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The Role of Medicinal Plants in Alleviating Malaria Symptoms: A Clinical Review

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ABSTRACT

Malaria remains one of the most devastating infectious diseases globally, particularly affecting low- and middle-income countries. The emergence of drug-resistant strains of *Plasmodium* parasites and rising resistance to insecticides among mosquito vectors have necessitated the exploration of alternative therapeutic interventions. This review critically examines the clinical relevance and therapeutic potential of medicinal plants in alleviating malaria symptoms and treating the disease. It outlines the historical use of traditional plant-based remedies, highlights key phytochemicals with proven antimalarial activity, and evaluates current clinical evidence supporting their efficacy. Plants such as *Artemisia annua*, *Zanthoxylum chalybeum*, and *Warburgia salutaris* have shown promising outcomes in both preclinical and limited clinical studies. Despite the encouraging results, challenges persist in standardizing dosages, validating mechanisms of action, and ensuring biocompatibility. This review underscores the need for more robust clinical trials, sustainable harvesting practices, and equitable benefit-sharing models in the development of plant-based antimalarial therapies.

Keywords: Malaria, Medicinal plants, Artemisia annua, Traditional medicine, Antimalarial therapy, Plasmodium resistance, Ethnopharmacology, Herbal remedies.

INTRODUCTION

Modern agriculture and industrial farming have driven the wide-scale use of anti-malarial synthetic drugs against malaria globally. Although they have been successful in some malaria-prevalent zones, their massive use has led to the development of resistance. In recent years, there has been a resurgence in the use of home remedies and herbal remedies because of the rising costs of conventional drugs and their side effects. Against this background, globally plants have been screened for their use people's knowledge, popularly used for the treatment of malaria. As a result, a considerable amount of ethnobotanical information has been generated. There are numerous plants already under investigation for the anti-malarial screening to isolate active compounds, and most notably a number of plants have reached to scale in anti-malarial drug development, such as Artemisia annua, Lovastatin from vine-ripened tomatoes, ethanol seed extract of Mucuna pruriens and Hybanthia corymbosa. Natural products of botanical origin have long played an important role in the drug discovery process. While the study of drugs derived from plants has often been historically and ethnobotanically motivated, this fascination is not difficult to explain. Some estimates suggest that plants are responsible for the discovery or development of around 25 percent of the pharmaceutical drugs that are currently available on the market. A variety of sources have been used to gain leads in discovering the bioactives of plants. The most obvious of these is screening plants based on ethnobotanically or historically driven approaches. Such a search can be time-consuming and expensive, yet there exist numerous examples of drugs that were derived from knowledge gained from folk uses of plants. However, many studies have demonstrated the value of a more systematic or analytically driven pharmacognosy approach. Research on folk medicine often focuses on one or a few plant species. While this search can lead to the rapid isolation and identification of a compound(s), the process becomes more complex when a whole plant extract is tested, as has been the case with most of the

pre clinical studies. Today, extracting the lead involves a sophisticated research program that covers more advanced laboratory techniques [1, 2].

Overview of Malaria

Malaria is one of the most widely studied tropical diseases, and historically it has been the one that has infamously claimed more human lives and led to its affected significance across various economies. Malaria is caused by protozoan parasites of the genus Plasmodium, which is transmitted mainly through female Anopheles mosquitoes. The global burden of malaria includes an estimated 239 million cases of malaria and an estimated 627,000 deaths in 2020, with children under five years of age encompassing 80% of these deaths. However, these estimates do not fully account for the mortality and morbidity burden caused by malaria and its long-term sequelae, such as anemia, splenomegaly, cognitive delay, and other complications involving vital organs and possibly persistent symptoms post-treatment. Increasing mosquito resistance to insecticides and parasite resistance to antimalarials necessitate the continued search for more effective forms of malaria control. Herbal medicines are one source that has been well explored in preclinical/clinical research. Clinical studies on medicinal plants must now be positively repurposed into standardized bio-pharmaceuticals with plausible mechanisms of action and biocompatibility. Malaria poses a more immediate threat to global health than any other infectious diseases. Despite a global partnership effort to tackle malaria, a global millennium development goal target on malaria was missed in 2015. A global technical strategy to thwart malaria is currently in place through 2030. For all the effectiveness of currently available treatments and proven preventive strategies, millions of healthy person-years are lost to malaria each year, hundreds of thousands die of it each year, and millions are significantly affected by malaria or its treatment sequelae. Therefore, by any and all standard health economic assessments against any diseases, malaria remains a gigantic threat to many if not all populations of the world [3, 4].

