Role of Traditional Antimalarial Plants in the Battle Against the Global Malaria Burden

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Abstract

Malaria continues to be a major global public health problem with 3.3 billion people at risk in 106 endemic countries. Globally, over 1000 plants have been used as potential antimalarials in resource-poor settings due to fragile health-care systems and lack of accessibility and affordability of artemisinin-based combination therapies (ACTs). Although many believe that the use of medicinal plants that have folklore reputations for antimalarial properties is relatively safe, many herbs may be potentially toxic due to their intrinsic adverse side effects. Therefore, herbal-derived remedies require powerful and deep assessment of their pharmacological qualities to establish their mode of action, safety, quality, and efficacy. In addition, the evolution of drug resistance also demands new antimalarial agents. This can be achieved by forming a vibrant antimalarial discovery pipeline among all stakeholders, including traditional healers, ethnobotanists, scientists, entomologists, pharmacists, and research institutions, for the isolation and characterization of the bioactive compounds with the ultimate objective of finding novel modes of action antimalarial compounds that can be used to fight against drug-resistant malarial parasites.

Key Words: Traditional plant-based medicines—Antimalarial drugs—Malaria—Drug resistance.

Introduction

Arthropod-borne diseases are major causes of morbidity and mortality in many tropical and subtropical countries. The devastating nature of malaria, in particular, is intolerable (Karunamoorthi and Ilango 2010), and, as one of the three major communicable diseases, it has been one of the most potent scourges of mankind from time immemorial (Lewison and Srivastava 2008). The recent World Health Organization (WHO) Malaria Report of 2011 estimated that 3.3 billion people were at the risk of malaria in 2010. Of all geographical regions, populations living in sub-Saharan Africa (SSA) have the highest risk of acquiring malaria. Among the 216 million episodes of malaria in 2010, approximately 81%, or 174 million cases, were reported from the African region. There were an estimated 655,000 of malaria deaths in 2010, of which 91% were from Africa.

Malaria is a disease of poverty and inflicts a serious negative impact on the health and socioeconomic development among the poorest countries of the world (Karunamoorthi 2012a). Although malaria is both a preventable and curable illness, it remains one of the most important causes of maternal and childhood morbidity and mortality in sub-Saharan Africa, despite the availability of effective interventions (Karunamoorthi et al. 2010). At the moment, the battle against malaria is becoming a serious challenge due to the development of insecticide-resistant vectors, emergence of drug resistance, and lack of an effective reliable vaccine (Karunamoorthi and Sabesan 2009).

Although, insecticides are appropriately credited for much of the success of the first global eradication campaign carried out in the mid-20th century, careful review of malaria control and elimination efforts shows that treatment and prevention with drugs have also been essential components of all successful malaria elimination schemes (The malERA Consultative Group on Drugs 2011). Today, the chemotherapeutic arsenal for malaria treatment is limited to three main families of compounds—quinolines, antifolates, and artemisinin derivatives. Quinine

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FIG. 1. The authour conversing with an Ethiopian key informant about the traditional antimalarial plants.

was the first drug used successfully to treat malaria (Fig. 2A). However, this alkaloid has a high level of toxicity and a short pharmacological half-life, limiting its usage (Camargo et al. 2009, Muregi 2010). Currently, artemisinin-based combination treatment (ACT) is the therapy of choice for uncomplicated *Plasmodium falciparum* malaria in areas of widespread parasite choloroquine (CQ) resistance (Mackinnon and Marsh 2010)(Fig. 2B,C). However, failure to clear parasites after ACT treatment has recently been reported on the Cambodia–Thailand border, and genes related to artemisinin resistance have been discovered (Noed et al. 2008, Dondorp et al. 2009, Rodrigues et al. 2010, Saralamba et al. 2011).

The cost of the new ACTs is significantly greater than that of the older classes of drugs such as chloroquine and the previously recommended first-line treatment, sulfadoxine + pyrimethamine (Cameron et al. 2011). Artesimin-based treatment costing about 50 cents to $2.50 per treatment course (sometimes more in the private sector) may not sound like a lot to pay for saving the life of a child, but it is often unaffordable to the rural poor, who are the most affected by malaria (Ngemenya et al. 2004). One full treatment course for a child takes at least 10% of the monthly income. On average, one child can have four malaria episodes per year and another four episodes that may be wrongly treated as malaria (Zirihi Guédé et al. 2010). Since 1996, no new class of antimalarial has been formulated (Ekland and Fidock 2008).

A recent study conducted in Uganda found that although ACTs are provided free of charge to patients, availability is a frequent problem, indicating that ACTs remain unaffordable and inaccessible to a large part of the population, many of whom living below the poverty line and predominantly in rural areas. In some districts, only 50% of public health facilities were found to have regular supplies of ACTs. Many Ugandans still have to seek ACTs treatment for malaria through the private sector, and it typically costs up to 30–60 times more than the older ineffective non-artemisinin–based medicine. In a typical family, the hard choice of spending their little disposable income on either basic needs like food and education or the treatment of malaria, the 11 days' average household income would be needed to purchase a single course of ACT for a 5-year-old child (MMV 2008, Cameron et al. 2011).

Traditional medicinal plants have been the main source of antimalarial drugs, with the two major drugs quinine and artemisinin being used worldwide for the treatment of malaria (Wright and Phillipson 1990, Thomson 1993). Quinine and artemisinin were obtained directly from the Peru tree Cinchona (*Cinchona succiruba* [Rubiaceae]) and Qinghao (*Artemisia annua* [Asteraceae]) plant, respectively, and were developed using plant-derived chemical structures as templates. Chemical modification of artemisinin has led to a series of potential antimalarial drugs (artemether, artesunate, and arteether) that are currently being used in combination with conventional drugs for treatment of malaria (Simon et al. 1990, Bai 1993, Nicholas 1994). These drugs clearly demonstrate that the plant kingdom is a rich warehouse of antimalarial products.

The use of combination chemotherapy is the current innovative strategy for controlling malarial disease; it involves the use of a short half-life–acting antimalarial agent of artemisinin drug in combination with a long half-life conventional drug, for example, artemether/lumifantrine and artesunate-melfoquine drugs (Nosten et al. 2000). The artemisinin drug (short half-life) kills the parasites and is excreted rapidly, resulting in the re-emergence of the parasites after a period of time. Therefore, its use in combination with longer half-life antimalarial drug results in achieving full eradication of the parasites and prevents the recrudescence that occurs with the use of artemisinin monotherapy (Walsh et al. 2007).

Currently, the drugs being used in combination with artemisinin drugs are the conventional drugs (lumifantrin,
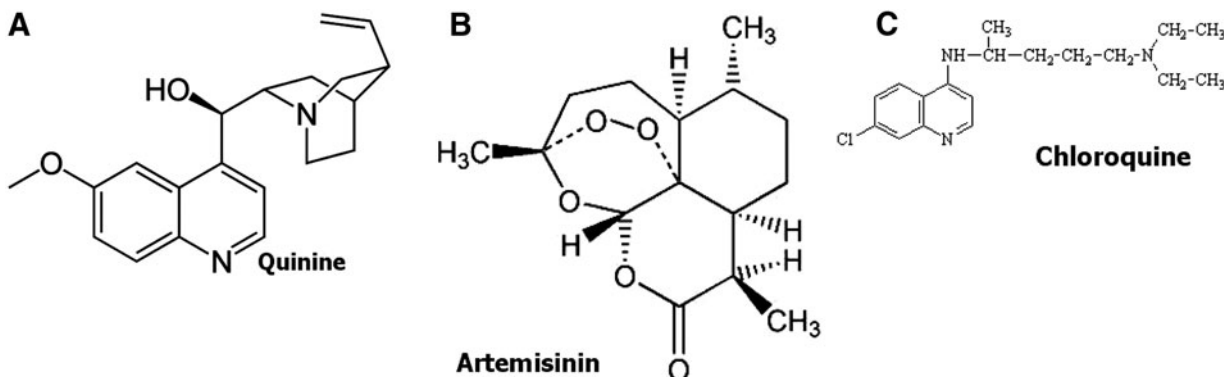

FIG. 2. Chemical structures of quinine (**A**), artemisinin (**B**), and chloroquine (**C**).

melfoquine, and amodiaquine), which have developed resistance to *P. falciparum* parasites when used in monotherapy. The use of the conventional drugs in combination therapy might not solve the problem of multidrug resistance of the parasites in the near future. There is an urgent need in discovering and developing new antimalarial drugs from traditional medicinal plants that can be used in combination therapy with artemisinin drugs to reduce the development of resistance and the occurrence of recrudescence (Kebenei et al. 2011). Because there is an urgent need for new, more affordable and accessible antimalarials possessing original modes of action, there is a revival of research interest in medicinal plants as sources of antimalarials.

This article reviews the current status of botanical screening efforts in Africa, Asia, the Middle East, Latin America, and beyond, as well as *in vitro* and clinical studies on antimalarial plants. It is also an attempt to document and preserve our traditional knowledge and to create a database of these plants that may pave way for policymakers with scientific consensus and researchers to formulate potential plant-based novel antimalarial drugs and traditional health care practices in the near future.

Importance of the Traditional System of Medicine

Despite recent scientific advancement and globalization, the system of traditional medicine (TM) and complementary/alternative medicine (CAM) is considered to be a primary health-care modality in resource-constrained health-care settings. Herbal medicinal system has been postulated and established through empirical observation and trial-and-error experiments since time immemorial to maintain good health and alleviate ailments and diseases. Even in the era of modern computational pharmacological approach, traditional medicinal plants are an important source, as well as a tool, for treating various ailments in developing countries (Fig. 1). The recent success of drug development from medicinal plants inspires and encourages many researchers to investigate and validate the uses of traditional medicinal plants (Karunamoorthi et al. 2012a,b).

Over 70,000 angiosperm plants of the 300,000 angiosperm plants recorded so far in the world are used for medicinal purposes by people of different cultures throughout the world (Pushpangadan 2006). Because of this strong dependence on plants as medicines, ethnopharmacological studies have been conducted to determine their safety and efficiency and on the other hand to find out new active principles from plants (Bruhn and Holmested 1981).

Indeed, the induction of modern health-care services has posed an immense threat to indigenous health practices because of their potential and speedy therapeutic effects. Therefore, in the recent past, the traditional system of medicine has been disappearing, displaced, and undervalued by the people (Karunamoorthi et al. 2012b). Over the past three decades, the worldwide scientific community is extremely inclined toward our long-standing traditional system of medicine to explore the opportunities to formulate the novel phytotherapeutic agents (Karunamoorthi 2012b).

Important Antimalarial Plants

It has been estimated that the number of medicinal plants in the world varies between 30,000 and 75,000 (Pampona-Roger 2001). To date, there are 1277 plant species from 160 families listed in a database that have been actually used to treat malaria or fever (Willcox and Bodeker 2004). One of the most compelling sagas in the history of medicine and therapeutics is the emergence of the Peruvian bark (*Cinchona*) and also of the pharmacologically active substance derived from it, quinine. Its discovery involved exploration, exploitation, and secrecy (Lee 2002a).

Cinchona: The tree of fever

For centuries there was no specific treatment for malaria, and it was not until the 17th century that Spanish colonizers brought back from Peru the tree bark from which quinine was later extracted. In the 20th century, synthetic alternatives to quinine were developed (Butler et al. 2010). The discovery of chloroquine and its subsequent worldwide use against malaria in the 20th century produced one of the greatest public health advances ever achieved by a drug against an infectious disease (Wellems 2002). Quinine was used as a template for the synthesis of another antimalarial drug, chloroquine, in 1940.

Cinchona has been known in the West for almost 400 years (Lee 2002a). The first widely used antimalarial drug was quinine, a natural product extracted from the bark of the tree *Cinchona calisaya*. Synthetic derivatives of quinine, such as 8-aminoquinoline primaquine and 4-aminoquinoline chloroquine, can be traced back to the pioneering work of Ehrlich on Methylene Blue in the late 19th century. These drugs cause parasite death by blocking the polymerization of the toxic byproduct of hemoglobin degradation, heme, into insoluble and nontoxic pigment granules, resulting in cell lysis and parasite cell autodigestion (Olliaro and Yuthavong 1999).

History of chloroquine: An incredible chapter in the control of malaria

In 1820, quinine was isolated by the French scientists Pelletier and Caventou from the bark of the *Cinchona* spp. (Oliveira et al. 2009). Many physicians are familiar with the story of the Countess of Chinchón, wife of the Viceroy of Peru. It was claimed by Bado that she was cured of a certain ague by *Cinchona* bark sometime in the late 1620s or early 1630s (Jaramillo-Arango 1949), and thus the genus *Cinchona* is said to have been named after the Spanish Countess of Chinchón (Garnham 1966).

The first definite written account of the medicinal properties of the bark appears to be that by Fray Antonio de la Calancha, an Augustinian missionary, in 1633, who wrote an account of "the fever tree" which "grows in Loja, Peru, the bark of which when made into a powder and given as a beverage, cured the tertian fevers." He also described its widespread use in Lima, the capital of Peru (Paredes-Borja 1946). In 1630, Juan Lopez, a missionary Jesuit, learned of the bark from Pedro Leiva, chieftain of the Malacatos tribe. He, and probably other Jesuits, took the knowledge of the bark and seeds back to their headquarters, St. Paul's at Lima, and then to Europe (Lee 2002a), where it was used for centuries to treat human malaria with efficacy.

