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Investigating the Pharmacological Mechanisms of Antimalarial Plants

Asiimawe Masika Agnovia

Department of Clinical Medicine and Dentistry Kampala International University Uganda
Email: agnovia.asiimawe@studwc.kiu.ac.ug

ABSTRACT

The global burden of malaria, especially from *Plasmodium falciparum*, underscores the urgent need for effective, affordable, and accessible treatments. Traditional medicinal plants have long served as a primary health resource in malaria-endemic regions, offering bioactive compounds with significant therapeutic potential. This study investigates the pharmacological mechanisms of antimalarial plants, emphasizing the isolation, characterization, and biological action of plant-derived compounds. Drawing upon both ethno botanical knowledge and modern pharmacological methodologies, it explores how these natural agents affect the parasite's lifecycle by targeting heme detoxification, protein kinases, mitochondrial electron transport, and biosynthetic pathways. Phytochemical analyses and in vitro/in vivo assays are reviewed to highlight their efficacy and safety profiles. Additionally, the paper discusses synergistic interactions with existing antimalarial drugs, isolation techniques, and the translational challenges from bench to bedside. By bridging traditional medicine and modern drug discovery, this research provides a foundation for the development of novel, plant-based antimalarial therapeutics with multi-target efficacy.

Keywords: Antimalarial plants, *Plasmodium falciparum*, phytochemicals, heme detoxification, drug resistance, ethnopharmacology, bioassay-guided isolation.

INTRODUCTION

Malaria is a fever produced by the parasite's release of toxins into the blood. There are 4 types of parasite causing malaria including P. falciparum (PF), P. vivax (PV), P. malarie (PM), and P. ovale (PO). PF is the most serious one, which can fastly infect red blood cells and kill patients. Therefore, it is urgent to find effective and cheap anti-PF medicines. Plant extracts are a good resource for drug discovery. Medicinal plants had been widely used in rural areas for chronic diseases. Currently, the development of modern pharmacology provides opportunities to identify bioactive compounds from medicinal plants. In addition, there are further demands of cheaper medicines for malaria treatment, because existing medicines, especially artemisinin derivatives, are very expensive, causing a high burden to malaria-endemic areas. Plants as primary sources of new lead compounds since ancient times. Some significant drug discoveries from natural products include nicoumalone, vincristine, paclitaxel, and artemisinin. Several medicinal plants are also reported to have anti-malaria effects such as A. annua, Bird pepper, Gardenia fruit, and Bidens pilosa. Therefore, the exploration of more anti-malaria plants is expected to find new lead compounds. Medicinal plants with folklore reputation for the treatment of malaria are listed in the NAPRALERT database. The plants are transsected into 52 genera. Plasmodium falciparum (Pf) is the most deadly malaria parasite in humans. Pf strain 3D7 is widely used for antimalarial pharmacological activity evaluation. A fetal bovine serum (FBS) red blood cell (RBC) system was established to culture and proliferate 3D7. The average proliferation rate is about 4.2% per day. The IC50 of the reference drug chloroquine (CQ) against the Pf strain 3D7 within 72 h was at 0.049 μM, while the coefficient of variation (CV) was 10.36%. The results suggested that this approach could be a good platform for the screening of antimalarial medicinal plants [1, 2].

Historical Context of Antimalarial Research

Malaria, prevalent in tropical and subtropical regions, causes approximately 27 million infections and over 619,000 deaths annually. Current treatments involve semi-synthetic or synthetic drugs, but emerging resistance of Plasmodium raises concerns about their long-term efficacy. This has led to investigating natural antimalarial products, as traditional societies have long utilized plant extracts to combat fevers. Consequently, the number of studies on plant-based malarial treatments has surged, particularly in journals focused on pharmacology and ethnomedicine. Research initially targeted non-alkaloidal, non-glycosidic plants using bioassay-guided methods, gradually shifting toward isolating active metabolites. However, many aspects of these plant remedies' bioactivity remain underexplored. Despite numerous reports on traditional plant usage for malaria, few have undergone thorough safety and efficacy testing. Clinical studies predominantly examine pure compounds with singular actions, while many medicinal plants contain diverse chemical mixtures that affect various biological targets. Additionally, effective natural compounds against malaria in livestock, insects, or humans often differ from those found in medicinal plants. Efforts to eliminate larvacidal plants may worsen transmission, and alternative botanical solutions, like fermented fruit as toxic bait, are seldom considered. Crude plant extracts frequently demonstrate greater effectiveness than isolated components against various organisms, with antimalarial activity in Plasmodium emerging from combined multi-target actions [3, 4].

