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INVITED REVIEW

Plant-Derived Antimalarial Agents: From Crude Extracts To Isolated Bioactive Compounds

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ABSTRACT

Despite decades of intense research, malaria remains a deadly disease of the developing worlds. Drug-resistance to limited available antimalarials, in part, has contributed to the persistence of this infectious disease. Likewise, the use of antimalarials such as artemisinin, though effective in global malaria control programs, is hampered by high cost and limited supply. Therefore, identification of an antimalarial drug that is easy to isolate and produce, inexpensive, and demonstrates little toxicity across a diverse population represents the ideal agent needed for global malaria control programs and eradication of this deadly disease. This review discusses several antimalarial compounds containing unique structural composition that have been isolated and characterized from plant sources. These compounds have exhibited promising antimalarial activities in vitro and in vivo. However, limitations such as toxicity, low bioavailability and/or poor solubility have probably restricted the scope of use for several plant products in humans. Nevertheless, plants provide novel leads, which can be developed into safe drugs by synthetic strategies as exemplified by artemether and quinoline class of antimalarials. Therefore, plant bioactive compounds described herein provide useful alternatives, 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, semi synthetic approaches to newer and modified antimalarials have provided useful insights into their applicability in antimalarial drug discovery.

Keywords: Malaria; plant products; *Plasmodium*; antiplasmodial activity

INTRODUCTION

Malaria remains one of the most important infectious diseases in the developing world affecting millions of people causing up to 3 million death annually [1, 2]. This vector-borne infectious disease affects the productivity of individuals, families and the whole society, since it causes more loss of energy, more debilitation, more loss of work capacity and more economic damage than any other human parasitic diseases [3]. Malaria is commonly associated with poverty, but is also a cause of poverty and a major hindrance to economic development. Malaria kills over a million people each year, with as many as 300-500 millions people being infected, with extremely high fatality rates among young children below 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 [4]. By the year 2000, the WHO Global Malaria Control Strategy aimed to reduce malaria mortality by at least 20%, compared with 1995, whereby the aim of control was merely in at least 75% of the affected countries.

The human malaria, transmitted by female *Anopheles* mosquitoes has four *Plasmodium* species as its aetiological agents, namely *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. 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 [5, 6, 7].

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A traditional antimalarial compound, Quinine (an aminoquinoline alkaloid) was isolated from the bark of *Cinchona* species (Rubiaceae) in 1820 by Pelletier and Caventou. It 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 *Plamodium falciparum*, and it has been considered that this compound was 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 [8, 9]. The appearance of drug-resistance *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 [10].

Currently the most promising active compounds are derived from Chinese medicinal plant, "Qinghasu" and especially artemisinin, one of the derived compound, has potential as an alternative to chloroquine. There is no single drug that is effective for treating multi-drug resistant malaria. Drugs combination which include artemisinin derivatives such as artesunate, or mixtures with older drugs such as the atovaquone – proguanil combination Malarone® [2, 10] provide effective combination therapy. Unfortunately first reports on drug resistance to artemisinin-derivatives [11] and to drug combination therapies [12] have appeared. So, in the absence of a functional, safe and widely available malaria vaccine, continuous efforts toward the development of new antimalarial drugs should be an urgent priority.

Natural products have been playing a dominant role in the discovery of leads for the development of drugs for the treatment of human diseases [13]. Undoubtedly, 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 the tropical plant sources, since biological chemodiversity continues to be an important source of molecular templates in the search for antimalarial drugs [14 - 16].

In Malaysia, chloroquine resistant case was first reported in 1963 [17, 18]. Subsequently, several chloqoquine resistant cases have been reported in Sabah, West Malaysia [19]. In addition, other drug resistant cases were also detected. For example, the combination of sulfonamides-pyrimethamine [20, 21] and sulfadoxine-pyrimethamine resistant [22, 23]. The study reported by Lokman *et al* (1996) revealed a widespread resistance of Falciparum malaria to both chloroquine and sulfadoxine-pyrimethamine in endemic areas of Peninsular Malaysia [24].