In the 17th century, Rome had been a malarious zone, and many Catholic cardinals died of the "malignant ague" (or malaria) while attending the papal congregations in the Eternal City. By the time of the Conclave of 1655, during

which Alexander VII was elected Pope, despite the availability of the bark, the "malignant ague" had not been recorded among the attendees, although Cardinal de Lugo died in 1660 due to the same malignant ague. Redi wrote some years later to the noted Jesuit Chircher that "the whole World owes a debt of gratitude to those Fathers of your most venerable Order who were the very first, much to their glory, to bring the bark to Europe." We would now add "and in particular to de Lugo and Puccerini" (Redi 1966). Cinchona plantations were established in Java, and they were the source of quinine supply until the Second World War (Krettli et al. 2001).

In 1940, the antimalarial drug chloroquine was synthesized. The structure of quinine was established by Rabe in 1908, and its synthesis was accomplished in 1944 by Woodward and Doering (Oliveira et al. 2009). However, this synthetic production is by industrial means and is both complex and costly. It is currently derived by extraction from the *Cinchona* spp., which grows wild in South America and is cultivated in Java (Boulos et al. 1997). Chloroquine became the chief replacement for quinine during the Second World War, and until recently this was the only drug used for the treatment of malaria (Bharel et al. 1996, Krettli et al. 2001).

Chloroquine resistance: A great disaster in the fight against malaria

Chloroquine was close to the ideal antimalarial drug and was used for decades due to its high efficacy against all species of malaria parasites and its high tolerance (Krettli et al. 2001). However, *P. falciparum,* the most malignant of the four human malaria parasite species, showed foci of chloroquine resistance (CQR) in Southeast Asia and South America in the late 1950s, Papua New Guinea in the 1960s, and East Africa in the late 1970s. The steady and unremitting spread of CQR from these foci could only be met by a few alternative drugs, all of which were more expensive and encountered resistance problems of their own, or were less safe and more difficult to use than chloroquine itself (Wellems 2002). Over the last 30 years, the increasing prevalence of resistant strains of *P. falciparum* was the major factor responsible for the increase in mortality that occurred mainly in Africa (World Malaria Report 2005).

Artemisia *(Qinghaosu or the sweet wormwood): The magical Chinese thyme*

The genus *Artemisia* is a member of the family Compositae and comprises more than 300 species of annual, biennial, and perennial herbs (and shrubs) (Hyam and Pankhurst 1995). The plants have pinnate, divided, silky, hairy leaves, and these are often grey to white in color. The flowers are pendant and daisy-like but with no rays (Lee 2002b). *A. annua* has been known to the Chinese herbal practitioners for at least 1000 years, but was introduced into Western medicine only during the past 30 years. A major difference between *Cinchona* and *Artemisia* is the speed with which the active principle of the latter, artemisinin was isolated, synthesized, and then modified to produce effective therapeutic entities, largely due to the efficiency of modern chemical techniques (Lee 2002b). In 1972, the artemisinin compound was isolated from *A. annua*; this plant species has had many traditional uses in China for several millennia (Wright 2005a).

History of artemisinin derivatives

In China, around 2800 BC, Shen Nung was known as the "Divine Ploughman" (Huang 1998), and his works were later set down by an anonymous scribe in 101 BC. He codified rules for the cultivation of crops such as rice and millet, and having tested many herbs himself, described those that were poisonous and those that might be useful in medicine. Amongst the herbs described by the Ploughman was Qinghaosu, an agent effective in the treatment of fever (Lee 2002b).

In the 1960s, China was fighting a war in the jungles of North Vietnam, a malarious region, and signs of chloroquine resistance were manifested. Unknown to the rest of the world, the Chinese government established a large research program to find a replacement for chloroquine (Li 2007). In 1967, more than 500 scientists from more than 60 institutions, including chemists, pharmacologists, medical entomologists, and doctors, were recruited by the Chinese government for the antimalaria drug project known as Project 523 (Butler et al. 2010).

Mao Zedong had insisted that traditional Chinese medicine was a "great treasure house," a phrase immortalized in "The Little Red Book" (Taylor 2005). The early studies of Qinghaosu established that this preparation was very active against malaria and that the active herb in the preparation was almost certainly *A. annua* (Qinghaosu Antimalaria Coordinating Research Group 1979, Li et al. 1982). Initial attempts to isolate the active principle or principles from the plant failed, but in 1971 success was achieved by extraction into diethyl ether at low temperature. The extract cured mice infected with *Plasmodium berghei* and, in 1972, further work culminated in the isolation of a crystalline compound called Qinghaosu (artemisinin) by the Chinese (Ying and Yu-Lin 1998).

Artemisinin chemical structure

The chemical structure of the active substance in this extract was identified in the late 1970s and was found, totally unexpectedly, to be sesquiterpene lactone peroxide. Pharmaceutical production of marketable drugs began in 1986. The WHO started to investigate artemisinin and its derivatives in the early 1990s and has promoted them on a large scale since 2004. Semisynthetic derivatives, including arteether, artemether, and sodium artesunate, are used increasingly more often (Wright 2005b). Although they are effective against CQ-resistant *P. falciparum* as single therapeutic agents, to minimize the risks of recrudescence and the development of resistance, a combination treatment with a second antimalarial drug is recommended (World Malaria Report 2005). The isolation of artemisin has inspired many research groups, since the early 1980s, to look for new plant-based antimalarial drugs to potentially contain malaria (Krettli et al. 2001). The first major hurdle in translating artemisinin into a global leader in malaria chemotherapy is its short half-life, which indicates the need for repeated doses and potential problems with treatment adherence and subsequent drug resistance (Awofeso 2011).

Ethnobotanical Studies on Traditional Antimalarial Plants

In light of this historic success and the fact that most indigenous people living in malaria endemic areas use

traditional medicines to fight this disease, there is every possibility that ethnopharmacological approaches could lead to new antimalarial agents (Phillipson and Wright 1991). The term "ethnobotany" refers to all studies that are related to the reciprocal relationship between plants and traditional peoples. Through an understanding of the biological and cultural aspects of these relationships, ethnobotany seeks to understand the practical, material, symbolic, and identity-formed potential of plants for human populations. Ethnopharmacological investigation has been found to be one of the most reliable and meaningful approaches to potent new drug discovery (Fabricant and Farnsworth 2001). This approach is based on plants used in organized traditional medical systems, such as Ayurveda, Unani, and traditional Chinese medicine (Bannerman et al. 1975, Bannerman 1979), or from herbalism, folklore, and shamanism, which concentrate on an apprenticeship system of information passed down form generation to generation through a traditional healer or herbalist (Rastogi and Dhawan 1982). This system of medicine is widely practiced in the developing countries, in particular Southeast Asia, South America, and Africa.

Plant usage custom is a result of thousands of years of experience. This expertise has been passed down to many generations chiefly through word of mouth. This mode of conveying information may result in distortion or loss of indigenous knowledge and usage custom of plants. Therefore, right now the documentation and safeguarding of these practices are becoming crucial core issues (Karunamoorthi et al. 2009a, 2009b). As a result, there is a renewed worldwide interest to explore plant-based antimalarial products by exploiting traditional medicinal systems (Karunamoorthi and Tsehaye 2012). Numerous ethnobotanical surveys on traditional antimalarial plants have been conducted to preserve traditional knowledge and to identify the people's usage customs. The most relevant studies are listed in the Table 1 (Leaman et al. 1995, Marshall et al. 2000, Randrianarivelojosia et al. 2003, Bidla et al. 2004, Asase et al. 2005, Njoroge and Bussmann 2006, Ouattara et al. 2006, Alshawsh et al. 2007, Botsaris 2007, Odugbemi et al. 2007, Roumy et al. 2007, Tene et al. 2007, Adekunle 2008, Ajibesin et al. 2008, Hlaing et al. 2008, Ramalhete et al. 2008, Kantamreddi et al. 2009, Al-Adhroey et al. 2010, Jain and Singh 2010, Karou et al. 2011, Nadembega et al. 2011, Namsa et al. 2011, Karunamoorthi and Tsehaye 2012).

The above-cited studies have specifically highlighted that the ethnopharmacological approach is the first phase for prioritizing plants as antimalarials and one of the most important and powerful tools for picking and choosing plants among the countless promising candidates to search future ideal antimalarial drugs. Although the use of crude extracts of various antimalarial plants is a custom of time immemorial, modern affordable potent antimalarial drugs can be formulated by conducting extensive investigation regarding their bioactivity, mode of action, pharmacotherapeutics, and toxicity after proper standardization and clinical trials. However, these ethnopharmacological surveys are commonly conducted among the rural poor in the resource-poor settings, where there is a lack of sophisticated equipment, laboratories, and skilled personnel to judge the bioactivities and efficacy of these traditional antimalarial plants. Therefore, further research must be carried out by international organizations like the WHO and collaboration with other agencies in the de-veloped/developing countries with adequate funds to measure/improve their effectiveness as modern antimalarial agents.

In Vitro *Antiplasmodial Activity of Traditional Medicinal Plants*

In the developing countries, where malaria is endemic, people heavily rely on traditional medicine, the health-care modality for the treatment of malaria. However, scientific data to validate the antimalarial properties of these herbal remedies are scarce. Consequently, it is important that antimalarial medicinal plants are investigated to establish their efficacy and to determine their potential as sources of new antimalarial drugs (Ramalhete et al. 2008). Numerous studies have been undertaken across the globe to assess the *in vitro* antiplasmodial activity of traditional medicinal plants. The most important and relevant of these studies is summarized in Table 2 (Gessler et al. 1995, Awe et al. 1998, El-Tahir et al. 1999, Marshall et al. 2000, Ancolio et al. 2002, Muregi et al. 2004, Garavito et al. 2006, Ouattara et al. 2006, Muthaura et al. 2007, Nguyen-Pouplin et al. 2007, Hlaing et al. 2008, Wangchuk et al. 2010).

The presence and/or quantities of bioactive compounds in plants are influenced by survival factors, including seasons, environment, plant part used, intraspecies variation, and plant age (Weenen et al. 1990). This may explain the discrepancies observed in *in vitro* activities of the plant parts reported. The major setback of *in vitro* studies is the antiplasmodial activity (half-maximal inhibitory concentration [IC_{50} μg/Ml]) of traditional medicinal plants, and in many cases it may not be comparable. The possible explanation could be that factors such as chemotypes, environmental parameters, harvesting, solvents, and storage conditions could collectively influence the plant metabolites prior to and following harvestings, which in turn, would be reflected in the bioactivity (Ramazani et al. 2010). The regions and periods of the year of plant collection are also known to play an important role in the variation of the type of compounds found in plants as well as their concentration.

Several pharmacologically active antimalarial compounds have been isolated from different plants used in ethnomedicine. Active compounds can be isolated from different parts of medicinal plants (such as leaves, roots, bark, fruits, or seeds) varying from species to species, and the active chemical ingredients of these parts can be different from one another (Van Wyk 2000, Pamplona-Roger 2001). One part of those plants may be quite toxic or useless and another may be quite harmless and useful. In traditional therapies, the whole plant is therefore rarely used for medicine. For example, the stem bark of *Gardenia jovistonatis* showed antiplasmodial activity against *P. falciparum* malaria, whereas no activity was found in the fruit of this species; the aerial part crude extract of *Cassia* species exhibits high antiplasmodial activity against different strains of *P. falciparum* (El-Tahir 1999).

With the problems of increasing levels of drug resistance and the difficulties in poor areas of being able to afford and access effective antimalarial drugs, traditional medicines could be an important and sustainable source of treatment (Willcox and Bodeker 2004). Over 1200 plant species are reportedly used for the treatment of malaria and fevers worldwide, and are potentially important sources of new antimalarial treatments (Willcox et al. 2004). According to

TABLE 1. THE BOTANICAL NAMES, FAMILY NAME, PLANT PARTS USED, MODE OF TRADITIONAL ADMINISTRATION
AND THE COUNTRY CROSS-REFERENCED IN PUBLISHED LITERATURE

