Antimalarial agents from plant sources

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The success of the antimalarial drug quinine and the discovery of artemisinin, the most potent antimalarial drug, both from plant sources, has led to the study of plants as antimalarial agents. The ethnopharmacological approach for the search of new antimalarial agents from plant sources has proved to be more predictive. This article gives a critical account of crude extracts, essential oils and secondary plant metabolites with diverse chemical structure possessing antimalarial activity against different malarial parasites. The major leads have been highlighted and some reported structure–activity relationships and their possible modes of action discussed.

MALARIA is the most prevalent among the insect-borne diseases. Every year it kills between one and two million people, with as many as 300–500 million people being infected. It is estimated that nearly half the world population is at risk, with fatal rates being extremely high among young children below 5 years of age. Malaria is a classic example of a disease that affects the productivity of individuals, families and the whole society. It is common in the poorer and less-developed countries of the world. Africa faces its greatest impact[1,2]. The other hard-hit tropical areas include East Asia, China and India. Experts estimated that as many as 40% of India's malaria cases is caused by *Plasmodium falciparum*[3].

The first antimalarial drug was quinine, isolated from the bark of *Cinchona* species (Rubiaceae) in 1820. It is one of the oldest and most important antimalarial drugs, that is still used today[4]. In 1940, another antimalarial drug chloroquine was synthesized and until recently, this was the only drug, used for the treatment of malaria[5]. Unfortunately, after an early success, the malarial parasite especially *P. falciparum* became resistant to chloroquine[6]. Treatment of chloroquine-resistant malaria was done with alternative drugs or drug combinations, which were rather expensive and sometimes toxic. Furthermore, these combinations were not always based on pharmacokinetic principles due to inadequate knowledge of metabolism and mechanism of action of most antimalarial drugs.

Hence several research groups are now working to develop new active compounds as an alternative to chloroquine, especially from artemisinin[8,9], a plant-based antimalarial drug isolated from the Chinese plant *Artemisia annua*[10]. Therefore, plants may well prove to be the source of new antimalarial drugs in view of the success with the two important chemotherapeutic agents, quinine and artemisinin, both of which are derived from plants. This article gives a critical account of crude extracts, essential oil and active constituents with diverse chemical structures from higher plants possessing significant antimalarial activity, reported during last ten years.

Crude extracts

In 1991, Carvalho *et al.*[8] studied the antimalarial activity of aqueous or organic extracts of forty-eight Brazilian plants selected on the basis of their use in folk medicine. Six plants, *Vernonia brasiliana* (Compositae), *Eupatorium squalidum* (Compositae), *Acanthospermum australe* (Compositae), *Esenbeckian febrifuga* (Rubaceae), *Lisianthus speciosum* (Gentianaceae) and *Tachia quianensis* (Gentianaceae), were partly active against rodent malaria. The remaining forty-two plants exhibited no antimalarial activity.

An aqueous decoction of the root bark of *Uapaca nitida* (Euphorbiaceae) is used in Tanzania to treat malaria. Alcoholic extract of the root bark showed antimalarial activity against *P. berghei* in mice[11].

Hernandia voyroni (Hernandiaceae) is another example of plant species traditionally used in Madagascar as a substitute for chloroquine. Neutral and basic alkaloidal extracts of this plant exhibited intrinsic *in vitro* antimalarial activity and chloroquine-potentiating action against chloroquine-resistant *P. falciparum* strain, FCM-29 (ref. 12).

In 1995, Valsaraj *et al.*[13] evaluated *Garcinia gummigutta* (Guttifereae) and *Mammea longifolia* (Guttiferae) against malarial parasite at a concentration of 100 mg/ml. The percentage of growth inhibition induced by *Garicinia* and *Mammea* was found to be 99.5 and 86%, respectively.

The antiplasmodial activities of organic and aqueous extracts from the West African plant *Picralima nitida* (Apocynaceae) were examined in an *in vitro* model, against asexual erythrocytic forms of *P. falciparum*. The highest activity was found in roots, stem bark and fruit rind extracts with IC50 values of 0.188, 0.545 and 1.581 μg/ml, respectively[14].

The *in vivo* antiplasmodial activity of total alkaloidal extract of *Golipea longiflora* has been confirmed in mice infected with *P. vinckei patteri*, when the infected mice were treated orally with a single dose of 50 mg/kg of the extract[15].

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Naphthylisoquinoline alkaloid-containing extracts of four plants of the family Ancistrocladeceae (*Ancistrocladus barteri*, *A. heyneanus*, *A. robertsoniorum* and *A. tectorius*), and *Triphyllum peltatum* (family Dioncophyllaceae) have been examined for their antiplasmodial activity against asexual erythrocytic forms of *P. falciparum* and *P. berghei*. Five of the examined extracts displayed high growth-inhibition activity in the *P. falciparum* system. Bark extract (CH_2Cl_2/NH_3) of *T. peltatum*, leaf extract (EtOH) of *A. tectorius* and leaf extract (CH_2Cl_2) of *T. peltatum* proved to be highly active in the test system. These findings confirmed that the extracts of species belonging to the family Ancistrocladeceae and Dioncophyllaceae have considerable antiplasmodial activity[16].