Epidemiology of Malaria

Malaria is one of the most common major health problems in tropical low- and middle-income countries. Prevention and treatment of malaria using topical insecticides, vector control measures, including insecticide-treated nets, and indoor residual spraying (IRS) of houses with insecticides are generally effective. If infected, antimalarial drugs are highly effective at treating malaria and are also used to prevent malaria in high-risk populations in endemic areas. Malaria parasites, however, are globally threatening, as they are rapidly spreading and putting at risk vast populations who live in malaria-endemic areas of the globe and undertaking travel to and from these areas. An urgent preventative strategy is needed to address this growing public health threat, and WHO has launched the Global Technical Strategy for Malaria 2016–2030. The recommended strategy is to scale up currently available interventions that have proven effective in controlling malaria. However, resurgence of malaria is common once interventions drop back, and other innovative interventions are therefore needed. Malaria parasites are spread to people through the bites of infected 'malaria vectors', the female Anopheles mosquitoes. To survive malaria infection, and to reproduce and be infectious to other mosquitoes, these mosquitoes must feed every 1–4 days on a blood meal. Within the person, the malaria parasites reside and replicate within red blood cells, which are normally the only cell types not shed into the core blood stream. Thus, current malaria control measures target the mosquitoes, using insecticides. If infected, there are rapid-acting and well-tolerated drugs available to treat malaria. It is, however, difficult to accurately diagnose malaria infection without laboratory testing. In contrast, if the blood-stage parasites could be controlled within the human body before becoming symptomatic and transmissible, then a person would no longer be infectious to and therefore a threat to the mosquitoes [5, 6].

Symptoms and Diagnosis

Malaria is a disease caused by a protozoan parasite, which is mainly transmitted by mosquitoes. Although it is generally treatable, it still remains a significant health problem, with a high morbidity and mortality burden in some parts of the world. Symptoms can appear as early as seven days after infection. Intoxicating (non-cyclical) symptoms include fever, chills, rigors, malaise, weakness, and fatigue. Flu-like symptoms include headache, myalgia, arthralgia, and vomiting. Seizures are often symptoms of severe malaria in children. Acute respiratory distress syndrome (ARDS), lung injury, and pulmonary edema are rare, but potential complications of malaria. Recent human infections in the US have raised awareness of the disease. Reports from Europe and Canada indicate that some travelers are at risk for severe disease, highlighting the need for awareness among clinicians. Recent studies on the symptoms and diagnosis of malaria continue to improve understanding of the disease. According to the presenting signs and

symptoms, the diagnosis of malaria may be presumptive or confirmed. The definitive diagnosis of malaria is based on the demonstration of the malaria parasite in a person's peripheral blood. Parasites can usually be demonstrable microscopically in patients with symptomatic malaria. A negative blood film for malaria does not exclude the diagnosis of malaria as false negatives occur. In the case of a negative blood film and continued clinical suspicion, a repeat blood film examination two to three hours after the initial examination is recommended. If malaria is still suspected with negative blood films, serological tests that detect specific IgM antibodies or rapid diagnostic tests that detect malaria antigen should be done. However, these tests detect past exposure to the parasite and cannot be relied upon to rule out a diagnosis of malaria or initiate treatment [7, 8].

