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Review Article

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Natural anti–malarials: A bright hope

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Abstract

Malaria is still an ever–continuing epidemic that claims a large number of lives in tropical and subtropical regions of the globe. The alarming rate at which the parasite, *Plasmodium* has developed resistance to currently used anti–malarial drugs makes it imperative to search for newer and more effective therapeutic agents. In this context, during last few decades several fundamental researches have been conducted to explore novel anti–malarial formulations. However, recent scientific evidences have indeed demonstrated that a variety of plant compounds may check the survival of *Plasmodium* both *in vitro* and *in vivo*. But, there is a need to evaluate and advocate their efficiency in a proper way, because reliable data on the clinical pharmacology and safety of such formulae are extremely scarce, preventing a responsible consideration of their potential benefits. Conclusively, after reviewing literatures it is very clear that plants with anti–malarial activity do not have fully defined this therapeutic property. Therefore, it is necessary to encourage multidisciplinary and interdisciplinary research, mostly those related to natural products enabling the discovery of new and appropriate anti–malarial pharmaceuticals.

Keywords: Malaria; *Plasmodium*; drug resistance; combination therapy; natural anti–malarials.

Introduction

Malaria remains the most important parasitic infection and one of the most prevalent infectious diseases in certain regions of Sub–Saharan Africa, Southeast Asia, Central and South America and Oceania. Human malaria transmitted by female *Anopheles* mosquitoes and caused by five species, *P. falciparum*, *P. vivax*, *P. ovale, P. berghei* and *P. malariae*. Most cases of malaria and deaths are caused by *P. falciparum* [1]. More than 800 million cases and at least one million consequent deaths are reported to occur annually, and more than one–half of the world's population lives in area where malaria is endemic [2] (Fig. 1). The life cycle, immunological defense mechanisms, and clinical development of malaria in humans is a complex process [3] (Fig. 2). Clinical malaria is characterized by periodic fever, which follows the lysis of infected erythrocytes, and caused mainly by the induction of cytokines, interleukin–1 and tumor necrosis factor [4]. *P. falciparum* infections can have serious effects, for example, anemia, cerebral complications (from coma to convulsions), hypoglycemia and glomerulonephritis. The disease is most serious in the non–immune individuals, including children, pregnant women and her developing fetus [5].

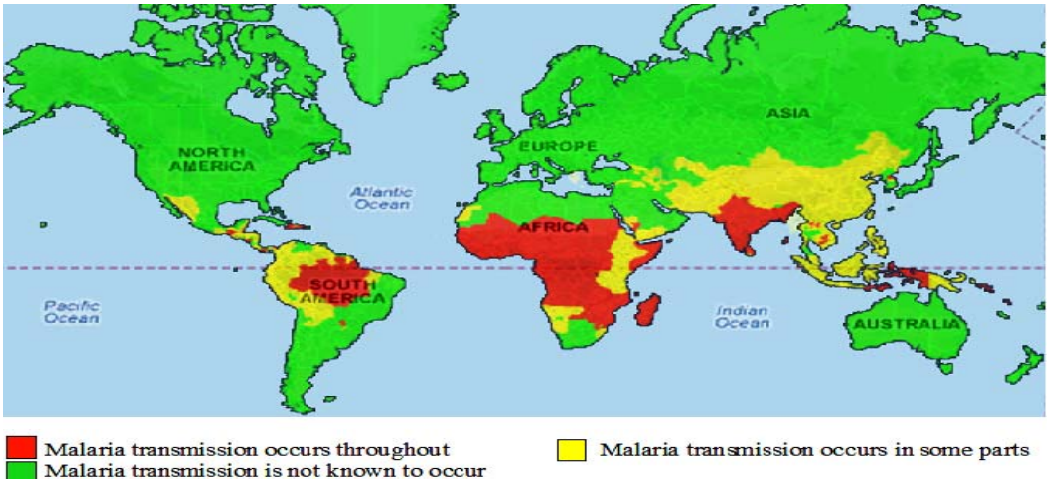

Figure. 1. This map shows an approximation of the parts of the world where malaria transmission occurs (CDC Malaria Map Application).

