

Review Article

Green solution for malaria: Unveiling the therapeutic potential of natural products in antimalarial studies

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Abstract

Malaria remains a major global health challenge, with the continued emergence of antimalarial drug resistance underscoring the need for new, effective, and sustainable therapeutic strategies. Natural products have historically served as an important source of antimalarial agents, exemplified by quinine and artemisinin, and continue to provide structurally diverse bioactive compounds with significant therapeutic potential. This narrative review synthesizes current evidence on the role of natural products in antimalarial drug discovery, emphasizing the integration of ethnopharmacological knowledge with green chemistry principles to support sustainable drug development. A structured literature search was conducted across PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar to identify relevant mechanistic, ethnobotanical, and pharmacological studies. The review highlights the antiparasmodial activities of major classes of natural compounds, including terpenoids, alkaloids, flavonoids, quinones, and other secondary metabolites, together with their mechanisms of action, drug discovery pipelines, and emerging technologies such as green extraction methods, nanotechnology-based delivery systems, and high-throughput screening. It also discusses the contribution of traditional medicinal knowledge to the identification of novel lead compounds and the importance of biodiversity conservation and equitable benefit-sharing. Despite persistent challenges related to standardization, bioavailability, pharmacokinetics, and clinical translation, natural products remain a promising foundation for the development of next-generation antimalarial therapies capable of addressing the growing burden of drug-resistant malaria through environmentally sustainable and culturally informed approaches.

Keywords: Antimalarial agents, Ethnopharmacology, Green chemistry, Malaria, Natural products

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INTRODUCTION

Malaria remains one of the most persistent global health challenges, affecting communities across Africa, Asia, Latin America, and parts of the Middle East [1]. The disease is caused by protozoan parasites of the genus *Plasmodium*, transmitted through the bite of infected female *Anopheles* mosquitoes (Figure 1) [1]. Among the six species known to infect humans, *Plasmodium falciparum* (*P. falciparum*) is responsible for the most severe and fatal form of malaria, particularly in Sub-Saharan Africa, where climatic conditions and weak health systems contribute to sustained transmission [2,3]. Despite ongoing control efforts, malaria continues to impede social and economic development by increasing healthcare costs, reducing agricultural productivity, and contributing to school and work absenteeism [4]. According to the World Health Organization (WHO) World Malaria Report 2023, approximately 249 million malaria cases were recorded globally in 2022, with Nigeria alone accounting for nearly 27 % of all reported cases and 40% of malaria-related deaths in children under five [5,6].

Current treatment strategies rely largely on four pharmacological classes: quinoline derivatives, antifolates, artemisinin-based compounds, and selected antimicrobials [7]. Artemisinin-based combination therapies (ACTs) remain the cornerstone of malaria management due to their rapid action and high efficacy [8]. However, the widespread emergence of drug-resistant *P. falciparum* strains threatens their long-term effectiveness [9]. Furthermore, the high cost of ACTs, coupled with limited access and supply instability in low-income regions, poses additional barriers to sustained malaria control [3,5]. These challenges underscore an urgent need for new, affordable, and sustainably sourced antimalarial therapies that can complement or replace current drug regimens.

The renewed interest in ethnopharmacology arises from the fact that traditional healing practices are built on generations of observation, experience, and refinement [10]. In many malaria-endemic regions, indigenous communities have developed detailed knowledge of medicinal plants, not only which species are effective, but also how they should be prepared, combined, and administered to maximize benefit and reduce toxicity [11]. This knowledge represents a living scientific tradition, passed orally and through practice. The successful translation of *Artemisia annua* from traditional Chinese medicine to the global antimalarial artemisinin exemplifies the value of

ethnopharmacological approaches, yet thousands of traditionally used antimalarial plants remain scientifically uninvestigated [11].

Thus, the purpose of this review is to provide a comprehensive overview of the therapeutic potential of natural products in antimalarial strategies, with a particular emphasis on green solutions for malaria, by revealing the diverse array of natural products with antimalarial properties and elucidating their mechanisms. This review aims to contribute to ongoing efforts to combat malaria and promote sustainable approaches to global health challenges by investigating the pharmacological properties of various natural products, discussing their potential as antimalarial agents, examining the challenges and opportunities associated with their development and use, and proposing future research and innovation directions in this field.

METHODS

This review was conducted using a structured literature search and narrative synthesis approach to gather and evaluate data on natural products with antimalarial activity with emphasis on ethnopharmacologically-validated compounds and green chemistry approaches.

Literature search strategy

Published articles, ethnobotanical surveys, and experimental studies were sourced from PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. The search strategy targeted: ethnobotanical surveys and ethnopharmacological studies, traditional medicine documentation, indigenous knowledge databases and cross-cultural antimalarial plant use patterns. Search terms combined: "malaria", "antiplasmodial", "*Plasmodium*" AND "natural products", "medicinal plants", "traditional medicine", "ethnopharmacology" AND compound classes ("terpenoids", "alkaloids", "flavonoids", "quinones") AND "antimalarial activity", "IC₅₀", "*in vitro*", "*in vivo*". Additional searches included "green chemistry," "drug resistance," and "sustainable extraction."

Study selection

Studies were purposively selected based on their contribution to understanding natural product antimalarial potential. Priorities included: documented traditional use for malaria/fever, clear botanical identification, pharmacological validation data, quantitative activity data and IC₅₀ values or *in vivo* efficacy, where available.

