responsible position is to treat sepsis as a future evidence question, not an existing indication (Wallis et al., 2023, Vande Walle and Lamkanfi, 2024, Coll and Schroder, 2025).

A comparison with non-tocotrienol metabolic immunomodulators helps define the limits of mechanistic extrapolation. Itaconate and fumarate derivatives can affect priming and canonical NLRP3 activation in macrophages, yet their effects are compound- and context-specific rather than evidence for interchangeable antioxidant modes of action. Macrophage glutamine utilization in tuberculosis provides a further example: metabolic substrates may support antimicrobial polarization rather than merely amplify damaging inflammation. Therefore, changing a metabolic pathway can create competing implications for pathogen control and tissue injury that must be tested in the same system (Hoyle et al., 2022, Jiang et al., 2022, Shi and Cai, 2022).

Type I interferon has also been observed to modify macrophage energy metabolism during mycobacterial infection, suggesting that infection-stage signals may substantially alter the apparent effect of a candidate metabolic intervention. This finding calls for explicit measurements of basal metabolic state and pathogen-specific innate signalling before and after γ-tocotrienol exposure. A broader contemporary account of inflammasome control in

metabolic and lifestyle-associated disorders further underlines that mechanisms characterised during sterile disease are not equivalent to a therapeutic profile during active infection (Olson et al., 2021, Ramachandran et al., 2024).

Finally, investigators should adopt validated biochemical and cellular assays rather than equating loss of inflammasome-associated fluorescence with disease control. Methodological literature provides detailed options for priming assays, NLRP3 assembly, caspase-1 function, and release of processed cytokines. These readouts must be combined with pathogen-directed measurements and careful cytotoxicity controls when studying lipophilic natural compounds (Zito et al., 2020, Hoyle et al., 2022, Yu et al., 2024).

Toward an integrated host-directed experimental program

A staged program would first verify source and molecular identity using validated high-performance liquid chromatography or mass spectrometry. A purified palm-derived γ-tocotrienol comparator and a compositionally standardized palm tocotrienol-rich fraction should be tested separately, accompanied by isomer-specific controls where scientifically relevant. Dose ranges must include realistic exposure windows rather than only concentrations chosen because they produce large cytokine reductions. Intracellular compound and metabolite concentrations should be quantified at baseline and during infection, and the stability and solvent burden of the preparation must be documented (Mohd Zaffarin et al., 2020, Wong et al., 2020, Ooi et al., 2026).

The second experimental stage should test proximal mechanism across at least two distinct activation systems, for example sterile LPS-plus-saturated-fat stress and live-pathogen infection under biosafety-appropriate conditions. Readouts should include NF-κB-dependent priming, ASC speck formation, caspase-1 processing, gasdermin D cleavage, cell viability, and IL-1β/IL-18 release, together with mitochondrial and lipid analyses. Genetic or highly selective perturbation controls should distinguish NLRP3 dependence from broader suppression of macrophage activation. This design allows a natural-product phenotype to be located on a mechanistic pathway without prematurely labeling the molecule a selective NLRP3 inhibitor (Yu et al., 2024, Xia et al., 2021, Olson et al., 2023).

Antibacterial competence should be represented by multiple orthogonal functional measurements rather than a single viability readout. Contemporary macrophage literature identifies phagocytosis-associated killing, antimicrobial metabolites, autophagy-related programmes and resource restriction as potentially nonredundant pathways. Because these mechanisms can be differentially susceptible to immunometabolic perturbation, parallel assays of bacterial uptake, viable intracellular organisms, phagosomal maturation and cellular survival provide a more defensible functional profile (Sweet et al., 2025, Mass et al., 2023).

A third stage should quantify infection function directly. In bacterial and fungal coculture experiments, investigators should measure viable organism numbers inside macrophages and in the extracellular compartment, phagocytosis, phagosome acidification, lysosome fusion, cell survival, and the integrity of host cell membranes. These should be repeated across early and late treatment windows and with clinically relevant antimicrobial co-therapy. The decisive outcome is not whether an immunological signal changes, but whether pathogen control and tissue-relevant cellular function improve together. If a treatment reduces cytokines yet increases viable bacteria, that observation should be reported as a host-defense liability even if other inflammatory biomarkers appear favorable (Jiang et al., 2022, de Sa et al., 2023, Gauthier and Chen, 2022).