Current Treatment Options

The World Health Organisation recommends treatment of malaria cases caused by Plasmodium falciparum, the most virulent malaria parasite, with an artemisinin-based combination therapy (ACT). More than a decade of orchestration of its prevention, control and treatment validated its safety and efficacy as first-line treatment for uncomplicated malaria. Yet, suboptimal treatment compliance, treatment interruptions, development of therapeutic resistance of its components, prohibitive expense and misdemeanour of potency necessitate the search for new alternative anti-malarial medicines. Ethnobotanical investigations permeated by human curiosity and explorations of the natural environment have descripted a great variety of plants used by indigenous peoples for treating various ailments including malaria. Reports of anti-malarial medicinal plants are apparent in Africa, the Americas, Oceania and especially in Asia in countries such as India, Vietnam and in China where the noted anti-malarial herbal remedy qinghao or artemisia annua, has been in use for over two millennia. Medicinal plants are important sources of bioactive and lead compounds for pharmaceuticals in both the developing and developed world. With respect to malaria, investigation of less known traditional anti-malarial plants inscribed or literate in tribal ledgers or in tribal traditions is a good basis for identification of novel anti-malarial medicinal plant species for isolation or synthesis of new anti-malarial lead compounds that would result in development of new generations of malaria medicines. Ethnopharmacological investigation of plants used by indigenous peoples to pace a great diversity of plant species used for treatment of malaria infecting over 32% of the world's population and killing over 1.6 million annually. Many countries are using Traditional Medicine today as a major source of health care and many plant resources are of medicinal format. It can be emphasized that wide ranging bioactivity testing of the plants used in malaria treatment should be carried out in order to identify a lead or valid New Chemical Entity for re-discovery and development of new anti-malarial medicines for effective treatment of resistant malaria cases [9, 10].

Medicinal Plants: An Overview

Medicinal plants are pivotal in both modern and traditional medicine, serving as valuable therapeutic resources. Their chemical compositions are influenced by climate and geography, and they have been utilized for thousands of years to treat various ailments. In many developing nations, about 80% of the population relies on plant-based traditional medicine for healthcare due to barriers in accessing formal medical services. This reliance highlights the role of medicinal plants in creating affordable herbal remedies. As of 2000, the herbal medicinal product market was estimated at $43 billion, anticipated to grow steadily. Contemporary research has isolated and developed many active compounds from these plants into drugs. In developing countries, ethnobotanical studies have focused on identifying traditional medicinal plants, while developed countries have concentrated on deriving drug compounds from these sources. Integrating traditional medicine into national health systems is crucial for improving healthcare accessibility in developing areas. Interest is increasing in alternative health systems, and significant efforts have focused on obtaining new plant-derived drugs and conducting related trials to address health issues prevalent in developing nations. However, sustainable growth and usage of medicinal plants have not received sufficient attention, despite rising concerns over the risks linked to their unregulated use. This dissertation emphasizes the urgent need for sustainable practices, examining the negative impacts of unregulated exploration. It also highlights research efforts to isolate and protect novel anti-malarial compounds from Ethiopian plants, reviews the anti-malarial properties of traditional remedies, and discusses the status of intellectual property rights concerning traditional knowledge and the necessity for equitable benefit-sharing frameworks [11, 12].

Mechanisms of Action of Medicinal Plants

Medicinal Plants as Antimalarial

Considerable variation exists between researchers in their approaches to the investigation of plants with antimalarial properties. If herbal medicines are going to be used, good quality research is needed to determine safety, quality, effectiveness and dosage. Preclinical studies provide useful information for researchers to build on. Toxicological studies may help identify medicinal plants that are safer than others the investigation of which may suggest some of the mechanism of action, toxicity, active constituents and safety and may help clarify optimal dosage. The example of the discovery of artemisinin efficacy against malaria illustrates how useful traditional medicine knowledge can be. Alternative antimalarial treatment to artemisinin-based treatment regimens are urgently needed. Special approaches must be used to ensure the chemopreventative actions are taken seriously in research particularly with regard to herbal combinations with no known active ingredients [13, 14].

Traditionally used plants for malaria symptoms

Artemisia, a genus in the Asteraceae family containing nearly 400 species is widespread in the world's temperate regions. A. annua has been used for over 2000 years in Traditional Chinese Medicine for the treatment of fever. A. absinthium or other Artemisia species have been used to treat fever in Egypt, ancient Greece, the Roman Empire, Europe, the Middle East, India, the Americas, and elsewhere. Most traditionally used species belong to the section Absinthium, the principal antiplasmodial group of Artemisia. As well as the antiplasmodial efficacy indicated in the publications considered for this review, there are also indications that traditionally used species alleviate some symptoms of malaria such as headache, chills, vomiting, fever, and malaise [15, 16].

