ANTIMALARIALS FROM SEMISYNTHETIC ORIGIN

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ABSTRACT
Malaria is still the most destructive and dangerous parasitic infection in many tropical and subtropical countries. The burden of this disease is getting worse, mainly due to the increasing resistance of Plasmodium falciparum against the widely available antimalarial drugs. So, there is an urgent need for the development of new treatments for malaria. Nature and particularly plants used in traditional medicine are a potential source of new antimalarial drugs as they contain molecules with a great variety of structures and pharmacological activities. A large number of antimalarial compounds with a wide variety of structures have been isolated from plants and can play a role in the development of new antimalarial drugs. Ethnopharmacological approaches appear to be a promising way to find plant metabolites that could be used as templates for designing new derivatives with improved properties. The literature from 1998 to October 2012 is reviewed. The review present literature compilation from plant and marine extracts, alkaloids (naphthylisoquinolines, bisbenzylisoquinolines, protoberberines and aporphines, indoles, manzamines, and miscellaneous alkaloids) terpenes (sesquiterpenes, triterpenes, diterpenes, and miscellaneous terpenes) quassinoids, flavonoids, limonoids, chalcones, peptides, xanthones, quinones and coumarines, and miscellaneous antimalarials from nature. The review also provides an outlook to recent semisynthetic approaches to antimalarial Drugs discovered from natural sources.

Keywords: antiplasmodial; malaria; plant compounds; Plasmodium falciparum; traditional medicine.

INTRODUCTION
Among all parasitic agents causing disease in humans, malaria is undoubtedly the single most destructive and dangerous infectious agent in the developing world \(^\text{[1,2]}\). This vector-borne infectious disease is a classic example of one that affects the productivity of individuals, families and the whole society, since it causes more energy loss, more debilitation, more loss of work capacity and more economic damage than any other human parasitic diseases \(^\text{[3]}\).

According to the World Health Organization (WHO), malaria remains a major health problem and affects more than 225 million individuals, causing approximately 700 thousand deaths each year. Plasmodium falciparum is the most common causative agent\(^\text{[4]}\).
Malaria is commonly associated with poverty, but is also a cause of poverty and a major hindrance to economic development. There were an estimated 247 million malaria cases among 3.3 billion people at risk in 2006, causing nearly a million deaths, mostly of children under 5 years of age. It is widespread in tropical and subtropical regions, including parts of the Americas, Asia and Africa. A total of 109 countries were endemic for malaria in 2008, 45 within the WHO African region [5]. Although human malaria transmitted by female Anopheles mosquitoes has four Plasmodium species as its aetiological agents – P. falciparum, P. vivax, P. ovale and P. malariae, the most widespread and severe disease is caused by P. falciparum, which transiently infects the liver before invading red blood cells of the mammalian host (Figure 1). Clinical manifestations occur at the erythrocytic stage and can include fever, chills, prostration and anaemia, as well as delirium, metabolic acidosis, cerebral malaria and multi-organ system failure, which may be followed by coma and death [6-8]. Quinine (1), an aminoquinoline alkaloid isolated from the bark of Cinchona species (Rubiaceae) in 1820 by Pelletier and Caventou, is one of the oldest and most important antimalarial drugs and is still used today. For almost three centuries, this alkaloid was the sole active principle effective against Plasmodium falciparum, and it has been considered the responsible, after the Second World War, for the development of synthetic antimalarial drugs belonging to the classes of 4- and 8-aminoquinolines, such as chloroquine and primaquine, among others. Until recently, chloroquine was the only drug used for the treatment of malaria [9,10].

Sporozoites, injected by Anopheles mosquitoes as they bite into the skin of mammalian hosts, rapidly enter the blood circulation to reach liver hepatocytes, where they mature in an entirely asymptomatic phase that lasts for approximately two weeks. Sporozoites of P. vivax and P. ovale remain dormant (hypnozoites) in the human hepatocyte, where they mature months to years later. These forms cause late malaria relapses under conditions that are not well understood and are related to host stress and low primaquine (PQ) doses [11]; such relapses require new drug treatment. The ideal antimalarial should destroy sporozoites soon after they are inoculated into the vertebrate host by the mosquitoes. However, no effective prophylactic anti-sporozoite drug is currently in use. Medicinal
plants that hamper sporozoite development in host cells have been reported and these plants appear to act as prophylactics, as further discussed below.