Animal studies would then need authentic infection endpoints, organism burden in tissues, histopathological damage, organ function, and survival, with carefully specified treatment timing and co-therapies. Results should be independently replicated with characterised preparations and should establish a pharmacokinetic-pharmacodynamic relationship between intracellular γ-tocotrienol exposure and the proposed causal mechanism. Only after these steps would disease-specific clinical feasibility be defensible. The path from nutrition-related studies of tocotrienol-rich fractions to a treatment for life-threatening infection cannot skip these intermediate tests (Looi et al., 2025, Sharif et al., 2023, Khor et al., 2021).

Translational decision gates and potential safety problems

Figure 4 translates the preceding synthesis into successive decision gates, each of which can halt or redirect development. The sequence starts with verified chemical and exposure profiles, proceeds through mechanistic engagement and preserved microbial clearance, and only then reaches preclinical benefit and appropriately justified human studies. This architecture is intended to prevent confirmation bias: failure at an infection-function gate cannot be rescued by a favourable change in a biomarker measured upstream (Coll and Schroder, 2025, Ranasinghe et al., 2022).

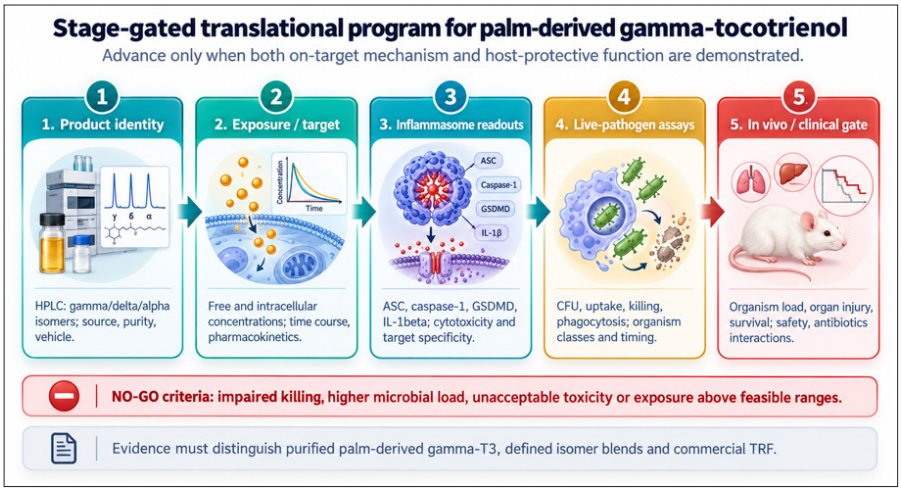


Figure 4: Five translational gates from compound identity to exposure, inflammasome assays, live-pathogen function and infected-host outcomes.

Figure 4 should be read from left to right as a set of falsifiable progression conditions. At each gate, investigators ask what observation could disconfirm the proposed benefit: unstable compound identity, unattainable intracellular dose, failure of NLRP3 dependency, increased microbial replication, or worsened organ injury. Passing one gate narrows uncertainty but does not guarantee passage through subsequent gates, making the framework suitable for prioritizing finite experimental resources and transparently reporting negative findings.

The principal safety concern is unintended interference with protective immunity. NLRP3-related responses and gasdermin-mediated cell fate can assist in pathogen containment, and natural-product pleiotropy may affect other innate pathways beyond the inflammasome. Furthermore, lipid delivery systems can alter tissue distribution or change interactions with other therapies. Research must therefore assess macrophage antimicrobial competence, pathogen replication, host cell viability, co-treatment interactions, and toxicological windows before human application is considered. Broad immune suppression should not be presumed safer merely because it is delivered by a food-derived constituent (de Sa et al., 2023, Sefik et al., 2022, Szewczyk et al., 2021).

