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Antimalarial Medicinal Plants: Evidence and Gaps

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ABSTRACT

Malaria remains a global health burden, particularly in sub-Saharan Africa, where rising drug resistance and treatment costs necessitate alternative therapeutic strategies. Medicinal plants, long central to traditional medicine, represent a valuable reservoir of bioactive compounds with proven and potential antimalarial properties. Historically significant agents such as quinine (from *Cinchona* bark) and artemisinin (from *Artemisia annua*) highlight the enduring importance of plant-derived compounds in malaria chemotherapy. Ethnobotanical surveys across Africa and Asia document thousands of plant species used in malaria management, though only a fraction have been systematically investigated. Phytochemicals including alkaloids, flavonoids, terpenoids, and phenolics demonstrate significant in vitro and in vivo antiplasmodial activity, acting through diverse mechanisms such as inhibition of hemozoin formation, interference with parasite metabolism, and immunomodulation. Despite promising laboratory findings, translation into clinical application remains limited due to variability in plant sourcing, extraction methods, bioavailability, and lack of mechanistic and safety studies. Regulatory and standardization challenges further hinder phytomedicine development. This review synthesizes evidence on antimalarial medicinal plants, highlighting validated agents, mechanisms of action, clinical potential, and the research and regulatory gaps that must be addressed to advance phytochemical-based malaria therapeutics.

Keywords: Antimalarial plants**,** Phytochemicals**,** Plasmodium resistance**,** Ethnobotany, and Drug discovery.

INTRODUCTION

Malaria is a major global health challenge, particularly in sub-Saharan Africa, where it causes high mortality. The growing resistance of Plasmodium parasites to current drugs and the development of adverse effects have intensified the search for new and effective treatments. Herbal medicine, used throughout human history and still integral to primary healthcare in many African communities, presents a promising avenue for discovering antimalarial agents. Approximately 80% of the world's population relies on traditional medicine, many on medicinal plants that contain bioactive compounds capable of inhibiting parasite growth. Several key antimalarial drugs, including artemether, quinine, and halofantrine, have been derived from plants, underscoring their therapeutic potential. The leaves and bark of several medicinal plants commonly used for malaria treatment in Kenyan communities have demonstrated inhibitory effects on Plasmodium falciparum in vitro, in vivo antimalarial activity, and antiplasmodial effects against multidrug-resistant strains. In vitro studies using the chloroquine-sensitive Nigerian strain (3D7) have shown a concentration-dependent decrease in parasite growth with extracts such as Annona senegalensis. Various assays (e.g., 3D7 method, pLDH, HRP 2) assess antiplasmodial activity, while in vivo tests in mice infected with Plasmodium berghei evaluate parameters like parasitemia levels, survival time, and optimal dosing. Ethnobotanical reports identify a substantial number of plant species used traditionally to manage malaria and fever-related illnesses, yet many of these remain scientifically unexplored at the phytochemical and pharmacological levels. Investigating these plants offers a pathway to developing novel antimalarial phytochemicals, highlighting the importance both of validating traditional knowledge and of addressing existing gaps in scientific understanding [1].

Historical Context of Antimalarial Plants

Plants have historically been a vital source of drugs against malaria, predominantly in the form of plant extracts and isolated compounds. Quinine (from Cinchona bark) and artemisinin (from Artemisia annua) form the basis of malaria chemotherapy worldwide. Indeed, more recent artemisinin derivatives and clinically developed antimalarial compounds, all of which are related chemically to plant secondary metabolites, are in current use or active development [1]. Phytochemical groups such as alkaloids, flavonoids, and terpenoids (including the artemisinins) have been implicated as the most important sources of antiplasmodial activity. Plant extracts or isolated compounds exhibiting antiplasmodial activity in vitro typically also show antimalarial activity in vivo, when tested at appropriate dosages or concentrations [2]. Most medicinal plant species suggested as antimalarials have not been properly investigated, and detailed analyses of many others remain outstanding. Naturally occurring antiplasmodial compounds play an important role in plant defence, and the corresponding plants will likely prove to be effective antimalarials. Field studies also indicate that patients who consult herbalists commonly enjoy rapid recoveries [1, 2].

Current Antimalarial Drugs Derived from Plants

Several drugs currently used for malaria treatment have been isolated from plants or are directly derived from their natural products [3]. The acute febrile illness caused by protozoans of the genus Plasmodium presents a significant challenge, with about half of the world's population at risk of infection and approximately one to two million deaths annually, mostly children from Africa 4. Improvements in malaria control strategies initially led to a global reduction in burden, but these gains were stalled in 2014–2015; the widespread emergence of resistance to existing drugs further complicated the scenario [3].