Country	Family	Plant name	Used plant parts	Mode of Administration	References
Brazil	Simarubacea	*Simaba ferruginea* A.	Barks and roots	NA	Botsaris 2007
	Gentianace	*Tachia guianensis*	Branches and roots	NA	
	Annonaceae	*Xylopia brasiliensis*	Seeds and barks	NA	
	Rubiaceae	*Remijia ferruginea*	Barks	NA	
	Simaroubacea	*Picrolemma sprucei*	Aerial parts and roots	NA	
Burkina Faso	Mimosaceae	*Albizzia chevalieri* Harms.	Root	Decoction	Nadembega et al. 2011
	Annonaceae	*Annona senegalensis* Pers.	Root	Charred	
	Liliaceae	*Allium sativum* L.	Bulb	Maceration	
	Combretacea	*Anogeissus leiocarpa* Guill. & Perr.	Leaf	Decoction	
	Fabaceae	*Arachis hypogaea* L.	Leaf	Maceration	
	Meliaceae	*Azadirachta indica* A. Juss.	Leaf	Decoction	
	Capparadaceae	*Bocia senegalensis* Lam.	Root	Powder	
	Capparaceae	*Cadaba farinosa* Fosrk.	Leaf	Decoction	
	Capparadaceae	*Capparis sepiaria* (L.)	Root	Decoction	
	Asclepiadaceae	*Caralluma dalzielli* N.E.Br.	Tubercle	Maceration	
	Solanaceae	*Capsicum frutescens* L.	Fruit	Maceration	
	Caesalpiniaceae	*Cassia mimosoides* L.	Stem bark	Decoction	
	Caesalpiniaceae	*Cassia nigricans* Vahl.	Whole plant	Decoction	
	Rutaceae	*Cochlospermum planchonii* Hook.	Tubercle	Inhalation	
	Combretaceae	*Combretum micranthum* DC.	Stem bark	Decoction	
	Caricaceae	*Carica papaya* L.	Leaf and fruit	Decoction	
	Zigophyllaceae	*Balanites aegyptiaca* (L.) Del.	Root	Maceration	
Burkino Faso	Leguminosae	*Swartzia madagascariensis*	Roots bark	NA	Ouattara et al. 2006
	Combretaceae	*Combretum glutinosum*	Tender leaves	NA	
	Menispermaceae	*Tinospora bakis*	Roots	NA	
Burma	Lauraceae	*Cinnamomum tamal*.F.Nees.	Leaves	NA	Hlaing et al. 2008
	Lauraceae	*Cinnamomum zeylanicum* Linn.	Barks	NA	
	Rutaceae	*Citrus medica*	Whole fruits	NA	
	Umbelliferae	*Ferula foetida* Regal.	Latex	NA	
	Myristicaceae	*Myristica fragrans*	Whole fruits	NA	
	Piperaceae	*Piper nigrum* Linn.	Seeds	NA	
	Zingiberaceae	*Zingiber cassumunar* Roxb.	R h i z o m e s	NA	
Cameroon	Annonaceae	*Annona muricana*	Leaves	Water decoction/oral	Bidla et al. 2004
	Anacardiaceae	*Mangifera indicus*	Leaves, roots	Water decoction/ oral and steam-baths	
	Euphorbiaceae	*Alcronanes difformis*	Leaf	Water decoction/oral	
	Menispermaceae	*Peniantus longifolius*	Stem bark	Water decoction/oral	
Cameroon	Melianthaceae	*Bersama engleriana*	Leaves	Water decoction/ oral, infusion and steam-baths	Ngemenya et al. 2004
	Combretaceae	*Terminalia superba*	Leaf	Water decoction/ oral	
	Simaroubaceae	*Odyendyea gabonensis*	Leaves	Water decoction/oral	
Côte d'Ivoire	Fabaceae	*Albizia ferruginea*	Leaf	Decoction and drink	Zirihi Guédé et al. 2010

(*continued*)

TABLE 1. (CONTINUED)

Country	Family	Plant name	Used plant parts	Mode of Administration	References
	Euphorbiaceae	*Alchornea cordifolia*	Leaf	Decoction and drink	
	Amaranthaceae	*Alternanthera pungens*	Whole plant	Decoction and drink	
	Loganiacee	*Anthocleista djalonensis*	Stem bark	Decoction and drink	
	Caesalpiniaceae	*Anthonotha macrophylla*	Stem bark	Decoction and drink	
	Melianthaceae	*Bersama abyssinica*	Leaf	Decoction and drink	
	Caesalpiniaceae	*Cassia alata*	Leaf	Decoction and drink	
	Sapotaceae	*Chrysophyllum perpulchrum*	Stem bark	Decoction and drink	
	Euphorbiaceae	*Erythrococca anomala*	Leaf	Decoction and drink	
	Asteraceae	*Microglossa pyrifolia*	Root bark	Decoction and drink	
Ecuador	Podocarpaceae	*Podocarpus sprucei* Parl.	Leaf	Aqueous infusion	Tene et al. 2007
	Mimosaceae	*Inga acreana* Harms	Stem and leaf	Aqueous infusion and drink	
	Commelinaceae	*Tradescantia* sp. L.	Stem	Aqueous infusion and drink	
Ethiopia	Lamiaceae	*Ocimum lamiifolium* Hochst. ex Benth.	Leaf	Concoction	Karunamoorthi and Tsehaye 2012
	Polygonaceae	*Rumex abyssinicus* Jacq.	Leaf & Stem	Crude extract/ Juice of the plant parts (herbal drug) is taken orally	
	Melianthaceae	*Bersama abyssinica* Fresen.	Leaf, root bark, and stem	Herbal drug and decoction are taken orally	
	Simaroubaceae	*Brucea antidysenterica* J.F. Mill.	Stem, bark seed	Decoction	
	Brassicaceae	*Brassica nigra* (L.) Koch.	Seed	Juice of crushed root with water is taken orally	
	Cucurbitaceae	*Zehneria scabra* (Lf.) Sond.	Root	Drinking juice of root	
	Phytolaccacaa	*Phytolacca dodecandra* L'Hér.	Leaf	Topical application	
	Verbenaceae	*Clerodendrum myricoides* (Hochst.) Vatke	Leaf	Leaf powder is sprinkled on burning charcoal and smoke is inhaled nasally	
	Acanthacea	*Justilia schimperand.* (Hochst ex Nees) T. Alnder	Root	Burning on charcoal and smoke is inhaled nasally	
	Zingiberaceae	*Zingiber officinale* Roscoe	Rhizome	Burning on charcoal and smoke is inhaled nasally	
	Asteraceae	*Vernonia amygdalina* Del.	Leaf	Decoction	
	Carcaceae	*Carica papaya* L.	Leaf	The seeds are pounded and the powder mixed with honey taken orally	

(continued)

TABLE 1. (CONTINUED)

Country	Family	Plant name	Used plant parts	Mode of Administration	References
	Lilliaceae	*Allium sativum* L.	Bulb	Oral	
	Mimosaceae	*Acacia catechu* (L.f.) Willd.	Leaf	The fresh leaves are soaked in warm water and the filtrate taken orally	
	Fabaceae	*Calpurna ourea* (Ait.) Benth	Leaf	The pounded leaves are lit with fire and the smoke inhaled	
	Euphorbiaceae	*Croton macrostachyus* Hochst. Ex Del.	Leaf/bark/roots	Juice from the boiled plant parts is drink orally	
Ghana	Rutaceae	*Afraegle paniculata*	Roots	Boil roots and drink as required.	Asase et al. 2005
	Anacardiaceae	*Haematostaphis barteri*	Leaves with leaves of *Pseudocedrela kotschyi* and *Ficus ghaphalocarpa*	Boil drink mornings and evenings and body massage	
	Leguminosae	*Indigoera pulchra*	Whole plants	Boil whole plants, drink and massage body	
	Anacardiaceae	*Ozoroa insignis*	Leaves and twigs	Boils leaves and twigs, and drink	
	Loganiaceae	*Strychnos spinosa*	Leaves and twigs	Boil leaves and drink. Grind twigs, add to pomade and smear on body	
Ghana	Rubiaceae	*Morinda lucida* Benth	Dried stem and roots	Boil in water or drink local gin infusions	Asase and Oppong-Mensah 2009
	Rubiaceae	*Nauclea latifolia* Sm.	Dried stems	Soak in water or add porridge, and drink	
	Apocynaceae	*Alstonia boonei* De.Wild.	Dried stem and roots	Boil in water and drink	
	Combretaceae	*Terminalia ivorensis* A. Chev	Dried stems	Boil in water and drink decoction	
	Rubiaceae	*Nauclea latifolia* Sm.	Dried stems	Soak in water or add porridge, and drink	
	Steruliaceae	*Theombroma cacao* L.	Fresh and dried leaves	Boil in water and drink decoction as required	
India	Acanthaceae	*Andrographis paniculata* Linn	Whole plant	One teaspoon decoction with *Tinospora cordifolia* is taken orally for 3 days	Jain and Singh 2010
India	Acanthaceae	*Andrographis paniculata*	Whole plant	Whole plant is boiled and decoction twice a day	Namsa et al. 2011
	Asteraceae	*Artemisia vulgaris* L.	Stem and flowering tip	Leaf decoction with honey orally thrice/day	
	Meliaceae	*Azadirachta indica* A. Juss	Bark and leaf	Leaf decoction with honey orally once/day	
	Ranunculaceae	*Coptis teeta* Wall	Seeds, Roots, Rhizomes	Smoke and root, seeds and rhizome decoction with honey thrice/day	

(continued)

TABLE 1. (CONTINUED)

Country	Family	Plant name	Used plant parts	Mode of Administration	References
	Menispermaceae	*Cissampelos pareira* L.	Roots	Smoke and root decoction is taken orally once/day	
India	Acanthaceae	*Andrographis paniculata* (Burm.f.) Nees	Whole plant	Water extract	Kantamreddi et al. 2009
	Barringtoniaceae	*Barringtonia acutangula* L.	Root	Root juice by grinding	
	Combretaceae	*Calycopteris floribunda* (Roxb.) Poir.	Leaves	Water extract of dry leaf	
	Lamiaceae	*Ocimum canum* Sims	Leaves	Fresh leaf juice	
	Lythraceae	*Woodfordia floribunda* Salisb	Leaves	Water extract of dry leaf	
	Moraceae	*Ficus hispida* L.f.	Fruits	Fruit juice by grinding	
	Rutaceae	*Toddalia asiatica* (L.) Lam.	Roots	Root juice	
	Sapindaceae	*Schleichera oleosa* (Lour.) Oken.	Bark	Bark juice	
	Scrophulariaceae	*Bacopa monnieri* (L.) Wettstein	Whole plant	Expressed juice of whole plant	
	Simaroubaceae	*Ailanthus excelsa* Roxb.	Leaves	Leaf juice or bark juice	
	Verbenaceae	*Vitex negundo* L	Leaves and flowers	Leaf decoction (as a tea form) or juice from fresh flower	
	Rubiaceae	*Adina cordifolia* (Roxb.) Hook.f.ex *Brandis*	Bark	Bark juice by grinding	
	Verbenaceae	*Clerodendrum viscosum* Vent.	Leaves	Leaf juice	
Indonesia	Annonaceae	*Annona muricata* L.	Leaves	Rubifacient+petrol	
	Araliaceae	*Schefflera* sp.	Leaves	Decoction	
	Piperaceae	*Piper betle* L.	Leaves	Decoction	
	Bombacaceae	*Eriodendron anfractosum* D.C.	Leaves+ rice water	Poultice	
	Piperaceae	*Piper arborescens* Miq.	Roots	Infusion	
Kenya	Fabaceae	*Tephrosia purpurea* (Linn.) Pers	Whole plant	Decoction (one teaspoonful) is given for 3 days	Njoroge and Bussmann 2006
	Caesalpiniaceae	*Caesalpinia volkensii* Harms	NA	NA	
	Loganiaceae	*Strychnos henningsii* Gilg	NA	NA	
	Lamiaceae	*Ajuga remota* Benth	NA	NA	
	Canellaceae	*Warburgia ugandensis* Sprague	NA	NA	
	Oleaceae	*Olea europaea* L.	NA	NA	
Madagascar	Canellaceae	*Cinnamosma fragrans* H. Bn.	Leaves and bark	A decoction of the leaf and bark is drunk	Randrian-arivelojosia et al. 2003
	Gramineae	*Andropogon schoenanthus/nardis* L.	Leaves	The leaf decoction is drunk with plenty of sugar and the fumes are inhaled as a febrifuge.	
	Leguminosae	*Desmodium mauritianum & Desmodium hirtum*	Leaf and bark	A decoction of the leaf and bark is mixed with a selection of five other plants—*Ficus megapoda, Nymphaea*	

TABLE 1. (CONTINUED)

Country	Family	Plant name	Used plant parts	Mode of Administration	References
				lotus, Noronhia linocerioides, Vepris ampody, Zanthoxylum madagascariense, Gambeya boiviniana, Peddia involucrata.	
	Moraceae	*Ficus megapoda* Bak.	Leaves and bark	A decoction of the leaf and bark is drunk (1 bowl, 3–4 times daily)	
Malaysia	Meliaceae	*Azadirachta indica*	Leaves	Decoction	Al-Adhroey et al. 2010
	Simaroubaceae	*Brucea javanica*	Leaves, fruits	Infusion	
	Fabaceae	*Cassia siamea*	Stem and bark	Decoction	
	Simaroubaceae	*Eurycoma longifolia*	Root	Decoction	
	Myrsinaceae	*Labisia pumila*	Leaves	Decoction	
	Zingiberaceae	*Languas galanga*	Rhizome	Decoction	
	Meliaceae	*Lansium domesticum*	Peel and bark	Infusion	
	Euphorbiaceae	*Elateriospermum tapos*	Leaves	Decoction	
	Zingiberaceae	*Curcuma domestica* L.	Root	Decoction	
	Ranunculaceae	*Nigella sativa* L.	Seeds	Infusion	
	Piperaceae	*Piper betle*	Leaves	Chewing	
	Apocynaceae	*Alstonia angustiloba*	Gum	Decoction	
	Phyllanthaceae	*Phyllanthus niruri*	Whole plant	Decoction	
	Gesneriaceae	*Aeschynanthus* sp. Jack	Leaves	Decoction	
	Lamiaceae	*Ocimum tenuiflorum* L	Leaves and seed	Decoction	
	Rubiaceae	*Morinda citrifolia*	Leaves and fruits	Decoction	
Mozambique	Fabaceae	*Acacia karroo* Hayne	Aerial parts	NA	Ramalhete et al. 2008
	Aloaceae	*Aloe parvibracteata* Schonland	Leaves	NA	
	Euphorbiaceae	*Bridelia cathartica* Bertol.f.	Roots	NA	
	Fabaceae	*Cassia abbreviate* Oliv.	Stem bark	NA	
	Fabaceae	*Cassia occidentalis* L.	Roots	NA	
	Lamiaceae	*Leonotis leonurus* (L.) R.Br	Aerial parts	NA	
	Cucurbitaceae	*Momordica balsamina* L.	Aerial parts	NA	
	Caesalpiniaceae	*Parkinsonia aculeata* L.	Aerial parts	NA	
	Plumbaginaceae	*Plumbago auriculata* Lam.	Aerial parts	NA	
	Araliaceae	*Schefflera actinophylla* (Endl.) Harms	Leaves	NA	
	Apocynaceae	*Tabernaemontana elegans* Strapt.	Leaves	NA	
	Meliaceae	*Trichilia emetica* Vahl	Seeds	NA	
Nigeria	Anacardiaceae	*Anacardium occidentale* L.	Bark	Boiled in water as decoction	Ajibesin et al. 2008
	Apocynaceae	*Alstonia boonei* De Wild.	Roots, leaves	Boiled in water as decoction	
	Bombacaceae	*Adansonia digitata* L.	Leaves	Boiled in water to make decoction	
	Caesalpiniaceae	*Daniellia ogea* (Harrms) Rolfe ex Holl.	Root	Boiled or macerated in water to make decoction or infusion	
	Euphorbiaceae	*Phyllanthus amarus* Schum & Thonn.	Leaves	Boiled in water as decoction	
	Gramineae	*Cymbopogon citratus* (DC) Stapf	Leaves	Boiled in water to make decoction	
	Labiatae	*Solenostemon monostachyus* (P. Beauv.) Briq	Leaves	Crushed in water and drink	