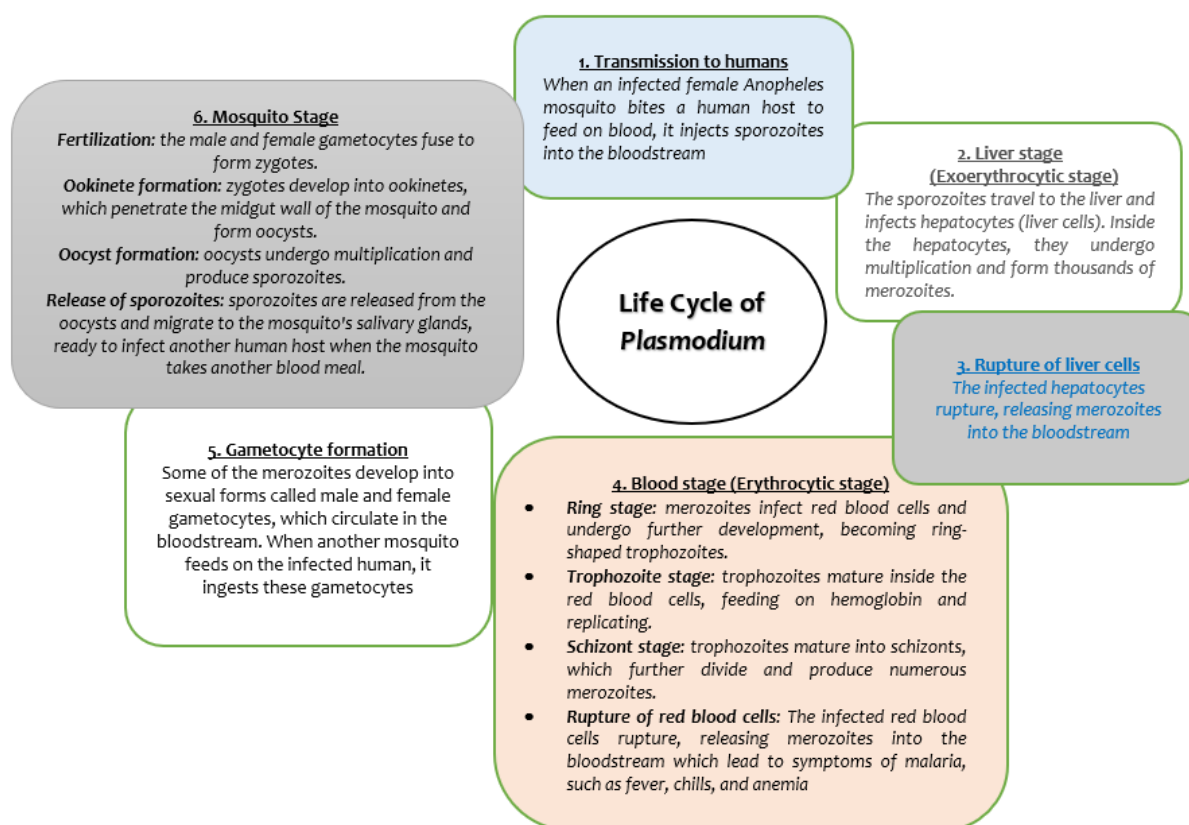


Figure 1: Life cycle of Plasmodium/malaria

Representative studies illustrated key concepts, major compound classes, and mechanistic insights rather than exhaustive coverage. Preference was given to high-quality recent studies, landmark discoveries (e.g., artemisinin), and research addressing drug resistance and sustainability.

Green solutions in antimalarial strategies

Green solutions in antimalarial research (Figure 2) focus on sustainable and environmentally responsible methods for malaria prevention and treatment [12]. These approaches combine the use of natural products, traditional ethnobotanical knowledge, eco-friendly vector control, community participation, and green chemistry innovations in drug discovery. The overall goal is to minimize environmental impact, improve accessibility, and support long-term malaria control, particularly in resource-limited regions.

A key aspect of these green strategies is the reliance on natural product-based therapies. Such treatments make use of bioactive compounds derived from plants, microbes, and marine organisms that can inhibit *Plasmodium* growth [11]. Ethnobotanical studies are vital in this process, as they help identify traditional medicinal plants that have been used for generations to treat malaria, providing a culturally

informed foundation for modern drug development [10]. To ensure sustainability and conservation, responsible sourcing practices are critical so that valuable medicinal species are not overexploited as their therapeutic potential becomes better known.

Another important part of green antimalarial research involves the use of eco-friendly extraction and formulation methods [13]. These technologies aim to reduce solvent toxicity, waste generation, and energy consumption during drug production. Researchers can create safer and more affordable antimalarial drugs by adhering to green chemistry principles. Nanotechnology-based delivery systems are also advancing these efforts by improving the solubility, stability, and effectiveness of natural compounds, often leading to stronger therapeutic outcomes with fewer side effects [14].

Combination therapies and multi-targeted approaches further enhance these sustainable treatments [15]. Natural compounds can work together with conventional drugs to increase effectiveness, clear parasites more efficiently, and slow the development of drug resistance [16]. Alongside laboratory advances, community engagement remains vital. When local communities participate in preventive efforts, plant cultivation, and health education, the

results are more sustainable and empowering for those most affected [16].

Recent genetic and molecular innovations, such as CRISPR/Cas9, have also expanded opportunities to study *Plasmodium* biology and identify new drug targets [17]. Although these tools are not inherently “green,” they strengthen the scientific foundation of sustainable drug development. Genetic engineering in *Plasmodium* research typically involves cultivating blood-stage parasites, introducing targeted genetic changes, and selecting modified strains, with electroporation being one of the most common methods for DNA delivery [17].

These green solutions aligned naturally with ethnopharmacological approaches, as traditional medicine essentially represents sustainable resource use, community-based health systems, and holistic environmental perspectives. Indigenous preparatory methods often reflect green chemistry principles by using water-based extractions, minimal processing, and locally available materials. Modern green chemistry thus represents a convergence of traditional wisdom and contemporary sustainability science [12].

Therapeutic potential of natural products

One of the basic pillars of green solutions in antimalarial research is the use of natural products from numerous sources, such as plants,

marine organisms, and microbes [12]. Natural products have a vast pool of bioactive molecules with various chemical structures and modes of action, making them promising candidates for antimalarial drug discovery and development [18]. Researchers capitalize on the inherent diversity of nature while reducing the ecological footprint associated with typical synthetic medications by using natural molecules as foundation for antimalarial therapeutics [18].

Natural products as rich source of bioactive compounds

Natural products have historically been an important source of bioactive molecules with therapeutic properties. Plants, for instance, produce a wide range of secondary metabolites to defend themselves against diseases, pests, and environmental stresses [10]. Alkaloids, terpenoids, flavonoids, and quinones are among the bioactive compounds that have been discovered to have antimalarial properties.

Terpenoids

Terpenoids, a diverse class of natural products, continue to play a vital role in antimalarial drug development due to their potent bioactive and structural versatility [19]. Artemisinin (1), a sesquiterpene lactone derived from *Artemisia annua*, remains the cornerstone of modern antimalarial therapy.