Mechanisms of Action of Antimalarial Compounds

Extraction from the sponge Diacarnus megaspinorhabdosa yielded new norterpene cyclic peroxides with inhibitory activity against malaria parasite clones. With over 80% of the global population still reliant on ethnopharmacologic modalities, plants remain a major resource for treating malaria where health services are limited [1]. Documented ethnomedicinal use spans cultures worldwide. Artemisinin, from Artemisia annua, is the most widely used plant-derived antimalarial, with ethnomedical application tracing back two millennia. Treatment practices vary considerably by region, ethnicity, and disease severity, and numerous species have been documented for antimalarial activity and toxicity [1]. The ongoing emergence of drug resistance underscores the need for continued investigation of herbal antiplasmodials, as many phytochemicals possess significant in vitro activity against Plasmodium falciparum. The pharmacological evaluation of African medicinal plants identifies non-alkaloid and non-terpenoid compounds with potential antimalarial effects [4]. Atranorin, specicoside, homogentisic acid derivatives, muzanzagenin, and spiroconazole A exemplify chemically diverse constituents exhibiting remarkable activity in vitro. Attempts persist to develop effective treatments against resistant P. falciparum strains, guided increasingly by integrative approaches that combine green phytomedicines with computer-aided drug discovery techniques such as docking and virtual screening [3]. Owing to their wide-ranging bioactivity and prevalence, alkaloids, terpenoids, and flavonoids constitute the primary focus of screening efforts. They are renowned as profoundly bioactive plant metabolites.

Ethnobotanical Studies on Antimalarial Plants

Historical literature and ethnobotanical studies on primary human health care strongly suggest that approximately 80% of the world's population relies on plant-based medicines. The discovery of quinine and the isolation of artemisinin triggered the search for medicinal plants exhibiting antiplasmodial activity 2. Numerous plants and herbal remedies demonstrating in vitro and in vivo antimalarial activities have been reported from countries with a tradition of herbal medication, such as Ethiopia, Ghana, Kenya, Madagascar, Mali, Mauritania, Nigeria, and Tanzania. Several of these plants have undergone clinical testing [5]. Although research on antimalarial activity among medicinal plants from different regions of Ethiopia is underway [6], much remains to be explored. In Ethiopian culture, where the management of endemic public health problems involves orthodox treatment, traditional medicine, or both, many plants are used, and traditional knowledge has been passed down through oral tradition [5, 6].

Traditional Uses in Various Cultures

Antimalarial medicinal plants have been widely used as primary health care remedies in many developing countries, either singly or in combinations, to treat various malaria-related symptoms. Plant-based remedies occupy a special position because they are perceived to be cost-effective, less toxic, and locally available than current expensive synthetic drugs [2]. Uganda is one of the countries in Africa with a high burden of malaria that recognizes plants as alternative malaria treatment options. Moreover, the increasing resistance to the current effective treatment requires identifying new plant species with antimalarial activity. Artemisia annua L. (qīng hāo)

is a well-known and famous medicinal plant with effective antimalarial activity. It has a long history of over 2000 years in China for treating malaria, fever, headache, and shingles [2]. The extract of the leaves has been used as traditional medicine by the Langa community in Limpopo Province, South Africa [7]. Artemisinin is an effective antimalarial compound isolated from the herb. This compound has been the leading medicine for malaria treatment over the last 20 years due to widespread Plasmodium falciparum resistance against previously available drugs such as chloroquine and mefloquine. More specifically, the current medicine worldwide for the early treatment of uncomplicated malaria is artemisinin combination therapy (ACT). The effectiveness of the extract from the leaves for the treatment of uncomplicated malaria has also been demonstrated in a murine model [6]. Both in vivo and in vitro studies of antimalarial plants and ethnobotanical surveys among different communities in Kenya have also been documented. Most antimalarial plants used among the communities have also been studied scientifically and demonstrated promising results. It is therefore necessary to review plants that have traditionally been used in Uganda to treat malaria, as an initial step in the search for alternative antimalarial drugs [6, 7].

Documentation and Validation of Ethnobotanical Knowledge

The documentation and validation of ethnobotanical knowledge constitute a fundamental step in the drug discovery process; drugs that have a historical ethnobotanical basis, such as quinine, have an increased probability of success in the discovery of efficacious drugs [6]. Ethnobotanical claims must therefore be subjected to scientific scrutiny to assess their validity and establish a firm biological rationale. Literature review demonstrates that several of the traditional claims in ethnobotanical surveys have been validated by scientific experiments, while others call for further experimentation. Consequently, it is not surprising that the search for antiplasmodial drugs continues to be guided by ethnobotanical information [7].

Phytochemical Constituents of Antimalarial Plants

Many classes of secondary metabolites from medicinal plants demonstrate antimalarial activity against Plasmodium falciparum both in vitro and in animal models. Alkaloids constitute the major group of antimalarial compounds and include quinoline alkaloids, proven antimalarial agents that act directly on the parasite. Wormwood (Artemisia annua) provided sesquiterpene lactones such as artemisinin and its derivatives, now front-line antimalarials. Other important groups consist of flavonoids and terpenoids [1]. Additional chemical groups contribute to the plants' antimalarial activity: phenolics, glycosides, tannins, and essential oils, for example, 3. These substances may act independently or in concert with other compounds to inhibit the malaria parasite or regulate metabolites and cell receptors implicated in the disease process. Hence, the ethnomedical use of several species has attracted extensive research in recent years [1].

