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*Review Article*

# *Goniothalamus macrophyllus*: A Comprehensive Review of Its Phytochemistry, Pharmacological Activities, and Therapeutic Potential

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ABSTRACT

*Goniothalamus macrophyllus*, a tropical species belonging to the Annonaceae family, has long been utilized in traditional Southeast Asian medicine for treating fevers, infections, and various other health conditions. This review provides a thorough examination of the plant's ethnomedicinal significance, phytochemical constituents, and pharmacological potential. A systematic review of the literature was conducted to collect data on its bioactive components, such as styryl-lactones, flavonoids, alkaloids, and acetogenins. Among these, goniothalamin, a major styryl-lactone, has been notably investigated for its cytotoxic effects, primarily through mechanisms like cell cycle arrest and apoptosis induction. Pharmacological investigations have highlighted the plant's notable anticancer, antimicrobial, antioxidant, anti-inflammatory, and antiparasitic activities. In vitro experiments have shown that both extracts and isolated constituents possess potent cytotoxic effects against various cancer cell lines, including those of breast, cervical, and hepatic origin. Moreover, antimicrobial assays have confirmed efficacy against both Gram-positive and Gram-negative bacterial strains. Antioxidant and anti-inflammatory activities further support its potential therapeutic versatility. However, its pharmacological promise is tempered by the scarcity of comprehensive toxicological studies and limited clinical data. Most findings are restricted to in vitro or preliminary in vivo models, and there is a lack of standardized protocols for extract formulation and compound isolation. In summary, *G. macrophyllus* represents a valuable natural resource for bioactive compounds with therapeutic potential, yet more extensive in vivo research and mechanistic studies are essential to substantiate its clinical applicability and safety.

**Keywords:** *Goniothalamus macrophyllus*, ethnomedicine, phytochemical constituents, pharmacological activities, natural product drug discovery

## Introduction

Medicinal plants continue to serve as an essential foundation for drug discovery and the development of new therapeutic agents. According to the World Health Organization, approximately 80% of the world's population relies on traditional medicine, which is largely based on plant-derived remedies.[1] The increasing global interest in natural products is driven by their chemical diversity, structural complexity, and broad spectrum of pharmacological effects. Southeast Asia, known for its rich floristic diversity, remains a promising region for the exploration of medicinal plants with untapped therapeutic potential.[2,3]

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Among the diverse plant families with documented ethnomedicinal uses, the *Annonaceae* family is noteworthy for its bioactive constituents, particularly styryl-lactones, acetogenins, alkaloids, and flavonoids. Species within this family, such as *Annona muricata*, *Polyalthia longifolia*, and *Goniothalamus spp.*, have been traditionally used for treating infections, inflammation, and even cancer.[4-6] *G. macrophyllus*, commonly found in Indonesia, Malaysia, and Thailand, is one such plant with a long history of traditional use in treating fever, menstrual disorders, postpartum care, and tumor-like conditions.[7,8] Despite its longstanding ethnomedicinal use, this species has not been comprehensively reviewed from a pharmacological and phytochemical perspective.

Phytochemical investigations of *G. macrophyllus* have identified a range of bioactive secondary metabolites, with styryl-lactones being the most prominent.[9,10] Among these, goniothalamin has garnered attention for its cytotoxic effects against various cancer cell lines, acting primarily through apoptosis induction and cell cycle arrest.[11-13] In addition to its anticancer potential, extracts and compounds from *G. macrophyllus* have demonstrated antimicrobial, antioxidant, anti-inflammatory, and antiparasitic activities in preliminary studies.[14]

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These pharmacological findings suggest that *G. macrophyllus* could be developed as a source of bioactive agents for drug discovery.
Nevertheless, existing data on *G. macrophyllus* remain scattered, predominantly comprising studies limited to isolated compounds or individual pharmacological assays. Comprehensive information on its complete phytochemical profile, underlying mechanisms of action, toxicological safety, and structure-activity relationships is notably lacking. Furthermore, few *in vivo* experiments or clinical assessments have been conducted to substantiate its traditional medicinal uses or to evaluate its therapeutic efficacy rigorously. This fragmented body of evidence significantly impedes the advancement and scientific validation of *G. macrophyllus* as a credible medicinal plant candidate.
Hence, the objective of this review is to systematically synthesize and critically appraise the existing literature concerning *G. macrophyllus*, with particular emphasis on its ethnomedicinal applications, botanical attributes, phytochemical composition, and pharmacological properties. By delineating bioactive compounds and exploring their potential mechanisms of action, this review seeks to establish a robust scientific foundation that supports further investigation and development of *G. macrophyllus* as a valuable natural resource for therapeutic agents.