Traditional and modern medicine share a common resource. They both utilize either plants, animals, micro-organisms or minerals. Malaysia, a developing country, is rich in natural resources. More than 20,000 species of angiosperms and 600 species of ferns in Malaysia, 1,082 species (15%) and 76 species (13%), respectively, are reported to have medicinal properties. A big portion of plants have long been in use by the Malay community because of their claim to be of medicinal value in the treatment of a variety of infections including malaria.

WHO estimates 80% of the world population uses herbal crude extracts for treatment of various ailments other than for culinary purposes. In addition the majority of the rural poplation in poor countries have limited access to formal health services and the distribution of health personnels and medical supplies are largely concentrated in the urban areas. Medicinal plants, whether prepared as crude extracts or in semi-purified forms are widely used in the treatment of a variety of disorders.

CRUDE PLANT EXTRACTS WITH ANTIPLASMODIAL ACTIVITY

Although many crude plant extracts often show only modest activity against the parasites in vitro or against malaria in mice, suggesting that the species in question probably have only a limited effect in man and that cure of the disease is unlikely. However, this may not necessarily mean that medicines made from these species are of no value, since partially effective treatments might be beneficial in those cases that the course of the disease is shortened by reducing anaemia and lowering the risk of death or serious illness from other anaemia-related diseases. Moreover, benefits may also include the alleviation of symptoms such as pain and fever and immunomodulation leading to increased immunity [25]. Finally, it is important to stress that plant extracts could also be effective against the parasite on hepatic stage [26].

In one study [27], crude extracts of ten Malaysian medicinal plants were screened for their antiplasmodial activity. These plants were selected based on their traditional claims for treatment of ailments or to relieve fever (Table 1). The 10 plants species selected in this study were: *Tinospora crispa, Xylocarpus granatum, Jasminium sambac, Andrographis paniculata, Physalis minima, Carica papaya, Ocimum sanctum, Nigella sativa, Ardisia crenata, Cinnamomum inners*. The 7-day suppressive test was employed to determine the parasitemia suppression of the plant extracts against *P. berghei*.

Out of 10 plants used in this study, 4 plants, *T. crispa, X. granatum, J. sambac and A. paniculata* showed very good in vitro antiplasmodial activities to *P. falciparum*. Their percentage inhibition were more than 50% inhibition (Table 2) to parasite growth at the 0.03 ug/ml extract concentrations. *T. crispa* showed the maximum at 90 % inhibition, followed

by *X. granatum* at 80 % and *J. sambac* and *A. paniculata* both at 70 %. These four plants showed minimal cytotoxicity on MDBK cells were *T. crispa, X. granatum, J. sambac* and *A. paniculata*. Their respective percent growth inhibition at 64 ug/ml concentration were 15.64 ± 1.19, 19.63 ± 0.62, 14.87 ± 0.47 and 18.89 ± 0.31 (Table 2).

Table 1. The local names of plants, parts used, method of consumption and their traditional

Plant	Local name	Plant part used and method of consumption
Tinospora crispa	Patawali	The stem is boiled and made into a drink to treat fever
Xylocarpus granatum	Nyireh	The stem is boiled and drunk for the treatment of fever, dysentery and filariasis.
Jasminum sambac	Melati or Melur	To treat a fever, drink water in which the flowers have been boiled
Andrographis paniculata	Hempedu bumi or Pokok Cerita	Water in which the leaves have been soaked drunk to treat a fever.
Physalis minima	Letup-letup	Water boiled with the plant is drunk to protect one against worm infestation and fever
Carica papaya	Papaya	Young leaves are pounded and mixed with water to create a drink
Ocimum sanctum	Selasih	Water that has been soaked with the seeds is drunk for coughs and to treat fever.
Nigella sativa	Jintan hitam	Water boiled with crushed seeds is drunk to cure rheumatism, fever and to improve general well-being.
Ardisia crenata	Mata ayam	To treat fever and diarrhea, the root is pounded till fine and eaten
Cinnamomum iners	Teja lawang	The root is boiled and water drunk for treating rheumatism and fever.

