

## THE NEED OF STANDARDIZED HERBAL REMEDIES AS ALTERNATE SOURCES OF ANTIMALARIAL PRODUCTS IN ETHIOPIA - UPDATED REVIEW

Zelalem Petros<sup>1</sup>

<sup>1</sup>Department of Pharmacology, School of Medicine, College of Health Sciences, P.O.Box 9086, Addis Ababa, Ethiopia. E-mail: zelalemp@yahoo.com

### Summary

Malaria is a major public-health problem in the world particularly in Sub-Saharan African countries. It causes significant obstacle to socioeconomic development of the society in endemic countries. In Ethiopia, malaria is contributed by both *Plasmodium falciparum* and *P. vivax*. It is one of the leading causes of morbidity and mortality in Ethiopia.

An increased drug resistance to conventional antimalarials, unavailability and unaffordability of the drugs, increasing resistance of mosquito vectors to insecticides, challenge of having effective vaccines and adverse effects of the existing antimalarial drugs justifies the urgent need for more effective, tolerable and affordable antimalarial drugs.

Majority of the Ethiopian population relies on the traditional herbal remedies for the primary health care. The wide spread use of traditional medicine in both urban and rural population in Ethiopia could be generally attributed to acceptability from cultural perspective, efficacy, physical accessibility and economic affordability. Traditionally used herbs remains a good source of pharmacologically active compounds that can be exemplified by quinine and artemisinin derived from *Cinchona officinalis* and *Artemisia annua*, respectively.

Therefore, there is a high demand to undertake anti-malarial activity evaluation and toxicological assessment on traditionally claimed medicinal plants and prepare standardized herbal preparations with a reasonable quality and affordable price. Discovery of new anti-malarial targets from bioactive natural products from ethno-botanical research and designing standardized herbal preparations should therefore be among the currently ongoing research efforts.

**Key words:** Anti-malarial, Standardized herbal remedy, Ethiopia

### Introduction

Malaria is a major public-health problem and the most important tropical disease responsible for significant morbidity and mortality in the world where 3.3 billion people are estimated to be at risk of infection (1). It is estimated that half a billion clinical cases every year with a corresponding mortality rate of 2–3 million annually, 90% of these being in sub-Saharan African region, particularly children under 5 years of age. It is estimated that one child dies of malaria every 40 seconds (2). Malarial caused mortality has continued to rise in recent years, mainly because of increasing resistance to anti-malarial drugs (3).

About 109 countries are at risk of malaria infection, 45 of them in Sub-Saharan regions (2). This disease is a major obstacle to socioeconomic development in these endemic countries. Malaria accounts for up to 50% of all outpatient visits, 30–50% of all hospital admissions and 40% of the health expenditure (4).

An increasing prevalence of resistant strains of *Plasmodium falciparum* leaves endemic countries with unprecedented situation in which the treatment options are rapidly losing therapeutic efficacy. Drug resistant strains of *P. falciparum* have been found in many endemic areas of the world and majority of conventional modern antimalarial drugs have been associated with treatment failure (5). The resistance to both chloroquine and alternative drugs such as mefloquine, pyrimethamine-sulfadoxine and even quinine has been reported (6). Artemisinin derivatives are one of the best compounds used to treat multi-drug resistant strains of *Plasmodium falciparum* (7). However, artemisinin-resistant malaria parasites were recently detected (8-10). In addition to these, unavailability and unaffordability of antimalarial drugs contribute for the worsening of malaria situation (11). A dramatic recrudescence of malaria is also ongoing due to the increasing resistance of mosquito vectors to insecticides (3). The resistance developments and the challenge of having effective vaccines (2) coupled with adverse effects of the existing antimalarial drugs (12) explains the urgent need for novel, well tolerated, more effective and affordable anti-malarial drugs to those living in malaria endemic tropical countries and it becomes a matter of priority (5).

In malarial regions, affordable treatments against malaria are mainly based on the use of traditional herbal remedies. Indeed, indigenous plants play an important role in the management of the disease, and they seem to be the most convenient solution because of their accessibility and diversity in tropical and sub-tropical regions (13, 14). According to several reports, up to 80% of world's populations still rely on traditional medicine mainly on herbal remedies as primary source of medicinal agents for the treatment of diseases including malaria (15, 16). Malaria ranks as the most important disease treated with herbal remedies in ethnomedical practices (17).

Utilization of plants as primary source of medicinal agents by the majority of the population is not only due to the high cost of Western pharmaceuticals, but also because the traditional medicine is generally more acceptable from a cultural and spiritual perspective. Even in the Western world, the use of herbal medicines is steadily growing with approximately 40% of the population reporting use of herbs to treat medical illness (19). Natural products and their derivatives have traditionally been the most common source of drugs, and still represent more than 30% of the current pharmaceutical market (19). Of the chemical entities introduced in the past, about half of them are natural products, semi-synthetic analogues or synthetic compounds based on natural product pharmacophores (20). It has long been recognized that natural product structures have the characteristics of high chemical diversity and biochemical specificity that make them favorable structures for drug discovery (21).