**Life cycle of plasmodium**

![Life Cycle of the Malarial Parasite](image_url)

Merozoites are liberated as merosomes from liver cells and then bud off from the hepatocytes to invade and develop in red blood cells (RBCs)\(^1\)[12]. In the RBCs, the parasites undergo asexual multiplication by schizogony and release merozoites, which invade other RBCs, thereby reinitiating the blood-stage cycle\(^2\)[13]. The infected RBCs (iRBCs) are responsible for the disease symptoms, i.e., high and periodic fever (paroxysms), headaches (common to all human malaria species) and anaemia. The symptoms of *P. falciparum* include cerebral malaria and respiratory distress (life-threatening manifestations that are related to iRBC cytoadherence on microvascular endothelial cells), blockage of deep capillaries with neurological symptoms and death. The pathogenesis of severe malaria is not completely understood, although proinflammatory cytokines are known to be involved\(^3\)[14] and these cytokines contribute to the suppression of erythropoiesis, particularly in infected children\(^4\)[15]. Evidence supports the role of type 1 pro-inflammatory cytokines that increase the expression of
adhesion molecules on vascular endothelium and iRBC sequestration \[16\]. Experimental data demonstrate that E6446, a synthetic antagonist of nucleic acid-sensing tool-like receptors (TLRs), diminishes the activation of TLR9 and prevents the increased production of cytokines in response to *Plasmodium* infections, consequently preventing severe malaria symptoms\[17\].

*Plasmodium ovale* and *Plasmodium vivax* can produce a dormant form, a hypnozoite, that can cause relapses of the disease months and even years after the original disease (relapsing malaria) because it's dormant in the liver cells. This is why it's important after these infections to be treated with primaquine to kill the liver stages. Primaquine cannot be used by people with a condition called G6PD-deficiency.

**Established natural product antimalarial drugs**

Cinchona species are well known for their antimalarial properties and the constituent alkaloid quinine is still acknowledged as an effective drug. Perhaps the less widely known stereoisomer quinidine (Figure 1) is at least as potent as, and possibly more potent than quinine \[18\]. The Chinese traditional treatment of malaria includes the use of *Artemisia annua* (Compositae) and its active compound, artemisinin, which are currently under considerable interest. (Figure 1) \[19\]. Artemisinin has a higher chemotherapeutic index than chloroquine and is effective in chloroquine-resistant strains of human malaria \[20\]. Another species used as an antimalarial drug in Chinese traditional medicine is *Dichroea febrifuga* (Saxifragaceae) \[21\]. The active principle, febrifugine (Fig. 1) has been used clinically against *P. vivax* and *P. ovale* but its liver toxicity makes it unacceptable as a useful antimalarial drug \[22\]. The use of plants for the treatment of malaria extends to at least three continents including several countries in Africa \[23\], Americas \[24\] and Asia \[25\].

The NAPRALERT natural product database lists species from 152 genera which have folklore reputations for antimalarial properties. It is important that using modern biological techniques plants with these traditional representations are investigated in order to establish their safety and efficacy, and to determine their value as the source of new antimalarial drug.
The discovery of the first antimalarial treatment almost 400 years ago resulted from observations that acutely ill patients were cured of malaria after treatment with infusions of bark obtained from plants growing in the Peruvian Amazon \[26\]. Such activity in *Cinchona calisaya* and *Cinchona succirubra* plants was later attributed to the alkaloid quinine (QN), which was characterized by French chemists in 1820. QN remains important for treating complicated *P. falciparum* malaria despite its toxicity when used for extended periods of time \[27, 28\].