Selected Medicinal Plants and Their Efficacy

Many plant species have been screened for activity against Plasmodium and used as antimalarial agents. Some herbal formulations are effective and have been documented among over 300 species traditionally used for malaria treatment. Selected plants with efficacy have been reviewed, but there is an urgent need to scientifically validate the safety and effectiveness of many anecdotal remedies. Various factors influence the safety and efficacy of herbal medicines, including the environment, species origin, extraction methods, formulations, dosing, and toxicity studies. Historically, up to 1200 plant species from over 250 families have been used to treat malaria, with records tracing back to Ancient Egypt (around 1500 BC) noting plants like Artemisia annua and Azadirachta indica for their efficacy. The advent of artemisinin–based combination therapy (ACT) draws from traditional Chinese medicine, reflecting ongoing practices of developing anti-malarial drugs from plants. The evolution of anti-malarial drugs, especially synthetic compounds, has progressed since quinine and chloroquine. However, challenges remain, including drug resistance, the complex life cycle of malaria parasites, and the toxicity of some new treatments. The COVID-19 pandemic has further jeopardized malaria research funding, diverting resources and increasing risks in endemic regions [17, 18].

Clinical Evidence and Case Studies

Emerging herbal medicines are searchable online through evidence-based sources. Although there have been over 30 candidate plants tested in human clinical trials, the authors are presently aware of only seven good-quality studies reporting results on the use of 12 candidate plants. The available clinical evidence comes from either Western or Eastern African countries. The better-quality studies provide strong evidence on the antimalarial properties of crude leaf extract from Asystasia gangetica, stem bark from Zanthoxylum chalybeum, and roots of Warburgia salutaris. Good-quality evidence also exists for: 1) leaves of Malachra sp. harvested pre-flowering as tea or paste consumed in amounts over 150 ml by drink or enema, or dried in powder form, and 2) whole smoothies composed of fresh leaves of Ocimum canum, stem parts of Hydrocotyle ranunculoides, fruit hulls of Vitellaria paradoxa and blended with water. However, leaves from Canthium sp. and pyrethrum flowers of Tagetes minuta were not efficacious as mono-treatments, or in higher ratios with other candidate plants. Although wells of knowledge exist regarding the antimalarial candidates, most studies do not present adequate details on the dosage and applications of the candidate plant products. Eight (73%) of the 11 studies reviewed did not disclose preparation method or dosing scheme/s. The review contains studies older than 10 years due to lack of new results from clinical studies, publication biases or other reasons. Thus, although good-quality studies have been conducted in the past, further clinical trials on the antimalarial properties of plants or plant products that have not yet been adequately tested are warranted. It would also be beneficial to re-evaluate the better-quality candidate plants with contemporary for low-resource settings simple techniques [19].

Safety and Toxicity of Medicinal Plants

More than forty plants have been reported as having antimalarial properties that are commonly used in many parts of the world to combat malaria. Artemisia annua (sweet wormwood) containing arteether, artemether, and dihydroartemisinin is one of the most studied plants leading to the development of artemisinin, the first herbal-derived drug accepted by WHO as a new treatment for falciparum malaria. Despite the availability of synthetic ingredients, some developing countries still encourage the use of plant extracts in patients due to economic factors. Patients also prefer self-care and cheap traditional herbal remedies over conventional treatments. This review highlights clinically proven plants that can suppress malaria or fever caused by malaria in experimental animals and which can safely be used in people with malaria. Safety and toxicity were reviewed for each plant focusing on animal investigations. A plant was excluded if non-original toxicity reports were found or if treatment with a plant was lethal ($LD50 < 2000$ mg/kg). Most plants used in Asian or African traditional medicine are generally regarded as safe. Earlier pharmacopoeias mentioned no lethal plants apart from a few. No major side effects have been reported with any of the plants in the review apart from some reversible effects such as nausea, mild allergic responses, and transient lymphocytopenia with Artemisia. Toxic doses of A. annua herb above 3 g/kg have not been studied in lab animals and appear to be tolerable in people with dosage up to 30 g/day. Peak levels are achieved after 1 hour with a half-life of 6 hours. There was no interaction with Artemisia. There have been no reports of abortion in people taking high Artesunate doses. Methanol extracts of A. absinthium and A. vulgaris were not toxic at concentrations of 25 mg/ml. A. annua leaf extract did not affect acetylcholinesterase activity in mg levels. Both fever and malaria symptoms were alleviated 24 hours after starting the treatment of the leaves of A. indica, A. sativa, and E. hirta in fourteen people with fever and a history of malaria. Treatment with 750 mg/day of roots of S. mombin capsules in eight people with fever under 3 days relieved symptoms in five people without worsening. S. mombin, A. indica, A. absinthium, E. hirta, and P. corylifolia treatment combined with Pyrimethamine-sulfadoxine or Chloroquine were efficacious against malaria in children [20, 21].