Table 2. *In vitro* inhibition of *P. falciparum* of methanol plant extracts and cytotoxicity to MDBK cells

Species	Plant part	Antiplasmodial activity (% of growth inhibittion or IC_{50})*	Cytotoxicity to MDBK cells (IC_{50})**
Tinospora crispa	Stem	>90	15.64 ± 1.19
Xylocarpus granatum	Barks	>80	19.63 ± 0.62
Jasminum sambac	Flowers	>70	14. 87 ± 0.47
Andrographis paniculata	Leaves	>70	18.89 ± 0.31
Physalis minima	Whole plant	34.68 ± 5.31	Not active
Carica papaya	Leaves	16.80 ± 1.29	Not active
Ocimum sanctum	Whole plant	14.20 ± 0.49	Not active
Nigella sativa	Seeds	18.03 ± 0.69	Not active
Ardisia crenata	Roots	9.95 ± 1.44	Not active
Cinnamomum iners	Roots	12.73 ± 3.04	Not active

* Results are recorded as the % of growth inhibition (or IC_{50}). The results for *T. crispa, X. granatum, J. sambac* and *A. paniculata* were given in percent of growth inhibition because the growth were beyond the 50 % level at the last concentration tested that is 0.03 ug/ml. All test samples were performed in triplicates and reported as mean ± SD. Not active because there was no growth inhibition.

**Cytotoxicity to MDBK cells. All tests were performed in triplicates and reported as mean ± SD

In mice infected with *P. berghei*, the group which received treatment with *T. crispa* showed the highest inhibitory effect (parasitemia suppression) on parasite growth *in vivo* (Table 3). At the end of day 5 all infected mice in the control groups died. Mean parasitemia suppression in the *P. berghei*-infected mice ranged from 1.14 ± 0.22 on day 1 to 50.73 ± 1.32 on day 6 (Table 3). By day 7 all mice died. Mice that survived until the sixth day were those treated with *T. crispa* (n=3) and *X. granatum* (n=2). The parasitemia suppression ranged from 50.73 ± 1.32 and 49.78 ± 2.30 for *T. crispa* and *X*. granatum respectively. Generally parasitemia suppression gradually increase and this probably extend the days of survival of treated mice to the infection. The mean percentage parasitemia per 1000 erythrocytes in the two control groups were between 1.67 ± 0.42 on day 1 to 40.68 ± 1.02 by day 4. There was a gradual increase in parasitemia which reached maximum of 40.68 ± 1.02. All control mice died by day 5.

Table 3. *In vivo* percentage parasitemia suppression* of *Plasmodium berghei* in mice treated with plant extracts and mean parasitemia in the control

No. of days	% parasitemia suppression in treated mice				**Control (% parasitemia per 1000 RBCs)
	T. crispa	*X. granatum*	*J. sambac*	*A. paniculata*	
Day 1	1.74±0.13	1.14±0.22	1.72±0.9	1.35±0.42	1.67±0.42
Day 2	1.26±0.25	2.89±1.05	2.94±0.71	3.17±0.69	6.94±1.10
Day 3	13.83±1.64	18.01±3.94	17.65±1.42	18.51±1.03	17.68±3.45
Day 4	32.11±1.78	34.28±5.90	26.44±5.19	28.38±2.26	40.68±1.02
Day 5	42.18±2.10	41.69±0.92	31.21±1.03	37.50±3.30	All died
Day 6***	50.73±1.32	49.78±2.30	All died	All died	
Day 7	All died	All died			

* Mice were divided into two experimental groups consisting of 8 mice per group and parasitemia suppression reported as mean ± SD each day for every plant extract

** Control received distilled water. Percentage of parasitemia was counted based on infected erythrocytes calculated per 1000 erythrocytes. Mice were divided into two control groups consisting of 8 mice per group and parasitemia levels reported as mean ± SD each day for every plant extract.