Phytochemical Components of Antimalarial Plants

Antimalarial medicinal plants are crucial for ethnopharmacology, with numerous indigenous species exhibiting antimalarial properties. This work focuses on plants with confirmed in vivo effects, highlighting their potential as sources of bioactive compounds with unique mechanisms for drug discovery. These compounds are also significant for chemical ecology and understanding plant or insect diversification. Literature indicates that various known and novel antiplasmodial metabolites can be isolated from these plants, often serving as lead compounds for structure-activity relationship studies or synthetic biology applications. Tropical rainforest plants represent a largely untapped resource for developing antimalarial compounds with innovative mechanisms. Furthermore, many isolated metabolites are toxic to fungi, bacteria, or insects, suggesting potential uses as agrochemicals or bioherbicides. The antimalarial efficacy of plant extracts and metabolites was assessed using standard phenotypic assays, producing IC50 values against P. falciparum strains. Standardized plant extracts, prepared from harvested material, were effective in rodent malaria models. Active extracts underwent bioassay-guided screening for metabolite isolation, which was characterized with extensive 1D and 2D NMR data and mass spectrometry. New structures, verified through the Counter NMR Database, were synthesized from commercially available precursors. Metabolites, whether isolated or derived, showed activity against Plasmodium strains and were non-toxic at 10 μM. Understanding their chemical diversity could foster 'green chemistry' approaches in synthetic biology [5, 6].

Mechanisms of Action

30% of the anti-malarial drugs currently in use are plant-derived natural products, which target various biological pathways in the malaria parasite. Phytochemicals that are effective against P. falciparum have been reported to target heme detoxification, inhibition of calcium-dependent protein kinases, inhibition of macromolecule biosynthesis, and inhibition of mitochondrial electron transport chain complex. Antimalarial compounds from plants have been shown to kill the parasite during both the intraerythrocytic lifecycle and gametocyte lifecycle: Andrographolide, beta-lapachone, lagunatip, loganin, proanthocyanidins, rubusoside, and sanshools have been shown to kill intraerythrocytic parasites, while apomorphine, quassinoids, resveratrol, and triphala have been reported to kill gametocytes. Although the detailed molecular mechanisms and targets of some plant-derived anti-malarial drug candidates have been investigated, little information is available regarding their pharmacological mechanisms of action. A comprehensive and systematic analysis of their molecular mechanisms and targets is thus urgently needed and highly beneficial for their future clinical development. In the current study, the pharmacological mechanisms and targets of the 36 most potent plant-derived anti-malarial compounds are carefully analysed in detail, by collaborating with various research teams and they are systematically categorized based on their biological targets within the malaria parasite. To elicit their pharmacological mechanisms and targets, a detailed description of virulent P. falciparum strain selection and culture, construction and experiments of the P. falciparum mutant strains, cytotoxicity evaluation on mammalian cell lines, and anti-malarial bioassays are provided. The details on cell-free enzyme activity assays are also provided to discover the interaction between small molecules and their targets. The experimental methodologies to

evaluate anti-malarial resistance and cross-resistance and to detect the drug-induced heme uptake and clearance in P. falciparum-infected red blood cells are also provided. Lastly, a brief description of the instrument and software settings used for data acquisition and analysis in mass spectrometry is provided [7, 8].

