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Review Article

Malaria and treatment: Herbal antimalarials as alternative to conventional medicine

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Abstract

For decades, malaria treatment has been championed by conventional medicine through chemotherapy. This was evident until the late 20th century when problems of treatment failure were observed as a result of the emergence of *plasmodium* parasite resistance. In addition, the safety of some of these drugs could not be guaranteed as were found to be toxic and produce adverse effect. In search for solution to the challenges of chemotherapy enveloped the emergence of herbal medicine as possible alternatives. Today herbal medicine is appreciated worldwide for the treatment of so many diseases including malaria. This paper review the current status of malaria and its management with reference to treatment by chemotherapy. It also enumerates the pitfalls of conventional medicine which laid the foundation of herbal medicine on treatment of malaria. Key herbal antimalarial plants and studies on their efficacy and safety are cited. In addition to their safety, some herbal plants were shown in some studies to be effective against resistant parasite strains. Herbal antimalarials are effective against malaria and are now becoming an alternative to the conventional drugs. However, there is need for improvement to ensure its efficacy and safety.

1. Introduction

Malaria is a one of the most dangerous disease in the world which is amongst the most prevalent communicable diseases worldwide [1]. Apart from being a major public health problem with high morbidity and mortality, it has also culminate other major socio-economic problems causing global instability as well as poverty [2]. The disease especially in Africa and Asia continue to be a major threat to mankind [3]. Due to the complexity of the parasite life cycle and transmission of the disease, combating it has been a very difficult task to overcome.

Malaria treatment using conventional (also called western or orthodox) medicine remains among the best methods for the disease management. Various forms of antimalarial treatments have been made available for the treatment of both simple and complicated malaria. Alongside the antimalarials used, antibiotics are also possible chemotherapy in cases of complicated malaria[4]. Though effective in treating malaria, orthodox medicine along the years has had some major drawbacks which have continued to question their supremacy in malaria management. So many, antimalarials such as chloroquine, amodiaquine, sulphadoxine-pyrimethamine etc. used in the nineties are no longer effective in treating malaria [5]. Rather, malaria parasite has become resistant against these treatments and continue to develop new mechanisms for survivals [5]. Chemotherapy today has sort for combination therapy; combining the existing antimalarials with new compounds of artemisinin base. Yet, cases of resistance against artemisinin based combination therapy (ACT) have been observed along the Thailand-Cambodian border in Asia with possibilities of spreading across the globe [6]. Also, apart from being ineffective, certain malaria treatment have also presented adverse effects and are toxic to the body [7]. This drives us to the question "is there no alternative to chemotherapy for malaria treatment?".

There are other types of medicine like naturopathy which have been used to manage malaria but their effectiveness still remain challenging. The most likely alternative to western medicine in recent time is herbal medicine. Herbal medicine which previously in the early 20th century was ignored in the global scenario of public health due to the rise of orthodox medicine is now gaining grounds in malaria treatment [8]. Artemisia *annua* plant used as folk Chinese herbal treatment for malaria which serves as the base for ACT is today widely used in various forms as herbal remedy for malaria [9]. This paper review the present state of malaria alongside the challenges of orthodox medicine in malaria management. It further emphasize on the contribution of herbal treatments in the management of malaria with possible suggestion for a better future for malaria management.

2. Burden of Malaria

Malaria situation is serious and getting worse around the world. Malaria threatens the lives of 40% of the world's population and over 2200 million people are affected by the disease [3]. Each year, there are an estimated 300-500 million clinical cases and an estimated 660 000 deaths [3, 10]. Malaria is estimated to kill more than 1 million people annually, the majority of whom are young children [10]. Ninety per cent of malaria cases in the world occur in Sub-Sahara Africa [11]. Children under 5 years of age and pregnant women are the most affected by malaria [12] and it is one of the leading causes of death among young children. Together with pneumonia, diarrhoea, measles and malnutrition, malaria is responsible for over 70% of deaths in young children especially in developing countries [13]. Malaria during pregnancy causes severe maternal illness and anaemia, and is also associated with low birth weight among newborn infants, a leading risk factor for infant mortality.