## Materials and Methods

The present review was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15,16] The workflow included the formulation of research objectives, identification and screening of relevant literature, application of inclusion and exclusion criteria, and synthesis of the collected data.[17] A flow diagram summarizing the literature selection process is presented in Figure 2. Relevant scientific literature was obtained through comprehensive searches of major online databases, including ScienceDirect, PubMed, SpringerLink, and Wiley Online Library. Additional sources such as Google Scholar, academic books, dissertations, and ethnobotanical reports were also used to enrich the context. The scientific name *G. macrophyllus* was validated using The Plant List (www.theplantlist.org) and Plants of the World Online (POWO). The search strategy involved combinations of the following keywords: "Goniothalamus macrophyllus", "Annonaceae", "ethnomedicine", "styryl-lactone", "goniothalamin", "phytochemical constituents", "cytotoxic activity", "traditional uses", "antioxidant", "anticancer", and "natural product". The retrieved articles were screened for content specifically related to traditional medicinal applications, phytochemical composition, pharmacological effects, mechanisms of action, and toxicological data. Only peer-reviewed journal articles, original research papers, and high-quality review articles published in English were included.
Studies that lacked clear data on *G. macrophyllus*, focused on unrelated species, or did not report original pharmacological or phytochemical findings were excluded. Inclusion and exclusion criteria were strictly applied during the screening of titles, abstracts, and full texts, as summarized in Table 1. The final selection was based on relevance to the review's objectives and data quality.

*Vernacular Names*
*G. macrophyllus* is referred to by a range of vernacular names across its native distribution in Southeast Asia. These names reflect its widespread traditional use and local familiarity. In Indonesia, the species is known as "keremuntingan", "merawan", or "ki selasih", especially in Java and Kalimantan.[7,18] In Malaysia, common names include "selasih hutan", "selasih jantan", and "pokok langir".[19] In Thailand, the plant is locally called "khanun ta pa", which translates to "forest jackfruit," due to the resemblance of its leaves to those of *Artocarpus heterophyllus.*[20] These vernacular names not only assist in field identification but also signify the plant's cultural and medicinal roles. However, due to the overlapping use of some names across different *Annonaceae* species, proper botanical identification is essential to ensure pharmacological accuracy.

*Morphology*
*G. macrophyllus* is an understorey shrub or small tree that typically grows up to 5-8 meters in height, occasionally reaching 10 meters under optimal conditions. The trunk is slender and unbuttressed with smooth grey-brown bark bearing small pale lenticels.[21] The leaves are large, oblong-lanceolate, leathery, and alternate, measuring 22-30 cm in

**Table 1:** Inclusion and exclusion criteria for papers.

| Inclusion criteria | Exclusion criteria |
|---|---|
| Journal articles, conference papers, and book chapters written between 1960 and 2025 | Papers written in languages other than English |
| Articles focused specifically on *G. macrophyllus* | Articles discussing other species of *Goniothalamus* without comparative context |
| Papers published with title, abstract and full text | Papers with no available full text |
| Papers about traditional uses, phytochemistry and pharmacological properties of *G. macrophyllus* | Abstract-only publications, conference posters, or editorials |

length and 6-11 cm in width (Figure 1). They are glabrous on both surfaces, with a distinctive granular texture beneath due to immersed tertiary veins.[22] Venation is pinnate, with 12-23 pairs of lateral veins. The petioles are short and stout, about 1-3 cm long. Flowers are solitary, bisexual, and fragrant, usually borne on older branches (cauliflorous). Each flower has three ovate sepals and six petals in two whorls.[23] The outer petals are oblong and creamy-white (up to 3 cm long), while the smaller inner petals are rhomboid, densely pubescent on the inside, and often enclose the reproductive organs. Numerous stamens and free carpels are present, with each carpel containing a single ovule.[24]
The fruit is an aggregate of 12-18 (sometimes more) sessile, ovoid monocarps, each about 1-2 cm long, turning red or orange-red when ripe. These fleshy, indehiscent fruits typically contain one ellipsoid seed each. The plant lacks specialized root structures, although it develops a lateral root system typical of tropical understorey trees. The roots and bark emit a spicy aroma when crushed, a trait linked to the presence of bioactive compounds. Morphological variation across regions is minimal, and diagnostic features such as leaf texture, floral structure, and fruit coloration help differentiate *G. macrophyllus* from other *Goniothalamus* species.[24]


**Figure 1**: Parts of the *G. macrophyllus* plant. (a) Leaves, (b) Stems, (c) Flowers, (d) Fruits

*Traditional Uses*
*G. macrophyllus* has been widely used in traditional medicine across Southeast Asia, particularly in Indonesia, Malaysia, and Thailand. In Indonesia, especially among communities in Kalimantan and Java, decoctions made from the leaves, roots, and bark have been used to

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treat fevers, headaches, rheumatism, and as a postpartum remedy for women to restore uterine health.[18,25] In Kalimantan, grated root preparations are sometimes applied externally to relieve muscular pain or inflammation, while infusions of the bark are consumed to alleviate symptoms of fatigue and chills.[7] The plant is also regarded as a general "tonic herb" and is often combined with other medicinal plants in traditional jamu formulations. Among the Dayak communities, parts of the plant are also used for postnatal bathing rituals and believed to protect against spiritual ailments. In Malaysia, traditional practitioners use *G. macrophyllus* under the names "selasih hutan" or "pokok langir." The root and bark are used in herbal mixtures for detoxification, menstrual regulation, and skin conditions, often administered as decoctions or pastes.[26] The plant is also used to promote sweating (diaphoretic effect) in cases of fever or to stimulate circulation after childbirth. In Thailand, particularly in the southern provinces, it is used as a traditional remedy for digestive disorders, snakebite, and to promote blood flow.[27] Despite the widespread traditional use of the species, standardized dosage forms and controlled pharmacological validations remain limited.