Alkaloids

Alkaloids are among the major active ingredients responsible for the antimalarial properties of plants. Representative alkaloids with significant antimalarial potential include quinine from Cinchona bark and ellipticine from Ochrosia elliptica Labill (O. elliptica). The increasing resistance to quinoline-type alkaloids has triggered a widespread search for novel antimalarial alkaloids containing different structural classes. Nitro-alkaloids such as nitidine and fagaronine have attracted attention due to their in vitro and in vivo chloroquine-like vitro activities and their efficacy against chloroquine-resistant strains [8]. Other classes of alkaloids reported in antimalarial plants include side chain alkaloids, N-containing heterocyclic alkaloids, and indole alkaloids. Although almost all possible alkaloid structural classes have been detected in such species, they are generally of minor importance. The sesquiterpene alkaloid furoquinoline is one of the exceptions and is well represented in a limited number of genera, including Acronychia, Evodia Schmidel (Evodia), and Ruta L. [2]. To date, no chloroquine-like activity has been demonstrated for furoquinolines, but a wide spectrum of biological activities has been recorded. Of particular relevance is sempervirine, an alkaloid present in medicinal plants traditionally used to treat malaria or malaria symptoms. Despite the well-documented antiplasmodial potential of alkaloids, few studies have investigated their modes of action. Some alkaloids have been reported to inhibit hemozoin formation, DNA, or protein biosynthesis [2, 8].

Flavonoids

Flavonoids represent a structurally diverse group of naturally occurring phenolic compounds characterized by a 15-carbon skeleton. While these compounds are widely recognized for antineoplastic and anti-inflammatory properties, emerging evidence indicates potential antimalarial activity [6, 9]. Several studies have assessed the inhibitory effects of common dietary flavonoids on the growth of two strains of the human malaria parasite Plasmodium falciparum, providing a foundation for further exploration of their therapeutic potential [9]. Although the evidence remains inconclusive, certain extracts appear to elicit clinical benefits against Plasmodium infections. The precise role of flavonoids in inhibiting parasite growth, either as direct mediators or synergistic enhancers of other active principles, warrants continuation of research efforts to resolve outstanding questions and enhance understanding of these mechanisms [6].

Terpenoids

Terpenoids constitute the largest group of secondary metabolites produced by many plant species 6. Terpenes are classified based on the number of linked isoprene C5 units: hemiterpenes (C5), monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), sesterterpenes (C25), triterpenes (C30), and tetraterpenes (C40). Terpenoids usually contain oxygen in the hydrocarbon skeleton; otherwise, they are referred to as terpenes [5]. To date, more than 55,000 terpenoids are known in nature, and they constitute the largest and most diverse class of natural products, with roles including plant hormones, pigments, modulators, and allelochemicals. Terpenoids are widespread in medicinal plants, both as bioactive principles and as starting materials for semi-synthesis of medicinal compounds. Many terpenoids display a wide range of pharmacological and biological properties, such as antiplasmodial, antitumoral, and anti-inflammatory activities [6].

In Vitro Studies of Antimalarial Activity

Plant extracts and isolated compounds have been evaluated for antimalarial effects against Plasmodium falciparum using in vitro techniques. Rapid and high-throughput fluorescent methods allow screening large numbers of samples for antimalarial activity [1]. In vitro analyses are vital for identifying and characterizing the antiplasmodial efficacy of plant-derived substances. Cultures of human malaria parasites in vitro facilitate measurement of antimalarial activity and enable detailed investigation of potential inhibitors [5]. Herbal preparations and phytochemicals are usually tested at various concentrations, covering the plant material and process parameters iteratively to obtain data comparable to conventional medicines. Quantitative information is also required to enable the most suitable candidates to be selected for further investigation [[1].

Cell Culture Techniques

Cell culture techniques are simple, inexpensive, and faster methods for investigating the antimalarial activity of medicinal plants 6. During such studies, strains of Plasmodium falciparum are cultivated in human erythrocytes suspended in RPMI-1640 medium. After adding various plant extracts to the erythrocytes, the degree of parasite growth or inactivation caused by the drugs is measured [1]. Different antimalarial assessment methods are applied for this purpose: the schizont maturation inhibition assay, [3H]hypoxanthine incorporation assay, parasite lactate dehydrogenase assay, and the parasite histidine-rich protein II (HRP-II) assay [5].

