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Review Article

Antimalarial Potential of Medicinal Plants: Phytochemical Insights and Host-Directed Strategies

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A B S T R A C T

Background: Malaria remains a significant global health threat, with rising drug resistance undermining the efficacy of standard therapies. Historically, plant-derived compounds such as quinine and artemisinin have served as cornerstones in antimalarial treatment.

Objective: This review explores the antimalarial potential of medicinal plants, emphasisingphytochemical classes, their mechanisms of action, and host-directed strategies to combat emerging resistance.

Methods: Relevant literature on alkaloids, terpenoids, flavonoids, coumarins, and phenolics with antiplasmodial activity was reviewed. Evidence from in vitro studies, animal models, and pilot clinical evaluations was analysed.

Results: Plant-derived compounds exert antimalarial effects via diverse mechanisms, including inhibition of heme detoxification, ROS generation, DNA intercalation, and modulation of host AMPK signalling. Flavonoids, in particular, restore cellular energy regulation by reactivating AMPK, depriving Plasmodium of critical metabolic substrates.

Conclusion: Phytochemicals offer a promising complementary strategy for malaria treatment. Their multi-target activity and host-directed actions present a low-resistance-risk profile. Future clinical translation requiresstanderisation, formulationoptimisation, and regulatory integration.

Keywords: Malaria, Medicinal Plants, Phytochemicals, Antimalarial, Flavonoids, Artemisinin, Quinine, Ampk, Host-Directed Therapy

Introduction

Malaria remains a persistent and deadly communicable disease, contributing to significant morbidity and mortality in tropical and subtropical regions. Despite reductions in disease burden in recent decades, progress has plateaued in many endemic areas due to health system gaps, socio-

economic disparities, and climate-induced changes in vector distribution. Vulnerable populations, particularly children under five and pregnant women, continue to experience disproportionate impacts.[1,2,3]

Pharmacological interventions have played a central role in malaria control, from early use of quinine to widespread implementation of chloroquine and sulfadoxine–pyrimethamine. However, the efficacy of these treatments has been repeatedly compromised by the emergence of drug-resistant Plasmodium strains. [6,7,8] The current reliance on artemisinin-based combination therapies (ACTs) is under threat due to delayed parasite clearance and resistance to partner drugs.[10]

These challenges point to the importance of novel therapeutic strategies with distinct mechanisms of action and a reduced likelihood of resistance development. Medicinal plants have historically served as a source of bioactive compounds, and notable antimalarials such as quinine and artemisinin were derived from botanical origins.[11,12,14,15] With advances in phytochemistry, molecular biology, and ethnopharmacology, the potential of plant-derived compounds to serve as both direct antiplasmodials and host-targeted adjuncts has garnered renewed interest.[10]

This review explores the antimalarial potential of medicinal plants, focusing on key phytochemical classes, their pharmacological profiles, mechanisms of action, and relevance to emerging resistance.[16,17,18] Particular attention is given to flavonoids and their role in activating host metabolic pathways, offering a promising avenue for resistance-resilient therapy.[23]

Malaria Pathophysiology and Therapeutic Targets

Plasmodium parasites cycle between Anopheles mosquitoes and human hosts, exploiting distinct cellular niches to ensure survival and transmission.[19,20] Sporozoites inoculated during a mosquito blood-meal rapidly home to the liver, traversing sinusoidal endothelium and invading hepatocytes. Here they undergo exoerythrocytic schizogony, generating tens of thousands of merozoites over approximately one week. Rupture of infected hepatocytes releases merozoites into the bloodstream to initiate the erythrocytic cycle.[3]

Within red blood cells, parasites progress through ring, trophozoite, and schizont stages. Haemoglobin catabolism supplies amino acids, but releases free haem, a pro-oxidant detoxified by conversion into the inert crystal hemozoin.[21,22] Interference with haem polymerisation is a validated drug target. Erythrocyte rupture occurs in a synchronised fashion, producing the characteristic febrile paroxysms and contributing to anaemia. In *Plasmodium falciparum* infection, surface expression of variant adhesins promotes cytoadherence and sequestration, a key driver of organ-specific pathology, including cerebral malaria.[23,24] Beyond parasite-intrinsic targets, host cell metabolism is co-opted. Evidence indicates that Plasmodium modulates AMP-activated protein kinase (AMPK) signalling, suppressing energy-conserving pathways and enhancing biosynthetic fluxes favourable to replication. Pharmacological reactivation of AMPK in host cells has emerged as a promising host-directed adjunct strategy that starves the parasite of critical precursors without exerting direct pressure on parasite targets.[5,6]

This review aims to systematically examine phytochemical classes with antimalarial properties, highlight pharmacological evidence across in vitro and in vivo models, and assess translational potential, especially in host-directed therapy.