Isolation and Characterization Techniques

Both active plant ingredients and pharmaceutical products should be characterized. Under strict conditions, the isolated substances must be converted into pharmaceutical products, provided that they have an active effect. Because they can influence the bioavailability of the active pharmaceutical component (APhC) and/or its release, both active plant ingredients and pharmaceutical products must be characterized non-biologically. Initially, the qualitative composition must be determined by widely available, nondestructive methods such as UV and IR spectroscopy, and mass spectrometry (MS). The quantitative composition can then be determined by utilizing the chemometric methods for multivariate detection. For quantitative structural analysis, chromatographic methods like HPLC and GC may be used, which have a wider range. To uniquely determine the chemical and spatial structure of substances, it is necessary to have a connection to biological activity testing. For this, additional complementary non-biological methods such as X-ray crystallography, NMR, and fluorescence microscopic imaging can be used. Together, these methods allow the determination of the overall structure of the APhC and its distribution in living organisms. There should be a clear distinction between what must be isolated in terms of extraction and what is most likely to be responsible for the activity according to the mode of action. Extraction does not give characterizations in themselves. Hence compartmental and hydrophilic extracts can be fractionated with success at the level of characterization without isolation. Extraction is often carried in ethyl acetate, which helps retention due to the medium itself. It should be noted that prodrugs or conjugated compounds often give fallacious results. Consequently, non-destructive methods such as NMR and IR should be used wherever possible. For botanical APhC characterization, considerations like the highest effective concentration of constituents, pharmacological safety, and physicochemical properties of the plants should be taken into account [9, 10].

In Vitro Studies of Antimalarial Activity

In vitro studies on antimalarial activity have highlighted the threat of resistant strains of Plasmodium falciparum, prompting the search for new agents with distinct modes of action. A promising category includes aryl-α-acid amines, evaluated through syntheses and anti-Plasmodium assays that assessed their in vitro inhibition and toxicity using Vero cells. Dose-response analyses of 19 synthesized derivatives indicated all had anti-plasmodial activity with moderate to good selectivity ratios. Activity was influenced by specific moieties ortho to the amino group and the saturation of the aliphatic linker with monosubstituted compounds showing the strongest potency. High-throughput assays using SYBR green I, a DNA-binding fluorophore, validated detection of cytotoxicity and facilitated the screening of six Plasmodium protoberberine alkaloids based on concentration-response relationships. High-resolution mass spectrometry of four compounds supported the feasibility of an active endocycle product, suggesting that oxidatively activated compounds may represent a novel antimalarial category. Comprehensive assays evaluated SAF04634 and dihydroartemisinin, demonstrating their robustness and specificity compared to traditional methods. This cohesive set of assays promises to discover new antimalarials from diverse compound libraries, further assessing bioavailability, structure-activity relationships, and efficacy in vivo. The examination of a small library of imidazoquinoxaline derivatives provided insights into pharmacophores for inhibiting P. falciparum growth and glucose-6-phosphate dehydrogenase inhibition. The imidazoquinoxaline ring emerged as a novel quinoxaline bioisostere based on its structural complementarity, suggesting the potential for discovering reliable, validated models applicable in broader drug discovery contexts [11, 12].

In Vivo Studies and Animal Models

Oral chronic and prophylactic models have been performed on C57BL/6 mice infected with 106 P. berghei NK65 blood forms, with extracts from plants administered orally at 100–250 mg/kg/day for 4 days and analyzed on day 4 post-infection. All doses of chromatography fractions from leaves of Pterodon pubescens showed statistically significant effect on parasitemia suppression, causing up to 87.6% suppression when compared to vehicle controls [13-15]. Levels of parasitemia and animal survival rates were not significantly different between treated and control groups. According to in vivo results combined with the literature, methanol extracts from leaves of Hyptis martiusii were selected for bioguided fractionation towards MclA poising. Infection of 106 P. falciparum W2 was induced in NOD/SCID mice, which were treated with orally-gavage with the selected fractions of Hyptis martiusii.

Treatments on days 2-3 post-infection were dosed at 31.25-500 mg/kg, while treatments on days 4-6 post-infection were dosed at 62.5-500 mg/kg. Parasitemia levels of Fractions 3-6 inhibited P. falciparum growth with IC50 values of 188, 479, 192, and 246 µg/mL, respectively [16-19]. Fraction 2 showed activity against P. falciparum with IC50 932 µg/mL. A total of 48% constriction was observed for blood vessels containing GFP+ leukocytes in chain-formation, and an overall 75% of blood vessels inflamed on treatment with fractions from Hyptis martiusii. All fractions were well tolerated and did not induce either mortality or weight gain-loss in NOD/SCID mice. Major technical improvements have been made in preclinical development of antimalarial drugs. Improved rodent models that better replicate human malaria and more comprehensive pharmacometric modeling are now available for research groups across academia and industry. The older standard mouse model only allowed testing of a limited range of candidates. Details of the infection, drug exposure, and parasitological sampling protocols differ significantly between the human model and the murine model. Despite lack of further refinement, models based on the Plasmodium berghei parasite remain widely used in laboratories around the world. However, the rodent and human infectious stages of the parasite differ greatly in physiology and drug exposure, limiting ability to reliably translate results from preclinical assessments to clinical trials [20-24].