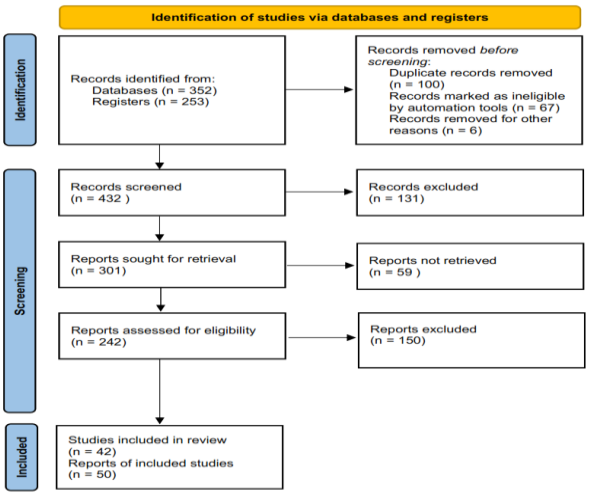


**Figure 2**: Diagram of search strategy

These ethnomedicinal applications highlight the cultural significance of *G. macrophyllus* and support further scientific investigation into its therapeutic potential.

*Phytochemistry*

Phytochemical analyses of *G. macrophyllus* have revealed a chemically diverse profile consisting of several major classes of secondary metabolites. These include styryl-lactones (notably goniothalamin and its analogues), which are characteristic of the genus and possess strong cytotoxic properties; alkaloids, such as anonaine, liriodenine, and oxostephanine, which exhibit antimicrobial and antiparasitic activities; and flavonoids, including quercetin, kaempferol, and their glycosides, known for their antioxidant and anti-inflammatory effects.[28] In addition,

the plant contains phenolic compounds and phenolic acids, which contribute to radical-scavenging activity, as well as acetogenins, which are polyketide-derived compounds associated with mitochondrial inhibition and anticancer effects. Minor constituents such as triterpenes (e.g., lupeol) and phytosterols (e.g., *β*-sitosterol and stigmasterol) have also been identified, supporting traditional applications related to inflammation and tissue recovery.[29] This rich chemical diversity underpins the wide range of pharmacological effects reported for the species and forms the basis for more detailed investigation into each compound group (Table 2).

*Polyketide-Derived Compounds (Styryl-Lactones)*

The most extensively studied group of compounds in *G. macrophyllus* is the styryl-lactones, which are biosynthetically derived from the polyketide pathway.[30] The principal compound in this class is goniothalamin, isolated from the roots of the plant.[31] Goniothalamin is an *α,β*-unsaturated γ-lactone bearing a styryl side chain, known for its potent cytotoxic and pro-apoptotic activities against various cancer cell lines.[10,32] Additionally, two novel compounds, goniolandrene A and goniolandrene B, have been isolated and structurally characterized from the root extracts.[33] These compounds represent new analogs within the styryl-lactone framework and were characterized using spectroscopic and circular dichroism analysis.[34,35] The presence of these compounds underscores the importance of the root as the richest source of polyketide-derived metabolites in *G. macrophyllus*.

*Flavonoids and Phenolic Compounds*

Flavonoids and related phenolic compounds are also present in *G. macrophyllus*, with (2S)-pinocembrin being the most notable compound reported.[36] Pinocembrin is a flavanone-type flavonoid that was isolated from the stem or root extracts, and it has been shown to possess anti-inflammatory activity, specifically by inhibiting prostaglandin E2 production in lipopolysaccharide (LPS)-stimulated macrophages.[28] This compound is widely known in other medicinal plants for its antioxidant, anti-inflammatory, and neuroprotective properties, and its identification in *G. macrophyllus* provides strong support for the presence of flavonoid-based bioactivity in the species.[37] While other flavonoids or phenolic acids have not been fully characterized from this plant, the isolation of pinocembrin confirms the relevance of this class within its phytochemical profile.