Antiplasmodial Activity Assessment

The evaluation of antiplasmodial activity from plants includes various in vitro models designed to identify candidates for in vivo experimentation. In vitro studies combine plant-derived substances with cultured Plasmodium species, allowing observation of parasite growth in the presence of these compounds [10]. Both the polar and non-polar fractions of medicinal plants have been examined using such in vitro methods. Employing the same extract for in vitro and in vivo procedures facilitates the determination of total activity and guides the isolation of active constituents [10]. Malaria poses widespread public health challenges, particularly in developing countries with limited access to antimalarial drugs. Following the initial characterization of quinine's antiplasmodial activity by Pelletier and Caventou in 1820, several plant-derived antimalarial compounds were isolated and commercialized, including quinine and artemisinin [6]. Ethnobotanical surveys record the use of thousands of plant species as antimalarials, though only a fraction have undergone pharmacological or clinical investigation. Of these, merely a few have progressed through clinical trials and received regulatory approval as standardized antimalarials. Consequently, the biological validation and pharmaceutical development of these plants necessitate extensive in vivo laboratory evaluations [6]. Besides in vitro models, in vivo experiments constitute a fundamental approach for screening the antimalarial potential of medicinal plants. Compared to cell cultures, estimating the activity of uncharacterized new compounds or crude plant extracts is more efficient in living parasites. In vivo methods encompass both prophylactic and curative protocols, each characterized according to antimalarial efficacy. Parameters such as percentage suppression, growth inhibition, and average survival time are measured to derive dose-dependent relationships. Commonly utilized rodent parasites include Plasmodium berghei, Plasmodium yoelli, Plasmodium chabaudi, and Plasmodium vinckei. Model selection depends on factors such as study duration, feasibility, and dose administration route. When these considerations are addressed, the 4-day suppressive test with P. berghei remains the most recognized and widely adopted in vivo rodent model [6, 10].

In Vivo Studies of Antimalarial Efficacy

Animal models are the starting point for in vivo evaluation of antimalarial activity, providing data on crude extract dosing levels, treatment schedules, and product safety. Frequently employed models include those based on rodent malaria parasites such as Plasmodium berghei, P. yoelii, P. chabaudi, and the simian parasite P. falciparum, with the P. berghei model historically the most popular [6]. Supplementary models exist, including humanized mouse models infected with P. falciparum and P. vivax and non-human primates. A variety of dosing

protocols and exposure durations are applied in vivo, most commonly a 4-day regimen with oral or intraperitoneal administration [6].

Animal Models for Testing

Animal models and clinical trials are also important for demonstrating the effectiveness of antimalarial pharmaceutical agents and medicinal plants as a preliminary step before administration in patients [11]. Studies of malaria in human beings are highly desirable but are often limited by restricted access to relevant tissues, the inability to manipulate the immune status, and the lack of a well-defined infection, such as primary or secondary. Experimental animal models are therefore essential for testing specific hypotheses, especially when human samples are unavailable or the removal of samples is not possible [11]. Funding is also needed to establish human sample repositories with well-annotated clinical samples to confirm or validate findings discovered in animal models. Although tightly controlled experimental infection of human individuals remains an important model, closer collaboration between scientists working on human malaria and those investigating animal models is necessary to determine which models most accurately represent different aspects of human infection. Antimalarial plants are usually tested using different animal models of Plasmodium infection such as the infected-mouse model, which is based on parasitaemia monitoring. These models are commonly used with regard to the antimalarial activity of pharmaceutical products for dose selection before clinical testing [11]. The search for active compounds or extracts demonstrating antimalarial activity is mainly carried out using the Plasmodium berghei-infected mouse model. Today, a representative of human malaria parasites is propagated in immunodeficient mice injected with human erythrocytes, adding a new model to the possibilities of investigations [11].

Dosing Regimens and Results

The efficacy of crude plant extracts against rodent malaria has led to a widely adopted experimental procedure for determining the optimal dosage and evaluating antimalarial activity in vivo [12]. Various plant parts can be extracted using solvents such as water, methanol, ethanol, chloroform, n-hexane, ethyl acetate, and petroleum ether. Therapeutic effects are then examined on infected laboratory mice to determine crucial parameters, including a suitable dosage that exceeds the minimum effective level, the administration route, and the treatment frequency [12]. Typically, dosage comparisons between certain plant extracts and standard drugs employ either the 4-day suppressive test, also known as Peter's test, for early and established infections or the curative test, known as Rane's test, for curative evaluation [6]. The suppressive test involves challenging mice with an inoculum containing standard quantities of P. berghei, followed by the administration of crude extracts or drugs orally once daily over four days, commencing three hours post-infection. At the conclusion of the fourth day (120 hours post-infection), parasitaemia levels are assessed; the percentage of suppression relative to negative controls is reported. Animals alive on the fifth day proceed to the curative assessment by receiving treatments for an additional five days, with parasitaemia monitored daily to gauge curative potential [6, 12].

Clinical Trials of Plant-Derived Antimalarials

Clinical trials represent the ultimate step in translating in vitro and in vivo research into approved drugs. Clinical trials range from early phase I safety and dose-finding studies to phase II-III efficacy and effectiveness studies, followed by phase IV post-marketing studies on treatment benefits and adverse effects [6]. While virtually all well-known antimalarial drugs have natural origins, plant-derived drugs have undergone very few clinical trials. Physicians and the public have shown interest in antimalarial plants in recent years, stimulated by reports of widespread resistance to antimalarial drugs, resulting in increased pressure to identify new antimalarial leads. The literature contains a wealth of studies on plants for malaria, some of which have already received clinical trial status [6]. Many plants can be administered as infusions, extracts, or powders, which offer a valuable alternative for malaria control, particularly in poor rural areas where access to treatment is difficult. Dried leaves can be actively stored for several months and therefore serve as a "dry-season medicine". Health personnel in rural areas can be quickly trained to prepare new remedies [6].