TABLE 1. (CONTINUED)

Country	Family	Plant name	Used plant parts	Mode of Administration	References
	Mimosaceae	*Cylicodiscus gabunensis* Harms	Leaves	Boiled in water as decoction	
	Rubiaceae	*Nuclea latifolia* Sm.	Root	Boiled or macerated in water to make decoction or infusion	
Nigeria	Apocynaceae	*Rauvolfia vomitoria*	Roots, barks, leaves	NA	Odugbemi et al. 2007
	Periplocaceae	*Mondia whitei*	Roots and whole plant	NA	
	Cannaceae	*Canna indica*	Leaves	NA	
	Solanaceae	*Solanum nigrum*	Leaves	NA	
	Poaceae	*Cymbopogon citratus*	Leaves	NA	
	Meliaceae	*Khaya grandifoliola*	Bark	Decoction, Infusion	
	Rubiaceae	*Morinda lucida*	Roots, leaves	Tincture, infusion	
	Meliaceae	*Azadirachta indica*	Bark, leaves	Decoction	
	Zingiberaceae	*Curcuma longa*	Rhizome	Tincture, Decoction	
	Caricaceae	*Carica papaya*	Fruit, leaves	Infusion	
	Compositae	*Vernonia amydalina*	Leaves	Infusion	
	Apocynaceae	*Rauvolfia vomitoria*	Root	Infusion	
	Apocynaceae	*Alstonia boonei*	Bark	Infusion, tincture, decoction.	
	Annonaceae	*Enantia chlorantha*	Bark	Decoction, tincture, infusion	
Nigeria	Alliaceae	*Allium ascalonicum*	Leaves	Boil with mango, neem, and dry pawpaw leaves as concoction	Adekunle 2008
	Anacardiaceae	*Anacardium occidentale*	Leaves	Boil singly or with other herbs decoction	
	Apocynaceae	*Alstonia boonai*	Leaves	Boil singly or in combination with other herbs	
	Bambusaseae	*Babusa vulgaris*	Leaves	Boil with other herbs decoction	
	Bignonaceae	*Newbouldia laevis*	Leaves	Boil with other herbs decoction	
	Caricaceae	*Carica papaya*	Leaves	Boil with other ingredients and drink	
	Sterculiceae	*Cola latertia*	Leaves	Boil with other herbs and drink the concoction	
	Rubiaceae	*Morinda lucida*	Leaves	Squeeze the leaves in water and drink the extracts. Cook with other herbs and drink as concoction	
	Bombacaceae	*Adansonia digitata*	Leaves	Boil singly and drink the extract	
	Combretaceae	*Combretum reticulatum*	Leaves	Boil singly and drink the extract	
	Compositae	*Sida acuta*	Leaves	Boil singly and drink the extract	
Peru	Menispermaceae	*Abuta rufescens* Aubl.	Stem	Decoction	Roumy et al. 2007
	Fabaceae	*Cassia loretensis*	Bark	Decoction	
	Solanaceae	*Cyphomandra hartwegii*	Leaves	Infusion, steaming bath with fresh leaf infusion for children	

(continued)

TABLE 1. (CONTINUED)

Country	Family	Plant name	Used plant parts	Mode of Administration	References
	Apiaceae	*Eryngium foetidum* L.	Leaves	Decoction	
	Lecythidaceae	*Grias neuberthii*	Stem and bark	Infusion of the stem and bark decoction	
	Lacistemaceae	*Lacistema aggregatum*	Wood	Decoction	
	Asteraceae	*Mikania congesta*	Aerial parts	Infusion	
	Rubiaceae	*Pagamea guianensis*	Dried stem	Decoction	
	Fabaceae	*Pithecellobium laetum* Benth.	Aerial parts	Infusion	
	Linaceae	*Roucheria punctata*	Bark	Decoction	
	Rubiaceae	*Sabicea villosa*	Leaves	Infusion	
	Verbenaceae	*Verbena litoralis* Kunth	Leaves	Infusion	
	Myristicaceae	*Virola calophylla*	Inner bark	Decoction	
	Fabaceae	*Zygia latifolia* (L.)	Leaves and resin	Infusion of the leaves, ingestion of the fresh bark resin	
Sierra Leone	Amaranthaceae	*Cyathula prostrata*	Leaves	NA	Marshall et al. 2000
	Annonaceae	*Uvaria chamae*	Wood	NA	
	Apocynaceae	*Catharanthus roseus*	Leaves	NA	
	Annonaceae	*Xylopia aethiopica*	Wood	NA	
	Euphorbiaceae	*Mareya micrantha*	Roots	NA	
	Passifloraceae	*Adenia lobata*	Wood	NA	
	Sapindaceae	*Paullinia pinnata*	Leaves	NA	
	Verbenaceae	*Lantana camara*	Leaves	NA	
	Rubiaceae	*Morinda geminata*	Leaves	NA	
Togo Maritime Region	Bombacaceae	*Adansonia digitata* L.	Leaves	Water decoction/oral	Karou et al. 2011
	Euphorbiaceae	*Alchornea cordifolia*	Leaves	Water decoction/oral	
	Apocynaceae	*Alstonia boonei*	Stem bark	Water decoction/oral	
	Arecaceae	*Borassus flabellifer* L.	Leaves	Water decoction/oral	
	Fabaceae	*Cassia siamea Lam.*	Leaves	Water decoction/oral	
	Rutaceae	*Citrus aurantiifolia*	Fruit	Juice/oral	
	Gramineae	*Cymbopogon citratus* (DC) Stapf	Leaves	Boiled in water to make decoction	
	Moraceae	*Ficus exasperata* Vahl	Leaves	Water decoction/oral	
	Malvaceae	*Gossypium hirsutum* L.	Leaves	Water decoction/oral	
	Sapindaceae	*Paullinia pinnata* L.	Leaves and stem	Water decoction/oral	
	Araceae	*Pistia stratiotes* L.	Whole plant	Water decoction/oral	
	Annonaceae	*Xylopia aethiopica* A.Rich	Fruit	Maceration/oral	
	Poaceae	*Zea mays* L.	Fruit	Maceration/oral	
Yemen	Euphorbiaceae	*Acalypha fruticosa* L.	Leaves	NA	Alshawsh et al. 2007
	Meliaceae	*Azadirachta indica* A. Juss	Leaves	NA	
	Burseraceae	*Boswellia elongata* Balf. f.	Bark	NA	
	Vitaceae	*Cissus rotundifolia* (Forssk.) Vahl	Leaves	NA	
	Cucurbitaceae	*Dendrosicyos socotrana* Balf. f.	Leaves	NA	
	Boraginaceae	*Echium vulgare* L.	Leaves	NA	

NA, related information not available.

TABLE 2. THE BOTANICAL NAMES, FAMILY NAME, PLANT PARTS TESTED, EXTRACTION TYPE, IN VITRO ANTIPLASMODIAL ACTIVITY [IC_{50} (μg/Ml)] OF TRADITIONAL MEDICINAL PLANTS AND THE COUNTRY OF CROSS-REFERENCED IN PUBLISHED LITERATURE

Country	Family	Plant name	Plant part tested	Malaria parasite species	Extract type	IC_{50} (μg/Ml)	Drug concentration (μg/mL)		References
							40	20	
Myanmar	Lauraceae	*Cinnamomum tamala.F.Nees.*	Leaves	*P. falciparum* CQ resistant strain	Crude-ethanolic	NA	100%	98.50%	Hlaing et al. 2008
	Lauraceae	*Cinnamomum zeylanicum* Linn.	Barks		Crude-ethanolic	NA	90.50%	76.20%	
	Rutaceae	*Citrus medica*	Whole fruits		Crude-ethanolic	NA	100%	88.90%	
	Umbelliferae	*Ferula foetida* Regal.	Latex		Crude-ethanolic	NA	100%	90.50%	
	Myristicaceae	*Myristica fragrans*	Whole fruits		Crude-ethanolic	NA	100%	92.90%	
	Piperaceae	*Piper nigrum* Linn.	Seeds		Crude-ethanolic	NA	100%	95.20%	
	Zingiberaceae	*Zingiber cassumunar* Roxb.	Rhizomes		Crude-ethanolic	NA	100%	100.00%	
Burkino Faso	Leguminosae	*Savartzia madagascariensis*	Roots bark	*P. falciparum* CQ resistant strain	Hydro-methanol	NA	NA	NA	Ouattara et al. 2006
	Combretaceae	*Combretum glutinosum*	Tender leaves		Hydro-methanol	NA	NA	NA	
	Menispermaceae	*Tinospora bakis*	Roots		Hydro-methanol	NA	NA	NA	
Sierra Leone	Amaranthaceae	*Cyathula prostrata*	Leaves	*P. falciparum* CQ resistant strain	Ethanol	50	NA	NA	Marshall et al. 2000
	Annonaceae	*Utvaria chamae*	Wood		Ethanol	125	NA	NA	
	Apocynaceae	*Catharanthus roseus*	Leaves		Ethanol	125	NA	NA	
	Annonaceae	*Xylopia aethiopica*	Wood		Ethanol	31	NA	NA	
	Euphorbiaceae	*Mareya micrantha*	Roots		Ethanol	500	NA	NA	
	Passifloraceae	*Adenia lobata*	Wood		Ethanol	125	NA	NA	
	Sapindaceae	*Paullinia pinnata*	Leaves		Ethanol	125	NA	NA	
	Verbenaceae	*Lantana camara*	Leaves		Ethanol	125	NA	NA	
	Rubiaceae	*Morinda geminata*	Leaves		Ethanol	125	NA	NA	
Nigeria	Anacardiaceae	*Mangifera indica* Linn.	Stem bark	*P. yoelii nigeriensis*	Methanol	NA	Schizontocidal effect during early infection, and also demonstrated repository activity	NA	Awe et al. 1998
Sudan	Aristolchiaceae	*Aristolchia bracteata*	Stem	*P. falciparum* Dd2 (chloroquine resistant and pyrimethamine sensitive)	Water	>500	NA	NA	El-Tahir et al. 1999.

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(continued)

TABLE 2. (CONTINUED)

Country	Family	Plant name	Plant part tested	Malaria parasite species	Extract type	IC$_{50}$ (μg/Ml)	Drug concentration (μg/mL) 40	20	References
	Aristolchiaceae	A. bracteata	Stem		Methanol	190	NA	NA	
	Aristolchiaceae	A. bracteata	Root		Methanol	5	NA	NA	
	Aristolchiaceae	A. bracteata	Seed		Water	>500	NA	NA	
	Aristolchiaceae	A. bracteata	Seed capsules		Methanol	260	NA	NA	
	Balantitiaceae	Balanites aegyptiaca	Mesocarp		80% Methanol	70	NA	NA	
	Balantitiaceae	Balanites aegyptiaca	Stem bark		80% Methanol	55	NA	NA	
	Caesalpiniaceae	Cassia tora	Aerial part		80% Methanol	3.3	NA	NA	
	Caesalpiniaceae	Tamarindus indica	Leaves		80% Methanol	220	NA	NA	
	Rubiaceae	Gardenia jovis tonatis	Leaves		80% Methanol	3.3	NA	NA	
	Rubiaceae	Haplophyllum tuberculatum	Aerial part		80% Methanol	1.5	NA	NA	
	Rubiaceae	H. tuberculatum	Root		80% Methanol	18	NA	NA	
Kenya	Labiatae	Ajuga remota Benth.	Leaves	*P. falciparum* (K 39) *CQ sensitive*	Methanol	21.6±1.36	NA	NA	Muregi et al. 2004
	Caesalpinaceae	Senna didymobotrya	Leaves		Methanol	>100	NA	NA	
	Menispermaceae	Stephania abyssinica	Roots		Methanol	63.8±3.44	NA	NA	
	Chrysobalanaceae	Parinari curatellifolia Benth.	Aerial parts		Methanol	>100	NA	NA	
	Cucurbitaceae	Cucumis figarei Naud.	Whole plant		Methanol	>100	NA	NA	
	Labiatae	Leonotis mollissima Gürke	Leaves		Methanol	80.7±4.07	NA	NA	
	Meliaceae	Ekebergia capensis Sparrm	Stem bark		Methanol	4.6±0.28	NA	NA	
	Meliaceae	Melia azedarach L.	Leaves		Methanol	80.7±4.07	NA	NA	
	Menispermaceae	Stephania abyssinica	Roots		Methanol	63.8±3.44	NA	NA	
	Mimosaceae	Acacia hockii De Wild.	Root bark		Methanol	>100	NA	NA	
	Verbenaceae	Clerodendrum myricoides (Hochst.) Vatke	Leaves/root bark		Methanol	8.6±3.51	NA	NA	
Vietnam	Bixaceae	Bixa orellana L.	Leaves	*P. falciparum* FcB1 (CQ Resistance Colombian strain)	Methanol	13.9±0.6	NA	NA	Nguyen-Pouplin et al. 2007
	Annonaceae	Annona muricata L.	Leaves		Cyclohexane	19.9±2.7	NA	NA	
	Apocynaceae	Wrightia dubia (Sims.) Spreng.	Leaves		Methylene chloride	17.3±1.1	NA	NA	
	Elaeocarpaceae	Elaeocarpus kontumensis Gagn.	Barks		Methanol	4.3±0.4	NA	NA	
	Elaeocarpaceae	E. kontumensis Gagn.	Barks		Crude extract	5.1±0.2	NA	NA	
	Fabaceae papilionoideae	Milletia diptera Gagn.	Barks		Cyclohexane	5.5±0.5	NA	NA	
	Verbenaceae	Clerodendrum inerme (L.) Gaertn.	Roots		Cyclohexane	10.0±1.5	NA	NA	
	Theaceae	Anneslea fragrans Wall.	Leaves		Cyclohexane	15.3±0.8	NA	NA	