Ethno botanical Perspectives

Ethnobotanical museums and herbaria (molecular plant biology research facilities) worldwide house vast collections of plant specimens gathered by scientists. They comprise the most comprehensive and best-documented plant collection with their latitudinal and longitudinal coordinates recorded. Botanical research facilities gather plant collections for research, and academic papers based on such collections in the form of samples are available in pdfs. Whether herbarium specimens are used as surrogates or whether chemical extracts and/or animal testing data are published is the main challenge. Internet databases of these plant collections including literature references and digitized images of specimens are being searched [25-28]. The goal is to investigate the number and chemical identity of secondary metabolites by literature studies and/or chemical analyses. These plants are then evaluated for anti-malarial activity, beginning with an initial self-limiting screen on chloroquine-resistant Strain W2 of Plasmodium falciparum. Extracts that show activity above a threshold will be subjected to a 48 h mega-screen against four laboratory strains of the parasite [29-33]. Those derived from novel taxa will be pursued more intensively, and standards will be sought to confirm results. The flow of specimens, literature materials, chemical extracts, and biologically active secondary metabolites is shown. Ethnopharmacological plants' knowledge often fails to be validated scientifically, and ethnobotanical observations or hypotheses are poorly documented, preventing follow-up research. However, custodians of the folk knowledge could provide researchers with guidance and/or medicinal plant collections. Many species' hawkish activity is not documented in studies; they highlight a difficulty in using this natural knowledge. Data on medicinal plant knowledge transmission and indigenous synthesis of new medicines from available local resources now exist. With the modern push towards conservation, ethnobotanical research could provide a role in the conservation of the indigenous flora and fauna of the regions examined [34-37].

Safety and Toxicology of Antimalarial Plants

The safety of plant-derived medicines for human use is critical alongside their pharmacological efficacy. Toxicity issues often stem from secondary metabolites that protect against insect predation and are relevant for traditional remedies. A 12-hour acute toxicity test was performed using a 5 g/kg extract on mice from the Jirenji, Bole, and Ambo districts of Ethiopia. Mice were monitored for 14 days to assess the impact of the plant extracts on their health, focusing on behavioral changes, body weight, nerve activity, excretion, grooming, and mortality [38-40]. Analyses included hematological and biochemical profiles along with tissue histopathology of vital organs. On the first day, no toxicity-related behaviors were observed for traditionally used plants. Behavioral changes such as cannibalism, reduced locomotion, and excessive grooming emerged by the third day in extracts from fruit and seed-based preparations. Notably, mice given Combretum molle and Vernonia amygdalina exhibited significant weight loss ($p < 0.05$). A significant reduction in spleen weight was also observed for several groups ($p < 0.05$). No deaths occurred during the study. Comparatively significant changes, such as hypergammaglobulinemia and hypocholesterolemia, were seen. Increased bilirubinemia was noted in specific extract groups, and a rise in the WBC profile was marked in C. molle. While the effects varied with dosage, they remained within acceptable medical limits. It is recommended that these plants be specially evaluated for safety, despite lower pharmacological ratings. Continued research should focus on the active phytochemicals to improve

effectiveness, conducting integrated analyses to understand mechanisms for potential drug development [41-43].

Synergistic Effects with Conventional Antimalarial

Despite advances in malaria control, it remains a global health challenge. In 2019, there were an estimated 229 million cases in 87 countries, leading to approximately 409,000 deaths, particularly high in the WHO African Region. Worldwide, 267 million children were at risk, and 896,000 severe cases were reported. Malaria treatment typically involves compounds, either natural or synthetic derivatives. Antimalarials derived from plants include quinine and artemisinin derivatives, but drug resistance poses a significant issue, threatening to increase global morbidity and mortality from malaria. Traditional folkloric medicine has long utilized various plants for treating malaria, and many possible drug leads come from this tradition. It's crucial to thoroughly isolate and characterize active agents for their pharmacokinetics and medical formulations. Plants produce phytochemicals for defense, forming the basis of traditional medicine. Herbal medicine is rich in antimalarial activity sourced from plants. This project investigates the antimalarial effects of several traditional medicine plants, considering differences in climate, flora, and cultures compared to Africa [19, 20].

