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PLANTS AS ANTIMALARIAL DRUGS: A REVIEW

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ABSTRACT

Malaria is a protozoa disease, transmitted by the Anopheles species of mosquito carrying the *Plasmodium* parasite. Despite the substantial progress made in the treatment of parasitic diseases, malaria remains a significant therapeutic challenge especially because of the wide spread resistance of malaria parasites to currently available anti-malarial agents, the resistance of the mosquito vectors to currently available insecticides, the limited success in the development of malarial vaccines and the debilitating adverse reactions of conventional anti-malarial drugs . These have stimulated the search for new pharmacologically active agents that can overcome these barriers. There is a long standing tradition for the use of phytomedicines for the treatment of malaria. The plant kingdom remains a major target in the search of lead compounds and new drugs to treat this debilitating parasitic disease. This review gives a detail account of plants possessing significant antimalarial activities.

KEYWORDS: Plants, Malaria, Traditional Medicinal Practitioners, Antimalarial herbal drugs, Active metabolite.

BACKGROUND

Malaria is a vector borne infectious disease caused by protozoan parasites of the genus *Plasmodium*.[1] The disease is widespread in tropical and subtropical regions, including parts of the Americas, Asia and Africa[2] as shown in Fig 1.

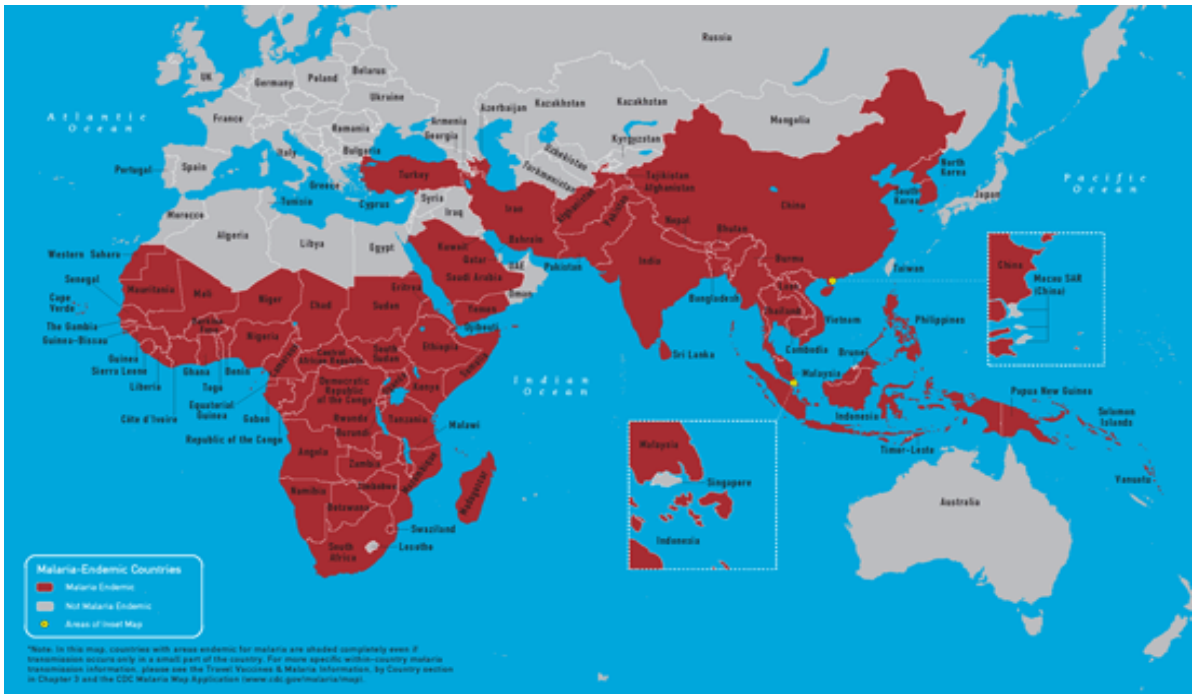


Figure 1: Malaria-endemic countries in the tropical and subtropical regions-Courtesy of CDC malaria MAP Application (www.cdc.gov/malaria/map)

Malaria has infected humans for over 50,000 years and *Plasmodium* may have been a human pathogen for the entire history of man. Also, a close relative of the human malarial parasites infects the chimpanzees.[3]

Human malaria is caused primarily by four species of *Plasmodium*, namely *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, and *Plasmodium ovale*. Each one has a distinctive appearance under the microscope, and produces a somewhat different pattern of symptoms.[4]