TABLE 2. (CONTINUED)

Country	Family	Plant name	Plant part tested	Malaria parasite species	Extract type	IC_{50} (µg/Ml)	Drug concentration (µg/mL) 40	20	References
	Theaceae	A. fragrans Wall.	Leaves		Methylene chloride	8.6±1.4	NA	NA	
	Simaroubaceae	Brucea javanica (L.) Merr.	Roots		Cyclohexane	1.1±0.2	NA	NA	
	Simaroubaceae	Eurycoma longifolia Jack	Barks		Methylene chloride	1.5±0.4	NA	NA	
Colombia	Menispermaceae	Abuta grandifolia	Leaves	P. falciparum CQ resistant (FcB2)	Alkaloid crude extract	<1	NA	NA	Garavito et al. 2006
	Mimosaceae	Acacia farnesiana (L.) Willd.	Barks		Ethanolic	1.3±0.2	NA	NA	
	Solanaceae	Acnistus arborescens (L.) Schltd.	Aerial part		Ethanolic	1.3±0.2	NA	NA	
	Asteraceae	Calea prunifolia Kunth.	Aerial part		Ethanolic	32±5	NA	NA	
	Euphorbiaceae	Croton leptostachyus Kunth.	Aerial part		Ethanolic	2.1±0.2	NA	NA	
	Piperaceae	Piper cumanense H.B. & K.	Fruit		Ethanolic	<1	NA	NA	
	Piperaceae	P. cumanense H.B. & K.	Leaves		Ethanolic	<1	NA	NA	
	Piperaceae	Piper holtonii C. DC.	Aerial parts		Ethanolic	<1	NA	NA	
	Annonaceae	Xylopia aromatica (Lam.) Mart.	Aerial parts		Ethanolic	<1	NA	NA	
Mozambique	Aloaceae	Aloe parvibracteata Schonland	Leaves	3D7 P. falciparum strain (susceptible to chloroquine)	Methanolic	>100	NA	NA	Ramalhete et al. 2008
	Fabaceae	Acacia karroo Hayne	Aerial parts		Methanolic	>100	NA	NA	
	Euphorbiaceae	Bridelia cathartica Bertol.f.	Roots		Methanolic	>100	NA	NA	
	Fabaceae	Cassia abbreviate Oliv.	Stem bark		Methanolic	>100	NA	NA	
	Lamiaceae	Leonotis leonurus (L.) R.Br	Aerial parts		Methanolic	>100	NA	NA	
	Cucurbitaceae	Momordica balsamina L.	Aerial parts		Methanolic	46.9±2.3	NA	NA	
	Plumbaginaceae	Plumbago auriculata Lam.	Aerial parts		Methanolic	80.0±15.1	NA	NA	
	Fabaceae	Senna didymobotrya Fresen.	Twigs		Methanolic	56.0±9.9	NA	NA	
	Apocynaceae	Tabernaemontana elegans Strapt.	Leaves		Methanolic	>100	NA	NA	
	Meliaceae	Trichilia emetica Vahl	Seeds		Methanolic	>100	NA	NA	
	Pittosporaceae	Pittosporum tobira	Aerial parts		n-Hexane	34.4±2.9	NA	NA	
	Araliaceae	Schefflera actinophylla	Leaves		Dimethyl sulfoxide	36.3±3.9	NA	NA	
Côte d'Ivoire	Fabaceae	Albizia ferruginea	Leaf	P. falciparum FcB1 (CQ Resistance Colombian strain)	Ethanolic	>50	NA	NA	Zirihi Gué dé et al. 2010

(continued)

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TABLE 2. (CONTINUED)

Country	Family	Plant name	Plant part tested	Malaria parasite species	Extract type	IC$_{50}$ (µg/Ml)	Drug concentration (µg/mL) 40	20	References
	Euphorbiaceae	Alchornea cordifolia	Leaf		Ethanolic	22.3±3.3	NA	NA	
	Amaranthaceae	Alternanthera pungens	Whole plant		Ethanolic	>50	NA	NA	
	Loganiacee	Anthocleista djalonensis	Stem bark		Ethanolic	>50	NA	NA	
	Caesalpiniaceae	Anthonotha macrophylla	Stem bark		Ethanolic	43.2±0.3	NA	NA	
	Melianthaceae	Bersama abyssinica	Leaf		Ethanolic	20.7±3.3	NA	NA	
	Caesalpiniaceae	Cassia alata	Leaf		Ethanolic	>50	NA	NA	
	Sapotaceae	Chrysophyllum perpulchrum	Stem bark		Ethanolic	12.8±4.2	NA	NA	
	Euphorbiaceae	Erythrococca anomala	Leaf		Ethanolic	13.1±3.0	NA	NA	
	Asteraceae	Microglossa pyrifolia	Root bark		Ethanolic	31.1±3.0	NA	NA	
	Rubiaceae	Morinda morindoides	Leaf		Ethanolic	9.8±0.3	NA	NA	
	Rubiaceae	Nauclea latifolia	Root bark		Ethanolic	7.3±1.3	NA	NA	
	Euphorbiaceae	Phyllanthus muellerianus	Leaf		Ethanolic	10.3±0.7	NA	NA	
	Menispermaceae	Rhigiocarya racemifera	Leaf		Ethanolic	>50	NA	NA	
	Rubiaceae	Scherbournia bignoniiflora	Leaf		Ethanolic	24.7±0.8	NA	NA	
	Rutaceae	Zanthoxylum gilletii	Stem bark		Ethanolic	2.8±1.0	NA	NA	
Mali	Combretaceae	Guiera senegalensis (Gmel.)	Root	P. falciparum W2 strain	Chloroform	<25	NA	NA	Ancolio et al. 2002
	Rubiaceae	Feretia apodanthera (Del.)	Leaves		Chloroform	<25	NA	NA	
	Combretaceae	Combretum micranthum (Don.)	Leaves		Metholic	>25	NA	NA	
	Polygalaceae	Securidaca longepedunculata (Fres.)	Root		Metholic	>25	NA	NA	
	Rubiaceae	Morinda citrifolia (Benth.)	Stem bark		Chloroform	<25	NA	NA	
	Myristicaceae	Pynanthus angolensis (Welw.)	Stem bark		Metholic	<25	NA	NA	
Kenya	Capparaceae	Boscia angustifolia A. Rich.	Stem bark	P. falciparum culture of D6 (CQ sensitive isolate from Sierra Leone)	Metholic	7.43±3.89	NA	NA	Muthaura et al. 2007
	Compositae	Schkuhria pinnata (Lam) O. Ktze	Whole plant		Metholic	1.30±0.11	NA	NA	
	Compositae	Sphaeranthus suaveolens (Forsk.) DC.	Whole plant		Metholic	7.93±1.04	NA	NA	
	Euphorbiaceae	Clutia abyssinica Jaub and Spach	Leaves		Metholic	7.83±1.17	NA	NA	

(continued)

TABLE 2. (CONTINUED)

Country	Family	Plant name	Plant part tested	Malaria parasite species	Extract type	IC_{50} (μg/Ml)	Drug concentration (μg/mL)		References
							40	20	
	Lauraceae	Ocotea usambarensis Engl.	Stem bark		Metholic	7.69±2.87	NA	NA	
	Lamiaceae	Fuerstia africana T.C.E. Fries	Whole plant		Metholic	0.98±0.05	NA	NA	
	Onagraceae	Ludwigia erecta (L.) Hara	Whole plant		Metholic	4.10±0.04	NA	NA	
	Pittosporaceae	Pittosporum viridiflorum Sims	Leaves		Metholic	18.9±1.70	NA	NA	
	Rubiaceae	Vangueria acutiloba Robyns	Stem bark		Metholic	13.36±3.4	NA	NA	
	Verbenaceae	Clerodendrum eriophyllum Guerke	Root bark		Metholic	9.51±0.52	NA	NA	
Bhutan	Fumariaceae	Corydalis calliantha Long	Whole plant	P. falciparum wild type (TM4) strain	Metholic	1.00±0.34	NA	NA	Wangchuk et al. 2010
			Whole plant	P. falciparum multidrug resistant (K1) strain	Metholic	2.56±0.46	NA	NA	
			Whole plant	P. falciparum wild type (TM4) strain	Crude alkaloid extract	0.33±0.03	NA	NA	
			Whole plant	P. falciparum multidrug resistant (K1) strain	Crude alkaloid extract	0.63±0.14	NA	NA	
Tanzania	Amaranthaceae	Achyranthes aspera L.	Root bark	P. berghei	Ethyl acetate	3	NA	NA	Gessler et al. 1995
	Araliaceae	Cussonia zimmermannii Harms	Root bark	P. berghei	Petroleum ether	3.3	NA	NA	
	Celastraceae	Maytenus senegalensis (Lam.) Excell	Stem bark	P. berghei	Ethyl acetate	0.2	NA	NA	
	Fabaceae	Erythrina sacleuxii Hua	Root bark	P. berghei	Ethyl acetate	3	NA	NA	
	Guttiferae	Harungana madagascariensis	Roots	P. berghei	Ethyl acetate	4	NA	NA	
	Malvaceae	Harungana madagascariensis	Stem bark	P. berghei	Petroleum ether	10	NA	NA	
	Menispermaceae	Abutilon grandiflorum G.Don	Roots	P. berghei	Ethyl acetate	10	NA	NA	
	Rubiaceae	Cissampelos mucronafa A. Rich.	Roots	P. berghei	Ethyl acetate	0.4	NA	NA	
	Rubiaceae	Keetia zanzibarica (Klotzsch) Bridson	Roots	P. berghei	Ethyl acetate	4	NA	NA	

IC_{50}, half-maximal inhibitory concentration; NA, not available.

Rukunga and Simons (2006), research on plant extracts carried out worldwide during the last decade covers over 300 extracts obtained from over 60 plant families. The antiplasmodial activity of these plants is assessed with various strains of the *Plasmodium* parasites.

A survey completed by WHO's Roll Back Malaria program showed that in Ghana, Mali, Nigeria, and Zambia, around 60% of all febrile cases in children, presumably due to malaria, are treated at home with herbal medicine (WHO 2002, 2004b). In many resource-poor settings, particularly in Africa, fever has been equated with malaria throughout most of the continent and the rest of the world. The assumption that fever equals malaria may be wrong as well as being a dangerous practice. It must be addressed effectively by developing appropriate communication strategy and health education campaigns in the malaria endemic settings.

Plants widely used as antimalarials by traditional healers are significantly more active *in vitro* and/or *in vivo* against *Plasmodium* spp. than plants that are not widely used, or not used at all, for the treatment of malaria (Brandão et al. 1985, Carvalho et al. 1991, Leaman et al. 1995, Krettli et al. 2001, Vigneron et al. 2005). The traditional antimalarial plants are a unique source of various types of compounds having diverse chemical structure; however, only limited amount of research has been carried out on the biological activity and plausible medicinal applications of these compounds, and therefore more extensive investigation is extremely important and inevitable to exploit their therapeutic utility to combat malaria effectively.

Clinical Studies: Clinical Safety and Efficacy of Herbal Preparations

Clinical observations on traditional remedies are feasible and useful. Some herbal remedies may be safe and effective for the treatment of malaria, as shown by many studies (Tsu 1947, CCRAS 1987, Guindo 1988, Boye 1989, Koita 1991, Yao-De et al. 1992, Valecha 2000, Benoit-Vical et al. 2003, Mueller et al. 2004) and reviewed by Willcox and Bodeker (2004). A recent study examined the efficacy and safety of an infusion of fresh *Vernonia* leaves for the treatment of uncomplicated malaria in patients aged 12 years and over. It found adequate clinical response (ACR) at day 14 in 67% of cases. However, complete parasite clearance occurred in only 32% of those with ACR, and of these, recrudescence occurred in 71%; there was no evidence of significant side effects or toxicity from the medication (Challand and Willcox 2009).

Patients being treated for malaria at an herbalists' clinic in southwestern Uganda were followed up, and their response to a particular herb, "AM," was monitored. Eighty-eight patients were enrolled; 72 were followed up for at least 2 days. Nearly 50% experienced minor side effects. Although complete parasite clearance was achieved in only one case, the geometric mean of parasite counts had declined significantly by day 7. There was also a marked symptomatic improvement in 17 of the 19 patients (Willcox 1999).