Malaria's cost to human and social well-being is enormous. The mosquito-borne disease typically strikes its victims not once but repeatedly. As a result, workers' output is diminished, and children miss school, often for periods of a week or more at a time. The economic loss from malaria was estimated at US$2 billion in Africa alone in 1997 [14]. Malaria is a major cause of poverty, and poverty exacerbates the malaria situation. Taken together, the effects of malaria on lives and livelihoods are devastating for economic progress in hard-hit countries. The World Health Organization and the World Bank rank malaria as the largest single component of the

disease burden in Africa, causing an annual loss of 35 million future life-years from disability and premature mortality [15]. In Africa, malaria is responsible for about 20-30% of hospital admissions and about 30-50% of outpatient consultations [15]. Malaria is also a major public health problem in parts of Asia, Latin America, the Middle East, Eastern Europe and the Pacific [16].

3. Malaria Parasite and Transmission

Malaria is a disease caused by the eukaryotic parasite of the genus *plasmodium* [17]. *Plasmodium* is a parasite that feeds on blood during which it invades the red blood cells (RBC) in humans and destroy them causing shock and fever characterized with high temperatures. Malaria is caused by principally five *plasmodium* species namely; *malariae, ovale, vivax, knowlesi* and *falciparum* [1].

Plasmodium falciparum is responsible for most malaria deaths, especially in Africa [18]. The infection can develop suddenly and produce several life-threatening complications. With prompt, effective treatment, however, it is almost always curable. *Plasmodium vivax*, the most geographically widespread of the species, produces less severe symptoms [19]. Relapses, however, can occur for up to 3 years, and chronic disease is debilitating. Once common in temperate climates, *P. vivax* is now found mostly in the tropics, especially throughout Asia. *Plasmodium malariae* infections not only produce typical malaria symptoms but also can persist in the blood for very long periods, possibly decades, without ever producing symptoms [20]. A person with understanding malaria asymptomatic (no symptoms) *P. malariae*, however, can infect others, either through blood donation or mosquito bites. *P. malariae* has been wiped out from temperate climates, but it persists in Africa. *Plasmodium ovale* is rare, can cause relapses, and generally occurs in West Africa [21]. *P. Knowlesi* is the most recent species discovered in Asia in 2005 responsible for malaria transmission from monkeys to humans [22].

Malaria parasite typically is transmitted to humans by mosquitoes belonging to the genus *Anopheles*. In rare cases, a person may contract malaria through contaminated blood, or a fetus may become infected by its mother during pregnancy. Because the malaria parasite is found in RBCs, malaria can also be transmitted through blood transfusion, organ transplant, or the shared use of needles or syringes contaminated with blood. Malaria also may be transmitted from a mother to her fetus before or during delivery ("congenital" malaria). Malaria parasite has a complex life cycle between humans and the mosquito vector anopheles [23].

4. Conventional Medicine for Malaria treatment

Effective malaria management must commence with laboratory diagnosis before administration of treatment. Malaria chemotherapy is complex and is dependent on certain factors. Treatments administered may vary depending on the *plasmodium* species present, the nature of the disease (simple or complicated malaria), human nature (children, adult, pregnant women), parasite geographical distribution and the intended therapeutic purpose (prophylaxis, Intermittent preventive treatment etc) as well as the drug susceptibility of the infecting parasite [24].

The first antimalarial chemotherapy belongs to the class of amino quinines. This class contains treatments such as chloroquine, mefluoquine, amodaquine, primaquine etc. [25]. Another class of antimalarials is those of the antifolates such as sulfonamide and pyrimethamine. Lumefantrine, and halofantrine antimalarials belong to another class. Recently, artemisinin derivatives of the endoperoxidase class in the forms of arthemeter, artesunate, dihydroartemisinin are shown to be the most effective group of antimalarials which can exist as singles treatment or combined with other antimalarials as combination therapies [26]. Though chemotherapy has dominated malaria treatment, challenges such as drug resistance by the parasite has emerge. Some antimalarials are toxic to humans causing adverse effects.

5. Antimalaria Drug Resistance

Chloroquine which was the first antimalaria is no more recommended for treatment due to the occurrence of resistance in 1959 [27]. The subsequent spread of chloroquine resistance set the scene for the discovery of new drugs. Antifolate combination, sulfonamide/pyrimethamine was the subsequent antimalarials used. After resistance to antifolates, there was increase deployment of quinine derivatives such as mefloquine, amodiaquine, and related lumefantrine, halofantrine antimalarial drugs. Resistance to antimalarials which originated in Asia has widely spread to South America and eastern parts of south Asia, and rapidly has gained ground in tropical Africa [28].