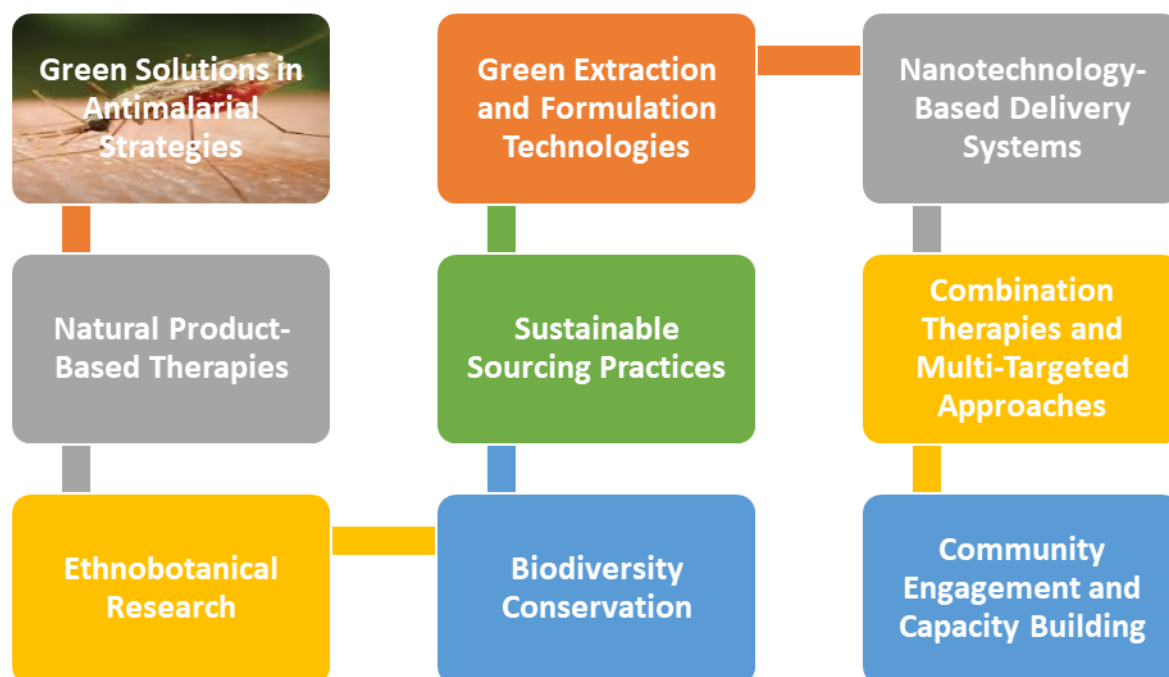


Figure 2: Green Solutions in Antimalarial Strategies

Other derivatives include dihydroartemisinin (DHA) (**2**) obtained by semisynthetic modification of artemisinin using sodium or potassium borohydride (Figure 3), which subsequently serves as a precursor for clinically important derivatives such as artemether (**3**), a methyl ether of DHA, and artesunate (**4**), a DHA succinate ester. These derivatives exhibit enhanced clinical efficacy, although their cost remains largely dependent on the availability and price of naturally sourced artemisinin. Beyond artemisinin, other terpenoids like limonoids (**5**) from citrus fruits and triterpenoids from medicinal plants such as *Centella asiatica* have shown promising antimalarial properties through diverse mechanisms of action [20]. The World Health Organization recommends artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated malaria [6]. Although, the artemisinin component provides rapid clearance of blood-stage parasites due to its short half-life, synthetic derivatives within ACTs offer prolonged half-lives and improved tissue distribution, enhancing treatment efficacy and reducing recurrence. Commonly used ACT regimens in endemic regions include artemether-lumefantrine, artesunate-amodiaquine, and dihydroartemisinin-piperaquine combinations [19-22].

Alkaloids

Alkaloids are a diverse group of naturally occurring nitrogen-containing compounds. They have long been recognised for their

pharmacological significance, particularly in the treatment of malaria [20]. Their antimalarial activity is mediated through multiple mechanisms, making them valuable candidates in the search for new therapeutics against *Plasmodium* spp. (Figure 4). One of the most historically significant antimalarial alkaloids is quinine (**6**), extracted from the bark of the *Cinchona* tree (family: Rubiaceae). Quinine has been used for centuries to treat malaria and remains a treatment option for severe and drug-resistant cases. Its antimalarial mechanism involves disrupting the parasite's heme detoxification pathway, leading to the accumulation of toxic heme and subsequent parasite death [21]. Despite its effectiveness, the clinical use of quinine is limited by adverse effects such as cinchonism and a narrow therapeutic window. Other notable alkaloids with antimalarial potential include isoquinoline alkaloids from *Papaver somniferum* (opium poppy), such as berberine (**7**), which is found in *Berberis* species. Berberine has demonstrated potent antiplasmodial activity in both in vitro and in vivo models [20-22], and its efficacy is further enhanced when used in combination with other antimalarial drugs. In addition, indole alkaloids from *Catharanthus roseus* (periwinkle), such as vincristine (**8**) and vinblastine (**9**), primarily known for their anticancer activity, have shown potential as antimalarial agents. These compounds inhibit parasite replication by interfering with cell division, representing a novel avenue for antimalarial drug development.

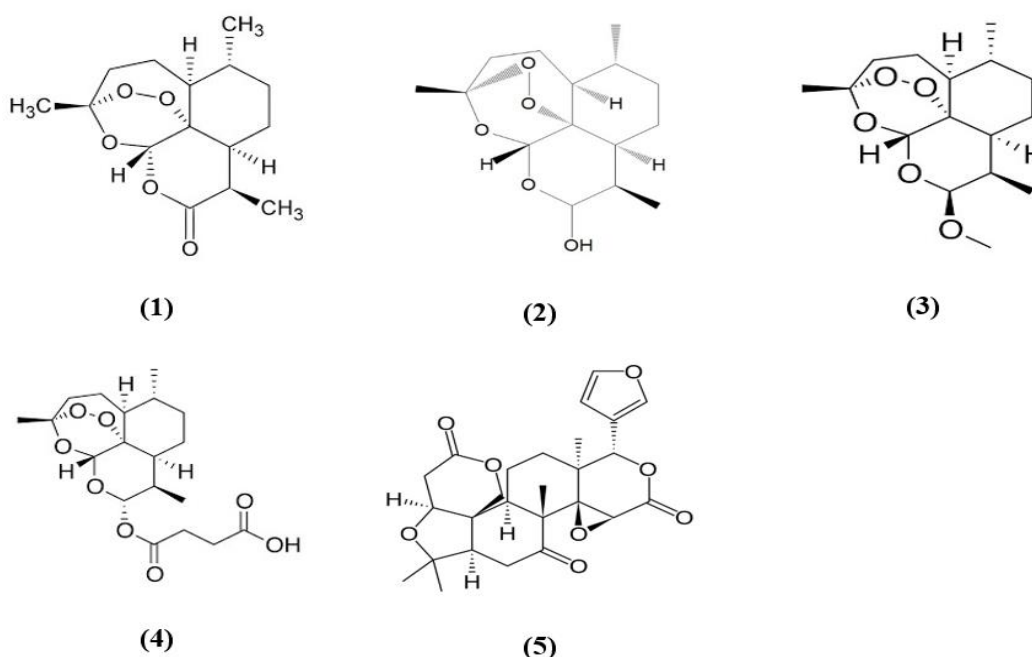


Figure 3: Terpenoids with antimalarial activity

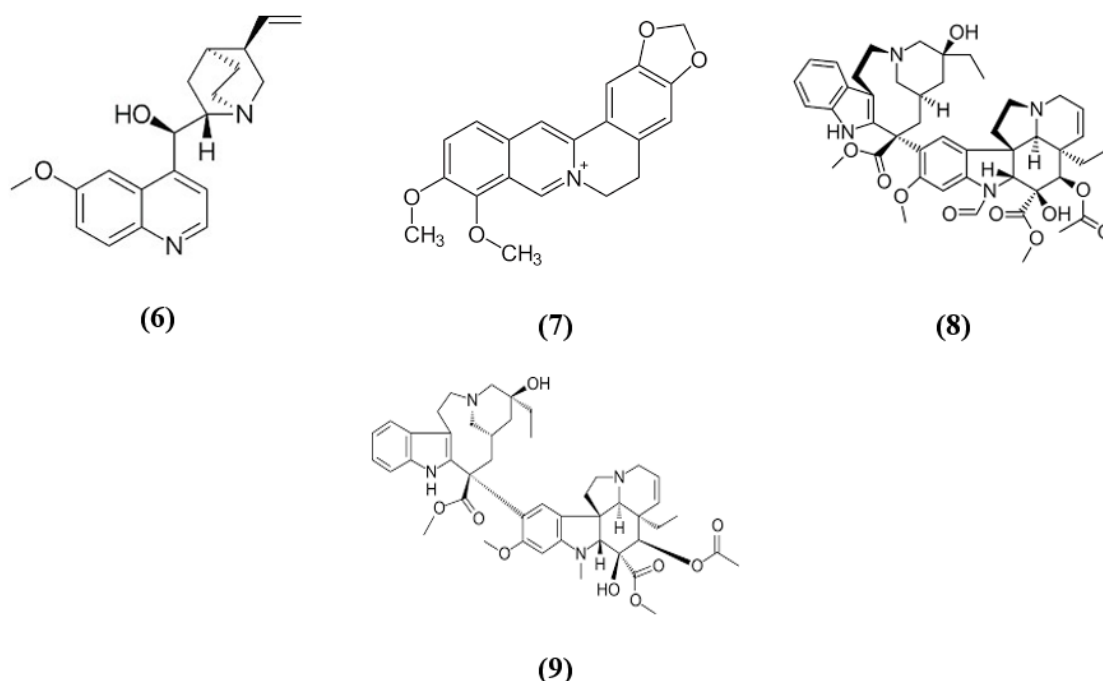


Figure 4: Alkaloids with antimalarial activity

Flavonoids

Flavonoids are a class of polyphenolic compounds widely distributed in plants, fruits, and vegetables. Several flavonoids have been investigated for their antimalarial activity; for instance, quercetin (**10**) (Figure 5), found in onions, apples, and tea, has shown potential as an antimalarial agent by inhibiting parasite growth and disrupting metabolic pathways. Similarly, flavonoids present in medicinal plants such as *Artemisia annua* and *Azadirachta indica* (Neem) exhibit antimalarial effects through various mechanisms [22]. *Cochlospermum planchonii* is rich in flavonoids that inhibit parasite protein synthesis.