Several 4-aminoquinolines were later synthesised based on the QN ring (Table 1). Among them, chloroquine (CQ) is the safest and least expensive drug and most
frequently was used to treat malaria worldwide as an essential component of the Global Malaria Eradication Campaign. This campaign, launched in 1955, was based on the treatment of malaria patients using CQ in association with mosquito control measures. In the late 1960s, \textit{P. falciparum} CQ-resistant strains appeared in Latin America and South East Asia and gradually spread to most endemic regions. This campaign was interrupted in the 1970s. Malaria had been eradicated in a few countries \cite{29}. Most importantly, multi-drug and cross-drug resistance among existing antimalarials, mainly the aminoquinolines, were reported. CQ is now used only in drug combinations against \textit{P. falciparum} or as the schizonticide of choice to treat \textit{P. vivax} and other human plasmodia species.

\textbf{ANTIMALARIAL DRUG RESISTANCE-}

The appearance of drug-resistance \textit{P. falciparum} strains since 1960, in particular to chloroquine, has made the treatment of malaria increasingly problematic in virtually all malarious regions of the world \cite{2}. Several researchers have dedicated efforts to the development of new active compounds, especially from artemisinin \cite{4}, as an alternative to chloroquine \cite{2}. Currently no single drug is effective for treating multi-drug resistant malaria, and effective combination therapy includes artemisinin derivatives such as artemusate \cite{5}, or mixtures with older drugs such as the atovaquone \cite{6} – proguanil \cite{7} combination Malarone\textsuperscript{®} \cite{2,30}. Unfortunately first reports on drug resistance to artemisinin-derivatives \cite{31} and to drug combination therapies \cite{32} have already appeared. So, in the absence of a functional, safe and widely available malaria vaccine, efforts to develop new antimalarial drugs continue being urgently needed now.

There is a consensus among the scientific community that natural products have been playing a dominant role in the discovery of leads for the development of drugs for the treatment of human diseases \cite{33}. Indeed, the vast majority of the existing antimalarial chemotherapeutic agents are based on natural products, and this fact anticipates that new leads may certainly emerge from tropical plant sources, since biological chemical diversity continues to be an important source of molecular templates in the search for antimalarial drugs \cite{34-36}.
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<tr>
<th>Antimalarial</th>
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<td>Dihydroartemisinin</td>
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<td>8-aminoquinoline</td>
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<sup>a</sup>: Bulaquine and tafenoquine are undergoing clinical screening and target the hepatic forms.
**THE PROMISE OF NATURAL PRODUCTS-**

The most significant recent development in naturally occurring antimalarial drugs is arguably the identification of artemisinin (Figure 1) as the active component of the plant Artemisia annua, which is used in traditional medicine as an antimalarial agent [37]. This unique sesquiterpene contains an endoperoxide group that appears to be an essential requirement for its activity. It is particularly active in vivo against chloroquine resistant *P. falciparum* and is reported to have relatively low toxicity. However, in the usual dose of 0.6 mg/day for 3 days, the average recurrence rate is more than 10% [37]. Due to its highly lipophilic nature, there are inherent problems with its administration as a drug and several derivatives have been prepared, including artemether (methyl dihydroartemisinin) and sodium artesunate (sodium dihyroartemisinin hemisuccinate). Artemisinin and its two derivatives have been used clinically for the treatment of cerebral malaria in an area where chloroquine resistance was endemic and the cure rate was greater than 90% [38]. The mode of action is not primarily at the level of nucleic acid synthesis but it appears to inhibit protein synthesis [39].