A prospective, dose-escalating, quasi-experimental clinical trial was conducted with a traditional healer using a decoction of *Argemone mexicana* for the treatment of malaria in Mali. The remedy was prescribed in three regimens: Once daily for 3 days (group A, $n = 23$); twice daily for 7 days (group B, $n = 40$); and four times daily for the first 4 days followed by twice daily for 3 days (group C, $n = 17$). Thus, 80 patients were included, of whom 80% were aged <5 years and 25% were aged <1 year. All presented to the traditional healer with symptoms of malaria and had a *P. falciparum* parasitemia >2000/μL but no signs of severe malaria. The proportions of ACR at day 14 were 35%, 73%, and 65% in groups A, B, and C, respectively ($p = 0.011$). Very few patients had complete parasite clearance, but at day 14, 67% of patients with ACR had a parasitemia <2000/μL (Willcox et al. 2007).

Current Development Efforts in Developing Plant-Based New Antimalarials

In malaria-endemic countries, traditional medicinal plants are frequently used to treat malaria. The analysis of traditional medicines that are employed for treatment of malaria represents a potential for the discovery of lead molecules and hence for further development as potential antimalarial drugs (Muthaura et al. 2007). New drugs are required to combat the emergence of antimalarials resistance. The main goal of ethnopharmacology is to discover novel plant-derived compounds based on the indigenous use of medicinal plants that can be developed into new pharmaceuticals. Historically, plants have proven to be a major source of drugs (Newman et al. 2003), with two of the most widely used antimalarials originating from plants. The quinoline-based antimalarials are modeled on quinine, derived from the bark of the Peruvian *Cinchona* tree, and the endoperoxide-based antimalarials originated from artemisinin, first isolated from the Chinese herbal medicine *A. annua* (Camacho et al. 2000).

In light of this historic success, there is every possibility that ethnopharmacological approaches could lead to new antimalarial agents (Phillipson and Wright 1991). ACTs have now been adopted globally as the first line of treatment. Together with mosquito-control measures such as insecticide-treated bed nets, ACTs have driven down malaria rates across sub-Saharan Africa (Eastman and Fidock 2009). The emergence and spread of drug-resistant malaria parasites is the major threat to effective malaria control. Experience has shown that resistance eventually curtails the life span of antimalarial drugs. If measures are not applied to contain resistance, the investment put into the development of new drugs will be squandered (Olliaro and Taylor 2003).

The discovery and development of new antimalarials are at a crossroads. Fixed-dose artemisinin combination therapy is now being used to treat a hundred million children each year, with a cost as low as 30 cents per child, and with cure rates of over 95%. They are also relatively safe, often with no serious adverse events seen in phase III trials of several thousand patients. However, in the long term, there will always be a need for new therapies, no matter how carefully the current medicines are used, and there is also the constant threat of resistance (Wells 2011). This is an early warning sign that new classes of antimalarials are needed and are an urgent priority. It takes at least 10 years to move a molecule from late in the discovery phase to completion of clinical trials. Herbal medicinal products carry one strategic advantage–in several cases we know that there is an activity in patients. Once the active ingredients are identified, it is likely that medicinal chemistry will be needed to optimize it for clinical use (Wells 2011).

Even though currently ACT serves a pivotal role to combat malaria, they are mostly inaccessible and unaffordable in the

resource-limited settings. Besides, there are signs of resistance to artemisinins and this has led to exploration for the low-cost and easily accessible plant species as a potential source of antimalarials in the near future (Karunamoorthi and Tsehaye 2012). However, the new antimalarial drugs must meet the requirements of rapid efficacy, minimal toxicity, and low cost.

The Role African or Asian Network on Drugs and Diagnostic Innovation

The African Network for Drugs and Diagnostics Innovation (ANDI) was conceived and launched as a concept at Abuja in 2008 by the WHO through TDR and its African and East Mediterranean Regional Offices, several African institutions, policy makers, Africans in the Diaspora, the African Development Bank (AfDB), and other stakeholders. ANDI intends to develop and fund a portfolio of collaborative network projects and leverage existing capacity in Africa in a manner that will support capacity and infrastructural development for product research, development, and delivery. The key objective is to discover, develop, and deliver affordable new drugs, vaccines, diagnostics, and other health products (including those based upon natural products and traditional medicines) to fight and prevent diseases that disproportionately affect the African continent (Addae-Mensah et al. 2011).

It is known that up to 80% of African populations use traditional medicines to address their health issues (WHO 2002). In spite of this, the biodiversity of Africa has yielded few examples of standardized phytomedicines, and only limited systematic analysis of available medicinal plants has been undertaken. The development of traditional medicines should not be seen as the answer to providing cheap treatments to poor populations. But it is important that such medicines are given the same scrutiny as any other pharmaceutical to ensure the protection of patients from any major adverse event and also to ensure the benefits of optimal efficacy. Research in support of the use of traditional medicines and natural products in disease prevention and control should also receive attention, for example, vector control (Addae-Mensah et al. 2011).

Major Challenges and Opportunities in Developing New Antimalarials

Continued and sustainable improvements in antimalarial medicines through focused research and development are essential for the world's future ability to treat and control malaria. Unfortunately, malaria is a disease of poverty, and, despite a wealth of scientific knowledge, there is insufficient market incentive to generate the competitive, business-driven industrial antimalarial drug research and development that is normally needed to deliver new products (Ridley 2002).

The challenge of any drug discovery effort is to identify and develop compounds with properties that are predictive of good efficacy and safety in humans. For malaria, additional hurdles that need to be overcome include the selection of compounds that are reasonably cheap to produce and that are effective against drug-resistant strains. The potential of a candidate compound to be used by the most vulnerable populations (young children and pregnant women) in disease-endemic countries also needs to be assessed as the candidate moves into development. In addition to being effective against uncomplicated *P. falciparum* malaria, compounds that can be easily formulated for severe disease (that is, amenable

to parenteral administration) bring an added benefit, as do compounds that work against *P. vivax* (Ridley 2002, Nwaka and Ridley 2003). Their ultimate success depends on the intrinsic qualities of the molecule, as well as how the development of the drug is planned and implemented (Fidock et al. 2004). Apart from these, further challenges and issues are discussed below.

Imprecise diagnosis and treatment

The WHO Global Malaria Programme recommended that all suspected cases of malaria receive an appropriate diagnostic test prior to treatment. But in malaria-endemic countries, economic and logistic reasons force entire populations to rely on clinical diagnosis. Each traditional system of medicine having its own unique diagnostic procedure, the diagnosis is involves examination of patient, reviewing physical signs such as complexions, color, smell, texture of the tongue, postures of the patient, and the patient's personal lifestyle. Unfortunately, the diagnoses in traditional healer systems of malaria are often error-prone as well as not precise. This remains one of the major setbacks to advocate the plant-based therapies for the treatment of malaria.

Randomized clinical trials

Although traditional medicine is widely used to treat malaria, and is often more available and affordable than Western medicine, it is not without limitations. First, there are few clinical data on safety and efficacy. Second, there is no consensus, even among traditional healers, on the selection of plants, preparations, and dosages that are the most effective. Third, the concentration of active ingredients in a plant species varies considerably, depending on several factors. However, these limitations are all remediable through research (Willcox and Bodeker 2004). Nevertheless, better evidence from randomized clinical trials is needed before herbal remedies can be recommended on a large scale. In remote settings with poor resources where modern antimalarials are not steadily available, research can provide an evidence base for traditional medicine to inform local treatment choices (Willcox and Bodeker 2004).

Lack of standardization on quality, efficacy, and safety

The identity, authenticity, and quality of crude plants are often uncertain and difficult to assess (Morris 1998). Traditional medicines are currently undergoing scrutiny to evaluate their effectiveness and to monitor their adverse effects (Normile 2003, Hsieh et al. 2006). The active ingredients used in many traditional medicines are potentially toxic, often containing dangerous elements, and they may include heavy metals (Garnier and Poupon 2006, Palombo 2006). Even the use of ineffective nontoxic remedies can be harmful if they delay effective treatment. For instance, fears have been expressed that, in Nigeria, witchcraft and traditional remedies of unknown efficacy are widely employed as treatments for malaria to delay the access to modern medicines of proven effectiveness (Okeke et al. 2006).

There are still certain inherent problems with the medicinal plants. A good number of medicinal plants are cross-pollinated, and therefore there are a large number of genetic variants in the population, which accounts for the variation in

chemical composition. Even the genetically similar plants behave differentially in different ecological, edaphic, and climatic conditions, leading to differences in the chemical composition and ultimately pharmacological action (Pushpangadan 2006). The medicinal plants may grow in areas of similar climatic conditions and soil, but the quality and composition of pharmacological components may be inconsistent in each and every harvest. In the case of *A. annua*, the concentration of artemisinin peaks around the time of flowering, although in some cases this may be just before flowering and in other cases during full flowering (Ferreira et al. 1995, Laughlin et al. 2002). The artemisinin concentration peaks at a slightly different time in different areas (Chang and But 1986).

Generally, the majority of the traditional healers treat their patients by administering various herbal medicines based on their previous knowledge and experience. However, the incorrect preparations, dosage, harmful side effects, and the end organ outcome are often ambiguous and unknown, and there could be potential risk if these medicines are not administered properly and appropriately (Robinson and Zhang 2011). The idea that just because traditional medicine products come from natural sources they are completely safe is dangerously false (Calixto 2000). Not everything that is natural is safe; traditional medicine products must be used judiciously and as indicated, just like any other medication, and with awareness of potential herb–herb and herb–drug interactions. The risks are relatively small when traditional medicines are used correctly, but they are still there and consumer understanding is generally low (Zhang et al. 2008). While acknowledging that all traditional medicines must be subject to evaluation of safety, therapeutic efficacy, quality control, and pharmacovigilance, according to prescribed criteria, we should, in conducting such evaluations, recognize the unique historical development of these products (WHO 2004a,b).

Lack of appropriate technology

In 1971, laboratory experiments verified the activity of extracts of a plant *A. annua* against *Plasmodium berghei*, using a mouse model of malaria (Schuster 2001). This discovery has since revolutionized the treatment of malaria around the world, but with little recognition for the traditional medicine practitioners of the African region who have used *Artemisia* spp. for centuries, but who lacked the technology or financing to prove its efficacy against malaria in a laboratory (Robinson and Zhang 2011).

The need for further research and development

Over the past several decades, numerous plants have been screened for their antimalarial bioactive compounds; however, this is a part of the minor-level research of the drug development program. Therefore, in-depth research is required to assess the antimalarial properties of such plants in terms of pharmacological investigation about their bioavailability, half-life, and interactions, etc. Furthermore, some of the plants may have potential antimalarial properties with a cytotoxic nature that may demand further extensive research.

Lack of accessibility of ACTs in the rural settings

Globally, many malaria-endemic countries have ACT-free treatment programs. However, these facilities are not reachable for the rural poor and those are living in the remote areas. For example, in 2005 more than half of the population of Ethiopia lived more than 10 km from health services (Bilal et al. 2010). These rural people must walk/travel a very long distance to reach the nearest health facility to access modern health-care facilities. Unfortunately, in malaria-endemic countries, many villages are not approachable by means of road. Even if they are reached, only a limited number of health facilities are found to have regular supplies of ACTs. From my personal observation in Ethiopia and India, of course, plant-based therapies are expensive in the urban areas but it is cheaper or inexpensive in the rural areas. I have witnessed in Ethiopia, where even the rural illiterate poor women prepare plant-based antimalarial therapy by using nearby freely available plants for their own children, who suffer from fever presumed as malaria. However, if the people consult a local traditional healer for herbal therapy, it may often be relatively expensive. It is purely because of the lack of accessibility and affordability toward effective antimalarial like ACTs. Therefore, the provision and scaling up ACTs along with rapid diagnostic tests (RDTs) at the village level must be implemented.

Conclusions

Traditional medicinal plants (TMPs) have been the main source of potential antimalarial drugs like quinine and artemisinin. Worldwide, over 1000 plant species have been used as a source of traditional antimalarial phytotherapy for many centuries. In the future, plant-derived compounds will still be an essential aspect of the therapeutic array of antimalarials. However their clinical efficacy, quality, and safety are a matter of grave concern. Because, in resource-poor settings, although traditional antimalarial therapy is certainly not a desirable one due to its safety and efficacy checkpoints, it is the accessible or possible one, because of remoteness, lack of affordability, and accessibility to ACTs. Therefore, the existing major issues, challenges, and risks must be addressed effectively and immediately by the public health experts for the betterment of traditional herbal systems of medicine and to develop potential antimalarial drugs. A vibrant antimalarial discovery pipeline must be formed by making collaboration among all stakeholders, like traditional healers, ethnobotanists, scientists, entomologists, pharmacists, and research institutions, to identify lead compounds and to develop usable antimalarials in the near future.

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Author Disclosure Statement

References

Addae-Mensah I, Fakorede F, Holtel A, Nwaka S. Traditional medicines as a mechanism for driving research innovation in Africa. Mal J 2011; 10(Suppl 1):S9.

Adekunle MF. Indigenous uses of plant leaves to treat malaria fever at Omo Forest reserve (OFR) Ogun state, Nigeria. Ethiop J Environ Stud Manag 2008; 1:31–35.

Ajibesin KK, Ekpo BA, Bala DN, Essien EE, et al. Ethnobotanical survey of Akwa Ibom State of Nigeria. J Ethnopharmacol 2008; 115:387–408.

Al-Adhroey AH, Nor ZM, Al-Mekhlafi HM, Mahmud R. Ethnobotanical study on some Malaysian anti-malarial plants: A community based survey. J Ethnopharmacol 2010; 132:362–364.