Phases of Clinical Trials

The human species has used medicinal plants to combat diseases across diverse cultures and regions since antiquity. Despite targeted eradication strategies, malaria persists as a leading global health challenge, necessitating exploration of safer and more effective agents [6]. Single-chemical antimalarial drugs exploit synergistic mechanisms by combining active phytochemicals from varying sources; however, the ability of these compounds to generate therapeutic blood concentrations remains unclear, hindering development. Plants with documented ethnomedical antimalarial credentials, yet lacking formal investigations, present promising avenues for clinical study [6]. Medicinal plants provide an economically viable strategy to combat emerging drug resistance and achieve large-scale malaria treatment coverage. In vitro and in vivo assays assess antiplasmodial activity, serving as preliminary indicators of antimalarial potential before clinical trials. Approximately 80% of

people in developing countries depend on traditional medicines for primary healthcare [6]. The World Health Organization promotes phytopharmaceuticals as complementary or alternative treatments in malaria control programmes. Pharmacinspector, a software tool, forecasts the likelihood of a compound becoming a successful drug with 95% accuracy by evaluating satisfactory ranges of phytochemical parameters." The mechanism of action of phytochemicals enables the development of efficient drugs compared to synthetic compounds, whose side effects remain a subject of investigation 6. Methods include: (i) schizonticide or blood schizontocidal, affecting the asexual blood stage; (ii) tissue schizonticide for the asexual exo-erythrocytic stage; (iii) gametocide acting on sexual erythrocytic stages, preventing fertilization; (iv) sporontocide influencing forms in the insect vector; (v) hypnozoitocide acting on dormant liver-stage parasites; and (vi) indirect action involving mechanisms such as immunomodulation [6].

Regulatory Challenges

The regulatory landscape for herbal medicines presents a complex array of challenges. National policies regarding herbal drugs often lack the infrastructural support necessary for effective administration, collaboration, and regulation, leading to gaps in the pharmaceutical industry that increase the likelihood of adverse reactions [6]. Around the 1990s, the Philippines sought to enhance the regulation of herbal medicines, yet stringent requirements imposed by the Food and Drug Administration (FDA) rendered compliance difficult, resulting in a mere handful of approved herbal drugs. Subsequently, the FDA issued a draft implementing rule on herbal drug registration; however, even this adaptation imposed burdensome demands that many Philippine herbal drug manufacturers were ill-equipped to satisfy [6]. Recognizing these obstacles, the Department of Health explored the adoption of complementary regulatory frameworks, notably the European Union's (EU) two-tiered approach to traditional herbal medicines. This EU model combines a simplified registration procedure with GMP-related quality controls, facilitating market access while maintaining safety standards. Nevertheless, the absence of a comprehensive regulatory framework specifically tailored to the Philippine context remains a significant impediment to the development and registration of phytomedicines [6].

Challenges in Researching Antimalarial Plants

Species source and extraction methods require standardization in antimalarial research. Practitioners enforcing remedies often use multiple herbs and extracts simultaneously because of communication gaps between traditional healers and scientific researchers, leading to inconsistent practices. The selection of plant parts and extraction solvents varies widely; the majority of ethnomedicinal reports lack disclosure of preparation details, hindering the reproduction of results. Post-preparation, extracts are dried using several methods (air, oven, and oven-air) and stored before evaluation, introducing further variability [7]. In vivo studies commonly employ rodents (murine and non-human primate models) infected with asexual-stage Plasmodium parasites to test the antimalarial activity of candidate plants [6, 13]. The widespread impact of infectious disease necessitates the control of pathogenic microorganisms. Bioactive molecules of plant origin with antimicrobial properties bear positive implications for combating infectious illness. The prophylactic or malarial control properties of plants remain unexploited for the benefit of humanity. Information on a range of medicinal plants illustrates the current extent of knowledge and knowledge gaps [7]. It is expected that this will provide the foundation for future development of medicinal plant-based antimalarials because new classes of malaria-fighting drugs play a significant role in overcoming resistant species of Plasmodium. The need for new drugs is urgent to avoid worldwide health implications and potential death. A variety of plants with proven antimalarial potential offers a sustainable route for the discovery of novel drugs. Improvements in technique for compound extraction and compound identification promise a revolution in traditional medicine. In addition to the above factors, competition for wild resources is the main reason why such plants cannot be developed effectively. Future research should focus on the isolation, characterization, and elucidation of the mechanism of antimalarial action of the bioactive compounds from these species [6, 13].