The current review provides an overview of a great number of bioactive natural products that have recently been described in the literature (from January 2009 to November 2010) as showing antiplasmodial activity (in vitro), along with a few compounds that were tested for antimalarial activity in animal models [40] using *Plasmodium knowlesi* (in simians), *Plasmodium yoelii*, *Plasmodium berghei*, *Plasmodium chabaudi* (in mice), and *Plasmodium gallinaceum* (in birds). In most of these bioassays, antiplasmodial activities were assessed using different *P. falciparum* strains, which include chloroquine-sensitive (NF54, NF54/64, 3D7, D6, F32, D10, HB3, FCC1-HN, Ghana, MRC-02, TM4), chloroquine-resistant (BHz26/86, Dd2, EN36, ENT30, FcB1, FCM29, FCR3, FCR-3/A2, FCR3F86, S20,W2,), chloroquine-resistant and pyrimethamine-resistant (K1, TM91C235), pyrimethamine-resistant (HB3), cycloguanil-resistant (CDC1), and chloroquine- and antifolate-resistant (K1CB1). Most of evaluations used the [3H]-hypoxanthine-incorporation assay to assess parasite inhibition of growth in the presence of the test-drugs. Antimalarial activity of new compounds has also been determined by using: i) the fluorometric method based on the intercalation of the fluorochrome PicoGreen (SYBR) in the parasite DNA, [41]; ii) enzyme-linked immunosorbent assays
(ELISAs) with monoclonal antibodies, which measure the \textit{P. falciparum}-specific antigen histidine-rich protein 2 (HRP2) or lactate dehydrogenase protein (pLDH). A chemical reaction using ferriprotoporphyrine biocrystallization (FBTI Inhibition Test) has been used to provide a possible action mechanism for presumed antimalarial compounds \cite{42}. Protein farnesyltransferase (FTase) bioassays have also been used to provide insight into their mode of action against \textit{P. falciparum} \cite{43}. The effects of natural products on glutathione (GSH), which plays a key role in redox mechanisms, and on cysteine (Cys), which is one of the substrates needed for the de novo synthesis of \textit{P. falciparum} GSH, as well as their impact on \(\beta\)-hematin formation have been investigated, since GSH participates in heme detoxification \cite{44}.

Several criteria have been proposed for considering a compound as active. Generally, a compound is considered to be inactive when it shows an IC50 > 200 \(\mu\)M, whereas those with an IC50 of 100-200 \(\mu\)M have low activity; IC50 of 20-100 \(\mu\)M, moderate activity; IC50 of 1-20 \(\mu\)M good activity; and IC50 < 1 \(\mu\)M excellent/potent antiplasmodial activity \cite{45}.

A total of 360 antiplasmodial natural products comprised of terpenes, including iridoids, sesquiterpenes, diterpenes, terpenoid benzoquinones, steroids, quassinoids, limonoids, curcubitacins, and lanostanes; flavonoids; alkaloids; peptides; phenylalkanoids; xanthones; naphthopyrones; polyketides, including halenaquinones, peroxides, polyacetylenes, and resorcylic acids; depsidones; benzophenones; macrolides; and miscellaneous compounds.

**Classes of natural product with antimalarial activity -**

**Alkaloids -**

Cassiarin A (2) from the leaves of \textit{Cassia siamea} (Leguminosae) showed promising antimalarial activities. Cassiarin A had inhibitory effects against \textit{P. falciparum} (IC50 = 0.02 \(\mu\)M). Antimalarial activity was assessed \textit{in vivo} using the 4-day suppressive test procedure. The ED50 value of cassiarin A was 0.17 \cite{46}.

Acridone alkaloids have been isolated from the fruits of \textit{Zanthoxylum leprieurii} (Rutaceae), and among them arborinine (3) and xanthoxoline (4) exhibited a good \textit{in vitro} antiplasmodial activity against the \textit{P. falciparum} strain 3D7, with IC50 values of 15.8 and 17.0 \(\mu\)M, respectively \cite{47}.
TERPENES-
SESQUITERPENES-
Antimalarial activity of sesquiterpene lactones from Neurolaena lobata has been
documented\cite{48}. Bioasay-guided fractionation of the extract from the wood-decayed
fungus Xylaria sp. BCC 1067 led to the isolation of elemophilane sesquiterpenes (+)-
phaseolinone (5) and (+)-phomenone (6)\cite{49}. Sesquiterpenes 5 and 6 known as
phytotoxins exhibited promising antimalarial activity (EC50 = 0.50 and 0.32
lg/mL, respectively).
TRITERPENES-
Fanta et al. reported the antiplasmodial activity of two triterpenoid saponins, glinoside A (7) and glinoside B (8) isolated from the aerial parts of Glinus oppositifolius. The crude extracts exhibited better antiplasmodial activity (IC50 = 31.8 lg/mL) than the pure saponins (7, IC50 = 42.3 lg/mL). An antimalarial tirucalla-type triterpene, epi-oleanolic acid (9, IC50 = 28.3 lM) has been reported from Celaenodendron mexicanum. A bis nortriterpene quinone methide, 20-epi-isoiguesterinol (10) isolated from the roots of Salacia madagascariensis showed potent activity against P. falciparum (IC50 = 68 ng/mL).
DITERPENES-
Tilley et al. performed molecular modeling studies on a series of diterpene isonitriles and isothiocyanates isolated from the tropical marine sponge Cymbastela hooperi, employing 3D-QSAR with receptor modeling methodologies. These studies showed that the modeled compounds like diisocyanoadociane (11) and axisonitrile-3 (12) exert their activities by: (i) inhibiting the decomposition of H2O2, (ii) inhibiting the peroxidative destruction of FP, and the GSH-mediated breakdown of FP, and (iii) interfering with β-hematin formation. Diisocyanoadociane (11) displayed IC50 of 14.48 nM against P. falciparum D6 strain.