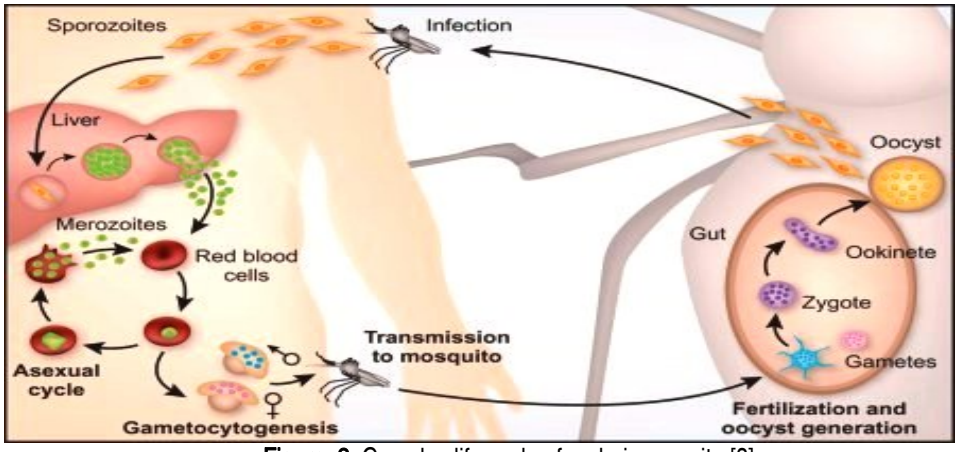

Figure. 2. Complex life cycle of malaria parasite [3]

Development of drug–resistance

Plasmodium falciparum, the most widespread etiological agent for human malaria has shown itself capable of developing multi–drug resistance to standard anti–malarials [6] that has further complicated it's management and only a few antibiotics are now effective in treatment of *falciparum* malaria [7]. Chloroquine has been used as a wonder anti–malarial drug in terms of it's efficacy, minimal side effects and affordability. Meanwhile, the development of widespread resistance to this molecule is the main reason for resurgence of *falciparum* malaria [8,9]. Replacement drugs such as sulphadoxine–pyrimethamine could not sustain for long time due to rapidity in development of resistance [10]. Other drugs such as amodiaquine, mefloquine, atovaquone, etc. could not fit the bill due to a variety of reasons, including development of cross–resistance, side effects and cost considerations [11]. The loss of effectiveness of chemotherapy constituted the greatest threat to the control of malaria.

Anti–malarials in current use

Basically, for anti–malarial chemotherapy quinoline and quinoline–based drugs have formed the mainstay from last 50 years. Anti–malarial drugs in current use are listed below

Quinine

Quinine, isolated from the bark of American *Cinchona* tree, which was the first reported anti–malarial compound in the seventeenth century [12]. Though it is curative to *falciparum* malaria, but fails against *vivax* malaria. It destroys trophozoites present in the erythrocytes, but has no effect on exo–erythrocytic stages that develop in the liver [13].

Chloroquine (CQ)

Chloroquine (CQ) was first used in the 1940s and found effective in curing all forms of malaria [14]. Chloroquine (CQ) remained the best drug for a long time because of its excellent clinical efficacy, safety and low cast. It is believed to act by inhibiting heme polymerization [15]. Unfortunately, most strains of *Plasmodium* are now resistant to this drug [16].

Mefloquine

Mefloquine is produced by Walter Reed Army Institute for Medical Research under Malaria Research Program established in 1963 [17]. Mefloquine is structurally related to quinine. It is selectively active against the intra–erythrocytic mature forms – trophozoites and schizonts of *Plasmodium* and has no activity against mature gametocytes [18]. Both *in vitro* and *in vivo* resistance has been reported against Mefloquine in malaria endemic regions [19].

Halofantrine

It was introduced in 1984 when clinical trials began against *P. falciparum* and found more active than Mefloquine [20]. It is used for treating mild to moderate acute malaria in sensitive strains of *P. falciparum* and *P. vivax* [21]. Exact mode of action of Halofantrine is not yet known [22]. Recent reports have raised serious questions concerning its safety [23].