Implications for palm bioactives research and scientific reporting
The palm sector offers a credible chemical source for studying tocotrienols, but commercial source identity is not equivalent to biological specificity. Research claims should state the exact isomer, analytical purity, relative composition of tocotrienol-rich fractions, source verification, carrier formulation, and achieved cellular exposure. Reporting a material only as vitamin E, palm antioxidant, or tocotrienol formulation loses information required to compare mechanisms across laboratories. Well-characterised plant bioactives could become valuable scientific probes even if they never mature into anti-infective drugs (Looi et al., 2025, Ranasinghe et al., 2022, Mohd Zaffarin et al., 2020).

A productive research program would also welcome negative or context-specific results. If γ-tocotrienol reduces inflammasome activity but does not improve infected-host survival, that is a substantive contribution that defines a mechanistic limit. If a standardized palm fraction performs differently from the purified gamma isomer, mixture synergy, antagonism, or pharmacokinetic effects become testable explanations rather than grounds for assuming a universally favorable nutritional mechanism. Comparative studies should thus avoid circular use of inflammatory biomarkers as both selection criteria and proof of efficacy (Zainal et al., 2022, Ooi et al., 2026, Khor et al., 2021).

Synthesis of the research questions
The first question—whether γ-tocotrienol is mechanistically relevant to macrophage inflammasome control—can be answered cautiously in the affirmative as a hypothesis grounded in lipid-signalling studies and subsequent critical reviews. The second—whether it selectively and directly inhibits NLRP3—remains unanswered without biochemical engagement and selective pathway controls. The third—whether it improves antimicrobial protection—has no established affirmative answer in the reviewed compound-specific evidence. These are different claims and should remain differently qualified in abstracts, media summaries, and research proposals (Ranasinghe et al., 2022, Fu and Wu, 2023, Li et al., 2024).

The fourth and fifth questions concern the conditions under which inflammation suppression might help or harm, and the barriers to translation. Infection studies support conditional benefit when destructive pyroptosis undermines phagocyte function, but they also document protective inflammasome roles in other host-pathogen systems. Bioavailability, dose, cell origin, treatment timing, and composition of source preparations remain unresolved. Consequently, the sixth question—what experimental criteria should precede clinical work—is answered by the proposed paired-endpoint system: reproducible target engagement, preserved or improved microbial clearance, improved host integrity, and achievable, safe exposure (Wang, Y. et al., 2022, de Sa et al., 2023, Sharif et al., 2023).

Conclusion and Future Directions
The relationship between palm-derived γ-tocotrienol and the macrophage inflammasome is scientifically promising but not yet clinically resolved. Evidence from tocotrienol pharmacology and contemporary inflammasome biology creates a plausible rationale for investigating modulation of NF-κB priming, lipid-derived inflammatory mediators, mitochondrial stress, caspase-1-associated signalling, and pyroptotic cell fate. Nevertheless, the literature does not justify inferring direct molecular blockade of NLRP3 or improved human infection outcomes merely from reduced cytokines in sterile macrophage assays. Chemical identity and biologically achieved exposure must remain explicit in every interpretation.

The most important conceptual conclusion is that host protection has two independent dimensions: containing pathogens and limiting harm to host tissues. Inhibiting an inflammatory pathway can strengthen one dimension while weakening the other, and the direction of the effect is strongly conditioned by pathogen, macrophage lineage, organ, and infection stage. Accordingly, anti-inflammatory activity should be described as a mechanism-associated phenotype, not automatically as host-directed therapeutic success. Purified γ-tocotrienol, standardized palm tocotrienol-rich fractions, and tocotrienols from other botanical sources warrant separate experimental interpretation.

Future research should progress through compound authentication, physiologically relevant intracellular pharmacology, orthogonal inflammasome measurements, macrophage-pathogen functional cocultures, and infected-animal models with paired microbial and organ-injury outcomes. Time-resolved dosing and explicit antimicrobial co-treatment should form part of that program. Only a reproducible improvement in both infection control and host function, supported by mechanistic dependency and safe exposure, could support advancement toward clinical testing. The proposed framework thus turns a credible natural-product hypothesis into a set of disprovable scientific questions while avoiding premature claims of infection therapy.

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