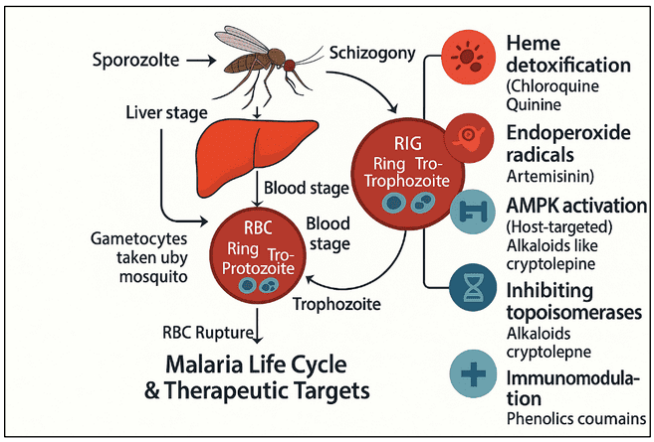

Figure 1. Schematic of the malaria life cycle with indicative therapeutic targets. Created by the authors

Historical Use of Medicinal Plants

The ethnopharmacological record chronicles centuries of empirical antimalarial practice. Cinchona bark decoctions, originating from Andean traditions, yielded quinine—an alkaloid that transformed nineteenth-century tropical medicine and enabled large-scale colonial enterprises. Quinine's success spurred medicinal chemistry programmes culminating in chloroquine and other 4-aminoquinolines that defined mid-twentieth-century therapy, until resistance emerged.[26]

A second epochal discovery arrived with artemisinin from Artemisia annua (Qinghao), rediscovered through a systematic review of classical Chinese materia medica and refined extraction. Endoperoxide-bearing sesquiterpene lactones derived from artemisinin became the fastest-acting antiplasmodials known, forming the basis of ACTs and contributing to dramatic declines in mortality. These exemplars validate plants as discovery engines and highlight the value of integrating traditional knowledge with rigorous pharmacology.[9,11]

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Phytochemicals with Antimalarial Activity

Plant secondary metabolites with antiplasmodial activity span multiple chemical classes. Below we summarise major classes—alkaloids, terpenoids, flavonoids, coumarins, and phenolics—emphasising representative compounds, sources, pharmacology, and translational considerations.[23,24,25]

Alkaloids

Alkaloids encompass nitrogen-containing heterocycles with diverse bioactivities. Quinine and quinidine remain archetypes that inhibit haem detoxification. Other notable examples include cryptolepine from Cryptolepis sanguinolenta, which intercalates DNA and inhibits topoisomerases, and febrifugine from Dichroa febrifuga, whose synthetic analogue halofuginone exhibits potent antiplasmodial activity albeit with dose-limiting toxicity. Continued work seeks scaffolds with improved safety margins.[29]

Terpenoids

Terpenoids include mono-, sesqui-, and diterpenes. Artemisinin derivatives (artesunate, artemether, and dihydroartemisinin) exemplify endoperoxide pharmacophores that generate reactive radicals within the parasite, damaging proteins and membranes. Beyond artemisinins, limonoids from Azadirachta indica (neem) and diterpenes from Andrographis paniculata have shown inhibitory effects in vitro and in vivo, meriting optimisation for potency and bioavailability.[9,11]

Flavonoids

Flavonoids such as quercetin, luteolin, apigenin, and catechins are widespread in diet and medicinal plants. Beyond modest direct antiplasmodial effects, an emerging theme is host-directed activity via AMPK activation and metabolic reprogramming that deprives parasites of lipids and nucleotides.[28,29,30] Flavonoids may also chelate iron, modulate redox status, and synergise with artemisinins, suggesting utility as adjunct.[9,11]

Coumarins and Other Phenolics

Coumarins (e.g., scopoletin) and simple phenolic acids exhibit antioxidant and immunomodulatory activities. While often less potent directly, they may attenuate inflammatory pathology, improve endothelial function, and enhance overall treatment response when integrated into multi-component phytochemical matrices.[26]