As a response to the antimalarial drug resistance situation, WHO recommended new treatment policies for *P. falciparum* malaria in all countries experiencing resistance to monotherapies, such as chloroquine, sulfadoxine/pyrimethamine, amodiaquine etc. to use combination therapies, preferably those containing artemisinin derivatives (Artemisinin-based Combination Therapy (ACT)) which are currently the most effective agents against multi-resistant malaria parasite strains. However, resistance due to *P. falciparum* against ACT has recently being observed along the Thialand-Cambodian border in Asia [29].

For simple malaria ACTs are recommended usually for oral administration route. In case where the illness is severe, intravenous or intramuscular route is used for antimalarials such as quinine or ACT which can be given in combination with some antibiotics such as clindamycin or doxycycline, tetracycline etc [4].

6. Antimalarials and Toxicity

Most antimalarial drugs have shown to be toxic to the body developing adverse effects [30]. Chloroquine and amodiaquine have been shown to have similar toxic effect. Overdose of chloroquine can lead to cardiac toxicity. Large doses of amodiaquine have been reported to cause syncope, spasticity, convulsions and involuntary movements. Sulfadoxine shares the adverse effect profile of other sulfonamides, although allergic reactions can be severe because of its slow elimination. Nausea, vomiting, anorexia and diarrhoea may occur. Crystalluria causing lumbar pain, haematuria and oliguria is rare compared with more rapidly eliminated sulphonamides. Hypersensitivity reactions may affect different organ system. Larger doses of pyrimethamine may cause gastrointestinal symptoms such as atrophic glossitis, abdominal pain and vomiting, haematological effects including megaloblastic anaemia, leukopenia, thrombocytopenia and pancytopenia, and central nervous system effects such as headache and dizziness. Intramuscular artemether and artemotil are subject to neurotoxicity cause an unusual selective pattern of neuronal damage to certain brain stem nuclei. Primaquine cause plasma levels of the latter to increase 10-fold and exacerbated the already notorious toxicity of that drug and was withdrawn from the market by the US government [31,32].

7. Herbal medicine versus Conventional Drugs

Herbal medicine differs from a conventional pharmacotherapy on two main important aspects [33].

Firstly, herbal medicine makes use of whole plant material containing several constituents and depends on synergic action for the effectiveness of the treatment. These plants constituents are of natural origin without any structural modification or chemical synthesis justifying the safety of herbal products. On the other hand, conventional medicine, sometimes certain plant constituents are fragmented and isolated to identify the principal active component which is chemical modified or synthesized as drugs.

Secondly, Herbal medicine does not depend on the paradigm for specificity which conventional medicine is solely based on (only one -target monopharmacy). Rather, multiple action is the

case of herbal medicine as a result of the presence of a population of various phytochemical constituents (polypharmacy) without a specific target. This mixture of phytochemical is believed to reduce the toxicity of some plants by buffering effect [33, 34].

8. Herbal medicine as malaria treatment

According to the World Health Organization (WHO), the use of herbal remedies throughout the world exceeds that of the conventional drugs by two to three times [35, 36]. The use of plants for healing purposes predates human history and forms the origin of much modern medicine. Many conventional drugs had their origin from plant sources. A few examples include aspirin (willow bark), digoxin (from foxglove), quinine (from cinchona bark), and morphine (from the opium poppy) [33].

Some of our most important medicines come from plants, including two major antimalarial classes used to treat severe malaria; the cinchona alkaloids and artemisinins [36]. The cinchona alkaloids, like quinine, are extracted from the bark of trees originally grown in Peru and have a history that goes back more than 350 years [37]. Artemisinin is extracted from a herb, *qinghao*, which in being documented in traditional Chinese pharmacopoeia for treatment of fevers over two millennia, has a longer history of use. In 1967, the Government of the People's Republic of China began a programme to identify antimalarial principles in plants used in traditional Chinese medicine [38]. By 1971, the Pharmaceutical Institute of the Academy of Traditional Chinese Medicine succeeded in showing that extracts of qinghao killed *Plasmodium berghei* invitro [39] and subsequently identified the active ingredient *qinghaosu* ("the active principle from qinghao") in 1972 which is now called artemisinin [40]. Artemisinin is still obtained by extraction from qinghao (*Artemisia annua* -sweet Annie, sweet wormwood), a genus of plant that also gives us absinthe [40]. Once the structure of artemisinin was solved in 1977 [41], modifications were introduced to improve solubility in both oil and water.