Standardization of Extracts

Extract standardization is critical to guarantee consistent and reproducible pharmaceutical quality of herbal medicines. The most common methods involve quantification of marker compounds using chromatographic and/or spectroscopic procedures. Significantly fewer articles provide reference ranges for marker compounds, posing a limitation for quality control and comparison of efficacy among different batches of extracts [6]. Nevertheless, standardization procedures represent essential contributions to guarantee worldwide access to reliable phytomedicines. Optimal extract standardization techniques should be selected according to the availability of equipment and specific requirements of the intended use; parameters such as dosage, preparation, harvesting time, and geographical source should also be considered [6]. Source materials comprising antimalarial preparations have been reported to include fresh and dry plant parts of the whole plant, leaves, roots, seeds, gels, and rhizomes. The precise source for acquiring the plant parts has rarely been mentioned in publications [6].

Variability in Plant Sources

Antimalarial medicinal plants are a valuable source of new antimalarial compounds, and the most widely used plants are well known to have these properties. Knowledge gaps exist in the understanding of less-studied plants and their mechanisms of action. The World Health Organization recommends the use of plant-based antimalarials through the second-class category. Variability in the sources of plants used for antimalarial studies adds complexity to the evaluation of these plants [7]. Over the past 30 years, ethnobotanical studies have increased considerably, documenting plants used against fever, malaria, and mosquito bites. Plant constituents (alkaloids, flavonoids, and terpenoids) often provide a starting point for understanding the mechanisms of an antimalarial agent. Extraction methods can influence the compounds present; e.g., water extractions are rich in tannins, while alcohol extractions yield terpenoids and alkaloids, affecting activities such as gametocidal properties and schizonticidal action [7]. There is ongoing debate about the origin of some medicinal plants, whether cultivated or wild, and a lack of information on the quantities used for treatment. A small number of plants dominate usage, often consumed as aqueous extracts in infusion or decoction form. Water-extracted compounds have shown considerable antiplasmodial activity [7].

Gaps in Current Knowledge

Despite growing interest in antimalarial plant research, significant gaps persist. Many plant species with ethnomedical records remain poorly studied [2]. The mechanisms of action of many antimalarial compounds remain unclear. Chemical compounds in plants often vary with geographic location and climatic conditions, making standardization difficult [2, 13].

Understudied Species

A substantial proportion of taxonomically identified plant species with documented traditional use against malaria remains unexamined. [2], Note that few of the approximately 1,200 plant species about genera widespread in tropical regions have been put under the lens of antimalarial activity. Similar lacunae pervade the considerable body of ethnomedical evidence compiled by the WHO, which cites fewer than 2,000 plant species globally as traditionally deployed against malaria, reflecting just a fraction of putative antimalarial herbs mentioned in ethnomedicine [6]. Where candidate plants within these inventories have been subjected to in vitro or in vivo scrutiny, their active compounds frequently elude unequivocal characterization; even when characterization succeeds, their precise modes of action are often conjectured by analogy with well-established antimalarial drugs that have rarely been subjected to rigorous experimental validation [2, 6]. These deficits curtail the translation of botanical leads into pharmacological interventions.

Lack of Mechanistic Studies

The majority of these plants have not been subjected to research delineating their mechanism of action [6]. Worldwide, a substantial number of plants are utilised for their antimalarial properties; however, there remains an evident and considerable absence of systematic evaluation to determine the precise mechanisms through which these plants exert their antiplasmodial effects [6]. Malaria, a parasitic disease of enduring global significance, continues to cause high mortality rates, predominantly in Africa and parts of Asia, underscoring the necessity of verifying and elucidating the antimalarial potential of various plants within these regions [6].

Future Directions in Antimalarial Plant Research

Plant species have been used for centuries as alternative therapies or sources of ingredients for the development of pharmaceutical drugs. However, to date, relatively few plant species have been investigated scientifically for their pharmacological activity and chemical constituents [3]. Advances in technology have created new opportunities for monetizing and advancing research on natural products in order to develop new antimalarial agents. Applications such as high-throughput screening, combinatorial chemistry, rational drug design, molecular modeling, and analytical techniques could be applied to the discovery of new antimalarial agents and facilitate studies related to activity, safety, and drug formulation [3]. Moreover, the integration of ethnomedicinal adaptive knowledge with global strategies for drug development could expedite and link the process of developing diagnostic tools, surveys, and drug resistance strategies with advances in natural medicine research and development [3]. The continued interactions of collaborating research institutions on venoms and natural product resources may lead to opportunities for supplementation of conventional antimalarial therapies through novel treatment avenues, which may ultimately result in new-generation antimalarial drugs [3].

Integrating Modern Techniques

The practical value of traditional medicine depends largely on good methods of quality assurance and quality control. Modern scientific techniques should be integrated where applicable. A new generation of technologies is needed that would enable the production of better herbal medicines incorporating a knowledge of manufacturing procedures and controls [3]. Collaborative research involving traditional healers and scientists from various disciplines is likely to generate innovative models for providing modern health care that are affordable, accessible,

and culturally acceptable [3]. Artemisia annua and Cinchona bark are two of the most important antimalarial plants in modern medicine. Both provided compounds whose synthetic derivatives continue to play a major role in combating the disease. Studies of plants with a claimed antimalarial use present an opportunity for the generation of data to support their potential use by traditional health practitioners [3]. Imparting knowledge of antimalarial plants is critical in communities without access to adequate health care, and in those where the prevalence of drug-resistant malaria is increasing [6].