Alshawsh MA, Mothana RA, Al-shamahy HA, Alsllami SF, et al. Assessment of antimalarial activity against Plasmodium falciparum and phytochemical screening of some Yemeni medicinal plants. eCAM 2007; 1–4. doi:10.1093/ecam/nem148.

Ancolio C, Azas N, Mahiou V, Ollivier E, et al. Antimalarial activity of extracts and alkaloids isolated from six plants used in traditional medicine in Mali and Sao Tome. Phytother Res 2002; 1:646–649.

Asase A, Oteng-Yeboah AA, Odamtten GT, Simmonds MSJ. Ethnobotanical study of some Ghanaian anti-malarial plants. J Ethnopharmacol 2005; 99:273–279.

Asase A, Oppong-Mensah G. Traditional antimalarial phytotherapy remedies in herbal markets in southern Ghana. J Ethnopharmacol 2009;126:492–499.

Awe SO, Olajide OA, Oladiran OO, Makinde JM. Antiplasmodial and antipyretic screening of Mangifera indica extract. Phytother Res 1998; 12:437–438.

Awofeso N. Project 523: Transformation of Artemisinin from traditional Chinese medicine to mainstream anti-malaria chemotherapy. Spatula DD 2011; 1:113–118

Bai D. Traditional Chinese medicines and new drug development. Pure Appl Chem 1993; 65:1103–1112.

Bannerman RHO. Acupuncture: The WHO View. World Health Magazine 1979; 24–29.

Bannerman RHO, Cummins A, Djukanovic V, et al. Indigenous system of medicine: Medicine in India. In: Djukanovic V, Mach EP, eds. Alternative Approaches to Meeting Basic Health Needs in Developing Countries. Geneva: WHO, 1975:84–91.

Benoit-Vical F, Valentin A, Da B, Dakuyo Z, et al. N'Dribala (Cochlospermum planchonii) versus chloroquine for the treatment of uncomplicated Plasmodium falciparum malaria. J Ethnopharmacol 2003; 89:111–114.

Bharel S, Gulati A, Abdin MZ, Srivastava PS, et al. Structure, biosynthesis and functions of artemisinin. Fitoterapia 1996; 67:387–399.

Bidla G, Titanji VPK, Jako B, Ghazali GE, et al. Antiplasmodial activity of seven plants used in African folk medicine. Indian J Pharmacol 2004; 36:245–246.

Bilal NK, Herbst CH, Zhao F, Soucat A, et al. Health Extension Workers in Ethiopia: Improved Access and Coverage for the Rural Poor. 2010. Available at http://siteresources.world bank.org/AFRICAEXT/Resources/258643-1271798012256/ Health_Extension_Workers_Ethiopia.pdf/. Accessed March 28, 2013.

Botsaris AS. Plants used traditionally to treat malaria in Brazil: The archives of Flora Medicinal. J Ethnobiol Ethnomed 2007; 3:18.

Boulos M, Dutra AP, Disanti SM, Shiroma M, et al. Avalia..o clínica do quinine para o tratamento da malária por Plasmodium falciparum. Rev Soc Bras Med Trop 1997; 30:211–213.

Boye GL. Studies on the antimalarial action of Cryptolepis sanguinolenta extract. Proceedings of an International Symposium on East–West Medicine, Seoul, Korea, 1989:242–251.

Brandão MGL, Botelho MDGA, Krettli AU. Quimioterapia experimental antimalárica com produtos naturais: I. Uma Abordagem mais racional? Ciência e Cultura 1985; 37:1152–1163.

Bruhn JG, Holmestedt B. Ethnopharmacology, objectives, principles and perspectives. In: Beal JL, Reihnard E, eds. Natural Products as Medicinal Agents. Stuttgart: Verlag, 1981:405–430.

Butler AR, Khan S, Ferguson E. A brief history of malaria chemotherapy. R Coll Physicians Edinb 2010; 40:72–77.

Calixto JB. Efficacy, safety, quality control, marketing and regulatory guidelines for herbal medicines (phytotherapeutic agents). Braz J Med Biol Res 2000; 33:179–189.

Camacho MDR, Croft SL, Phillipson JD. Natural products as sources of antiprotozoal drugs. Curr Opin Investig Drugs 2000; 2:47–62.

Camargo LMA, Oliveira S, Basano S, Garcia CRS. Antimalarials and the fight against malaria in Brazil. Ther Clin Risk Manag 2009; 5:311–317.

Cameron A, Ewen M, Auton M, Abegunde D. The World Medicines Situation 2011. Medicines prices, availability and affordability. WHO/EMP/MIE/2011.2.1Available at www. who.int/medicines/areas/policy/world_medicines_situation/ WMS_ch6_wPricing_v6.pdf/. Accessed March 28, 2013.

Carvalho LH, Brandao MG, Santos-Filho D, Lopes JL, et al. Antimalarial activity of crude extracts from Brazilian plants studied in vivo in Plasmodium berghei-infected mice and in vitro against Plasmodium falciparum in culture. Braz J Med Biol Res 1991; 24:1113–1123.

CCRAS. (Central Council for Research in Ayurveda and Siddha). Ayush-64: A New Antimalarial Herbal Compound. Delhi: CCRAS, 1987.

Challand S, Willcox M. A clinical trial of the traditional medicine Vernonia amygdalina in the treatment of uncomplicated malaria. J Altern Complement Med 2009; 15:1231–1237.

Chang HM, But PPH. Pharmacology and Applications of Chinese Materia Media, vol. 1. Singapore: World Scientific Publishing, 1986.

Dondorp AM, Nosten F, Yi P, Das D, et al. Artemisinin resistance in Plasmodium falciparum malaria. N Engl J Med 2009; 361:455–467.

Eastman RT, Fidock DA. Artemisinin-based combination therapies: A vital tool in efforts to eliminate malaria. Nature Rev Microbiol 2009; 7:864–874.

Ekland EH, Fidock DA. In vitro evaluations of antimalarial drugs and their relevance to clinical outcomes. Int J Parasitol 2008; 38:743–747.

El-Tahir A, Satti GMH, Khalid SA. Antiplasmodial Activity of Selected Sudanese Medicinal Plants with Emphasis on Acacia nilotica. Phytother Res 1999; 13:474–478.

Fabricant DS, Farnsworth NR. The value of plants used in traditional medicine for drug discovery. Env Health Persp 2001; 109(S):69–75.

Ferreira JFS, Simon JE, Janick J. Developmental studies of Artemisia annua: Flowering and artemisinin production under greenhouse and field conditions. Planta Med 1995; 61:167–170.

Fidock DA, Rosenthal PJ, Croft SL, Brun R, et al. Antimalarial drug discovery: Efficacy models for compound screening. Nature 2004; 3:509–520.

Garavito G, Rincón J, Arteaga L, Hata Y, et al. Antimalarial activity of some Colombian medicinal plants. J Ethnopharmacol 2006; 107:460–462.

Garnham PCC. Malaria Parasites and Other Heamosporidia. Oxford: Blackwell Scientific Publications, 1966:1114.

Garnier R, Poupon J. Lead poisoning from traditional Indian medicines. Presse Med 2006; 35:1177–1180.

Gessler MC, Tanner M, Chollet J, Nkunya MHH, et al. Tanzanian medicinal plants used traditionally for the treatment of malaria: In vivo antimalarial and in vitro cytotoxic activities. Phytother Res 1995; 9:504–508.

Guindo M. Contribution à l'étude du traitement traditionnel du "Suma" (Paludisme). PhD thesis, National School of Medicine and Pharmacy, Bamako, Mali, 1988.

Hlaing AKS, Oo ZK, Mon HM. Evaluation of the Antimalarial Activity of Selected Myanmar Medicinal Plants. GMSARN International Conference on Sustainable Development: Issues and Prospects for the GMS, November 12–14, 2008.

Hsieh SC, Lai JN, Chen PC, Chen HJ, et al. Development of active safety surveillance system for traditional Chinese medicine: An empirical study in treating climacteric women. Pharmacoepidemiol Drug Saf 2006; 15:889–899.

Huang KC. The Pharmacology of Chinese Herbs, 2nd ed. Boca Raton: CRC Press, 1998;1–14.

Hyam R, Pankhurst R. Plants and their Names: A Concise Dictionary. Oxford: Oxford University Press, 1995:40–41.

Jain SP, Singh J. Traditional medicinal practice among the tribal people of Raigarh (Chhatisgarh), India. Indian J Nat Prod Resourc 2010;1.

Jaramillo-Arango J. A critical review of the basic facts in the history of Cinchona. J Linnaean Soc 1949; 53:1272–1309.

Kantamreddi VSS, Parida S, Kommula SM, Wright CW. Phytotherapy used in Orissa State, India for treating malaria. Phytother Res 2009; 23:1638–1641.

Karou DS, Kokou K, Essien K, et al. An ethnobotanical study of antimalarial plants in Togo Maritime Region. J Ethnopharmacol 2011; 134:183–190.

Karunamoorthi K. Global malaria burden: Socialomics implications. J Socialomics 2012a; 1:e108.

Karunamoorthi K. Neem oil: Biological activities and usage. In: Govil JN, Bhattacharya S, eds. Recent Progress in Medicinal Plants (RPMP), vol. 33: Fixed Oils and Fats of Pharmaceutical Importance. Houston, TX: Studium Press LLC, 2012b.

Karunamoorthi K, Ilango K. Larvicidal activity of Cymbopogon citratus (DC) Stapf. and Croton macrostachyus Del. against Anopheles arabiensis Patton (Diptera: Culicidae), the principal malaria vector. Eur Rev Med Pharmacol Sci 2010; 14:57–62.

Karunamoorthi K, Sabesan S. Relative efficacy of repellents treated wristbands against three major mosquitoes (Diptera: Culicidae) vectors of disease, under laboratory conditions. Int Health 2009; 1:173–177.

Karunamoorthi K, Tsehaye E. Ethnomedicinal knowledge, belief and self-reported practice of local inhabitants on traditional antimalarial plants and phytotherapy. J Ethnopharmacol 2012; 141:143–150.

Karunamoorthi K, Ilango K, Endale A. Ethnobotanical survey of knowledge and usage custom of traditional insect/mosquito repellent plants among the Ethiopian Oromo ethnic group. J Ethnopharmacol 2009b; 125:224–229.

Karunamoorthi K, Mulelam A, Wassie F. Assessment of knowledge and usage custom of traditional insect/mosquito repellent plants in Addis Zemen Town, South Gonder, North Western Ethiopia. J Ethnopharmacol 2009a; 121:49–53.

Karunamoorthi K, Bishaw D, Yilkal T. Knowledge and practice concerning malaria, insecticide-treated net (ITN) utilization and antimalarial treatment among pregnant women attending specialist antenatal clinics. J Pub Health 2010; 18:559–566.

Karunamoorthi K, Jegajeevanram K, Jerome X, Vijayalakshmi J, et al. Tamil traditional medicinal system—Siddha: An indigenous health practice in the international perspectives. Int J Genuine Trad Med 2012a; 2:2.e Available www.e-tang.org/. Accessed on March 28, 2013.

Karunamoorthi K, Jegajeevanram J, Vijayalakshmi J, Mengistie E. Traditional medicinal plants: A source of phytotherapeutic modality in resource-constrained health care settings. J Evid Based Complementary Altern Med 2012b; doi: 10.1177/2156587212460241.

Kebenei JS, Ndalut PK, Sabah AO. Synergism of artemisinin with abyssinone-V from Erythrina abyssinica (Lam. ex) against Plasmodium falciparum parasites: A potential anti-malarial combination therapy. J Med Plants Res 2011; 5:1355–1360.

Koita N. A comparative study of the traditional remedy "Suma-Kala" and chloroquine as treatment for malaria in the rural areas. In: Mshigeni KE, Nkunya MHH, Fupi V, Mahunnah RLA, et al., eds. Proceedings of an International Conference of Experts from Developing Countries on Traditional Medicinal Plants, Arusha, Tanzania, February 18–23, 1990. Dar Es Salaam: Dar Es Salaam University Press, 1991.

Krettli AU, Andrade-Neto VF, Brandão MGL, Ferrari WMS. The search for new antimalarial drugs from plants used to treat fever and malaria or plants randomly selected: A review. Mem Inst Oswaldo Cruz 2001; 96:1033–1042.

Laughlin JC, Heazlewood GN, Beattie BM. Cultivation of Artemisia annua L. In: Wright CW, ed. Artemisia. London: Taylor & Francis, 2002.

Leaman DJ, Arnasona JT, Yusuf R, et al. A quantitative assessment of local consensus as an indicator of biological efficacy. J Ethnopharmacol 1995; 49:1–16.

Lee MR. Plants against malaria. Part 1: Cinchona or the Peruvian bark. J R Coll Physicians Edinb 2002a; 32:189–196.

Lee MR. Plants against malaria. Part 2: Artemisia annua (Qinghaosu or the sweet wormwood). J R Coll Physicians Edinb 2002b; 32:300–305.

Lewison G, Srivastava D. Malaria research, 1980–2004, and the burden of disease. Acta Trop 2008; 106:96–103.

Li GQ, Guo XB, Jin R, et al. Clinical studies on treatment of cerebral malaria with Qinghaosu and its derivatives. J Trad Chinese Med 1982; 2:125–130.

Li Y, ed. Discovery and Development of New Antimalarial Drug (Artemisinin). Shanghai: Scientific & Technical Publishers, 2007.

Mackinnon MJ, Marsh K. The selection landscape of malaria parasites. Science 2010; 328:866–871.