*** Day 6 : T. crispa: 3 survived and 2 survived with J. sambac

Nor Rain *et al.* in 2007[28] similarly studied antiplasmodial activities of plant extracts using the pLDH assay to *Plasmodium falciparum* D10 strain (sensitive strain) while the cytotoxic activities were carried out towards Madin-Darby bovine kidney (MDBK) cells using MTT assay. The concentration of extracts used for both screening assays were from the highest concentration 64 µg/ml, two fold dilution to the lowest concentration 0.03 µg/ml. *Goniothalamus macrophyllus* (stem extract) showed more than 60% growth inhibition while *Goniothalamus scortechinii* root and stem extract showed a 90% and more than 80% growth inhibition at the last concetration tested, 0.03 µg/ml. The *G. scortechini* (leaves extract) showed an IC50 (50 % growth inhibition) at 8.53 µg/ml, *Ardisia crispa* (leaves extract) demonstrated an IC50 at 5.90 ± 0.14 µg/ml while Croton argyratus (leaves extract) showed a percentage inhibition of more than 60% at the tested concentration. *Blumea balsamifera* root and stem showed an IC50 at 26.25 ± 2.47 µg/ml and 7.75 ± 0.35 µg/ml respectively. *Agathis borneensis* (leaves extract) demonstrated a 50% growth inhibition at 11.00 ± 1.41 µg/ml.

Riduan *et al.* 2006[29] studied the enhancement of antimalarial properties combination of goniothalamin with chloroquine. Percentage of parasite growth on treated infected mice were determined based on 4 Day Test. Oral treatment with 1 mg/kg BW of chloroquine on experimental mice suppressed 70% and 76.7% of both *Plasmodium yoelii* and *Plasmodium berghei*, respectively. The infection of *P. berghei* in mice was inhibited less than 50% by goniothalamin individual treatment at all doses in this study. About 27.8% and 18.5% inhibition of infection were observed in *P. yoelii* infected mice treated with 30 mg/kg and 60 mg/kg of goniothalamin respectively and the suppression exceed more than 50% at higher doses (90 and 120 mg/kg). Combination of 1 mg/kg chloroquine with either 30 mg/kg or 60 mg/kg of goniothalamin decreased the parasitemia of *P. yoelii* infected mice more than 90% and prolong the survival up to 100% after treatment. Similar treatment to *P. berghei* infected mice only shows about 60% reduction of parasitemia. The study findings showed that antimalarial property of goniothalamin was enhanced by combination with chloroquine at lower dose of each drug.

ISOLATED PLANT ANTIPLASMODIAL BIOACTIVE COMPOUNDS

Several classes of bioactive compounds isolated from plants possess antimalarial activity. However, the most important and diverse biopotency has been observed in alkaloids, quassinoids and sesquiterpene lactones. The chemical structures of some traditional antimalarials are shown in Figure 1.

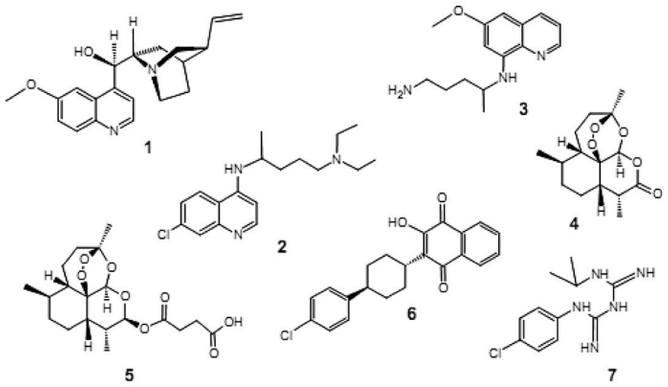

Figure 1. Chemical structures of some traditional antimalarial drugs. 1) Quinine (1), chloroquine(2), primaquine (3), artemisinin (4), artesunate (5), atovaquone (6) and proguanil (7)

Quinine, 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 *Plamodium falciparum*, and it has been considered 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 [30].

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The appearance of drug-resistance *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. Several researchers have dedicated efforts to the development of new active compounds, especially from artemisinin, as an alternative to chloroquine. Currently no single drug is effective for treating multi-drug resistant malaria, and effective combination therapy includes artemisinin derivatives such as artesunate, or mixtures with older drugs such as the atovaquone–proguanil combination [31] provide effective combination therapy. Unfortunately first reports on drug resistance to artemisinin-derivatives and to drug combination therapies have appeared. So, in the absence of a functional, safe and widely available malaria vaccine, research to develop alternative therapies is greatly needed. To this end, plants used in traditional medicines may offer a promising source of compounds with antimalarial activity. Indeed, plant products and their derivatives have traditionally been a common source of drugs.