Collaborative Research Initiatives

Initiated in 1999, the Research Initiative on Traditional Anti-malarial Methods (RITAM) has consolidated knowledge on traditional antimalarial approaches, identified research priorities, devised optimal methodologies, and prevented redundant investigations [14]. The Alliance for Biodiversity maintains a database encompassing over 1,300 species of plants reputed to have antimalarial activity [14]. Collaboration among ethnobotanists, ethnopharmacologists, and the global pharmacological research community is essential to translate traditional knowledge into clinically viable medicines [6]. Whatever the scale or form, such phytopharmaceutical factories are likely to have wide economic and social impacts on the producing regions [14].

Implications for Public Health

By 2016, plant-derived antimalarials represented 34% of all drugs in clinical use and 44% of those of natural origin [2]. The affordability and widespread availability of medicinal plants create opportunities to improve conditions and reduce the costs associated with accessing antimalarial treatments [6]. Another potential impact concerns public health and educational outreach in tropical zones. Research activities can increase knowledge and scientific interest, enabling students and the general population to build confidence in the public health system. Current challenges include many species studied only in vitro or in mixed extracts, whose specific activity must be confirmed [2]. This difficulty is greater for numerous species identified by ethnomedicine but lacking systematic screening due to factors such as political instability, financial constraints, or during ongoing epidemics.

Access to Herbal Medicines

The access to herbal medicines remains a significant consideration in both resource-limited and developed countries [6]. Malaria is a disease of poverty, often without access to adequate health-care services, but it also affects developed countries with a high population of immigrants. Many of the existing antimalarial drugs used to treat chloroquine-resistant Plasmodium falciparum malaria are derived from medicinal plants. The need for new malaria treatments is more urgent than ever with the emergence of artemisinin and multidrug resistance. Well over 1200 plants have been described with antimalarial activity through ethnobotanical studies conducted across malaria-endemic regions [6]. A significant proportion of these plants have been subjected to scrutiny since the isolation of the active ingredient; lead optimisation and synthetic works are central to current investigations. It is important to re-evaluate plant extracts such as Artemisia annua L. (Asteraceae) for potential clinical treatment of malaria in a setting that is relevant at the start of the 21st century. Plant remedies remain a valuable source for the development of new antimalarial drugs under the framework of current biological tests [6].

Education and Awareness

Within endemic malaria regions, the availability and affordability of current antimalarial drugs diminish considerably. As a result, reliance upon traditional medicine, steeped in cultural customs and practices, remains paramount [2]. Malaria also threatens military personnel traveling to or stationed within endemic areas. During international missions, such as United Nations peacekeeping, a lack of access to regular supplies of anti-malaria pharmaceuticals frequently increases the distribution of traditional medicines among these groups [2]. Given the complexities inherent in modern antimalarial drug synthesis, such plants serve as valuable basic resources for drug preparation or development. Nonetheless, limited knowledge, particularly regarding plants not yet subjected to scientific evaluation, perpetuates continued reliance on traditional remedies [2]. Furthermore, the inaccessibility of information concerning proper dosages impedes effective delivery of preventative care or treatment in endemic regions. Education, therefore, constitutes a fundamental pillar in awareness campaigns and efforts to empower local communities to manage pandemics. As a global public-health concern, appropriate attention must consequently focus upon a comprehensive understanding of local conditions, involving multiple stakeholders in addressing pertinent challenges [2]. This awareness further informs strategies utilized by health practitioners operating within these endemic regions. Antimalarial education programmes remain an essential endeavour to curb the development of harmful diseases worldwide and contribute significantly towards improving communal resilience across the globe [6]. Nonetheless, disparities exist with respect to the accessibility and application of antimalarial information. Developing nations habitually suffer from severe deficiencies in available material resources required to undertake educational initiatives, thereby limiting production and distributional capacities [2, 6].

Regulatory and Ethical Considerations

The application of medicinal plants in malaria control raises challenges related to commercial exploitation, intellectual property rights, and the protection of indigenous knowledge [6]. Market demand for antimalarial products sourced from particular plants in limited habitats can compromise natural availability and threaten the survival of these plants. Unregulated harvesting from the wild can lead to the overexploitation and extinction of these valuable resources, with consequences for cultural continuity and ecological balance. Sustainable cultivation and stewardship of antimalarial plants are therefore important strategies to ensure future access and conservation [6].