*Phytosterols*

As part of its lipophilic secondary metabolites, *G. macrophyllus* has been reported to contain *β*-sitosterol, a common phytosterol found in higher plants. This compound was identified from the hexane fraction of the roots, likely during general screening of nonpolar constituents.[38] Although *β*-sitosterol is not unique to *Goniothalamus* species, its presence supports the existence of terpenoid-derived sterols in *G. macrophyllus.*[39] *β*-sitosterol is known for its anti-inflammatory, cholesterol-lowering, and immunomodulatory effects in other medicinal plants, and it may contribute to some of the traditional uses of *G. macrophyllus*, particularly in formulations aimed at postpartum trecovery or internal cleansing.[40]

*Alkaloids*

Although many species within the *Goniothalamus* genus are known to produce isoquinoline and aporphine alkaloids (e.g., liriodenine,anonaine, oxostephanine),[41,42] no specific alkaloid compound has been conclusively isolated or reported from *G. macrophyllus* to date.[35,43,44] This is in contrast to related species where such alkaloids are commonly detected and attributed with antimicrobial, antiplasmodial, and cytotoxic activities.[45,46] The absence of alkaloid reports in *G. macrophyllus* may reflect a gap in phytochemical investigation or indicate trace-level presence that has not been prioritized in published studies. Further targeted alkaloid screening would be necessary to confirm or refute their presence in this species.

*Biological Activities*

*Anticancer Activity*

Several constituents from *G. macrophyllus* exhibit potent cytotoxic (anticancer) effects, primarily by inducing apoptosis in cancer cells: Goniothalamin (styryl-lactone), a major bioactive compound isolated from *G. macrophyllus.*[47,48] It has shown strong cytotoxicity against various cancer cell lines (e.g., $IC_{50} \approx 0.42$ μM in P388 murine leukemia cells).[49] Notably, goniothalamin is relatively selective for tumor cells, concentrations up to 20 μM were non-toxic to normal human blood cells (peripheral blood mononuclear cells) while still impairing cancer cell viability.[29] Mechanistic studies indicate goniothalamin triggers mitochondrial-mediated apoptosis (associated with Bax upregulation) and interferes with pro-survival signaling. For example, at sub-apoptotic doses (5-20 μM) it inhibits NF-κB activation in tumor cells, blocking p50/p65 nuclear translocation and reducing NF-κB dependent IL-8 expression. This NF-κB inhibition can sensitize cancer cells to apoptosis and underlies its anti-leukemic activity.

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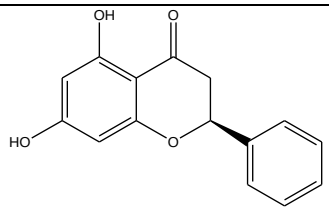
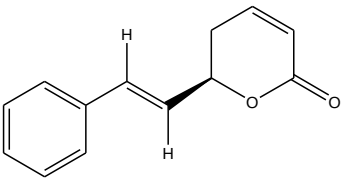
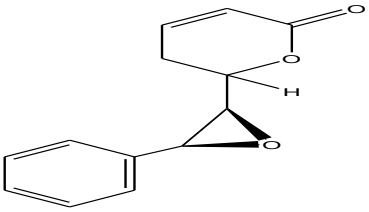
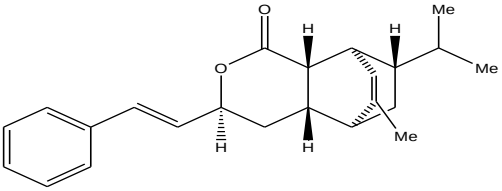
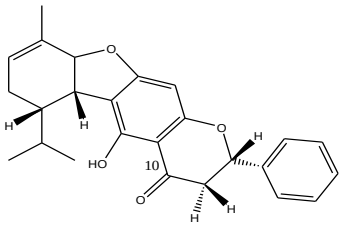
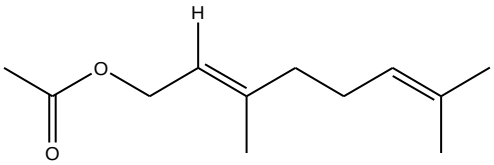
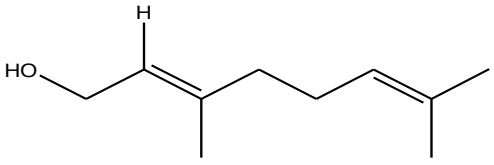
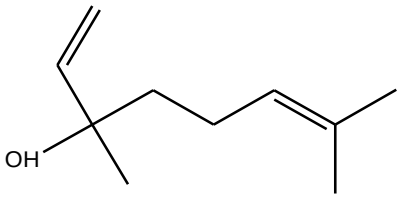
**Table 2**: Phytochemicals and bioactive compounds isolated from *G. macrophyllus*