Pharmacological Evidence

A substantial body of evidence supports the antiplasmodial activity of plant-derived compounds, spanning in vitro assays, animal models, and early-phase human evaluations. In vitro studies have demonstrated that alkaloids (e.g., cryptolepine, quinine), terpenoids (e.g., artemisinin), and flavonoids (e.g., quercetin, luteolin) exhibit inhibitory effects against chloroquine-sensitive and -resistant strains of *Plasmodium falciparum*. Half-maximal inhibitory concentrations (IC_{50}) for potent isolates range from sub-micromolar to low micromolar levels.[10]

In vivo studies using murine models (*P. berghei*, *P. yoelii*) have shown reductions in parasitemia, delayed onset of symptoms, and improved survival rates upon treatment with phytochemical-rich extracts. Combination regimens, particularly those involving flavonoids and artemisinin derivatives, have revealed synergistic or additive effects, supporting their use as adjunct therapies to prevent resistance selection.[9,11]

Clinical data remain limited but are emerging. Standardisedextracts of *Artemisia annua, Azadirachta indica*, and *Andrographis paniculata* have undergone pilot studies in human subjects, demonstrating potential efficacy as supportive therapies. However, heterogeneity in extract preparation, dosing, and trial design hinders widespread clinical adoption. Future research should prioritisephar-macokinetic/pharmacodynamic (PK/PD) characterisation, toxicity profiling, and harmonised clinical endpoints to facilitate translational progress.[9,11]

Table 1.Representative plant-derived antimalarial phytochemicals, sources, and salient notes.

Class	Representative compounds	Plant source(s)	Notes
Alkaloids	Quinine, Cryptolepine, Febrifugine	Cinchona spp.; Cryptolepis sanguinolenta; Dichroa febrifuga	Heme detox inhibition; DNA intercalation/ topoisomerase inhibition
Terpenoids	Artemisinin, Limonoids, Diterpenes	Artemisia annua; Azadirachta indica; Andrographis paniculata	Endoperoxide radicals; redox stress
Flavonoids	Quercetin, Luteolin, Apigenin	Citrus spp.; Artemisia; many others	Host AMPK activation; synergy with ACTs
Coumarins/Phenolics	Scopoletin, Caffeic acid	Multiple medicinal plants	Immunomodulation; adjunct potential

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Table 2.Illustrative pharmacology of selected phytochemicals and extracts (in vitro and in vivo

Entity	Model/Strain	IC50 / Effect	Key finding	Notes
Quercetin	P. falciparum (resistant)	IC50 ~ 5–15 µM	Moderate direct inhibition	Synergy with artemisinins reported
Cryptolepine	P. falciparum	IC50 < 1–2 µM	Potent but toxicity concerns	DNA intercalation/ topoisomerase inhibition
Artemisinin	Multiple strains	Sub-micromolar	Rapid parasite kill	Endoperoxide activation
Neem limonoids	Murine *P. berghei*	↓parasitaemia; ↑survival	Adjunct benefit	Immunomodulatory contributions

Mechanisms of Action

Parasite-targeted mechanisms include:

- **Inhibition of heme detoxification:** Alkaloids such as quinine prevent conversion of free heme into non-toxic hemozoin, leading to oxidative damage in parasites.[10]
- **Radical-mediated damage:** Artemisinin's endoperoxide bridge is activated by heme iron, generating carbon-centered radicals that alkylate parasite proteins and lipids.
- **DNA damage and enzyme inhibition:** Compounds like cryptolepine intercalate DNA and inhibit topoisomerases, halting parasite replication.

Host-directed mechanisms represent a novel and resistance-resilient approach:

- **AMPK activation:** Flavonoids (e.g., quercetin, luteolin) reactivate AMP-activated protein kinase (AMPK) pathways in infected host cells. AMPK reprograms cellular metabolism, suppressing biosynthetic pathways critical to parasite development.[5]
- **Redox modulation and iron chelation:** Polyphenols modulate redox status, chelate iron, and reduce oxidative stress in host tissues, thereby enhancing the host's immune response and impairing parasite survival [24,25].
- **Endothelial and immune modulation:** Certain coumarins and phenolics reduce inflammatory cytokines and support endothelial integrity, mitigating severe complications such as cerebral malaria.

Multiple, partially overlapping mechanisms explain the antiplasmodial activity of plant-derived molecules. Heme detoxification inhibition by quinoline alkaloids increases free haem and ROS, damaging parasite membranes and proteins. Artemisinin's endoperoxide bridge is activated by haem iron to generate carbon-centred radicals that alkylate essential parasite targets.