Malaria causes about 400-900 million cases of fever and approximately 1-3 million deaths annually.[5] This represents at least one death every 30 seconds. The vast majority of cases occur in children under the age of 5 years, pregnant women are also especially vulnerable.[6] The economic impact of malaria has been estimated to cost Africa $12 billion every year.[7] The economic impact includes costs of health care, working days lost due to sickness, days lost in education, decreased productivity due to brain damage from cerebral malaria, and loss of investment and tourism. In some countries with a heavy malaria burden, the disease may account for as much as 40% of public health expenditure, 30-50% of inpatient admissions and up to 50% of outpatient visits.[8]

Accurate diagnosis is a vital part of good malaria case management and is becoming increasingly important as the need for presumptive treatment of fever declines along with malaria burden in many areas. The proportion of people treated for malaria who have a confirmed diagnosis is low in the African Region compared with other regions of the world[9] with the result that anti-malarials could be used to treat patients without malaria.

The reemergence of malaria in many parts of the world is due to the rapid increase of resistance to most of the available antimalarial drugs, as well as resistance of vectors to insecticides.[10] Drug resistant strains of *P. falciparum* have been found in many endemic areas of the world and many of conventional antimalarial drugs have been associated with treatment failure. Furthermore, the difficulty of creating efficient vaccines and also adverse side-effects of the existing antimalarial drugs highlight the urgent need for novel, well-tolerated antimalarial drugs[11] for both prophylaxis and treatment of malaria.

TRADITIONAL TREATMENT OF MALARIA

In Africa, people use different parts of plant such as leaf, bark, stem, root, fruit etc. to treat malaria. Many of the herbal remedies may also be prepared by decoction in order to imitate the ethnomedicinal method of preparation by the Traditional medicinal Practioners (TMP).[12, 13] Researches conducted by [14-16] indicated that many medicinal plants used in herbal medicine for the treatment of malaria were taken orally in the form of infusions (hot teas), decoctions (boiled teas), tinctures (alcohol and water extracts), paste, powder and macerations (cold-soaking).

Table 1 indicates modes of preparation of antimalarial medicinal plants in different African countries.

Table 1. Modes of preparation of African antimalarial medicinal plants

No	Plant	Part	Vernacular	Preparation	Country	Reference
1	*Agelanthus dodoneifolius*	Leaves, Young twig	Kauchi	Decoction	Nigeria	[17]
2	*Azadirachta indica*	Leaves, Barks	Nim, Dogonyaro	Decoction	Ghana, Nigeria	[16,18]
3	*Carica papaya*	Leaves, Fruits	Gwanda, Brofe	Infusion, Decoction	Nigeria Ghana	[16,18]
4	*Cymbopogon citratus*	Leaves	Tea leaf, Elephant grass	Decoction	Ghana, Nigeria	[16,18]
5	*Khaya senegalensis*	Leaves	Mahogany	Decoction, Infusion	Ghana	[18]

6	*Mangifera indica*	Root bark, Leaves	Mango, Mangoro	Decoction	Ghana, Nigeria	[16,18]
7	*Morinda lucida*	Aerial part, stem bark , root bark	Nimo, Konkroma	Decoction, Infusion	Nigeria, Ghana	[18,19]
8	*Musa sapientum*	Leaves, Fruits	Ayaba	Decoction	Nigeria	[16]
9	*Nauclea latifolia*	Stem	Ogewu	Decoction	Ghana	[18]
10	*Parkia biglobosa*	Stem bark, Leaves, Pulp	Dorowa, Nere	Decotion, Powder,Poutices	Nigeria, Senegal	[20]
11	*Psidium guajava*	Barks, Leaves, Stem, Root	Guava	Decoction, Infusion	Nigeria, Ghana	[16,18]
12	*Phyllanthus amarus*	Stem, Whole plant	Boma	Decoction	Ghana	[18]
13	*Vernonia ambigua*	Whole plant	Orungo	Decoction	Nigeria	[21]
14	*Vernonia amygdalina*	Leaves	Chuaka, Awonoo	Decoction	Nigeria, Ghana	[16,18]
15	*Zanthoxylum zanthoxyloides*	Leaves	Okanto	Decoction	Nigeria	[16]

The first effective treatment for malaria was the bark of cinchona tree, which contains quinine, this tree grows on the slopes of the Andes, mainly in Peru.[22] This natural product was used by the inhabitants of Peru to control malaria as shown in Fig 2.