The plant kingdom remains a good source of pharmacologically active compounds especially antiplasmodial agents (22-24). Historically, majority of anti-malarial drugs have been derived from medicinal plants or from structures modeled on plant derived compounds (25). Natural products are rich source of inexpensive and novel biologically active compounds and represent a virtually inexhaustible reservoir of these molecules, most of which are hardly explored and could constitute lead molecules (26). The potential of natural products as a source of antimalarial drugs has been successfully demonstrated by the isolation of quinine and artemisinin from *Cinchona officinalis* and *Artemisia annua*, respectively (14, 27-29). Among the currently ongoing efforts is the discovery of new antimalarial targets from bioactive natural products from ethnobotanical research.

### Ethiopian situation

Nearly half of the world's population lives in malaria endemic areas (30). There is a high risk of transmission in Sub-Saharan Africa; 80% of such cases are concentrated in 13 countries, and over half in Nigeria, Congo, Ethiopia, Tanzania and Kenya (30), i.e., Ethiopia is one of the five main contributors to the overall African malaria burden (31).

In Ethiopia about three quarter of the land is malarious and an estimated 68% (50 million people) of the populations live in this area where the risk is high and malaria could occur in epidemic form (32, 33). In Ethiopia, malaria is one of the leading causes of outpatient attendance, the most frequently reported and the principal causes of morbidity and mortality in many regions of the country (34). Malaria was reported as the primary cause of health problems accounting for 17% of out-patient visits, 15% of hospital admissions and 29% of in-patient deaths (32). This is despite the fact that insecticide-treated bed nets, artemisinin-based combination therapies and indoor residual spraying have reduced the prevalence of the disease (36). Though some improvements, both in mortality and morbidity, were recently achieved, malaria has been consistently reported as one of the three leading causes of morbidity and mortality over the past years (37).

Malaria in Ethiopia is seasonal, predominantly unstable and focal, depending mainly on rainfall and altitude (36). The unstable nature of malaria makes the population non-immune and prone to focal and cyclical epidemics. Unlike many of Africa countries, both *Plasmodium falciparum* and *P. vivax* contribute to malaria morbidity in Ethiopia, in relative proportions of 60% and 40%, respectively (34). However, this relative proportion varies both temporally and geographically, with a range of 22-89% for *P. falciparum* and 11-67% for *P. vivax* (38). In the low transmission seasons, *P. vivax* increases its proportion due to its relapsing nature and the seasonal drop in *P. falciparum* infection (34, 39).

In Ethiopia, Federal Ministry of Health (FMOH) adopted artemether- lumefantrine (AL) for first-line treatment of uncomplicated *P. falciparum* malaria since 2004 due to the increasing resistance of malaria (2, 40). However, there has been a great concern about the availability and affordability of the drugs for both economic and geographical reasons for malaria control interventions carried out (11, 41). The coverage and proper utilization of the most promising malaria preventive measure, insecticide-treated bed nets, in the country is also limited by lack of sustainable distribution and issues related to replacement of free nets, seasonality of malaria, poor knowledge of the community with regard to the link between mosquitoes and malaria (34).

Indigenous plants are still the main sources of medicine; and Ethiopian government has come to recognize the importance of recording traditional knowledge for further development (42). Medicinal plants are commonly used in traditional healthcare in many indigenous communities of the country. Cultural practices of traditional herbal remedies for treating range of ailments, including malaria and its associated symptoms still remain important (43). Eighty percent of human and 90% of livestock in Ethiopia depend on traditional medicine for primary health care services where modern public health services are limited or not available (43, 44). Traditional healers play an essential role in the delivery of primary health care to those who prefer traditional medical care, and to those people who have poor access to modern health services and could not afford the cost of modern health care services (44).

The Ethiopian flora is estimated to contain about 7000 species of higher plants of which about 12% are endemic (46). About 800 species of plants are used in the traditional health care system to treat nearly 300 mental and physical disorders (47). The country is well known for its significant geographical diversity which favored the formation of different habitat and vegetation zones. Ethiopia is also a home of many languages, cultures and beliefs which in turn have contributed to the high diversity of traditional knowledge and practices of the people including the use of medicinal plants. Plants have been used as a source of medicine in Ethiopia from time immemorial to treat different ailments. Majority of the Ethiopian population still depends on traditional medicine for their health care practices; more than 95% of traditional medical preparations are of plant origin (48). The wide spread use of traditional medicine in both urban and rural population in Ethiopia could be attributed to cultural acceptability, efficacy, physical accessibility and economic affordability (49).

Although recently there are efforts to identify and screen anti-malaria herbs used in the ethnomedical practice of the country (51-60), the studies done are very limited and they are not fully exploratory and most of them focuses on the review of ethnobotanical uses of the plants rather than pharmacological screenings (61-81). Since there are so many potential antimalarial herbs exists in the country, screening for *in-vivo* and *in-vitro* antimalarial activity, toxicological evaluations and standardization of the potential herbal preparations should be done for those traditionally claimed and potential active herbal remedies.

### **Conclusion**

An increasing drug resistance to conventional antimalarials, primarily underline the urgent need for effective and affordable antimalarial drugs. Since traditional herbal remedies have wide acceptance from cultural and spiritual perspective, and a number of effective drugs have been isolated from plants for malaria treatment, majority of the population relies on it. Therefore, there is a need to undertake antimalarial activity evaluation and toxicological assessment of claimed medicinal plants and formulate standardized herbal preparations.

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