The *n*-hexane extract, the crude and purified fractions of the stem bark of the plant *Khaya grandifoliola* exhibited the most active antimalarial activity with about 91% chemo suppression *in vivo*, with IC50 values of 1.4 μg/ml (for multi-drug-resistant clone) or 0.84 μg/ml (for Nigerian *P. falciparum* isolates)[17]. The stem bark extracts of *Mangifera indica* showed schizontocidal effect during early infection and also demonstrated repository activity when evaluated against *P. yoelii nigeriensis*[18]. The different fractions of the plant *Morinda lucida* revealed schizontocidal activity against early infection of *P. berghei* in mice[19]. Aqueous extracts obtained from the stem and root parts of *Nauclea latifolia* were tested on two strains of *P. falciparum*. The aqueous extract of *N. latifolia* inhibited *P. falciparum* (FCB1 strain) mainly at the end of the erythrocytic cycle 32nd to 38th h (ref. 20).

In vitro and *in vivo* studies revealed that *Piper sarmentosum*, *Andrographis paniculata* and *Tinospora crispa* produce considerable antimalarial effects. *In vivo*, *A. paniculata* demonstrated higher antimalarial effect than the other two plant species. Chloroform extract of *A. paniculata in vitro* showed better efficacy than the methanolic extract. The chloroform extract showed complete parasite growth inhibition at a concentration as low as 0.05 mg/ml within 24 h of incubation period compared to the methanolic extract, which has a concentration of 2.5 mg/ml, but under the incubation time of 48 h (ref. 21).

Essential oil

The essential oil from the leaves and stem of *Tetradenia riparia* was tested. Moderate antimalarial activity was recorded against two strains of *P. falciparum*[22].

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 μg/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 μg/ml[23].

Secondary plant substances

Several classes of the secondary plant substances are responsible for antimalarial activity, but the most important and diverse biopotency has been observed in alkaloids, quassinoids and sesquiterpene lactones. We highlight the various classes of secondary plant substances which have been assessed either for *in vitro* activity against *P. falciparum* or *in vivo* activity against *P. berghei*. The structure–activity relationship and mechanism of action of some compounds reported earlier have also been discussed.

Alkaloids

Alkaloids are one of the major classes of compounds possessing antimalarial activity. In fact, one of the oldest and most important antimalarial drugs, quinine, belongs to this class of compounds and is still relevant. Alkaloids are the physiologically-active nitrogenous bases derived from many biogenetic precursors. A number of naturally-occurring alkaloids belonging to different groups are arranged in Table 1 (refs 24–57), which have been reported to possess antimalarial activity against different malarial models.

A new bisbenzylisoquinoline alkaloid named as (+)-2-*N*-methyltelobine (**13**) together with twelve known alkaloids (**14–25**) 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*. With regard to the structure of these compounds, it is of interest to note that for each pair of 2-*nor*-alkaloid and its di-*N*-Me counterpart, the 2-*nor*-alkaloid which has only one Me group on the 2′-*N*, was always more active against both susceptible and resistant strains of Plasmodium as compared to the di-N-Me derivative, which bears Me groups on both nitrogens. For example ED50 value for (+)-2-*nor*-thalrugosine (**17**) was lower than those of (+)-thalrugosine (**18**). Similar observations were noted for compounds (**15**, **16**, **22–25**)[29].

It was observed that augustine (**27**) exhibited significant antimalarial activity, which might be due to presence of epoxide functionality that can result in the formation of adducts with nucleophiles in the biological system thereby leading to non-selective toxicity. While some other naturally occurring substances, which lack the oxirane ring in their structure were not active. However, (+)-crinamine (**28**) deferring from (**27**) in its absolute