Marshall SJ, Russell PF, Phillipson JD, Kirby GC, et al. Antiplasmodial and antiamoebic activities of medicinal plants from Sierra Leone. Phytother Res 2000; 14:356–358.

MMV. Understanding the antimalarials market: Uganda 2007. An overview of the supply side. A study by Medicines for Malaria Venture, in collaboration with Ministry of Health Uganda, HEPS and WHO. Geneva, Medicines for Malaria Venture, 2008. Available at: www.mmv.org/newsroom/publications/understanding-antimalarials-market-uganda-2007-overview-supply-side. Accessed May 7, 2013.

Morris K. Tackling thorny issues of herbal medicines worldwide. Lancet 1998;351:9110-9116.

Mueller MS, Runyambo N,Wagner I, Borrmann S, Dietz K, Heide L. Randomized controlled trial of a traditional preparation of Artemisia annua L in the treatment of malaria. Trans R Soc Trop Med Hyg 2004; 98:318–321.

Muregi FW, Chhabra SC, Njagi ENM, Lang'at-Thoruwa CC, et al. Anti-plasmodial activity of some Kenyan medicinal plant extracts singly and in combination with chloroquine. Phytother Res 2004; 18:379–384.

Muregi FW. Antimalarial drugs and their useful therapeutic lives: Rational drug design lessons from pleiotropic action of quinoline and artemisinins. Curr Drug Discov Technol 2010; 7:280–316.

Muthaura CN, Rukunga GM, Chhabra SC, Omar SA, et al. Antimalarial activity of some plants traditionally used in Meru district of Kenya. Phytother Res 2007; 21:860–867.

Nadembega P, Boussim JI, Nikiema JB, et al. Medicinal plants in Baskoure, Kourittenga Province, Burkina Faso: An ethnobotanical study. J Ethnopharmacol 2011; 133:378–395.

Namsa ND, Mandal M, Tangjang S. Anti-malarial herbal remedies of northeast India, Assam: An ethnobotanical survey. J Ethnopharmacol 2011; 133:565–572.

Newman DJ, Cragg GM, Snader KM. Natural products as sources of new drugs over the period 1981–2002. J Nat Prod 2003; 66:1022–1037.

Ngemenya MN, Tane P, Berzins K, Titanji VPK. Antiplasmodial activity of some medicinal plants used in Cameroon: Preliminary toxicity studies of highly active extracts. XIth Annual Conference of The Cameroon Bioscience Society 2004:16–18.

Nguyen-Pouplin J, Tran H, Tran H, Anh Phan T, et al. Antimalarial and cytotoxic activities of ethnopharmacologically selected medicinal plants from South Vietnam. J Ethnopharmacol 2007; 109:417–427.

Nicholas JW. Artemisinin, current status. Trans R Soc Trop Med Hygiene 1994; 88:3–4.

Njoroge GN, Bussmann RW. Diversity and utilization of antimalarial ethnophytotherapeutic remedies among the Kikuyus (Central Kenya). J Ethnobiol Ethnomed 2006; 2:8.

Noed H, Se Y, Schaecher K, Smith BL, et al. Evidence of artemisinin-resistant malaria in western Cambodia. N Engl J Med 2008; 359:2619–2620.

Normile D. The new face of traditional Chinese medicine. Science 2003; 299:188–190.

Nosten F, van Vugt M, Price R. Effects of artesunate-mefloquine combination on incidence of Plasmdium falciparum malaria and melfloquine resistance in Western Thailand: A prospective study. Lancet 2000; 356:297–302.

Nwaka S, Ridley RG. Virtual drug discovery and development for neglected diseases through public-private partnerships. Nature Rev Drug Discov 2003; 2:919–928.

Odugbemi TO, Akinsulire OR, Aibinu IE, et al. Medicinal plants useful for malaria therapy in

Okeigbo, Ondo state, southwest Nigeria. Afr J Trad CAM 2007; 4:191–198.

Okeke TA, Okafor HU, Uzochukwu BSC. Traditional healers in Nigeria: Perception of cause, treatment and referral practices for severe malaria. J Biol Soc Sci 2006; 38:491–500.

Oliveira AB, Olabela MN, Braga FOC, Jácome RLRP, et al. Plant-derived antimalarial agents: New leads and efficient phytomedicines. Part I. Alkaloids. An Acad Bras Cienc 2009; 81:715–740.

Olliaro PL, Taylor WRJ. Antimalarial compounds: From bench to bedside. J Exp Biol 2003; 206:3753–3759.

Olliaro PL, Yuthavong Y. An overview of chemotherapeutic targets for antimalarial drug discovery. Pharmacol Ther 1999; 81:91–110.

Ouattara Y, Sanon S, Traoré Y, et al. Antimalarial activity of Swartzia madagascariensis desv. (Leguminosae), Combretum glutinosumguill. & perr. (Combretaceae) and Tinospora bakis miers. (Menispermaceae), Burkina faso medicinal plants. Afr J Trad CAM 2006; 3:75–81.

Palombo EA. Phytochemicals from traditional medicinal plants used in the treatment of diarrhoea: Modes of action and effects on intestinal function. Phytother Res 2006; 20:717–724.

Pamplona-Roger MDGD. Encyclopaedia of Medicinal Plants. Education and Health Library, vols.1 and 2. 2001.

Paredes-Borja V. Contribucion del Ecuador a la Materia Quimica: La Quina. Ecuador; January–December, 1946:217 et sequitur.

Phillipson JD, Wright CW. Can ethnopharmacology contribute to the development of antimalarial agents? J Ethnopharmacol 1991; 32:155–165.

Pushpangadan P. Important Indian Medicinal Plants of Global Interest. 2006. Available from: http://herbalnet.heal-threpository.org/bitstream/123456789/2075/16/7.%20Ayur-94-109.pdf/. Accessed March 29, 2013.

Qinghaosu Antimalaria Coordinating Research Group. Antimalaria studies on qinghaosu. Chinese Med J 1979; 12:811–816.

Ramalhete C, Lopes D, Mulhovo S, Rosário VE, et al. Anti-malarial activity of some plants traditionally used in Mozambique. Workshop Plantas Medicinais e Fitoterapêuticas nos Trópicos. IICT/CCCM, October 29–31, 2008.

Ramazani A, Zakeri S, Sardari S, Khodakarim1 N, et al. In vitro and in vivo anti-malarial activity of Boerhavia elegans and Solanum surattense. Mal J 2010; 9:124.

Randrianarivelojosia M, Rasidimanana VT, Rabarison H, Cheplogoi PK, et al. Plants traditionally prescribed to treat tazo (malaria) in the eastern region of Madagascar. Malaria J 2003; 2:25.

Rastogi RP, Dhawan BN. Research on medicinal plants at the Central Drug Research Institute, Lucknow (India). Indian J Med Res 1982; 76(S):27–45.

Redi F. Opere de Francesco Redi. Venice: Ertz 1966:1712–1750.

Ridley RG. Medical need, scientific opportunity and the drive for antimalarial drugs. Nature 2002; 415:686–693.

Robinson MM, Zhang X. The World Medicines Situation 2011. Traditional medicines: Global situation, issues and challenges. Available at http://digicollection.org/hss/en/m/abstract/Js18063en/. Accessed March 30, 2013.

Rodrigues LA, Henriques G, Borges ST, Hunt P, et al. Experimental evolution of resistance to artemisinin combination therapy results in amplification of the mdr1 gene in a rodent malaria parasite. PLoS One 2010; 5:e11593.

Roumy V, Garcia-Pizango G, Gutierrez-Choquevilca AL, Ruiz L, et al. Amazonian plants from Peru used by Quechua and Mestizo to treat malaria with evaluation of their activity. J Ethnopharmacol 2007; 112:482–489.

Rukunga G, Simons AJ. The potential of plants as a source of antimalarial agents. A review. Africa herbal antimalarial meeting. CDE and ICRAF. World Agroforestry Centre, 2006.

Saralamba S, Pan-Ngum W, Maude RJ, Lee SJ, et al. Intrahost modeling of artemisinin resistance in Plasmodium falciparum. Proc Natl Acad Sci USA 2011; 108:397–402.

Schuster B. Demonstrating the validity of natural products as anti-infective drugs. J Alt Compl Med 2001; 7(Suppl 1):S73–S82.

Simon JE, Charles D, Cebert E, Grant L, et al. Artemisia annua L.: A promising aromatic and medicinal. In: Janick J, Simon JE, eds. Advances in New Crops. Portland, OR: Timber Press, 1990:522–526.

Taylor K. Chinese Medicine in Early Communist China, 1945–63. London: Routledge Curzon, 2005.

Tene V, Malagón O, Finzi PV, et al. An ethnobotanical survey of medicinal plants used in Loja and Zamora-Chinchipe, Ecuador. J Ethnopharmacol 2007; 111:63–81.

The malERA Consultative Group on Drugs. A Research Agenda for Malaria Eradication: Drugs. PLoS Med 2011; 8:e1000402.

Thomson RH. The Chemistry of Natural Products, 2nd Ed.; Springer Verlag, Blackie: Glasgow and London, 1993, pp. 117–121.

Tsu CF. Chang Shan in the treatment of malaria. Trop Med Hygiene 1947; 50:75–77.

Valecha N, Devi CU, Joshi H, Shahi VK, et al. Comparative efficacy of Ayush-64 vs chloroquine in vivax malaria. Curr Sci 2000; 78:1120–1122.

Van Wyk BV, Oudtshoorn BV, Gericke N. Medicinal Plants of South Africa. Pretoria, South Africa: Briza Publications, 2000.

Vigneron M, Deparis X, Deharo E, Bourdy G. Antimalarial remedies in French Guiana: A knowledge attitudes and practices study. J Ethnopharmacol 2005; 98:351–360.

Walsh JJ, Coughlan D, Heneghan N, Gaynor C, et al. A novel artemisinin—quinine hybrid with potent antimalarial activity. Bioorg Med Chem Lett 2007; 17:3599–3602.

Wangchuk P, Bremner JB, Samten, Rattanajak R, et al. Anti-plasmodial agents from the Bhutanese medicinal plant *Corydalis calliantha*. Phytother Res 2010; 24:481–485.

Weenen H, Nkunya M, Bray DH, Mwasumbi LB, et al. Anti-malarial activity of Tanzanian medicinal plants. Planta Med 1990; 56:368–370.

Wellems TE. Plasmodium chloroquine resistance and the search for a replacement antimalarial drug. Science 2002; 298: 124.

Wells TNC. Natural products as starting points for future anti-malarial therapies: Going back to our roots? Mal J 2011; 10(Suppl 1):S3

WHO. 2002. Traditional medicine strategy 2002–2005. Geneva: World Health Organization, 2002. (WHO/EDM/TRM/2002.1). Available at whqlibdoc.who.int/hq/2002/who_edm_trm_2002.1. pdf/. Accessed March 28, 2013.

WHO. 2004a. Guidelines for the regulation of herbal medicines in the South-East Asia Region. New Delhi, World Health Organization Regional Office for South-East Asia, 2004. (SEA-Trad. Med.-82).

WHO. 2004b. Guidelines on registration of traditional medicines in the WHO African Region. Brazzaville, World Health Organization Regional Office for Africa, 2004. (AFR/TRM/04.1). Available at http://whqlibdoc.who.int/afro/2004/AFR_TRM_04.1.pdf /. Accessed March 30, 2013.

Willcox ML. A clinical trial of 'AM', a Ugandan herbal remedy for malaria. Public Health Med 1999; 21:318–324.

Willcox M, Bodeker G. Traditional herbal medicines for malaria. Br Med J 2004; 329:1156–1159.

Willcox M, Bodeker G, Rasoanaivo P. *Artemisia annua* as a traditional herbal antimalarial. In: Willcox M, Bodeker G, Rasoanaivo P, eds. *Traditional Medicinal Plants and Malaria.* Boca Raton, FL: CRC Press, 2004:43–59.

Willcox ML, Graz B, Falquet J, Sidibé O, et al. Argemone mex-icana decoction for the treatment of uncomplicated falciparum malaria. Trans R Soc Trop Med Hyg 2007; 101:1190–1198.

World Malaria Report 2005. Geneva: World Health Organization, 2005. Available at www.who.int/malaria/publications/atoz/9241593199/en/. Accessed March 30, 2013.

World Malaria Report 2011. Geneva: World Health Organization. Available at www.who.int/malaria/world_malaria_report_2011/en/. Accessed March 30, 2013.

Wright CW. Traditional antimalarial and the development of novel antimalarial drugs. J Ethnopharmacol 2005a; 100:67–71.

Wright CW. Plant derived antimalarial agents: New lead and challenges. *Phytochem Rev* 2005b; 4:55–61.

Wright CW, Phillipson JD. Natural products and development of selective antiprotozoal drugs. Phytother Res 1990; 4:127–129.

Yao-De W, Qi-Zhong Z, Jie-Sheng W. Studies on the antimalarial action of gelatin capsule of *Artemisia annua*. Clin J Parasitol 1992; 10:290–294.

Ying LI, Yu-Lin WU. How Chinese scientists discovered Qin-ghaosu (Artemisinin) and developed its derivatives. What are the future perspectives? Med Trop 1998; 58(3 Suppl):45–47.

Zhang AL, Story DF, Lin V, Vitetta L, et al. A population survey on the use of 24 common medicinal herbs in Australia. Pharmacoepidemiol Drug Saf 2008; 17:1006–1013.

Zirihi Guédé N, N'guessan K, Etien Dibié T, Grellier P. Ethno-pharmacological study of plants used to treat malaria, in traditional medicine, by Bete Populations of Issia (Côte d'Ivoire). J Pharm Sci Res 2010; 2:216–27.

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