Host-directed mechanisms are increasingly recognised. Flavonoid-mediated activation of AMPK resets host cellular metabolism toward catabolism, reducing lipid and nucleotide synthesis required by intracellular parasites. In parallel, antioxidant and anti-inflammatory phenolics may mitigate endothelial activation and microvascular dysfunction, complementing direct parasiticidal effects.[5]

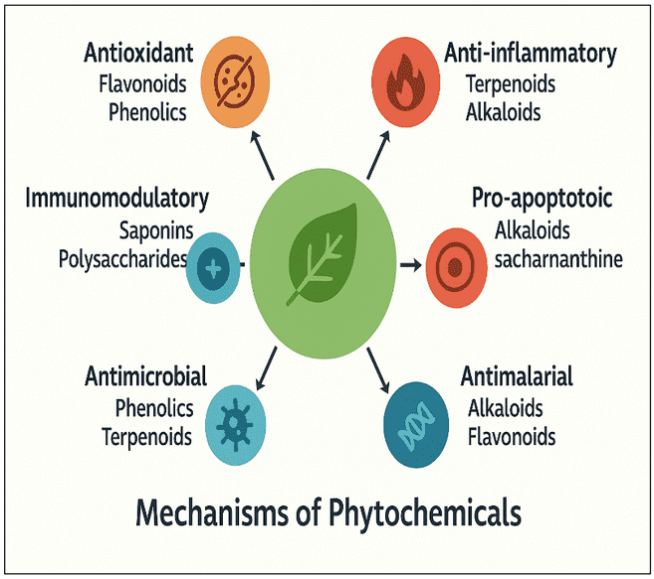

Figure 2. Schematic summary of mechanisms attributed to major phytochemical classes. Created by the authors

Regional Evidence of Medicinal Plants

The use of medicinal plants in antimalarial therapy is deeply rooted in traditional medical systems across diverse geographic regions. Ethnobotanical practices have guided the discovery of several potent antiplasmodial agents.

India: Traditional Ayurvedic and tribal medicine systems have utilised plants such as Azadirachta indica (neem), Swertia chirayita, Andrographis paniculata, and Curcuma longa for fever and malaria-like symptoms. Extracts from these plants—rich in limonoids, flavonoids, and xanthones—have demonstrated in vitro efficacy, and neem-based formulations are currently under evaluation in community trials.[13]

Africa: The plant Cryptolepis sanguinolenta is widely used in West African ethnomedicine. Its major alkaloid, cryptolepine, has shown potent antiplasmodial activity,

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though its therapeutic index requires further investigation due to potential genotoxicity. Artemisia annua, now cultivated in parts of East Africa, is traditionally consumed as herbal tea, but concerns remain regarding standardisation, dosage, and safety in long-term use.[9,11]

South America: The bark of Cinchona species, historically the source of quinine, remains symbolic of indigenous knowledge in the Andean regions. Other lesser-known genera such as Aspidosperma and Simaba contribute indole alkaloids and quassinoids that have shown investigational antimalarial activity. These compounds warrant further pharmacological evaluation and development.[10]

A comparative analysis of these regional sources highlights the global relevance of medicinal plants and underscores the importance of aligning traditional practices with modern scientific validation.

Challenges and Limitations

- **Standardisation:** Variability in phytochemical profiles driven by genotype, geography, harvest timing, and processing complicates dose reproducibility. Robust quality-control frameworks, validated analytical markers, and Good Agricultural and Collection Practices are prerequisites for clinical development.
- **Safety and toxicity:** While many phytochemicals have favourable safety profiles, certain alkaloids (e.g., cryptolepine analogues) exhibit cytotoxicity and genotoxicity at higher doses. Systematic toxicology, drug–drug interaction assessments, and prudent patient selection are critical.[13]
- **Pharmaceutical developability:** Poor aqueous solubility and rapid metabolism limit oral bioavailability for many leads. Enabling formulations (lipid systems, nanoparticles) and structure–property optimisation can address these deficits.[13]
- **Evidence generation:** Randomised controlled trials with rigorous endpoints remain sparse. Bridging the translational gap requires harmonised protocols, registrational-quality data, and alignment with regulatory expectations.

Future Directions

The therapeutic potential of medicinal plants in malaria management is well-recognized, but several scientific and translational challenges must be addressed to realize their clinical application.