Figure 2: Peru offered a branch of cinchona to Science (from a 17th-century engraving): *Cinchona*, the source of Peruvian bark, as an early remedy against malaria.

However, it was not until 1820 that the active ingredient quinine was isolated and made available by the French Chemists Pierre Joseph Pelletier and Joseph Bienaime Caventou. [22] This in addition also contains three other antimalarial compounds, namely, quinidine, cinchonine, and cinchonidine. [23] Quinine served as a lead structure for the synthesis of several antimalarial drugs such as chloroquine, mefloquine, pyrimethamine, proguanil, atovaquone (sold together with proguanil as "Malarone"), or primaquine. Quinine (alone or in combination with doxocycline, tetracycline or clindamycin) is still used today to treat acute cases of severe *P. falciparum* infections. [24]

Artemisia annua is another medicinal plant which was rediscovered in China in the seventies as an important source of the antimalarial artemisinin. [25, 26] Artemisinin-combined therapies (ACT) were formally adopted as first-line treatment of uncomplicated malaria in Nigeria from 2005 onwards [27] and atovaquone (Malarone®), which is a synthetic compound (2-alkyl-3-hydroxynaphthoquinone) analogue of lapachol from the Tabebuia species (Bignoniaceae). [28]

Another plant species used as an antimalarial drug in Chinese ethno-medicine is *Dichroea ferifuga*. The active principle, febrifugine, has been used clinically against *P.vivax and P.ovale* but its liver toxicity makes it unacceptable as a useful antimalarial agent.[29]

TRADITIONAL ANTIMALARIAL DRUGS

Traditional medicine encompasses the utilization of substances, dosages and practices based on socio-cultural norms and religious beliefs as well as witnessed experiences and observations of a specific group. This knowledge is handed down from generation to generation in order to diagnose, prevent or eliminate a physical, social or spiritual imbalance.[13]

In some communities in Africa excessive mortality due to the disease has been reduced by the ability of the local TMP to manage the disease. [30] Plants from different botanical sources have been used by various TMP for the treatment and cure of malaria. [15, 31] Numerous claims by the TMP on the potency and use of various plant species for the treatment of malaria abound. Only few of these claims have been authenticated by scientific investigations. [32]

Traditional drugs may be collected from wild or cultivated plants, it is known that the active constituents of medicinal plants are affected by many factors such as time of the year, time of

the day, stage of maturity and age and these may vary during the course of plant growth. Proper time of collection is very important to obtain a drug of good quality.[33]

Fresh or dried plant material can be used as a source for secondary plant components, drying of the crude drugs is by natural, artificial method or Lyophilization (Freeze-drying).[34] The reasons for using dried plant materials in phytochemistry of traditional drugs are (i) there are fewer problems associated with the large scale extraction of dried plant material than with fresh material, (ii) the time delay between collecting plant material and processing it makes it difficult to work with fresh material because differences in water content may affect solubility or subsequent separation by liquid-liquid extraction, (iii) many , if not most plants are used in the dried form or as aqueous extract by TMP), (iv) to ensure apparent stability and antimalarial activity of the drug,[35] for example the antimalarial activities of many medicinal plants were assessed in lyophilized forms.[12, 36]

ANTIMALARIAL SCREENING OF TRADITIONAL DRUGS

The testing of new anti-malarial drugs in natural products requires that at least two steps are undertaken before testing in humans may take place. In the first step, the new drug is tested *in vitro* and then if promising results are obtained it is tested *in vivo*. In the first step of the process, assays have been developed that focus on the drug's ability to affect parasite growth in red cells. In these assays, *P. falciparum* is the parasite used if the drug is intended for humans. In the second step of the process, animal models, usually rodents are used to test the drug efficacy. In this step, species-specific parasites such as *P.berghei* are used.[37]

Plasmodium species that cause human disease are essentially unable to infect non primate animal models. So, *in vivo* evaluation of antimalarial compounds begins with the use of rodent malaria parasite.[38] The *P. berghei*-infected mouse model has been widely used as a preliminary test for the in *vivo* activity of potential antimalarial agents, as it provides a preclinical indication of any *in vivo* potential bioactivity as well as possible toxicity of the sample tested.[39] Rodent malaria parasite *P.berghei*, has proved to be valuable for estimation of activity in chemotherapeutic research programs in which more than 300,000 compounds have been screened.[40] *Plasmodium berghei* 4 day suppression test is the most widely used preliminary test, in which the efficacy of a compound is assessed by comparison of blood parasitemia and mouse survival time in treated and untreated mice.[41] To compare the effect of a standard inoculum of *P.berghei* , which kills mice within 6 days with extension of survival time to 12 days by a single dose of test compound Rane test is used.[42] Compounds

are also tested for prophylactic activity by administrating them prior to infection, followed by daily examination of smears in prophylactic test.[41]

Chloroquine phosphate has been used as the standard antimalarial drug for curative, suppressive and prophylactic antiplasmodial assessment because of its established activity on *P. berghei*,[43] P. *berghei* a rodent malaria parasite though, not able to infect man and other primates has been used because of its sensitivity to chloroquine.[44] The *in vivo* antimalarial activity of some plant extracts are listed in table 2.