9. Herbal antimalarial Plants and Studies

Today, several plants have been useD in the world as treatment for malaria and presented in different forms as teas bags, blisters, solutions, capsules, tablets etc. Over one hundred thirty nine medicinal plants have been reported for their use as antimalarials as stated by Satish and Kale [42]. Large numbers of plant species have been identified as antimalarial medicinal plants. A wide variety of plants belonging to several families have been identified through ethnobotanical and ethnopharmacological studies as antimalarial medicinal plants. A study by Willcox showed 1277 plant species from 160 families listed that has been used to treat malaria [43]. Unfortunately five plants species used are among the endangered species thus cannot be further evaluated. Also, of these plants 47 species are used on 2 continents and 11 species on all 3 tropical continents are used as antipyretics or antimalarials. In northeast India 65 medicinal plants from 38 different families have been reported to treat malaria, [44] while in South Viet Nam, of 49 plants identified as traditionally used for malaria, forty-six showed in vitro activity at 10 µg/mL [45]. Approximately 64% of the traditional malaria remedies in Kenya have been found in an *in vitro* model to exhibit anti-plasmodial activity [46].

Among others, some of these medicinal plants have undergone clinical trials with good results. Notably, *Cinchona* spp. and *A. annua*, include the Ugandan formula "AM" in which 55% of patients had adequate clinical responses and 8% had clearance of parasites [47]. *Terraplis interretis* showed high rates of adequate clinical response to the point of clinical cure. [48]. *Cryptolepsis sanguinolenta* (Asclepiadaceae) has demonstrated activity similar to that of chloroquine; the extract cleared fever 12 hours faster, and cleared parasites within 24 hr [49].

Some plants have shown to be effective against certain resistant parasite strains. *Bidens pilosa* (Asteraceae) has shown activity against drug resistant *P. falicparum* parasites *in vitro* and *in vivo* in rodents [50, 51].

10. Conclusion

Herbal medicine is widely used for the treatment of malaria in our world today. Several studies have confirmed the effectiveness of some herbal product in treating malaria in *in vitro* as well as *in vivo* studies using animals and in clinical trials. The increase used of herbal medicine over the conventional medicine in the treatment of malaria has been as a result of three main factors notably their safety, cost effectiveness and possible abilities of overcoming resistant parasite strains. However, though herbal medicine seem promising, its future and sustainability will only be achieved if the necessary standard practices are encouraged to improve on the efficacy and safety through clinical trials as well as building the capacity of herbal practitioners with professional ethics to assure the quality of the products by applying good manufacturing practices.

Reference

[1] Snow RW, Guerra CA, Noor AM, Myint HY, Hay SI, 2005. The global distribution of clinical episodes of *Plasmodium falciparum* malaria. *Nature*, 434:214-217.

[2] John Luke Gallup and Jeffrey D. Sachs, 2001. The Economic Burden of Malaria. *Am. J. Trop. Med. Hyg.,* 64(1, 2) S: 85–96

[3] World Malaria Report, 2012. Fact Sheet. www.who.int/malaria, December 2012.

[4] World Health Organisation, 2010. Guidelines for the treatment of malaria, 2nd edition. WHO Library Cataloguing-in-Publication Data.

[5] David Bell and Peter Winstanley, 2004. Current issues in the treatment of uncomplicated malaria in Africa. *British Medical Bulletin* 71: 29–43.

[6] Harald Noedl, Youry Se, Sabaithip Sriwichai, Kurt Schaecher, Paktiya Teja-Isavadharm, Bryan Smith, Wiriya Rutvisuttinunt, Delia Bethell, Sittidech Surasri, Mark M. Fukuda, Duong Socheat, and Lon Chan Thap, 2010. Artemisinin Resistance in Cambodia: A Clinical Trial Designed to Address an Emerging Problem in Southeast Asia. *Clinical Infectious Diseases*, 51(11):e82–e89

[7] Taylor WR and White NJ, 2004. Antimalarial drug toxicity: a review. Drug Saf. 27(1):25-61.