Quinones

Quinones are aromatic compounds characterized by a conjugated ring structure with two carbonyl groups. Natural quinones have been recognized for their diverse biological activities, including antimalarial properties (Figure 6) [23]. *Plasmodium* parasites rely on heme metabolism for survival, and quinones interfere with this process, leading to parasite death. Examples of natural quinones with antimalarial activity include lapachol (**11**) from the bark of the Lapacho tree (*Tabebuia* species) and atovaquone (**12**), a synthetic analogue of ubiquinone derived from a natural product source. *Picrorhiza kurroa* contains iridoid glycosides with moderate antimalarial activity, and *Terminalia bellirica* also

contains ellagitannins (**13**) that demonstrate *in vitro* efficacy [24].

Other bioactive compounds

Many other bioactive compounds derived from natural products have been found to possess antimalarial properties in addition to the previously described classes of natural product compounds; these consist of lignans, polyphenols, saponins, and essential oils. For instance, the neem tree (*Azadirachta indica*) produces a number of bioactive compounds with antimalarial qualities, such as azadirachtin (**14**), nimbin (**15**), and nimbidin (**16**) [25]. Strychnine (**17**) and brucine (**18**), two alkaloids with antimalarial properties, are also found in the bark and leaves of the *Strychnos* species (Figure 7).