11. Diisocyanoadociane

12. Axisonitrile-3
Clarkson et al. studied the effect of two diterpenes 13 and 14 isolated from Harpagophytum procumbens, on erythrocyte shape to determine the selectivity of their antiplasmodial activity.\textsuperscript{[54]} It was observed that 13 and 14 did not alter erythrocyte shape at the concentrations which resulted in the inhibition of parasite growth (0.76 and 0.95 lg/mL, respectively) or at the highest test concentration (100 lg/mL). This suggested that the mechanism of action of these compounds is different from dehydroabietinol (15) despite of structural similarities. Ziegler et al. have reported that antiplasmodial activity
of 15, an abietane-type diterpene from Hyptis suaveolens was due to erythrocyte membrane modification. Diterpene 15 inhibited parasite growth (IC50 = 25.6 lM) at similar concentrations at which cytotoxicity was observed (IC50 = 28.0 lM).

Miscellaneous terpenes -

Recently, Moein et al. isolated and characterized a terpene, 12,16-dideoxy aegyptinone B (17) from the roots of Zhumeria majdae, which exhibited promising antiplasmodial activity (IC50= 1.3 and 1.4 lg/mL against chloroquine sensitive and resistant strains, respectively).

![12,16-Dideoxy aegyptinone B](image)

17. 12,16-Dideoxy aegyptinone B

**Flavonoid-**

The exact mechanism of antimalarial action of flavonoids is unclear but some flavonoids are shown to inhibit the influx of L-glutamine and myoinositol into infected erythrocytes.

Exiguaflavanone A (18a) and exiguaflavanone B (18b) from Artemisia indica exhibited in vitro antiplasmodial activities (IC50= 4.6 and 7.0 lg/mL, respectively.)
18a. Exiguaflavanone A, R=H

18b. Exiguaflavanone B, R=CH₃

20. Acacetin

(\_\_)-cis-3-Acetoxy-40,5,7-trihydroxyflavanone (19, IC₅₀ = 24.3 lg/mL) was isolated from the lipophilic extract of leaves of Siparuna andina which showed higher in vitro antimalarial activity (IC₅₀ = 3.0 lg/mL).[59] Although obtained from an active fraction, 19 was less active (IC₅₀ = 24.3 mg/mL). 3.32 IM against K1 and NF54 strains, obtained from Vriesea sanguinolenta,[59] acacetin (20, IC₅₀ = 5.5 and 12.6 lg/mL against poW and Dd2 strain, respectively), 7-methoxyacacetin, and genkwanin isolated from A. afra,73 possessed considerable antiplasmodial activity.

Quinones-
Quinone methides 21 and 22 were isolated from the roots of Salacia kraussii. The isolates showed high antiplasmodial activity (IC₅₀ = 94.0 and 27.6 ng/mL, respectively).[61] The
mode of action of these furano and hydroxy-naphthoquinones appears to be the inhibition of mitochondrial electron transport and respiratory chain by reduced oxygen consumption similar to that of atovaquone.

Phenylanthaquinones like (23) and knipholone (24) were isolated from Bulbine frutescens.