[8] Gyasi RM, Mensah CM, Adjei PO & Agyemang S, 2011. Public Perceptions of the Role of Traditional Medicine in the Health Care Delivery System in Ghana. *Global Journal of Health Science*, 3 (2) 40-49: doi:10.5539/gjhs.v3n2p40.

[9] Dana G. Dalrymple, 2012. *Artemisia annua*, Artemisinin, ACTs & Malaria Control in Africa. *Tradition, Science and Public Policy.* Politics & Prose Bookstore, 5015 connecticut ave, N.W. Washington D.C.

[10] World Health Organization, 1999. Malaria, 1982–1997. *Wkly Epidemiol Rec* 74: 265–270.

[11] World Health Organization, 1997. World malaria situation in 1994, part I. *Wkly Epidemiol Rec* 72: 269–274.

[12] The Prescriber, 2000. Promoting Rational Use of Drugs and Correct Case Management in Basic Health Services. UNICEF Programme Division, 3 UN Plaza, New York 10017

[13] Tobler W, Deichmann U, Gottsegen J, Maloy K, 1995. *The Global Demography Project.* National Center for Geographic Information and Analysis. Technical Report TR-95-6.

[14] World Bank, 1998. *World Development Indicators 1998 CDROM.* Washington, DC: International Bank for Reconstruction and Development.

[15] World Health Organization, 1992. World malaria situation in 1990, part II. *Wkly Epidemiol Rec 67:* 169–174.