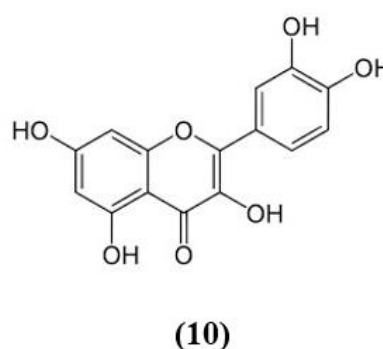


Figure 5: Chemical structure of quercetin

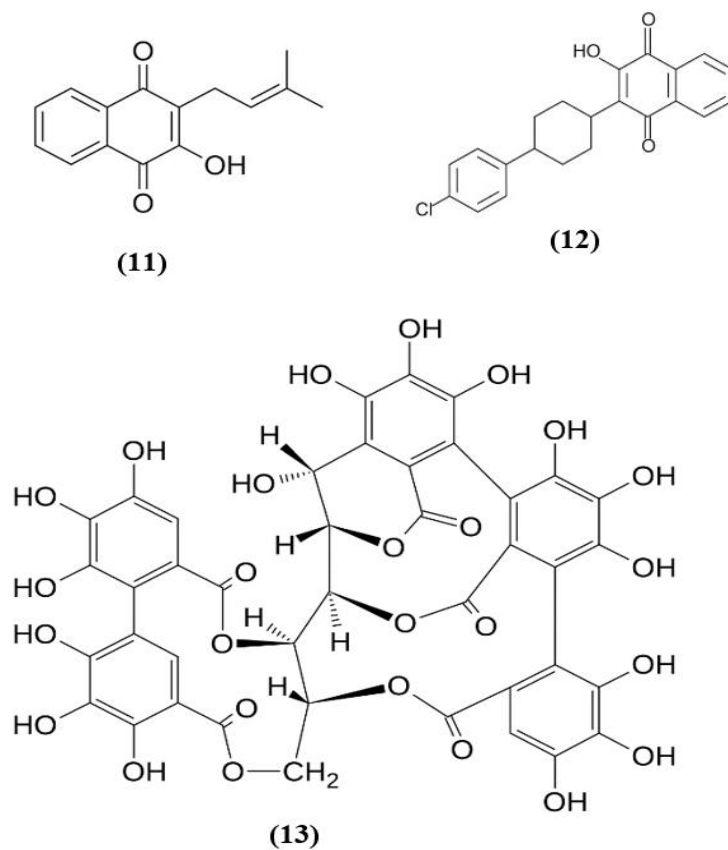


Figure 6: Quinones with antimalarial activity

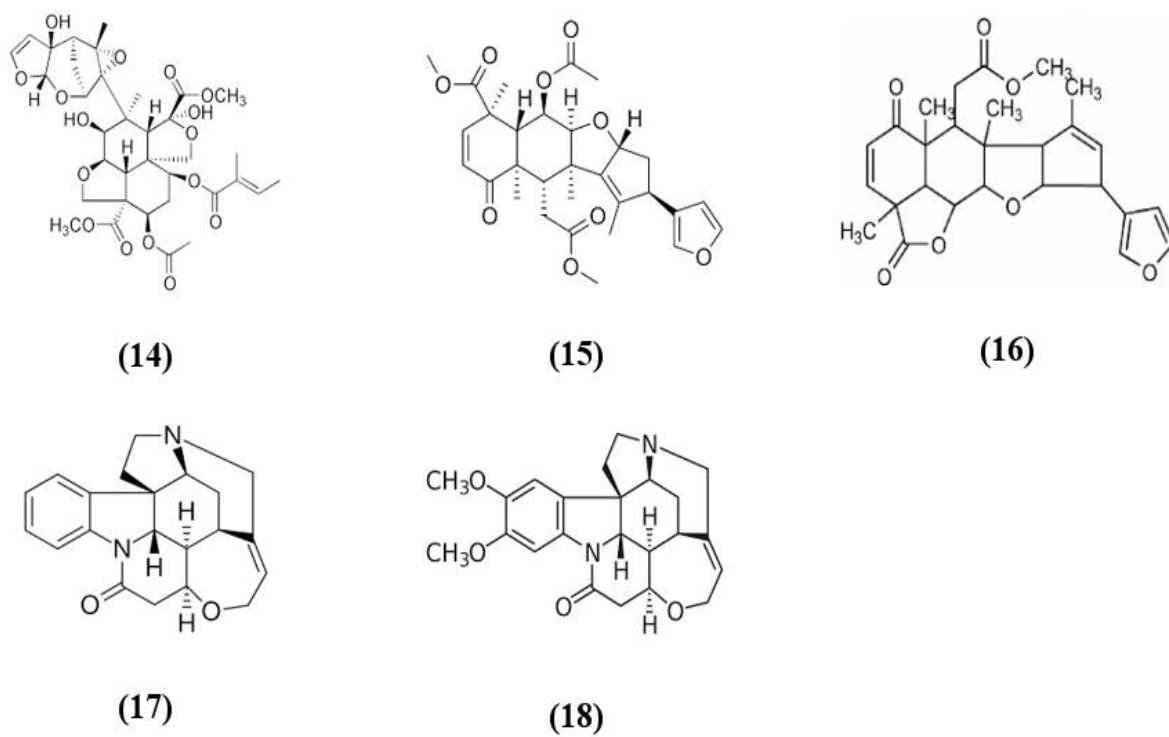


Figure 7: Other bioactive compounds with antimalarial activity

Ethnopharmacology and traditional knowledge in malaria treatment

For centuries, indigenous communities in malaria-endemic regions have developed sophisticated botanical pharmacopeias that continue to inform modern drug discovery. Ethnopharmacological studies have systematically documented these traditional antimalarial remedies, revealing a remarkable diversity of bioactive compounds [26]. For example, *Cryptolepis sanguinolenta*, widely used in West African traditional medicine, contains alkaloids with demonstrated in vitro activity against chloroquine-resistant *Plasmodium falciparum* strains. Similarly, *Azadirachta indica* (neem) produces limonoids with significant antimalarial properties, operating through mechanisms distinct from conventional therapeutics [27]. Additional medicinal plants with reported antimalarial activity are presented in Table 1. One of the most prominent examples of integrating traditional knowledge into modern medicine is the development of artemisinin-based combination therapies (ACTs). Tu Youyou, awarded the 2015 Nobel Prize in Physiology or Medicine, pioneered the extraction of artemisinin from *Artemisia annua* after a detailed review of ancient Chinese medical texts [27]. This discovery revolutionised malaria treatment, especially for drug-resistant cases. Phytochemical investigations have since revealed that many traditional formulations contain multiple active constituents acting synergistically to enhance efficacy and reduce toxicity [27]. For instance, alkaloids from the Malagasy plant *Strychnopsis thouarsii* have been shown to work in concert, reflecting the polypharmacological strategies now employed in combination therapies [26-28]. Furthermore, metabolomic profiling of traditional preparations has led to the identification of novel chemotypes with unique mechanisms of action. Compounds such as febrifugine from *Dichroa febrifuga* and gedunin from *Azadirachta indica* have shown activity against parasite targets that differ from those of current antimalarials, offering promising avenues to overcome drug resistance [26].

West Africa, Southeast Asia, and Madagascar stand out as regions with exceptionally rich traditional knowledge about antimalarial plants and practices. This deep ethnopharmacological expertise reflects both the high malaria burden in these areas and their extraordinary biodiversity. Yet much of this valuable knowledge is at risk. Urbanisation, the decline of traditional healing practices, and poor documentation are eroding centuries of accumulated understanding. Balancing biodiversity conservation with the

safeguarding of traditional knowledge offers both significant challenges and opportunities for sustainable drug discovery. Ethical research in this space must align with international standards, such as the Nagoya Protocol on Access and Benefit-Sharing, which ensures that benefits from using traditional knowledge are shared fairly. Promising examples come from community-based participatory research and well-structured benefit-sharing agreements, which acknowledge and compensate indigenous communities for their vital role in developing new therapeutic compounds [6].

Indigenous knowledge often includes sophisticated preparation methods that enhance bioavailability or reduce toxicity. For example, Wilcox *et al.* [28] demonstrated that decoction methods for preparing *Argemone mexicana* yielded higher concentrations of active alkaloids compared to simple infusions. Integrating ethnopharmacological insights with modern drug discovery tools (such as high-throughput screening) has accelerated the identification of potent candidates active against multiple stages of the *Plasmodium* life cycle [28]. As resistance to existing therapies continues to rise, traditional medicine remains a vital resource for discovering novel antimalarial agents. Indigenous cultures have long relied on natural products for treating malaria and other diseases, reinforcing the relevance of this knowledge in addressing present and future global health challenges (Table 1).

Drug discovery and development

Natural products are vital in the discovery and developmental activities of malaria medication [34]; numerous natural compounds with the promise of antimalarial activity have been found using traditional and high-throughput screening procedures [34]. These compounds serve as starting points for future optimization and development into effective antimalarial medicines; the successful development of antimalarial drugs from natural products typically begins with the identification of biologically active compounds through well-structured screening programs [35]. These programs play a foundational role in evaluating the efficacy of natural extracts, isolated compounds, and synthetic derivatives against *Plasmodium* species through both traditional bioassays and advanced high-throughput screening (HTS) technologies [36]. This initial screening phase is crucial for selecting promising candidates that can be further optimized through medicinal chemistry and preclinical evaluation.

Table 1: Traditional medicines and cultural practices for treatment of malaria

Plant	Formulation	References
<i>Aegle marmelos</i>	The decoction of leaves is to be taken orally.	Taek et al [29]
<i>Allium sativum</i>	The bulb of this plant can be used for the preparation of concoctions, tinctures and infusion	Odugbemi et al [30]
<i>Alstonia boonei</i>	Stem, root, leaves and bark can be used for treating malaria. Infusion, tincture and decoction can be prepared	Odugbemi et al [30] Ogbuehi and Ebong [31]
<i>Anacadum occidentale</i>	Leaves are washed and boiled in water for 20–50 min. 300 ml of the same is taken once a day for 1 week or until the symptoms disappear.	Omosun et al [32]
<i>Andrographis paniculata</i>	Decoction of whole plant can be used and the same can also be used to have bath with.	Taek et al [29]
<i>Azadirachta indica</i>	Decoction of stem bark and leaves is used.	Odugbemi et al [30], Ogbuehi and Ebong [31]
<i>Azadirachta indica, Carica papaya, Psidium guajava, Eucalyptus citisodora, Mangifera indica</i>	Leaves are sun-dried and then pounded and mixed with water then filtered. For 7 days, 300 ml of filtrate is taken twice.	Omosun et al [32]
<i>Azadirachta indica, Ocimum gratissimum</i>	Leaves are washed and pounded or squeezed and the juice is filtered. The filtrate is consumed twice daily.	Omosun et al [32]
<i>Azadirachta indica, Psidium guajava, Carica papaya</i>	Leaves are washed and boiled in water for 30–50 min. For 7 days, 300 ml of the concoction is taken twice.	Omosun et al [32]
<i>Bambusa vulgaris, Uwaria chamae, Cymbopogon citratus</i>	Aqueous decoction of mixed fresh leaves is prepared and 300 ml of the same is taken 4 times daily until malarial symptoms disappear.	Omosun et al [32]
<i>Cactus opunita</i>	Leaves are sun-dried and pounded, the mixture is poured into cold water and left to stand for 5 min and then filtered. 300 ml of the decoction is taken daily.	Omosun et al [32]
<i>Carica papaya</i>	Fruit, seeds and leaves of this plant are used as infusion.	Odugbemi et al [30] Ogbuehi and Ebong [31]
<i>Carica papaya, Mangifera indica</i>	Leaves are washed and boiled in water for 30 min and 300 ml of the concoction is taken twice daily for 10 days.	Omosun et al [32]
<i>Carica papaya, Psidium guajava, Eucalyptus, Mangifera indica</i>	Leaves are washed and boiled in water for 20–50 min. 300 ml of the concoction is taken two times for 10 days and the water is used for bathing through the duration of treatment.	Omosun et al [32]
<i>Citrus aurantifolia</i>	Leaves are washed and boiled in water. The juice from the fruit is squeezed separately. 300 ml of tisane is taken once a day and 10 ml spoonful of the squeezed juice is taken 3 times daily.	Omosun et al [32]
<i>Cymbopogon citratus, Eucalyptus citriodora, Phyllanthus amarus</i>	Fresh leaves are to be macerated in water and 300 ml of extract is taken 3- or 4 times daily for 10 days.	Omosun et al [32]
<i>Cymbopogon citratus</i>	Leaves are washed and boiled water is added to it and allowed to stand for 10–50 min. 300 ml of the infusion is taken twice daily until symptoms disappear.	Omosun et al [32]
<i>Enantia chlorantha</i>	Decoction, tincture and infusion of bark are used.	Odugbemi et al [30]
<i>Ficus megapoda</i>	A decoction of the leaf and bark is drunk (1 bowl, 3–4 times daily) to alleviate malarial symptoms.	Randrianarivelojosia et al [33]
<i>Khaya grandifoliola</i>	Bark can be used to make decoction and infusion.	Odugbemi et al [30]
<i>Leconiodiscus cupanioides</i>	Decoction of roots is used.	Odugbemi et al [30]
<i>Magnifera indica, Citrus aurantifolia</i>	Roots and leaves are boiled in water for 50 min and 300 ml of extract is taken 3 or 4 times daily for 5 days.	Omosun et al [32] Ogbuehi and Ebong [31]
<i>Morinda lucida</i>	Stem, roots and leaves are used as tincture and infusion.	Odugbemi et al [30] Ogbuehi and Ebong [31]
<i>Nauclea latifolia</i>	Tincture and decoction of bark and roots are to be consumed.	Odugbemi et al [30]
<i>Vernonia amygdalina</i>	Decoction of leaves is used to reduce the symptoms of malaria.	Odugbemi et al [30] Ogbuehi and Ebong [31]
<i>Vernonia amygdalina, Gongronema latifolium</i>	Leaves are washed and pounded or squeezed and the juice is filtered. 300 ml of the concoction is taken for 10 days.	Omosun et al [32]