SECONDARY PHYTOCHEMICALS

Several classes of the secondary phytochemicals possess antimalarial activity. However, the most important and diverse biopotency has been observed in alkaloids, quassinoids and sesquiterpene lactones. The chemical structures of some traditional antimalarials are shown in Figure 1.

Alkaloids are the physiologically-active nitrogenous bases derived from many biogenetic precursors. A new bisbenzylisoquinoline alkaloid named as 2-N-methyltelobine together with twelve known alkaloids [32, 33, 34] of the same group were isolated from *Stephania erecta* (Menispermaceae). All the alkaloids inhibited the growth of cultured chloroquine-resistant and sensitive strains of *P. falciparum* [35, 36, 37, 38, 39].

A bisbenzylisoquinoline alkaloid dehatrine [40] isolated from the wood of *Beilschmiedia madang* (Lauraceae), exhibited potent inhibitory activity (IC50 0.017 mM) against the proliferation of malaria pathogen *P. falciparum*, which was comparable to quinine. Cryptolepine is an indolisoquinoline antimalarial alkaloid with IC50 value approximately

half that of chloroquine. In view of this high degree of in vitro activity, it was surprising that the isolated alkaloid proved to be inactive in mouse against the *P. berghei* model [41, 42, 43]. It was shown that the alkaloid might interact with DNA, and it appeared that two nitrogen atoms N and N-CH3 of cryptolepine interact with adenine–thymine base pair. There is also a possibility of formation of p–p charge transfer complex between purine–pyrimidine bases and cryptolepine [44, 45, 46].

Another interesting antimalarial compound tubulosine was found active in vitro against both sensitive and resistant strains of *P. falciparum* [47, 48, 49]. The indol moiety in tubulosine enhances the affinity for protozoan receptor, when compared with psychotrine and cephaeline [50, 51]. The relative in vitro inactivity of in comparison with can be explained by its double bond in ring C, which enhances the coplanar conformation and electron environment [52].

Quassinoids.

The quassinoids are heavily oxygenated lactones with majority of C20 basic skeleton named as picrasane. A wide spectrum of biological properties was reported for this class of compounds, of which antineoplastic and antimalarial have equal and parallel importance [53] The quassinoids brusatol, bruceantin and brucein A, B and C differ only in the nature of the ester moiety [54] Its IC_{50} values were similar for chloroquine-resistant and sensitive strains, suggesting that quassinoids may act upon malarial parasites by means of a fundamentally different mechanism from that of chloroquine. Cedronin possesses some of the structural requirements for cytotoxic activities. The results also suggested cedronin exhibits lower selective toxicity against Plasmodium than against mammalian cells [55] .

Sesquiterpenes

The discovery of Qinghaosu (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. Artemisinin is a new class of antimalarials, where the endoperoxide moiety plays an important role. The definitive mode of action of this series of drugs is still not known. After being opened in the *Plasmodium* it liberates singlet oxygen and forms a free radical, both being strong cytotoxins. In vitro-testing using the inhibition of radio-labelled hypoxanthine uptake as an index of drug effect on parasite growth suggests that artemisinin causes a marked diminution of nucleic acid synthesis. The drug effect on this process is, however, rather slow; well-defined concentration response curves being generated only after a 6–8 h incubation period. Dihydroartemisinin is over 200 times more effective than artemisinin in reducing 3H-hypoxanthine uptake. The inhibitory action of artemisinin on the incorporation of 3H-leucine into the parasite protein is much more rapid than that of hypoxanthine, which has led some researchers to hypothesize that protein synthesis may be one of the prime targets of drug action. Unlike chloroquine, artemisinin does not directly cause malaria parasite haemozoin to clump, but it does inhibit clumping caused by subsequent exposure to chloroquine. It has also been reported that one of the mechanisms of action is due to its inhibition of cytochrome oxidase, which occurs at the plasma, the nuclear and the food vacuole-limiting membranes as well as in the mitochondria of the trophozoites of *P. berghei*. It was demonstrated in neurolenin B, that a, b -unsaturated keto function is one of the structural requirements for high in vitro antiplasmodial activity. Additionally, a free OH function at C-8 increases and at C-9 decreases the activity. The two endoperoxides: nardoperoxide and isonardoperoxide isolated from the roots of *Nardostachys chinensis*, showed strongest antimalarial effects. It is noteworthy that activity and selectivity of isonardoperoxide was comparable to those of quinine, a clinically used drug. Nardoperoxide and isonar doperoxide seem to be the promising lead compounds for antimalarial drugs [56, 57].