The glycoside 23 displayed better activity than 24 (IC50 = 0.41 and 0.67 lg/mL, respectively), whose antiplasmodial activity appears to be associated intrinsically with the complete molecular array of a phenylanthaquinone including the stereogenic axis. \[^{62}\]

**Xanthones**

The xanthone 1,5-dihydroxy-3,6-dimethoxy-2,7-diprenylxanthone (25) showed selective activity against *P. falciparum* with an IC50 value of 7.25 μM. When screened for activity against *T. cruzi*, *T. brucei*, *L. infantum* (Ghana strain), *S. aureus*, and *E. coli*, and for cytotoxicity against MRC-5 cells, it showed IC50 values >64 μM. \[^{63}\] Xanthones 26-27 and their analogues 28,29 have been isolated from *Cratoxylum maingayi* and *Cratoxylum cochinchenense* (Clusiaceae). \[^{64}\] These compounds showed antiplasmodial activity against *P. falciparum* at concentrations of 11.0 to 1.9 μM. Most of these compounds also showed cytotoxicity toward the NC1-H187 cancer cell line. \[^{64}\]
Coumarins-

Biologically guided fractionation of the methanolic extract of the roots of Zanthoxylum flavum Vahl. (Rutaceae) led to the isolation of isoimperatorin (30) which displayed IC50 values of 5.5 and 2.7 mM against D6 and W2, respectively. A new coumarinolignan was isolated from a sample of Grewia bilamellata Gagnep. (Tiliaceae), grewin (31), which displayed antimalarial activity against D6 and W2 (IC50 11.2 mM and 5.5 mM, respectively) without significant cytotoxicity. Shows coumarins with moderate or promising activity in vitro against various strains of P. falciparum.
Phenols-

The petroleum ether extract of Viola websteri Hemsl. (Violaceae) was investigated and the main antiplasmodial compound was 6-(8’Z-pentadecenyl)-salicylic acid (32) with an IC50 of 10.1 mM (D10). [47]
Dictyochromenol (33) and a known compound, 2’E,6’ E 2-farnesyl hydroquinone (34) obtained from the petroleum ether extract of the whole plant of Piper tricuspe C.DC. (Piperaceae) showed antimalarial activity against FcB1 with IC50 values of 9.58 and 1.37 mM while the selectivity index suggests their high toxicity\cite{67}. 

\[32.\]

\[33.\]

\[34.\]
Lignans-
From the hexane extract of holostylis reniformis duch(aristolochiaceae) three lignans were isolated: (7'R,8S,8'R)-4,5 dimethoxy-3',4'-methylene dioxy-2,7' – cyclo lignan-7-one(35)(IC50=0.20 (IC50 = 0.26 mM), (7'R,8S,8'R)-3',4,4',5-tetramethoxy-2,7'-cyclolignan-7-one (36) (IC50 =0.32 mM), (7'R,8R,8'S)-3',4,4',5-tetramethoxy-2,7'-cyclolignan-7-one (37) (IC50 =0.20 mM). Most compounds possessed high antiplasmodial activity against BH26/86 and low toxicity on hepatic cells. Therefore, these compounds are potential candidates for the development of antimalarial drugs.\[^{[68]}\]

CONCLUSIONS
Medicinal plants have provided valuable and clinically used antimalarials like quinine and artemisinin. In past few years, not only plants but fungi, bacteria and marine organisms have also been intensively investigated for obtaining new antimalarial agents. As discussed in this review, several compounds containing unique structural composition have been isolated and characterized from natural sources. These natural products have exhibited promising antimalarial activities in vitro and in vivo. However, limitations such
as toxicity, low bioavailability and/or poor solubility have restricted the scope of use for several natural products in humans. Nevertheless, nature provides novel leads, which can be developed into safe drugs by synthetic strategies as exemplified by artemether, and quinoline class of antimalarials. Therefore, compounds described herein provide useful bioactive synthons, which could be modulated to obtain antimalarials active against not only drug-sensitive, but also drug-resistant and multi-drug resistant strains of Plasmodium. In this direction, semisynthetic approaches to newer and modified antimalarials have provided useful insights into their applicability in antimalarial drug discovery.

To conclude, nature has been generous in providing several remedies for the treatment of disease like malaria. However, still there is vast unexplored flora and fauna, which when systematically explored will provide additional new leads and drugs for malaria chemotherapy.

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