| Compound Name | Structure | Pharmacological Activity | References |
|---|---|---|---|
| (2S)-Pinocembrin |  | Anti-inflammatory (suppresses LPS-induced $PGE_2$ production via MAPK inhibition); Larvicidal (toxic to *Aedes aegypti* larvae) | [28] |
| (R)-(+)-Goniothalamin |  | Anti-inflammatory (inhibits TNF-*α*-induced NF-κB activation, reduces IL-8 expression); Anticancer (cytotoxic to leukemia and other cancer cells at low μM) | [29] |
| Goniothalamin epoxide |  | Anticancer (potent cytotoxicity against human liver cancer (HepG2) and other cancer cell lines; $IC_{50}$ ~0.19–0.64 μg/mL) | [90] |
| Goniolandrene A |  | Anticancer (cytotoxic to murine leukemia P388 cells, $IC_{50}$ ~0.42 μM) | [49] |
| Goniolandrene B |  | Anticancer (cytotoxic to murine leukemia P388 cells; $IC_{50}$ up to ~160 μM) | [49] |
| Geranyl acetate |  | Antimicrobial (major twig/root oil constituent; contributes to antibacterial activity against *Staphylococcus* and *Candida* species) | [58] |
| Geraniol |  | Antimicrobial (present in active essential oils; inhibits growth of bacteria and yeast) | [58] |
| Linalool |  | Antimicrobial (present in active essential oils; broad-spectrum antimicrobial) | [58] |

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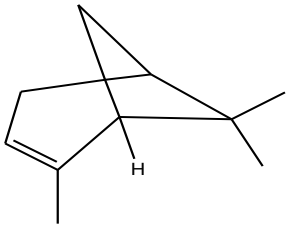
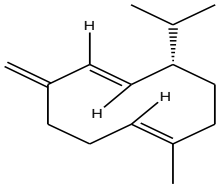
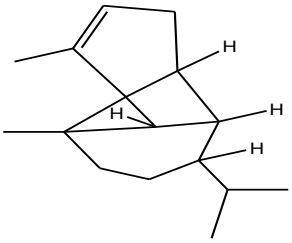
|---|---|---|
| *α*-Pinene |  | Antimicrobial (strong activity against Gram-positive bacteria and fungi; e.g., *Staphylococcus aureus*, *Candida albicans*; MIC as low as 0.3–2.5 mg/mL) [58] |
| Germacrene D |  | Antibacterial (broad-spectrum antibacterial properties reported for this common sesquiterpene) [91] |
| *α*-Copaene |  | Insect repellent/larvicidal (strongly repels insects such as the Asian citrus psyllid at very low doses) [92] |

Altholactone (styryl-lactone), another cytotoxic lactone identified in *G. macrophyllus*. Altholactone has been reported to induce apoptosis in human carcinoma cells via the extrinsic (Type II) pathway.[50] In HeLa cervical cancer cells, it triggers the caspase cascade associated with extrinsic death receptors (Type II apoptosis involves mitochondrial amplification of the death signal), leading to cell death.[51] This compound's pro-apoptotic effect is selective to cancer cells; however, it is also known to generate oxidative stress in tumor cells, which contributes to apoptosis induction in a caspase-dependent manner (as seen in related *Goniothalamus* species).[52]

*G. macrophyllus* (Annonaceae) also produces long-chain polyketide acetogenins. Two novel linear acetogenins, goniolandrene A and B, were isolated from *G. macrophyllus* roots and tested for cytotoxicity.[49] These showed activity against P388 cells, though with higher $IC_{50}$ values (up to tens of μM) compared to goniothalamin.[53] Goniothalamin itself (a styryl-lactone rather than an acetogenin) was the most potent in the same study ($IC_{50}$ ~0.42 μM).[54] The cytotoxic acetogenins are thought to act by disrupting mitochondrial function in cancer cells, a hallmark mechanism for many Annonaceous acetogenins.[55,56] In summary, the anticancer efficacy of *G. macrophyllus* is largely attributed to styryl-lactones (like goniothalamin and altholactone) and related compounds that induce apoptosis and inhibit survival pathways in tumor cells.

*Antimicrobial Activity*

*G. macrophyllus* has demonstrated broad-spectrum antimicrobial effects, attributable to both its essential oils and solvent-extractable phytochemicals. The plant's essential oils are rich in mono- and sesquiterpenes (e.g., *α*-pinene, geraniol, linalool, bicyclogermacrene) which show significant antimicrobial activity.[57] In one study, *G. macrophyllus* root oil exhibited a notable inhibitory effect at ~0.3 mg/mL against vancomycin-intermediate resistant *S. aureus* (VISA), *S. epidermidis*, and the yeast *C. albicans*. Among the isolated oil components, *α*-pinene was identified as a key antimicrobial agent, it inhibited bacterial growth at 0.3 mg/mL and fungal growth at 2.5 mg/mL, outperforming other constituents like linalool, geraniol, and geranyl acetate.[19,58] These findings suggest the essential oil's efficacy against Gram-positive bacteria and yeasts, aligning with traditional uses for treating skin infections and wounds.[59] (Gram-negative bacteria tend to be less susceptible to these terpenes, as is often the case with essential oils.)

Ethanol extracts of *G. macrophyllus* (non-volatile compounds) also show pronounced antimicrobial effects. Recent tests of leaf and root extracts revealed strong growth inhibition of *C. albicans* (yeast), *P. acnes* (a Gram-positive bacterium implicated in acne), and *S. mutans* (Gram-positive bacterium causing dental caries). The phytochemical profile of these extracts includes alkaloids, flavonoids, saponins, tannins, and triterpenoids,[60] all of which can contribute to antimicrobial activity. For instance, tannins and flavonoids can disrupt microbial membranes or enzymes, while aporphine alkaloids (common in Annonaceae) may intercalate DNA or inhibit protein synthesis in microbes.[61] The broad inhibition of both fungi and bacteria by *G. macrophyllus* extracts underscores its potential as a source of natural antimicrobial agents. Indeed, local communities use the bark and roots as antiseptics, and these laboratory results validate such traditional applications.