Primaquine

Primaquine is effective against the liver stages of parasite's life cycle [24]. Its use is imposing great limitations because of inherent side effects like haemolysis in glucose–6–phosphate dehydrogenase deficient cases, anaemia and methaemoglobin toxicity [25].

Sulphonamides and Sulfones

These are basically antibacterial but during the Second World War these were used successfully in cure of malaria in war affected areas. Malaria parasites, like many bacteria are unable to utilize preformed folic acid and require *p*–amino benzoic acid as a substrate in order to synthesize it. Sulphonamides and sulfones act as competitive antagonists of this substrate [26]. These are slow

acting blood schizontocide that are more active against *P. falciparum.* But, there is a report that *P. falciparum* has developed resistance against sulphonamides and show serious toxicity in some individuals [27].

Antifolate

This class of anti–malarial includes compounds like pyrimethamine and trimethoprim. These are always given in combination with either a sulphonamide or sulfone and have been used extensively for prophylaxis and suppression of human malarias especially those with chloroquine resistant *P. falciparum* strain [28]. Serious side effects to this combination are now widespread and therefore it is not recommended [29].

Combination therapy

The basic principle of combination therapy is that the probability of resistance developing simultaneously to two chemotherapeutic agents with independent mechanisms of action is extremely low. This frequency is the product of the probabilities of the acquisition of a resistant mutation to each drug multiplied by the number of parasites in a typical infection [30]. However, the effect of combination therapy is enhanced by the inclusion of an artemisinin derivative [31]. Artemisinin anti–malarials decrease parasite density more rapidly in combination with some older drugs such as atovaquone [32], proguanil [33], and malarone [34]. Furthermore, combination drugs have not been found easy to reach poor people due to its high cost. Hence, combination therapy could not fully bill the need and there is an urgent need to explore some novel formulations with a different mode of action and low cost.

Plants as a source of anti–malarial drug

There is a consensus among the scientific community that natural products have been playing a dominant role in the discovery and development of drugs for the treatment of human diseases [35]. Indeed, the vast majority of the existing anti–malarial chemotherapeutic agents are based on natural products, and this fact anticipates that new leads may certainly emerge from the tropical plant sources, since biological chemo–diversity continues to be an important source of molecular templates in the search for anti–malarial drugs [36-38]. However, on the basis of the plants which appear to be widely used in traditional medicine for fever and joint pains as symptoms of malaria (Listed in Table 1), researches were moved toward the search of wonder anti–malarial compound that would have unending power to fight with this deadly parasite [39]. Therefore, time to time different plants have been screened for their anti–malarial potential. *Bowdichia virgilioides* a traditionally reputed plant among American natives was found active against *P. falciparum*–MRC–20 and *P. berghei* infected mice in dose of 250mg/kg [40]. Marcela *et al.* [41] experimentally evaluated the plasmodicidal activity of *Solanum nudum*, a plant that have already been used in traditional medicine in Colombia to cure malaria. Oliveira *et al.* [42] have demonstrated the anti–malarial activity of *Bidens pilosa*, in patients infected respectively with *P. falciparum* and *P. berguei* in Brazilian endemic area. Similarly in a laboratory experiment, methanol extract of *Remijia ferruginea* (Brazilian plant) was found active in *P. berghei* infected mice [43]. Okunade and Lewis [44] reported the anti–malarial activity of leaves and stem extracts of *Lantana cujabensis* Schauer, a shrub found in the Amazonian and Andean forests of South America. Mcphail *et al.* [44] evaluated the anti–malarial activity of the ethyl acetate extract of marine cyanobacterium *Lyngbya majuscula* (Oscillatoriaceae) *in vitro* model for *P. falciparum*.