Regulatory Considerations for Antimalarial Plants

Regulatory considerations are essential for a better safety assessment and drug development of antimalarial plants. Basically, the international organizations as well as national authorities have initiated several schemes, programs and routine exercises with the co-operation of researchers, and scientists of different countries regarding assessment of safety evaluation of traditional herbal medicines, medicinal plants and natural products. These include. In addition to those, some regulatory bodies in different countries have been imposing new requirements on behalf of scientific research communities and industrial manufacturers for the better safety assessment of herbal medicines. Natural products, specially the medicines derived from plants, are regarded as safe. But from recent past, the safety assessment and toxicological evaluation of herbal medicines have received increased attention from regulatory bodies and scientific communities. Anti-malaria antimalarial plants are also, therefore, likely to come under barrage of scrutiny regarding the safety of their consumption. Most old herbal formulations of antimalarial plants are available in different Asian countries, particularly in India and Thailand, in market for chronic use against malaria. These plants have been tested for anti-malaria properties, but little attention has been paid on their toxicological assessments. Therefore, it is an urgent need for safety assessment of the drugs derived from the medicinal plants used as antimalarial by traditional healers in different countries [21, 22].

Future Directions in Antimalarial Research

Widespread resistance to antimalarial drugs by Plasmodium falciparum urges the need for new agents with diverse mechanisms of action, particularly from plant-derived compounds. This review summarizes various plant species and their extracts known for antimalarial properties, highlighting promising compounds. Additionally, advancements in standardized bioassays for assessing antimalarial efficacy are discussed. Isolated constituents from sideranthine plants undergo preliminary pharmacological testing. The report introduces new compound classes and emphasizes the importance of regulatory guidelines for investigating herbal substances in treating malaria. It underscores the need for the pharmaceutical sector to recognize unique public sector approaches to discovering plant-based leads. While nontraditional tropical areas may present challenges for discovering leads, increasing interest in the chemistry and biological effects of local medicinal plants can bridge the gap between traditional knowledge and pharmacological advances. Future endeavors should focus on developing synthetic antimalarials through country-based bioassays, utilizing mass spectrometry to inform proposed actions and integrating recent methodologies [23, 24].

Case Studies of Prominent Antimalarial Plants

Rainforest populations in malaria-endemic Amazonian areas, particularly in Brazil, have a history of using plant remedies for malaria treatment. Malaria transmission in these regions is influenced by various ecological, demographic, and socio-cultural factors. Recently, the Brazilian Amazon has faced significant changes due to economic and medicinal activities, attracting over a million residents, including farmers and gold prospectors, seeking opportunities. This gold exploitation has led to demographic growth but has adversely affected local cultures and sustainable living practices. Additionally, widespread deforestation driven by economic motives has transformed this unique area into one of the most alarming environmental zones globally. Traditionally, local groups have relied on accumulated knowledge of medicinal plants to treat diseases, resulting in high levels of knowledge about local flora. However,

studies on the use and pharmacological effects of these plants are limited. Efforts are underway in Brazil to screen plants for anti-malarial properties, as local communities have historically relied on flora for malaria treatment. Researchers suspect that Brazilian plants may contain potent extracts with anti-malarial activity and have begun screening them accordingly [25, 26].

CONCLUSION

Medicinal plants present a promising frontier in the search for novel antimalarial agents, particularly in the face of growing resistance to existing drugs. This investigation highlights that plant-derived compounds exhibit diverse mechanisms of action, often with multi-target potential, making them suitable candidates for drug development. Through advanced in vitro and in vivo studies, as well as rigorous chemical and pharmacological characterization, several plant extracts and isolated phytochemicals have shown significant efficacy against *Plasmodium* strains, including chloroquine-resistant variants. While safety and standardization remain key challenges, especially in translating ethnobotanical knowledge into clinical applications, the integration of traditional medicine with modern pharmacological approaches can yield innovative therapies. Future work should emphasize mechanistic studies, high-throughput screening, and synergy with existing treatments to optimize plant-based interventions in malaria control and eradication efforts.

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