Integrated Discovery Approaches

Combining ethnopharmacological knowledge with high-throughput phenotypic screening and metabolomic profiling can accelerate the identification of bioactive compounds. Emerging technologies such as AI-assisted phytochemical mining and network pharmacology offer tools to decode multi-component synergistic effects inherent in botanical extracts.[13]

Formulation and Delivery Technologies

Poor water solubility and bioavailability limit the clinical utility of many phytochemicals. Nanoformulations, lipid-based carriers, and solid dispersion techniques are promising platforms to enhance systemic exposure and therapeutic efficacy. These strategies can also allow dose reduction, improving safety profiles.[13]

Host-Directed Therapeutics

Targeting host pathways such as AMPK, mTOR, and endothelial integrity offers resistance-resilient strategies. Further research should explore the immunomodulatory and anti-inflammatory roles of plant compounds in mitigating disease severity and complications such as cerebral malaria.[5]

Clinical and Regulatory Integration

Clinical development should focus on generating registrational-quality evidence through randomized controlled trials in endemic settings. Standardization of extracts, validated chemical markers, and quality-control frameworks aligned with WHO TDR and national pharmacopoeias are essential for regulatory approval and policy adoption.

With coordinated global efforts, medicinal plants can be repositioned from traditional remedies to evidence-based therapeutic agents contributing to malaria elimination.[9]

Table 3.Illustrative pharmacology of selected phytochemicals and extracts (in vitro and in vivo)

Region	Plant (scientific name)	Principal constituents	Notes
India	Azadirachta indica (Neem)	Limonoids (azadirachtin)	Adjunct immunomodulation; vector deterrence
India	Swertia chirayita	Xanthones, secoiridoids	Traditional antipyretic; in vitro activity
Africa	Cryptolepis sanguinolenta	Cryptolepine alkaloids	Potent in vitro; toxicity to be managed
Africa	Artemisia annua	Artemisinin	Backbone of ACTs; standardisation essential

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South America	Cinchona spp.	Quinine alkaloids	Historic mainstay; resistance shaped policy
South America	Aspidosperma spp.	Indole alkaloids	Investigational antiplasmodials

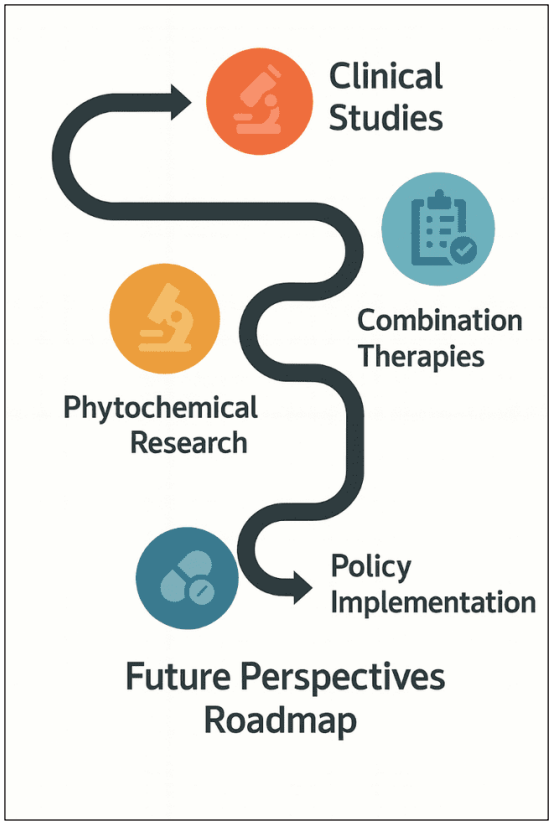

Figure 3.Development roadmap for plant-based antimalarial strategies from standardisation to policy adoption. Created by the authors

Conclusion

Medicinal plants offer a scientifically validated and historically grounded avenue for antimalarial drug discovery. Their diverse phytochemical profiles present unique structural and mechanistic advantages, including multi-target activity and the ability to modulate host metabolism[1,2,3,4].

In the current landscape of growing resistance to artemisinin-based therapies, the integration of plant-derived compounds—especially those with host-directed mechanisms like AMPK activation—can serve as adjuncts to existing regimens and potentially delay resistance evolution.

To unlock their full potential, efforts must focus on standardizing phytochemical content, overcoming formulation challenges, and conducting robust clinical trials. Bridging traditional knowledge with modern pharmacology can enrich the antimalarial arsenal and support global elimination efforts, particularly in resource-limited and endemic regions.[13]

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Declaration of Generative AI and AI-Assisted Technologies in the Writing Process: None

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