Table 1. List of some plants traditionally used to treat malaria in different countries

Family	Species	Countries
Bixacea	*Bixa orellana*	Brazil and Peru
Boraginaceae	*Heliotropium indicum*	Venezuela
Caricaceae	*Carica papaya*	Brazil and Surinam
Compositae	*Parthenium hysterophorus*	Venezuela
Compositae	*Vernonia spp*	Brazil, Colombia and Venezuela
Cucurbitaceae	*Momordica charantia*	Colombia, Guyana and West Indies
Lamiaceae	*Ocimum sanctum*	India
Leguminosae	*Senna occidentalis*	Brazil
Liliaceae	*Allium sativum*	India
Meliaceae	*Azadirachta indica*	India and Sudan
Myrtacea	*Eucalyptus globulus*	Venezuela
Phytolaccaceae	*Phyllanthus niruri*	Cuba and Surinam
Piperaceae	*Piper nigrum*	India
Verbenaceae	*Verbena litoralis*	Venezuela
Zingiberaceae	*Curcuma longa*	India
Zingiberaceae	*Zingiber officinalis*	India

Moreover, various plants of Indian subcontinent have also been used in anti–malarial research including *Citrus cinensis*, *Carcia papaya*, *Swertia chirata* [46], *Bidens pilosa* [47], *Ocimum sanctum* [48], *Piper sarmentosum*, *Andrographis paniculata* and *Tinospora crispa* [49]. Coppi *et al.* [50] tested stage specific activity of 'allicin', isolated from garlic and found that a 4–day regimen of allicin administered either orally or intravenously significantly decreased parasitemias or increased the survival of infected mice by 10 days. In the light of some advance researches it was come out that use of purified plant secondary substances than crude extracts might be better practice. However, the most important and diverse biopotency has been observed in naturally occurred plant secondary substances belonging to different groups, listed in Table-2 [51–60]. These substances interestingly show synergism with crude plant extracts and other plant metabolites as well. Mishra *et al.* [61] has documented the synergistic activity of curcumin, with crude extracts of *Andrographis paniculata* and *Hedyotis corymbosa*. Evidently, curcumin is a novel compound isolated from *Curcuma longa* that has already been reported for its anti–malarial potential [62]. Further, its efficacy has also evaluated and advocated in combination with artemisinin (derived from *Artemisia annua*) against *Plasmodium* [63]. Recently, Mishra *et al.* [64] has reported for the first time Andrographolide as the major bioactive anti–malarial constituent of the plant, *Andrographis paniculata* using both *in vitro* and *in vivo* approaches and evaluated the interaction of Andrographolide with other established anti–malarial compounds such as curcumin and artesunate. This has added new information on combination of potent anti–malarial compounds for novel combinatorial drug therapy against drug–resistant malaria.

Table 2. A short list of anti-malarial plant secondary substances

Plant	Compound	Activity*	References
Artemisia annua	Artemisinin	0.01µg/ml (EC_{50})	[50]
Azadirachta indica	Gedunin	0.72 mg/ml (IC_{50})	[51]
	Nimbinin	0.77 mg/ml (IC_{50})	[51]
	Meldenin	5.23 mg/ml (IC_{50})	[52]
	Isomeldenin	50.0 mg/ml (IC_{50})	[52]
Cyperus rotundus	α–Cyperone	5.5 µg/ml (IC_{50})	[53]
Erycoma longifolia	Eurycomanone	48.1 ng/ml (EC_{50})	[54]
Morinda lucida	Digitolutein	12.92 µg/ml (EC_{50})	[55]
Rosa rugosa	Rugosal A	1.4 µg/ml (EC_{50})	[50]
Siparuna andina	Sipandinolide	46.2 µg/ml (IC_{50})	[56]
Salacia kraussii	Celastrol	180.9 ng/ml (IC_{50})	[57]
Triphyophyllum peltatum	Betulinic acid	10.46 µg/ml (IC_{50})	[58]
Xanthium strumarium	Tomentosrin	7.8 µg/ml (IC_{50})	[59]

*activity against *P. falciparum*

Conclusion

Off course, the gravity of the situation has been compounded by the absence of a vaccine for protection. Further, plant compounds and its derivatives would only be a viable option for the treatment of drug resistant malaria. However, not a lot, but a satisfactory report has been found in favor of herbal anti-malarials. These drugs would have novel modes of action or be chemically different from the drugs in current use. The effective anti–malarial activity of some plant–based formulations has recently generated much interest to explore plant resources for their possible anti–malarial efficacy, specially based on ccombination therapy, which have become the practice of choice because of their increased therapeutic efficacy over monotherapy and the other benefits include decreased cytotoxicity, delay or prevention of the development of drug resistance.

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