Intellectual Property Issues

The intellectual property dimension is a major issue that arises within the context of the research. In many Indigenous societies, traditional knowledge, including knowledge related to biodiversity, culinary practices, medicines, and health sciences, is an important part of their cultures and traditional heritage and is passed down, often orally, from generation to generation [6]. Indigenous or traditional knowledge is generally acquired or disclosed through unwritten custom and practice, informed by existing social, cultural, spiritual, or environmental values, and often forms part of the customary laws and practices that govern societies [6]. Within the context of research related to the evaluation of medicinal plants, it is paramount that the principles and customary laws that govern, control, and protect access to such traditional medicinal knowledge are respected. Research must still take place, but obtaining prior informed consent of local custodians or holders of traditional knowledge before commencing should be a first step toward facilitating research and ensuring mutually beneficial outcomes [15]. Moreover, it is useful to have a peer-reviewed standard that encourages international research collaboration and facilitates reporting of the research approach and results, on the one hand, and the ethical and legal approach to indigenous knowledge, on the other. To help address the matter of access and benefit sharing, the World Intellectual Property Organization (WIPO) is currently dedicated to fostering and promoting an effective international intellectual property system that balances the interests of rights holders with the wider public interest. Its objectives include promoting creativity and innovation for the economic, social, and cultural development of all countries, particularly developing countries [6, 15].

Ethical Harvesting Practices

As malaria continues to affect millions, traditional medicines derived from plants remain critical worldwide. However, there are legal and ethical concerns regarding the commercialization of some medicinal plants. Unauthorized human activity and over-collection of certain species threaten delicate forest ecosystems and the recirculation of organic materials [2, 6]. Major concerns have arisen about the sustainability of harvesting certain important antimalarial species like Prunus africana (sasafrasa or red stinkwood): widespread collection of its bark (often done destructively) is leading to dramatic population declines in many countries [6]. A need to devise methods of harvesting the bark sustainably is evident, and the Crown Land Forestry Department of Ghana has imposed certain sanctions on the extraction of Prunus africana bark to curb the damage. The collection and trafficking of medicinal plants often occurs illegally, in contravention of official legislation. The development and implementation of appropriate management practices are needed for the sustainable harvest of many important medicinal plants. Development projects and land clearance will also have an impact on naturally occurring medicinal plants [2].

Case Studies of Successful Antimalarial Plants

Two prominent examples emphasize the potential and practicality of medicinal plants as sources of antimalarial drugs. Artemisinin, obtained from Artemisia annua (sweet wormwood), represents a cornerstone of modern antimalarial therapy [7]. Artemisinin-based compounds rapidly clear parasitaemia and form the basis of combination therapies that constitute the current global standard. Likewise, drugs derived from cinchona bark (notably quinine and related compounds) have historical and ongoing importance in malaria control [2]. Extracts have served as precursors for the synthesis of many synthetic and semi-synthetic molecules, effectively bridging traditional and modern approaches [7].

Artemisia annua

Artemisia annua is one of the most widely known antimalarial herb species, and nonmolecular aspects associated with its medicinal use, such as permeability through the duodenal wall, clinical drug response, metabolic activity, and safety of administration, are well-established [16]. High antiplasmodial potency is evidenced by the green extract components, the ability to consistently develop candidate molecules in a lead optimisation program, and a wide range of purchased accessions essential for regional drug development [16].

Cinchona bark

The Peruvian bark of Cinchona was introduced into France in 1640, and the active components were purified at the end of the 19th century. Quinine is a diastereomer of quinidine with the same alkaloid formula ($C_{20}H_{24}N_2O_2$).

These two isomers and their derivatives, including mefloquine, are among the most effective antimalarial drugs 6. Artemisia annua and Cinchona bark are perhaps the only two plants with clearly established efficacy against malaria in a clinical setting [16]. The Peruvian bark of Cinchona was introduced into France in 1640, and the active components were purified at the end of the 19th century. Quinine is a diastereomer of quinidine with the same alkaloid formula (C20H24N2O2). These two isomers and their derivatives, including mefloquine, are among the most effective antimalarial drugs. Artemisia annua and Cinchona bark are perhaps the only two plants with clearly established efficacy against malaria in a clinical setting [16].

CONCLUSION

Medicinal plants continue to play a pivotal role in the fight against malaria, offering both historical precedents and future promise in the discovery of novel antimalarial agents. Landmark compounds such as quinine and artemisinin demonstrate the therapeutic value of ethnobotanical knowledge and plant-derived phytochemicals. Contemporary research has identified diverse secondary metabolites, particularly alkaloids, flavonoids, and terpenoids, with significant in vitro and in vivo activity against *Plasmodium* species, including resistant strains. However, critical gaps persist: most ethnomedicinally cited species remain uninvestigated, mechanisms of action are poorly understood, and standardization of extracts is inconsistent. Regulatory frameworks are fragmented, limiting the translation of traditional knowledge into evidence-based phytomedicines. Advances in high-throughput screening, molecular docking, and integrative research initiatives such as RITAM provide new opportunities to bridge these gaps. Collaborative efforts among ethnobotanists, pharmacologists, and regulatory bodies are essential to validate efficacy, ensure safety, and promote quality control. By uniting traditional knowledge with modern scientific approaches, medicinal plants can serve as affordable, accessible, and sustainable resources for combating malaria and overcoming the challenge of drug resistance.

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