The following section highlights the various screening strategies employed in antimalarial drug discovery.

Screening programs

Screening programs are essential components of drug discovery efforts aimed at identifying novel antimalarial compounds [36-38]. These programs encompass both traditional and high-throughput screening approaches. Traditional screening methods involve the testing of natural extracts or fractions derived from plants, microorganisms, or marine organisms for their antimalarial activity using *in vitro* assays or animal models. High-throughput screening, on the other hand, utilizes automated platforms to rapidly screen large libraries of natural product extracts or synthetic compounds for their antimalarial properties [37].

Natural compound libraries

Natural compound libraries represent a critical resource in antimalarial drug discovery, providing structurally diverse molecules derived from plants, microorganisms, and marine organisms [35]. These libraries serve as the basis for initial screening efforts aimed at identifying novel compounds with antiplasmodial activity [37]. Advances in isolation, dereplication, and analytical techniques have expanded the availability of well-characterised libraries, enabling efficient high-throughput screening against various *Plasmodium* life cycle stages. The unique chemical scaffolds found in natural products often offer distinct mechanisms of action, making them valuable leads in the development of next-generation antimalarial agents.

Identification of lead compounds

A variety of natural compounds with putative antimalarial action have been found through screening techniques. These compounds, known as lead molecules, have substantial inhibitory effects on the malaria parasite *in vitro* and *in vivo* [37-39]. Lead compounds are chosen based on factors such as effectiveness, selectivity, safety, and chemical tractability. Natural compounds with promising pharmacological properties are prioritised for further improvement and development as antimalarial medicines [37].

Mechanism of action studies

Understanding the mechanism of action of lead compounds is crucial for rational drug design and optimisation; natural product-derived antimalarials may target various stages of the

malaria parasite's life cycle, including inhibition of parasite growth, disruption of metabolic pathways, or modulation of host immune responses [39]. Mechanistic studies involving molecular biology, biochemistry, and pharmacology elucidate the molecular targets and pathways involved in the antimalarial activity of lead compounds [38-40]. For example, artemisinin is a sesquiterpene lactone and all of its derivatives have a peroxide bridge. Reduction of this bridge with Fe^{2+} ion causes the production of radical compounds, which subsequently alkylate proteins and kill parasites in the blood stage of malaria.

Lead optimization

Lead optimization involves chemical modification and structural optimization of lead compounds to enhance their potency, selectivity, pharmacokinetic properties, and safety profile [40]. Medicinal chemistry techniques such as structure-activity relationship (SAR) analysis, scaffold hopping, and combinatorial chemistry are employed to optimize the chemical structure of lead molecules while preserving their antimalarial activity. Iterative cycles of synthesis, testing, and structure-activity optimization lead to the development of more potent and efficacious antimalarial candidates [40].

Preclinical and clinical development

Antimalarial candidates derived from natural products undergo preclinical evaluation to assess their safety, pharmacokinetics, and efficacy in animal models of malaria [41]. Promising candidates progress to clinical trials, where their safety and efficacy are evaluated in human volunteers. Clinical development involves multiple phases, including dose escalation studies, efficacy trials in malaria-endemic regions, and post-marketing surveillance [41]. Antimalarial drugs derived from natural products must undergo rigorous regulatory review and approval processes before they can be marketed for use in malaria-endemic areas. Ciprogammin (**55**), formerly known as KAE609 and formerly referred to as NITD609, is one of several novel antimalarial compounds being developed in the pursuit of next-generation antimalarials (Figure 8). It is presently undergoing phase 2 clinical development for the treatment of uncomplicated malaria and has promising properties that indicate action against all parasitic blood stages. A lead-optimization procedure produced ciprogammin, a member of the spiroindolones. Spiroindolones are a unique class of new antimalarial drugs that work by upsetting the parasite's intracellular Na^+ homeostasis through

a mechanism that has not been used before. The molecule has an indolone ring that has been spiro-configured with another ring [41].

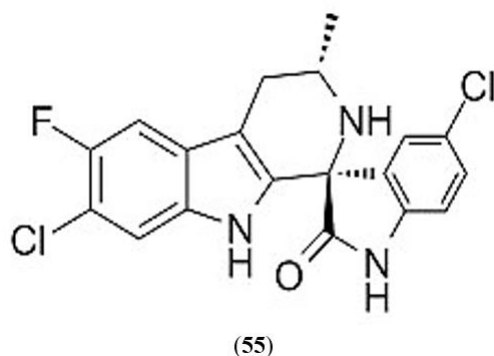


Figure 8: Chemical structure of Ciprogamin

Pipeline for antimalarial drug discovery

The pipeline for the discovery and development of antimalarial drugs is greatly aided by natural products (Figure 9) [41]. According to Siqueira-Neto *et al* [42], they offer a sustainable and renewable source of bioactive chemicals with a variety of chemical structures and modes of action. Utilizing the therapeutic potential of natural products offers a promising strategy for discovering new antimalarial agents, particularly in overcoming challenges such as drug resistance and toxicity associated with

conventional therapies. As illustrated in Figure 3, the antimalarial drug development pipeline follows a systematic process, starting with primary screening of natural compounds, followed by lead optimization, preclinical studies, and ultimately clinical trials and deployment [41-43]; this structured approach ensures the identification and advancement of safe, effective candidates for the treatment of malaria.

Mechanisms of action

Natural products with antimalarial activity exert their effects through various mechanisms, including inhibition of parasite growth, disruption of parasite metabolism, and modulation of host immune responses [43]. For example, artemisinin, derived from the plant *Artemisia annua*, disrupts the malaria parasite's cell cycle by targeting heme detoxification pathways.