Table 2. *In vivo* antimalarial activity of some plant extracts

No	Plants	Extracts	% Inhibition	Reference
1	*Agelanthus dodoneifolium*	Aqueous	80.1	17
2	*Alstonia bonnie*	Ethanol	100	45
3	*Annona senegalensis*	Methanol	91.1	43
4	*Artemisia annua*	Hexane	52.8	46
5	*Boerhavia elogans*	Ethanol	66.2	47
6	*Crossopteryx febrifuga*	Methanol	84.7	48
7	*Languas galangal*	Methanol	67.0	*49*
8	*Lippia multiflora*	Ethanol	69.2	50
9	*Morinda lucida*	Ethanol	100	*45*
10	*Morinda morindiode*	Fermented-Maize-starch	70.0	51
11	*Parkia biglobosa*	Aqueous	55.6	12
12	*Parkia biglobosa*	Methanol	100	52
13	*Paullina pi*nnata	Ethanol	85.0	53
14	*Phyllanthus fraternus*	Aqueous	86.4	54
15	*Solanum surattense*	Ethanol	58.1	47
16	*Tinospora crispa*	Methanol	50.1	14
17	*Vernonia ambigua*	Aqueous	57.7	21
18	*Vernonia amygdalina*	Ethanol	82.3	55

In vitro screens for activity constitute a key component for antimalarial drug screening. It is based on the ability to culture *Plasmodium falciparum* in human erythrocytes *in vitro*. The development of techniques for continuous cultivation of *Plasmodium falciparum* is a reliable source, for continuous stock culture of parasite, apart from drug screening and long term assessment. *Plasmodium falciparum* can now be maintained in continuous culture in human erythrocytes incubated at 37oc in RMPI 1640 medium with human serum or albumax.[42]

The most commonly used method for the antimalarial *in vitro* testing for resistance is Micro-test (Mark III). It provides information on the quantitative drug response of *P.falciparum* irrespective of the patient's immune system.[56] Historically, the most widely *in vitro* technique for assessment of drug resistance is the microscopic quantification of parasite

maturation.[57, 58] This approach is laborious, time consuming and unpopular with microscopists.[59]

To circumvent these problems, light microscopic evaluation as the primary assay is increasely replaced by new methods incorporating automated analysis of assay plates. The most widely used are (i) quantitation of titrated hypoxanthine incorporated into parasite DNA by scintillation counting,[60, 61] (ii) colorimetric measurement of Plasmodium lactate dehydrogenase (LDH), [62, 63] and (iii) histidine rich protein II quantitation by Enzyme linked immunosorbent assay.[59]

Recently, the feasibility of using Sybr Green (SG) nuclei acid gel stain and florescence based analysis has been investigated.[64, 65] Yolanda *et al* (2004) had also carried out microfluorimetric assay to measure inhibition of *Plasmodium falciparum*. [66] Bealmans *et al* (2000) screened 178 plants extracts for their ability to inhibit the polymerization of heamatin.[67] Builders *et al*., (12, 17, 21, 52,), evaluated *in vitro* antiplasmodial activites of some plant extract with cyscope fluorescene microscope. Table 3 shows the *in vitro* antimalarial activities of some of these plant extracts.

Table 3. *In vitro* antimalarial activities of some plant extracts

No	Plants	Extracts	IC $_{50}$ (µg/ml)	References
1	*Acalypha fructicosa*	Methanol	1.6	68
2	*Agelanthus dodoneifolium*	Aqueous	21.5	17
3	*Anogeissus leiocarpus*	Methanol	2.6	69
4	*Aspillia Africana*	Ethyl acetate	9.3	70
5	*Boerhavia elogans*	Ethanol	12.0	47
6	*Caesalpinia pluviosa*	Stem barks	8.0	67
7	*Cassia accidentalis*	Ethanol	2.8	*71*
8	*Eurycoma longifolia*	Butanol	0.3	62
9	*Holarrhena pubescens*	Ethanol	28.0	73
10	*Nauclea latifolia*	Aqueous	0.6	74
11	*Parkia biglobosa*	Methanol	0.12	52
12	*Swartzia madagascariensis*	Aqueous	15.5	60
13	*Terminalia glaucescens*	Aqueous	2.4	75
14	*Trichilia rubescens*	Methanol	12.0	76
15	*Trigonella foenum*	Ethanol	8.8	77
16	*Vernonia ambigua*	Aqueous	31.6	21
17	*Vernonia amygdalina*	Ethanol	9.8	*45*