Triterpenoids

Triterpenoids isolated from different medicinal plants exhibit antimalarial property, for example, Gedunin activity of which is about three times higher than chloroquine, but twenty-times lower than quinine. Comparison of activities of gedunin and dihydrogedunin suggested that the reduction of the double bond in a ,b -unsaturated keto function lead to a decrease of antimalarial activity and increase in toxicity [58].

Flavonoids and xanthones

The antimalarial activity from these classes of compounds has not been described earlier, although it constitutes one of the most characteristic classes of compounds in higher plants. Flavonoids isolated from *Artemisia annua* were not found active against *P. falciparum*, but demonstrated a marked and selective potentiating effect on the antiplasmodial

activity of artemisinin [59, 60].

Quinones

Chemically, quinones are compounds with a 1,4-diketo-cyclohexa-2,5-dienoid or a 1,2-diketocyclohexa-3,5-dienoid moiety [61] The structure of many naturally-occurring quinones is based on the benzoquinone, naphthoquinone or anthraquinone ring system. Napththoquinones are rather promising as blood schizonticides, since they are highly active against *P. falciparum* in vitro [62] Roots of Nepenthes thorelii yielded plumbagin and 2-methylnaphthazarin both of which were evaluated against *P. falciparum*. The quinone structure was regarded essential for the activity of naphthoquinones like plumbagin[63, 64].

Miscellaneous compounds and Essential Oil

Various compounds with different chemical structures possessing antimalarial activity have been isolated from plants. The active constituents isolated from *Piptadenia pervillei, Moronobea coccinea, Holostylis reniformis* were phenolic compounds, benzophenones and aryltetralone lignans respectively. All these compounds were shown to possess significant antimalarial activity due to the presence of a, b - unsaturated carbonyl moiety [65, 66, 67]. The a, b -unsaturated carbonyl moiety was suspected to undergo a Michael reaction with nucleophilic sites in the parasite DNA molecule, thereby inhibiting the growth of *P. falciparum*.

The essential oil from the leaves and stem of *Tetradenia riparia* was tested. Moderate antimalarial activity was recorded against two strains of *P. falciparum*. Essential oils of *Artemisia vulgaris, Eucalyptus globulus, Myrtus communis, Juniperus communis, Lavandula angustifolia, Origanum vulgare, Rosmaricus officinalis* and *Salvia officinalis* were tested against two strains of *P. falciparum*, FcB1-Columbia and a Nigerian chloroquine resistant strain. Concentrations ranging from 150 mg/ml to 1 mg/ml inhibited 50% of the parasite growth in vitro which is obtained after 24 to 72 h of contact between the oil and parasite culture. The best results were obtained with *M. communis* and *R. officinalis* oils, which inhibited P. falciparum at a concentration ranging from 150 to 270 mg/ml [68].

CONCLUSION

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. There is an urgent need for new, more affordable and accessible antimalarial agents possessing original modes of action. Plant products have played a dominant role in the discovery of leads for the development of drugs to treat human diseases, and this fact anticipates that new antimalarial leads may certainly emerge from tropical plant sources. The recently developed new isolation and characterization techniques together with development of new pharmacological testing undoubtedly shall further facilitate discovery of newer derivatives with improved properties. The search for additional antimalarials from higher plants must continue to fight the disease.

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