Inhibition of parasite growth

One of the primary mechanisms by which natural products exert their antimalarial effects is by inhibiting the growth and replication of the malaria parasite [41]. This can occur through various molecular targets within the parasite, including enzymes involved in essential metabolic pathways, structural proteins, or organelles crucial for parasite survival.

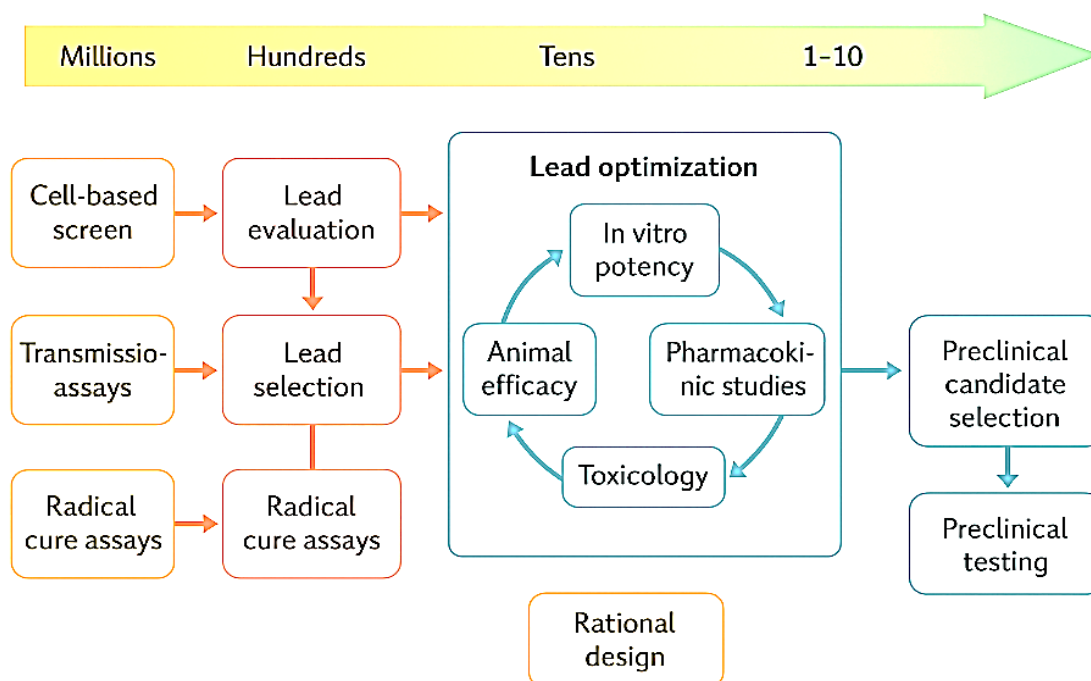


Figure 9: Pipeline of antimalarial evaluation and development

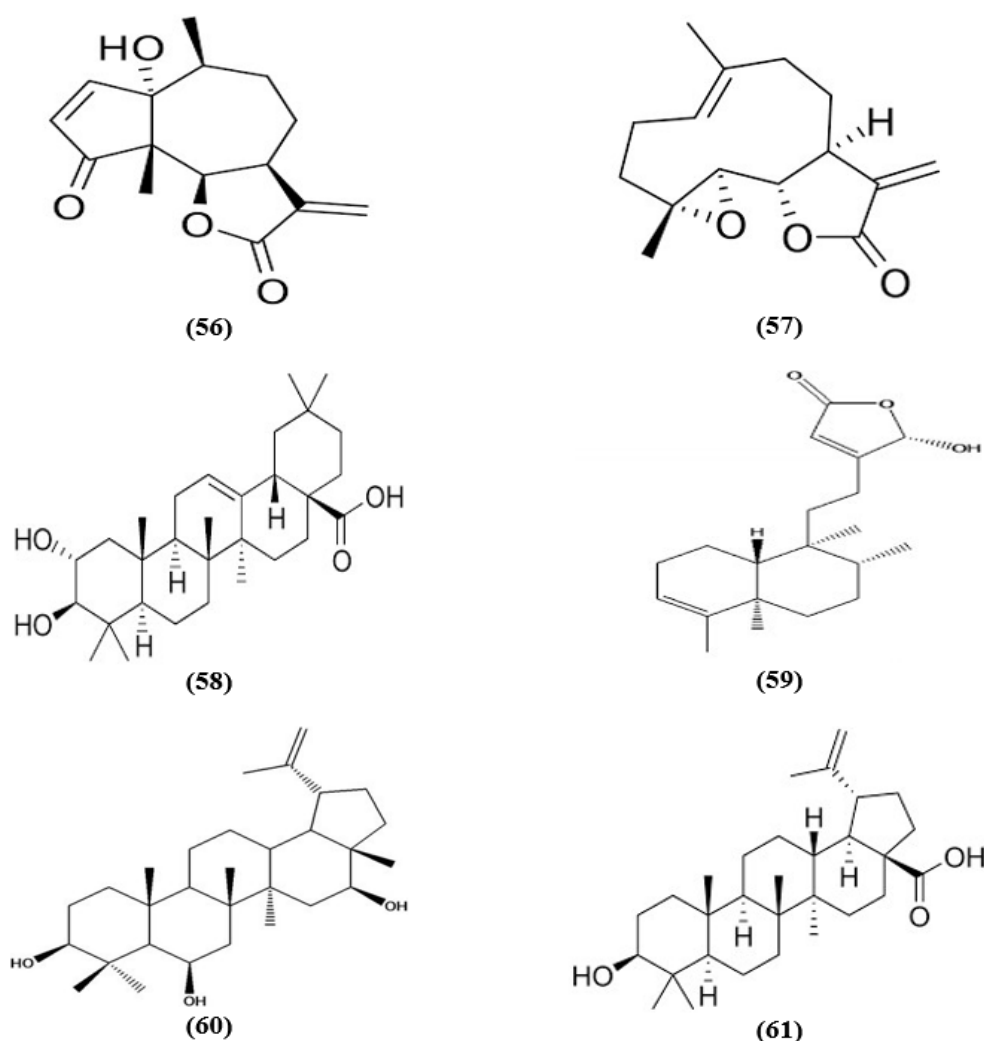


Figure 10: Antimalarial compounds that act by inhibiting the growth and replication of the malaria parasite

Natural compounds may disrupt key processes such as DNA replication, protein synthesis, or membrane integrity, ultimately leading to parasite death. The sesquiterpenoids, parthenin (**56**) and parthenolide (**57**) were reported to induce DNA damage in different life stages of *Plasmodium falciparum*. A triterpenoid, maslinic acid (**58**), inhibited DNA replication in the same parasite as assessed by a microfluorimetric DNA-based assay [44]. In another study, the sesquiterpenoid 16a-hydroxycyclohexa-3, 13(14) Z-dien-15, 16-olide (**59**) was shown to interact with recombinant leishmanial DNA-topoisomerase I leading to apoptosis. Similarly, interference with DNA metabolism may be insinuated for lupeol (**60**), betulin (**61**) and its derivatives possibly via inhibition of DNA-topoisomerase I (Figure 10). However, the evidence for this assertion was a result of an observation of the interaction of the compounds in *in silico* simulations or with a recombinant *Leishmania donovani* topoisomerase.