*Antioxidant Activity*

Antioxidant activity in *G. macrophyllus* has not been as extensively characterized as its other activities, but available evidence and its phytochemistry suggest the plant can scavenge free radicals.[62] *G. macrophyllus* contains significant amounts of phenolic compounds, which are known antioxidants. Phytochemical screening of the leaves and roots shows the presence of flavonoids, tannins, and other phenolics.[60] These compounds (e.g., flavanones like pinocembrin, and various tannins) can donate hydrogen atoms or electrons to neutralize reactive oxygen species.[63,64] The mere presence of such constituents implies that extracts of the plant are likely to exhibit free-radical scavenging activity.[65] For example, flavonoid antioxidants typically inhibit lipid peroxidation and protect against oxidative stress in biological systems.[66]

Direct antioxidant assays specific to *G. macrophyllus* are somewhat limited in the literature. However, studies on related *Goniothalamus* species support its potential. A comparative example is *Goniothalamus velutinus* (another member of the genus), whose bark and leaf extracts showed significant DPPH free radical scavenging activity correlating with high total phenolic content.[64] By analogy, a methanolic extract of *G. macrophyllus* would be expected to exhibit similar antioxidant effects given its phenolic makeup. In line with this expectation, many *Goniothalamus* species have been noted in reviews to possess antioxidant activity (often mentioned alongside their antimicrobial and anti-inflammatory properties).[67] In summary, while *G. macrophyllus*' antioxidant capacity needs further quantification (e.g., $IC_{50}$ in DPPH or ABTS assays), its rich phenolic profile strongly suggests a protective effect against oxidative damage. This could contribute to its traditional use in treating inflammatory conditions and general "health tonic" uses in folk medicine.

*Anti-inflammatory Activity*

Traditional uses of *G. macrophyllus* (e.g. to alleviate inflammation and swelling are supported by modern findings that its compounds interfere with key inflammatory pathways. Beyond its cytotoxicity, goniothalamin exerts anti-inflammatory effects by targeting the NF-κB pathway.[28] NF-κB is a transcription factor that controls the production of many pro-inflammatory cytokines (like TNF-*α*, IL-1*β*, IL-6) and chemokines.[68] Goniothalamin was shown to suppress TNF-*α*-induced NF-κB activation in cell-based assays at low micromolar levels.[29] In TNF*α*-stimulated leukemia cells, it prevented the p50/p65 NF-κB heterodimer from translocating to the nucleus and binding DNA, which in turn reduced the expression of interleukin-8 (IL-8), a key inflammatory chemokine. This blockade of NF-κB signaling occurred at non-apoptogenic concentrations (5-10 μM),[29] indicating a direct anti-inflammatory action separate from its cytotoxic effect. By inhibiting NF-κB, goniothalamin can down-regulate numerous inflammatory mediators and adhesion molecules, thereby exhibiting an anti-inflammatory and potential anti-tumor-promoting effect in the context of chronic inflammation.

(2S)-Pinocembrin isolated from *G. macrophyllus* stem bark, has emerged as a potent anti-inflammatory agent in its own right.[69,70] In an in vitro study, (2S)-pinocembrin significantly suppressed prostaglandin $E_2$ ($PGE_2$) production in activated macrophages.[28] Specifically, when RAW 264.7 (mouse) and U937 (human) macrophage cells were stimulated with bacterial lipopolysaccharide (LPS), treatment with (2S)-pinocembrin markedly reduced the levels of $PGE_2$, a pro-inflammatory eicosanoid involved in fever, pain, and swelling.[71] Mechanistic experiments revealed that (2S)-pinocembrin achieves this by inhibiting MAPK signaling, particularly the p38 and ERK1/2 pathways, which are upstream of cyclooxygenase-2 (COX-2) induction.[28] By attenuating p38/ERK activation, the compound likely reduces COX-2 expression or activity, thus lowering $PGE_2$ synthesis. Docking studies in the same work supported that (2S)-pinocembrin can bind to the kinase sites, corroborating the in vitro findings. This mechanism indicates a COX-2 modulatory effect analogous to NSAIDs, though via upstream kinase inhibition.[72] The anti-inflammatory efficacy of pinocembrin is noteworthy because excessive $PGE_2$ is implicated in conditions like rheumatoid arthritis and even cancer progression.[73] By curbing $PGE_2$, (2S)-pinocembrin could help ameliorate inflammation-related symptoms (it has even been suggested as potentially beneficial in preventing septic shock exacerbation).[74,75] Notably, pinocembrin is already known for its anti-inflammatory and neuroprotective profiles in other contexts, and its presence in *G. macrophyllus* adds to the plant's overall anti-inflammatory arsenal.[76] In summary, *G. macrophyllus* exhibits anti-inflammatory activity via compounds that modulate key signaling pathways (NF-κB and MAPK/COX-2). These molecular actions validate the ethnomedicinal use of the plant for swelling, fever, and inflammatory pain.