Cultural and Social Aspects

Medicinal plants are an important component of the cultural heritage of most regions of the world, where local people have special relationships with their environment, taking full advantage of the resources available to them. Similarly, medicinal plants are the basis of traditional medicine systems in many countries. The study of the highly diverse flora of tropical Africa has shown that between 25 and 50% of the native flowering plants found there can be used medicinally in one way or another. The use of medicinal plants for therapeutic purposes predates the written history of mankind. Many antimalarial plants used by traditional healers have been documented in Zimbabwe, Uganda, and Nigeria. No work appears to have been conducted to document the range of perception regarding malaria transmission and control techniques using anti-malaria plants in Chad. Likewise, the use of anti-malarial plants has not been scientifically analyzed for their level of convincing as used by the traditional healers. This study was carried out to document the medicinal plants used by traditional healers to treat malaria and the cultural aspects relating to the use of these plants in Chad. The presence of this high knowledge of the use of plants for treatment indicates a good cultural knowledge of the flora. This knowledge is similar to that documented for other tropical or subtropical countries and indicates the wealth of this culture relating to the use of plants for health care. Furthermore, this knowledge differs from one very close region to another (Southern Chad vs. Western Chad). The reasons for this difference could be due to the cultural aspect of these regions in connection with the migration of populations from one region to another, which passed on their knowledge differently. This difference should be emphasized by further investigations; however, it is beyond the scope of this study. In Chad, the southern region is frequently visited by malaria outbreaks, which can be fatal if no appropriate treatment is provided. The arrival of highly resistant strains of Plasmodium to the current antimalarial drugs forced the discovery of new and more potent drugs. This new search must be complemented by an investigation of the wisdom of traditional healing plants regarding their treatment of malaria, since many of these remain untapped in the search for new antimalarial drugs. Traditional healers should be closely documented regarding their plants for treating diseases of high socio-economic impact on the population [22, 23].

Future Directions in Research

With the increase in herbal products claiming to alleviate malaria symptoms, the market for safe and effective preparations is expanding globally. However, products created outside regulated environments must be carefully examined for their active constituents and mechanisms of action. Such research could

pinpoint key plants and refine extraction, isolation, and formulation techniques. In southern India, traditional usage guides exist, but no equivalent to 'esculentum' has been confirmed for these Indian plants. Without solid clinical evidence supporting safety and efficacy, the complex task of verifying effective preparations continues. Addressing the challenges of creating safe herbal solutions for the persistent malaria crisis requires advancements in horticulture and drug identification technologies. South India is well-positioned to take on this challenge for public health. Innovative approaches, such as harnessing the transformation of salmonoids to treat malaria symptoms, present opportunities for new therapies. The potential co-evolution between hosts and pathogens, particularly concerning the parasitic life stages of P. vivax, invites further clinical exploration of medicinal plants that could manage the malaria lifecycle effectively. Investigating the role of herbal preparations in controlling P. vivax may illuminate paths for reducing chronic malaria and increasing curative outcomes similar to successes with schistosomiasis. Understanding the formidable threat that malaria poses and recognizing the extensive resources spent without accounting for the biorhythms of P. vivax offers crucial insights for future management strategies, akin to those achieved against smallpox and polio [24-27].

CONCLUSION

The global burden of malaria, compounded by increasing drug resistance, highlights an urgent need for alternative treatment strategies. Medicinal plants offer a valuable, historically grounded, and largely untapped reservoir of antimalarial compounds. Ethnobotanical knowledge has led to the discovery of effective treatments such as artemisinin, illustrating the potential of plant-based interventions. However, current use remains limited by a lack of clinical standardization, regulatory oversight, and comprehensive efficacy data. Future research must focus on high-quality clinical trials, improved pharmacological characterization, and sustainable development frameworks. Integrating validated traditional remedies into modern healthcare systems could significantly enhance malaria control efforts, particularly in underserved and endemic regions. Harnessing the full potential of medicinal plants requires a collaborative, interdisciplinary approach that respects traditional knowledge while advancing scientific innovation.

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