Disruption of parasite metabolism

The ability of malaria parasite to obtain nutrients, generate energy, or detoxify metabolic byproducts is disrupted by many natural products [43]. For instance, artemisinin and its derivatives target the heme detoxification pathway in *Plasmodium*-infected red blood cells, forming reactive intermediates called free radicals that alkylate heme molecules and produce cytotoxic compounds that kill the parasite. Other natural products may inhibit particular enzymes involved in glycolysis, nucleotide biosynthesis, or lipid metabolism, which further hinders the growth and survival of the parasite [43].

Modulation of host immune responses

Additionally, natural compounds can improve the body's ability to fight off the parasite by modifying the host's immune response to malaria infection [45]; this could entail triggering innate immune pathways, including the generation of pro-

inflammatory cytokines and chemokines, triggering natural killer cells and macrophages, or altering the function of antigen-presenting cells. Natural products aid in reducing the severity of sickness and controlling parasite burden by improving immune surveillance and activation. Furthermore, several natural substances have immunomodulatory qualities that help lessen the severe tissue damage and inflammation linked to severe malaria [45].

Induction of parasite death pathways

Certain natural products induce programmed cell death pathways (apoptosis) or other forms of cell death in the malaria parasite; this may involve the activation of signaling pathways that lead to mitochondrial dysfunction, caspase activation, DNA fragmentation, or membrane permeabilization [46]. Natural compounds promote the demise of the parasite while minimizing collateral damage to host cells by triggering intracellular signaling cascades.

Synergistic interactions

Natural products may exhibit synergistic interactions when used in combination with conventional antimalarial drugs or other natural compounds [43]. Synergy occurs when the combined effect of two or more compounds is greater than the sum of their individual effects. Synergistic combinations enhance the potency, efficacy, and durability of antimalarial treatment, overcome drug resistance, and reduce the likelihood of treatment failure. Identifying synergistic interactions between natural products and conventional drugs is a promising strategy for improving malaria treatment outcomes [43].

Combination therapies

Combination therapies, such as artemisinin-based combination therapies (ACTs), are commonly used as first-line treatments for malaria due to the emergence of drug-resistant strains of the disease [47]. Natural products are frequently used in combination with synthetic antimalarial drugs to increase efficacy, lower the risk of drug resistance, and mitigate side effects [47].

Bioavailability and pharmacokinetics

Despite their therapeutic potential, natural products often face challenges related to bioavailability, pharmacokinetics, and formulation. Efforts to improve the delivery and pharmacokinetic properties of natural compounds are essential for maximizing their

efficacy as antimalarial agents [48]. Nanotechnology-based approaches, encapsulation techniques, and prodrug strategies are being explored to address these challenges.

Natural products (such as antimalarial agents) often encounter limitations in bioavailability and pharmacokinetics, hindering their efficacy as therapeutic agents. These challenges include poor solubility, permeability, and stability, coupled with rapid metabolism and clearance. To address these issues, various strategies are being explored, including formulation approaches such as solid dispersion, lipid-based formulations, and cyclodextrin complexes, aiming to enhance solubility, stability, and absorption. Additionally, nanotechnology-based approaches like nanoparticulate systems offer promising avenues for encapsulating natural compounds and facilitating targeted delivery [48]. Pro-drug tactics can maximize pharmacokinetic characteristics, while encapsulation methods in biocompatible carriers can shield substances from deterioration and extend systemic circulation. Additionally, enhancer-based combination medicines offer chances to boost systemic exposure and absorption. These tactics seek to optimize the therapeutic potential of natural products in the fight against malaria through further research and innovation in medication delivery and formulation technology.

Sustainability and conservation

The sustainable utilization of natural resources for drug discovery is paramount for ensuring their long-term availability while safeguarding environmental integrity [49]. These imperatives underscore the need for ethical considerations, biodiversity conservation efforts, and the promotion of equitable access to medicinal plants. Ethical considerations encompass respect for indigenous knowledge, cultural traditions, and the rights of local communities involved in the collection and utilization of natural resources [49]. Biodiversity conservation efforts aim to preserve the rich biodiversity of ecosystems, recognizing the interconnectedness between medicinal plants and their habitats. Furthermore, promoting equitable access to medicinal plants involves addressing issues of intellectual property rights, benefit-sharing, and ensuring that local communities receive fair compensation for their contributions. Collaboration among scientists, local communities, and policymakers is essential to develop and implement sustainable practices in natural product-based drug discovery. This collaboration facilitates knowledge exchange, capacity building, and the development of

conservation strategies that balance the pursuit of therapeutic innovation with environmental and social responsibility. The continued availability of natural resources for future generations can be ensured by integrating sustainability principles into drug discovery programs, while supporting biodiversity conservation and respecting the rights and well-being of local communities.

Prospects

The future of green solutions in malaria treatment is highly promising, driven by advances in natural product-based drug discovery and interdisciplinary collaboration. Emerging technologies such as high-throughput screening, genomic sequencing, and bioinformatics are facilitating the identification of novel bioactive compounds from diverse natural sources, offering new therapeutic leads. Integrating sustainable practices into drug development is essential to preserve biodiversity and ensure equitable access to medicinal resources. This includes collaboration with local communities and policymakers to promote ethical sourcing and conservation.

Innovations in formulation science, including nanotechnology and targeted drug delivery systems, present opportunities to improve the bioavailability, stability, and efficacy of natural compounds. Furthermore, combining natural products with conventional antimalarials in multi-targeted therapies may help overcome drug resistance and enhance treatment outcomes. Overall, sustained research and responsible utilization of natural resources will be critical in advancing effective, sustainable strategies toward malaria control and eventual elimination.

CONCLUSION

The persistent global burden of malaria, along with the escalating issue of drug resistance, calls for a transition toward more sustainable and innovative therapeutic strategies. The exploration of green solutions for malaria through the therapeutic potential of natural products represents a promising frontier in antimalarial strategies. This review highlights the significant potential of natural products derived from plants, microorganisms, and marine organisms as promising sources for the development of next-generation antimalarial agents.

From both traditional knowledge and modern high-throughput screening methods, researchers have identified a wide variety of bioactive compounds, including terpenoids, alkaloids, flavonoids, and quinones, each demonstrating

distinct mechanisms of action against *Plasmodium* species. In addition, the adoption of green approaches such as eco-friendly mosquito control measures, the use of biopesticides, and the application of green chemistry in drug synthesis highlights the growing importance of environmentally responsible strategies in malaria control. Ultimately, a multidisciplinary approach that combines ethnopharmacological knowledge, modern scientific tools, and sustainability principles provides a comprehensive framework for malaria control. Continued investment in natural product-based research, coupled with ethical collaboration with indigenous communities, will be essential in the global effort to develop effective therapies while safeguarding biodiversity and promoting environmental stewardship.

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Use of Artificial intelligence/Large language models

The authors confirm that AI-based tools were used solely for language editing and manuscript polishing purposes (e.g., grammar, phrasing, and clarity). No AI tools were used to generate content, interpret data, or influence study design, results, or conclusions. All intellectual contributions, study analyses, and interpretations reported in the manuscript are the original work of the authors.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this

article will be borne by the authors. AJY: conceptualization, investigation, supervision, project administration, funding acquisition, writing-original draft preparation. AAU: methodology, data curation, formal analysis, writing-review and editing. COA: Validation, supervision, resources, visualization, writing-review and editing. KGI and FAG: formal analysis, visualization, writing-review and editing. JA and MS: data curation, visualization, formal analysis, writing-review and editing. JP: data curation, formal analysis, writing-review and editing.

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