*Antiparasitic Activity*

The antiparasitic effects of *G. macrophyllus* are most prominently noted against the malaria parasite (*Plasmodium* spp.), consistent with its use in traditional medicine for treating malarial fevers.[62] In Malaysia and Indonesia, decoctions of *G. macrophyllus* roots have been used to treat fever and malaria for generations. This folk use suggests the plant contains antipyretic and antiplasmodial constituents. Malaria is caused by *Plasmodium* parasites; thus, a medicinal effect against "malaria" implies the plant might inhibit parasite growth or alleviate symptoms (or both). Indeed, *G. macrophyllus* is locally known as "penawar hitam," reflecting its reputation as a remedy for intermittent fevers like malaria.[58] Such use set the stage for scientific evaluation of its antiparasitic properties.

A screening study of Malaysian medicinal plants provided experimental evidence for *G. macrophyllus*' antimalarial activity. In an in vitro assay against *P. falciparum* (human malaria parasite, strain D10), the stem extract of *G. macrophyllus* achieved >60% inhibition of parasite growth. This was at the highest test concentration (64 μg/mL), indicating moderate antiplasmodial potency. While an $IC_{50}$ was not reached in that initial screening (unlike extracts of some other species, which were more potent), a >60% growth inhibition is a promising result for a crude extract. It suggests that one or more constituents can affect the parasite's viability or development. This aligns with the traditional use and supports that *G. macrophyllus* indeed has antimalarial principles. It's worth noting that another *Goniothalamus* species (*G. scortechinii* ) showed even higher activity in the same study (90% inhibition at 0.03 μg/mL),[77] implying the genus broadly is a rich source of antiplasmodial agents.

Although specific antiprotozoal compounds from *G. macrophyllus* have not been definitively isolated in the context of malaria, the plant's known chemical classes provide clues. *Goniothalamus* species are known to produce acetogenins and styryl-lactones that are cytotoxic,[56] and some of these have shown antimalarial effects in related studies.[58] For example, certain Annonaceous acetogenins (like bullatacin and squamocin from other genera) are potently antiplasmodial by disrupting parasite mitochondrial function.[78] It is conceivable that *G. macrophyllus*' acetogenins (e.g., the goniolandrenes or others) and styryl-lactones contribute to the observed activity by a similar mechanism, attacking parasite mitochondria or inhibiting critical enzymes.[79,80] Additionally, the presence of flavonoids (like pinocembrin) could add antiparasitic synergy, as some flavonoids inhibit plasmodial proteins or enhance immune response.[81,82] While more research is needed to pinpoint the exact mechanism in *G. macrophyllus*, the existing data firmly establish it as having antiparasitic (antimalarial) potential. This justifies its traditional usage and highlights it as a candidate for further bioactive compound isolation against malaria. (There are no specific reports on its efficacy against other parasites such as leishmania or trypanosomes yet; current evidence is focused on plasmodial activity.)

*Antidiabetic*

To date, no direct study has evaluated *G. macrophyllus* for glucose-lowering or antidiabetic activity. The plant is not prominently documented in traditional medicine for diabetes. However, its phytochemistry suggests possible antidiabetic effects worth exploring. The bark and leaves contain flavonoids and saponins,[60] which in other plants have been shown to improve insulin sensitivity or inhibit carbohydrate-digesting enzymes.[83,84] Notably, some Annonaceae alkaloids can inhibit *α*-glucosidase,[85] an enzyme that breaks down sugars; for instance, alkaloids from a related custard-apple family plant (*Polyalthia* sp.) showed potent *α*-glucosidase inhibition in vitro. [67] By analogy, any alkaloids in *G. macrophyllus* might exhibit similar activity. Thus, while *antidiabetic effects have not been reported* for this species, it has the chemical repertoire (flavonoids, tannins, etc.) that could confer antihyperglycemic or *α*-glucosidase inhibitory activity. This remains a potential pharmacological facet for future investigation.

*Hepatoprotective Activity*

There is no evidence so far that *G. macrophyllus* protects the liver; in fact, available data suggest caution. Traditional usage of this plant does not specifically include liver ailments, and scientific studies have not reported any hepatoprotective assays. On the contrary, some constituents might be hepatotoxic at high doses rather than protective. For example, the styryl-lactone altholactone (discussed above for anticancer) was noted to elevate liver enzymes in an animal study, it significantly increased serum alanine aminotransferase (ALT) levels, a marker of liver injury.[52] This was associated with its potent bioactivity and suggests it can stress hepatocytes. Thus, *G. macrophyllus* extracts would need careful toxicity evaluation before considering any hepatoprotective claims.[86] At present, no hepatoprotective effect is reported, and some components like goniothalamin are quite bioactive (potentially harmful to rapidly dividing cells, including hepatocytes at high concentration). Any use of the plant for liver health in folk medicine is not well documented, so hepatoprotection remains an unlikely or at least unproven activity for now.