ANTIMALARIAL ACTIVITIES OF ACTIVE METABOLITES ISOLATED FROM MEDICINAL PLANTS

Many secondary plant substances had been assessed either for *in vitro* activity against *P.falciparum* or *in vivo* activity against *P.berghei*.[78] Alkaloids are one of the major classes of compounds possessing antimalarial activity. In fact, one of the oldest and most important antimalarial drugs, quinine, belong to this class of compounds and are still relevant. A number of naturally occurring alkaloids belonging to different groups, oxyacanthine from *Dehaasia incrassate*, alstonerine from *Alstonia angustifolia*, cryptolepine from *Crytolepsis sanguinolenta*, had been reported to possess antimalarial activity against different malarial models.[79,80]

The discovery of quighaosu (artemisinin), a novel sesquiterpene lactone endoperoxide antimalarial constituent from the Chinese plant Qinghao (*Artemisia annua*), prompted the investigation of some other naturally occurring peroxides for their schizonticidal activity. Various sesquiterpenoids reported for their antimalarial activity include peroxyachifolid from *Achillea millefolium*, patchoulenone from *Cyperus rotundus* and neurolenin from *Neurolaena lobata* .[81, 82]

Some triterpenoids isolated from different medicinal plants (Gedunin from *Azadirachta indica*, *Khaya grandifolia*, *Cedrela odorata*, *Guarea multiflora*) were found to exhibit antimalarial property.[78] Isopreterpenoid compound such as azadirachtin obtained from *Azadirachta indica* possessed antiplasmodial activity.[83]

The antiplasmodial activities of many phenolic compounds had been described.[84, 85] Active compounds such as prunetin, genistein derived from *Andira inermis* are commonly implicated in the antiplasmodial activity of many plants.[86] The antiplasmodial activity of gerontoxanthone isolated from *Cratoxylum maingayi* had described by.[87] Phyllanthrin , a lignin isolated from *Phyllanthrus amarus* is a polyphenolic compound with antiplasmodial activity.[88]

The antiplasmodial activities of tannins were found in *Acalypha fruticosa*, *Boswellia elongate*, *Terminalia belerica* Roxb had been reported.[88] *Indigofera* species exhibited antiplasmodial activity due to the presence of glycosides.[89]

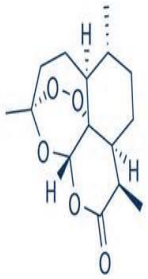
Saponins found in *Petersianthus macrocarpus* possessed antiplasmodial activity.[90,91] Anthraquinones were found in *Morinda lucida* and their antiplasmodial activities were investigated . [71,92] Naturally –occuring quinone digitotutein had been isolated from *Morinda lucida* with antiplasmodial activity . [78] The pharmaceutically important carbohydrates are polysaccharides found in *Acaypha fructicosa*, *Azadirachta indica*, *Boswellia elongate* and *Echium rauwalfii* indicated antiplasmodial activities reported. [68]

Alshwash *et al.*, 2007 investigated the *in vitro* antiplasmodial activity of *Cissus rotundifolia* and *Dendrosiccyos socotrana*, proteins were some of active constituents present in these plant extracts.[68]

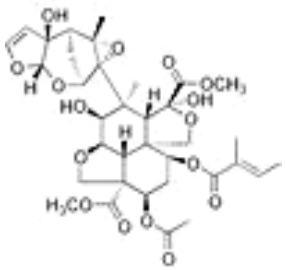
Essential oils in *Stephania erecta* , *Myrtus communis* and *Rosmaricus officinalis* exhibited antiplasmodial activities (Saxena *et al*., 2003). Milhan *et al*. (1997) reported the antiplasmodial activity of Cepharanthine isolated from *Stephania erecta* .[78, 93]

Steroidal compounds present in many species such as *Cissus rotundifolia* , *Parkia biglobosa* and *Vernonia ambigua* displayed antiplasmodial activities.[12, 21, 52, 68]

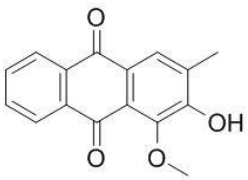
Chemical structures of some of these secondary metabolites with antimalarial activities are presented in Fig 3.