[16] Pampana EJ, Russell PF, 1955. *Malaria: A World Problem.* Geneva: World Health Organization.
[17] Ascenzi A, 1999. Malaria diseases and parasites. Parassitologia, 41:33-38.
[18] Carucci DJ, Hoffman SL, Newbold C, Davis RW, Fraser CM, Barrell B, 2002. Genome sequence of the human malaria parasite *Plasmodium falciparum. Nature*, 419:489-511.
[19] Shortt HE, Garnham PCC, Covell G, Shute PG, 1948. The pre-erythrocytic stage of human malaria *Plasmodiun vivax*. *Brit Med J,* 1:547.
[20] Bray RS, 1960. Studies on malaria in chimpanzees. VIII. The experimental transmission and pre-erythrocytic phase of Plasmodium malariae with a note on the host range of the parasite. *Amer J Trop Med Hyg*, 9:455-65.
[21] Garnham PCC, Bray RS, Cooper W, Lainson R, Awad FI, Williamson J, 1954. Preerythrocytic stages of human malaria: Plasmodium ovale. A preliminary note. Brit Med J, 1:257.
[22] Singh B, Lee KS, Matusop A, Radhakrishnan A, Shamsul SSG, Cox-Singh J, Thomas A, Conway DJ, 2004. A large focus of naturally acquired *Plasmodium knowlesi* infections in human beings. *Lancet*, 363:1017-24.
[23] Francis EG Cox, 2010. History of the discovery of the malaria parasites and their vectors. Cox Parasites & Vectors, 3:5. http://www.parasitesandvectors.com/content/3/1/5
[24] CDC treatment guidelines, 2013 Treatment of Malaria (Guidelines For Clinicians). http://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf
[25] World Health Organization. Malaria eradication in 1965.*WHO Chron* 1966; 20: 286–300.
[26] Sanjeev Krishnaa, Anne-Catrin Uhlemanna, Richard K. Haynesb. Artemisinins: mechanisms of action and potential for resistance. Drug Resistance Updates 2004; 7: 233–244.
[27] Talisuna AO, Langi P, Bakyaita N, Egwang T, Mutabingwa TK, Watkins W, Van ME, and D'Alessandro U. Intensity of malaria transmission, antimalarial-drug use and resistance in Uganda: what is the relationship between these three factors? *Transaction of the Royal Society of Tropical Medicine and Hygiene*, 2002; 96:310–7.
[28] Wernsdorfer H. N, and Walther H. Molecular markers for drug resistance in malaria: use in treatment, diagnosis and epidemiology. *Current Opinion in Infectious Diseases*, 2003; 16:553–558.
[29] Rogers W, Sem R, Tero T, *et al*. Failure of artesunate-mefloquine combination therapy for uncomplicated *Plasmodium falciparum* malaria in southern Cambodia. *Malaria J 2009;* 8(1):1-9.
[30] Taylor WR, White NJ. Antimalarial drug toxicity: a review. *Drug Safety,* 2004; 27:25–61.
[31] Surgeon General of the United States. In: The drug treatment of malaria, suppressive and clinical. Circular letter no. 153. *J. Am. Med. Assoc.* 1943; 123: 205–208.
[32] Baird, J.K. Resistance to chloroquine unhinges vivax malaria therapeutics. Antimicrob. *Agents Chemother*. 2011; 55, 1827–1830.
[33] Sanjoy Kumar Pal, Yogeshwer Shukla. Herbal Medicine: Current Status and the Future. *Asian Pacific J Cancer Prev*, 2003; 4: 281-288
[34] Vickers A and Zollman C. ABC of complementary medicine: herbal medicine. *BMJ*, 1999; 319, 1050 -3.
[35] World Health Organization, 1998. Quality control methods for medicinal plants materials. Geneva.
[36] Evans M, 1994. A guide to herbal remedies. *Orient Paperbacks*.
[37] Dobson MJ. Bitter–sweet solutions for malaria: exploring natural remedies from the past. *Parassitologia* 1998; 40, 69–81.
[38] Greenwood D. The quinine connection. *J. Antimicrob. Chemother*. 1992; 30: 417–427.
[39] Klayman DL. Qinghaosu (artemisinin): an antimalarial drug from China. *Science* 1985; 228, 1049–1055.
[40] Qinghaosu C-ORGo. Kuo Xue Tung Bao 1977; 22, 142.
[41] Qinghaosu C-ORGo. Antimalaria studies on Qinghaosu. *Chin. Med. J. (Engl.)* 1979; 92, 811–816.
[42] Satish Bahekar1, Ranjana Kale. Herbal Plants Used For the Treatment of Malaria- A Literature Review. Journal *of Pharmacognosy and Phytochemistry.* 2013; 1 (6): 141-146
[43] Willcox ML, Bodeker G, Traditional herbal medicines for malaria. *BMJ.* Nov 2004; 13329(7475):1156-1159.
[44] Bora U, Sahu A, Saikia AP, Ryakala VK, Goswami P. Medicinal plants used by the people of Northeast India for curing malaria. *Phytother Res.* 2007; 21(8):800-804.
[45] Nguyen-Pouplin J, Tran H, Tran H, *et al*. Antimalarial and cytotoxic activities of ethnopharmacologically selected medicinal plants from South Vietnam. *J Ethnopharmacol.* 2007; 109(3):417-427.
[46] Muregi FW, Chhabra SC, Njagi EN, *et al*. Anti-plasmodial activity of some Kenyan medicinal plant extracts singly and in combination with chloroquine. *Phytother Res.* 2004; 18(5):379-384.
[47] Willcox ML. A clinical trial of 'AM', a Ugandan herbal remedy for malaria. *J Public Health Med.* 1999; 21(3):318-324.
[48] Muregi FW, Chhabra SC, Njagi EN, *et al*. Anti-plasmodial activity of some Kenyan medicinal plant extracts singly and in combination with chloroquine. *Phytother Res.* 2004; 18(5):379-384
[49] Bletter N. A quantitative synthesis of the medicinal ethnobotany of the Malinke of Mali and the Ashaninka of Peru, with a new theoretical framework. *J Ethnobiol Ethnomed.* 2007; 5; 3(1):36.
[50] Carraz M, Jossang A, Franetich J-F, *et al*. 2006. A Plant-Derived Morphinan as a Novel Lead Compound Active against Malaria Liver Stages. *PLoS Med.* 2006; 3(12):e513.
[51] Tran QL, Tezuka Y, Ueda JY, *et al. In vitro* antiplasmodial activity of antimalarial medicinal plants used in Vietnamese traditional medicine. *J Ethnopharmacol.* 2003; 86(2-3):249-252.