*Antinociceptive/Analgesic Effects*

Analgesic (pain-relieving) potential of *G. macrophyllus* has not been formally studied, but folk medicine hints at it. The plant has been used as a post-partum remedy and to treat "body pains" and aches in certain local traditions.[87] In some regions, concoctions of *G. macrophyllus* (or its relatives) are applied to relieve rheumatism and muscular pain.[88]

These uses suggest the plant may have antinociceptive compounds (perhaps acting as mild sedatives or muscle relaxants). Some Annonaceae plants contain morphine-like alkaloids or central nervous system depressants, though *Goniothalamus* is better known for cytotoxic agents. It is possible that the anti-inflammatory effects (NF-κB and COX-2 inhibition by goniothalamin and pinocembrin) also contribute to pain relief, since reducing inflammation often alleviates pain. Without direct studies, one can only say *G. macrophyllus* has a potential analgesic effect as evidenced by traditional usage, but this remains to be pharmacologically validated.

*Insecticidal and Insect-Repellent Activity*

*G. macrophyllus* is well-known in indigenous practice as a natural insect repellent. The smoke from burning the dried leaves or bark is used to repel mosquitoes and other insects.[60] In Malaysia, people have observed that the burnt leaves produce a fragrant smoke that is highly effective at keeping mosquitoes away.[89] This aligns with the presence of volatile terpenoids in the plant's essential oil; many of those (e.g., geraniol, citronellol, *α*-pinene) are known mosquito repellents. Modern studies confirm this traditional knowledge: ethanol extracts of *G. macrophyllus* have shown mosquitocidal activity. In a laboratory larvicidal assay, the root extract caused up to 88% mortality of *Aedes* mosquito larvae at 15% concentration.[60] Such efficacy is comparable to some conventional larvicides. The extract likely contains a blend of compounds that are toxic to the larvae (possibly an overlap of antimicrobial terpenes that also disrupt insect physiology). Additionally, earlier reports noted that various parts of *G. macrophyllus* are effective against pests. The fragrance of the leaves deters adult insects and even the planted tree is said to have fewer insect herbivores relative to other species (an observation that prompted chemical analysis of its volatiles). Therefore, *G. macrophyllus* can be considered to have insecticidal properties, especially as a repellent and larvicide. This justifies its local use in preventing mosquito-borne illnesses and as a botanical insect control agent.

*Abortifacient (Embryotoxic) Effect*

An important traditional use of *G. macrophyllus* (and several *Goniothalamus* spp.) is as an abortifacient to induce miscarriage. The bark or root decoction was given to women post-partum or to terminate unwanted pregnancy. Chemical studies have provided a basis for this effect: goniothalamin and goniothalamin oxide, two styryl-lactones from *G. macrophyllus*, were found to have embryotoxic properties. In laboratory assays (e.g., on embryonic tissues or pregnant animal models), these compounds caused fetal resorption or embryo lethality.[58] The mechanism is presumably related to their cytotoxicity, they can induce apoptosis in rapidly dividing embryonic cells and possibly cross the placental barrier. Because of this, *G. macrophyllus* is known as "gajah beranak" (literally "elephant giving birth") in Malay, alluding to its use in difficult childbirth and abortion. While this embryotoxic/uterotonic effect is a hazard in terms of toxicity, it was harnessed in folk medicine. Modern users should be cautious, as the same compounds with anticancer activity can harm reproductive cells. Nonetheless, this is a documented pharmacological effect of the plant (albeit a harmful one), and it underscores the potency of *G. macrophyllus*' bioactive constituents on physiological processes.

## Conclusion

In conclusion, *G. macrophyllus* exhibits significant therapeutic promise based on its diverse phytochemical profile and extensive pharmacological activities. The ethnomedicinal applications of *G. macrophyllus* across Southeast Asia are well supported by scientific evidence, particularly regarding its cytotoxic, antimicrobial, antioxidant, anti-inflammatory, antiparasitic, and insecticidal properties. The prominent bioactive compounds, notably goniothalamin and related styryl-lactones, along with flavonoids like pinocembrin, underpin these biological effects through mechanisms such as apoptosis induction, NF-κB inhibition, and MAPK/COX-2 modulation. However, the review also highlights critical gaps, such as the limited in vivo validation, insufficient toxicological data, and lack of standardized preparation methods. Future research should prioritize comprehensive toxicological studies, clinical validations, and mechanistic explorations to facilitate the translation of *G. macrophyllus* from traditional use into evidence-based therapeutic applications. By addressing these research needs, *G. macrophyllus* could significantly contribute to the development of novel natural product-based therapeutics, thus reinforcing its role in contemporary medicine.

## Conflict of Interest

The authors declare no conflict of interest.

## Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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