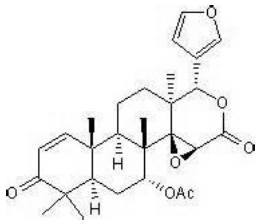
Artemisinin



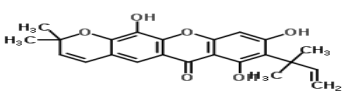
Azadirachtin



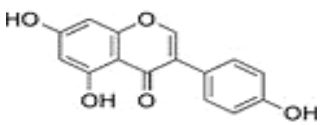
Digitolutein



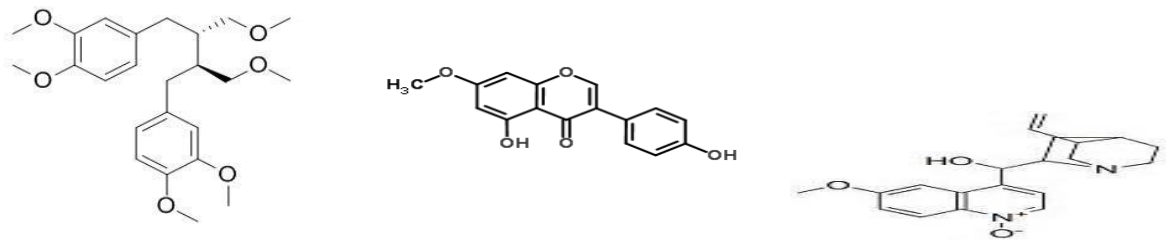
Gedunin



Gerontoxanthone



Genistein



Phyllanthin **Prunetin** **Quinine**

Figure 3: Secondary metabolites isolated from plants

MODES OF ACTION OF ANTIMALARIAL TRADITIONAL DRUGS

Many of the plants which produce alkaloids (families Papaveraceae, Berberidaceae, Menispermaceae, Ranunculaceae) elicit their antiplasmodial activities by Intercalating DNA. For example quinoline alkaloids (such as quinine), furanoquinoline alkaloids (Rutaceae), emetine (*Cephaelis acuminata*, Rubiaceae), beta-carboline alkaloids (e.g., in *Peganum harmala*, Nitrariaceae), anthraquinones (many Polygonaceae, Rhamnaceae), and furanocoumarins (many Apiaceae, Fabaceae) produce their antiplasmodial activities by damaging DNA.[94]

The peroxide bridge in the trioxane pharmacophore is essential for the expression of antimalarial activity of Artemisinin-based compounds.[26] The antioxidant flavonoids and phenolic compounds containing plants such as (*Parkia biglobosa, vernonia ambigua, Cratoxylum maingayi* and *Cratoxylum cochinchinense*) have also been shown to exert antiplasmodial activity by elevating the red blood cell oxidation and inhibiting the parasite's protein synthesis and also counteract the oxidative damage induced by the malaria parasite.[12, 21, 52, 95]

The postulated mechanisms of action for other antimalarial herbal drugs include hemozoin polymerization parasite inhibition for *Caesalpina pluviosa* and Trichilia *pleenea*,[67] *Plasmodium falciparum* lactate dehydrogenase inhibition for *Ajuga remota and Caesalpinia volkensi* ,[96] and inhibition of formation of mobile microgamates for *Azadirachta indica*,[97, 98] proteolytic processing circumsporozoites protein inhibition for *Allium sativum* [99] and alkalytion for *Khaya grandifoliola*. [100]

CONCLUSION

Plant kingdom has proven an effective source of antimalarial drugs in the past, and since about 1,200 plant species are used in traditional medicines of the world for treatment of

malaria, they are being used in medicine from time immemorial because they have fitted the immediate personal need, they are accessible and inexpensive. Natural antimalarial products have traditionally provided most of the antimalarial drugs in use, with the achievements of synthetic chemistry and the advances towards rational antimalarial drug design, herbal antimalarial drugs continue to be essential in providing antimalarial medicinal compounds and as starting points for the development of antimalarial synthetic analogues. However, to ensure the safety of these herbal antimalarial drugs, there must be adequate information on the contra-indications, drug interactions and toxicities of these drugs and there should also be proper standardization and clinical trials of these plant products.

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