Table 1. Antimalarial activity of alkaloids against *P. falciparum*

Compound (Structure no.)	Plant (plant parts)	Activity *In vitro* (strain)		Reference
Oxyacanthine (**1**)	*Dehaasia incrassata* (L, Bk)	IC 50 μg/ml	0.31** (KI)	24
7-Methoxy-***b***-carboline-1-propionic acid (**2**)	*Eurycoma longifolia* (Rt)	IC 50 ng/ml	2978** (W-2) 314.4* (D-6)	25
Alstonerine (**3**)	*Alstonia angustifolia* (Rt)	ED 50 μM	46.3* (KI)	26
Alstophylline (**4**)	*Alstonia angustifolia* (Rt)		82.5** (KI)	26
Macrocarpamine (**5**)	*Alstonia angustifolia* (Rt)		9.36** (KI)	26
11-Methoxyakuammicine (**6**)	*Alstonia angustifolia* (Rt)		41.3** (KI)	26
nor-Fluorocurarine (**7**)	*Alstonia angustifolia* (Rt)		129** (KI)	26
Pleiocarpamine (**8**)	*Alstonia angustifolia* (Rt)		20.5** (KI)	26
Villastonine (**9**)	*Alstonia angustifolia* (Rt)		2.92** (KI)	26
Vincamajine (**10**)	*Alstonia angustifolia* (Rt)		138** (KI)	26
7-*O*-Demethyltetraandrine (**11**)	*Strychnopsis thouarsii* (L)	IC 50 nM	740** (FCM-29)	27
Limacine (**12**)	*Spirospermum penduliflorum* (St, Rt)	ED 50 ng/ml	789** (FCM-29)	27
	Cyclea barbata (Rt)		164** (W-2) 52.7* (D-6)	28
(+)-2-*N*-Methyltelobine (**13**)	*Stephania erecta* (T)		255.7** (W-2) 97.4* (D-6)	29
(+)-1,2-Dehydrotelobine (**14**)	*Stephania erecta* (T)		256.4** (W-2) 306.7* (D-6)	29
(+)-2-*nor*-Isotetrandrine (**15**)	*Stephania erecta* (T)		45.3** (W-2) 66.1* (D-6)	29
(+)-Isotetrandrine (**16**)	*Stephania erecta* (T)		54.6** (W-2) 165.1* (D-6)	29
(+)-2-*nor*-Thalrugosine (**17**)	*Stephania erecta* (T)		125.1** (W-2) 68.6* (D-6)	29
(+)-Thalrugosine (**18**)	*Stephania erecta* (T)		229.7** (W-2) 120.6* (D-6)	29
	Cyclea barbata (Rt)		78.0** (W-2) 65.1* (D-6)	28
(+)-Homoaromoline (**19**)	*Stephania erecta* (T)		288.3** (W-2) 104.6* (D-6)	29
	*Cyclea barbata (*Rt)		451** (W-2) 232* (D-6)	28
(+)-Stephibaberine (**20**)	*Stephania erecta* (T)		310.0** (W-2) 130.0* (D-6)	29
(+)-Dephnandrine (**21**)	*Stephania erecta* (T)		223.2** (W-2) 63.0* (D-6)	29
(+)-2-*nor*-Cepharanthine (**22**)	*Stephania erecta* (T)		129.4** (W-2) 46.6* (D-6)	29
(+)-Cepharanthine (**23**)	*Stephania erecta* (T)		294.8** (W-2) 140.4* (D-6)	29
(+)-*nor*-Obaberine (**24**)	*Stephania erecta* (T)		93.7** (W-2) 45.9* (D-6)	29
(+)-Obaberine (**25**)	*Stephania erecta* (T)		216** (W-2) 231* (D-6)	29
(–)-Lycorine (**26**)	*Crinum amabile* (B)	ED 50 ng/ml	300** (W-2) 320* (D-6)	30
	Brunsvigia littoralis (B)	IC 50 μg/ml	0.7** (FAC-8) 0.62* (D-10)	31
	Brunsvigia radulosa (B)	IC 50 μg/ml	0.7** (FAC-8) 0.6* (D-10)	32
(–)-Augustine (**27**)	*Crinum amabile* (B)	ED 50 ng/ml	180** (W-2) 140* (D-6)	30
(+)-Crinamine (**28**)	*Crinum amabile* (B)	IC 50 μg/ml	2520** (W-2) 2180* (D-6)	30
	Brunsvigia radulosa (B)		3.4** (FAC-8) 2.8* (D-10)	32
(–)-Asimilobine (**29**)	*Stephania pierrei* (T)		470** (W-2) 950* (D-6)	33
(–)-Anonaine (**30**)	*Stephania pierrei* (T)		1900** (W-2) 1290* (D-6)	33
(–)-Isolaureline (**31**)	*Stephania pierrei* (T)		1610** (W-2) 2560* (D-6)	33
(–)-Xylopine (**32**)	*Stephania pierrei* (T)		2270** (W-2) 440* (D-6)	33

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Table 1. (*Contd…*)

Compound (Structure no.)	Plant (plant parts)	Activity *In vitro* (strain)		Reference
(–)-Roemeroline (**33**)	*Stephania pierrei* (T)		1780** (W-2) 3150* (D-6)	33
(–)-Dicentrine (**34**)	*Stephania pierrei* (T)		2550** (W-2) 1260* (D-6)	33
(–)-*nor*-Dicentrine (**35**)	*Stephania pierrei* (T)		1030** (W-2) 470* (D-6)	33
(–)-Phanostenine (**36**)	*Stephania pierrei* (T)		2880** (W-2) 2010* (D-6)	33
(–)-Cassythicine (**37**)	*Stephania pierrei* (T)		2260** (W-2) 2290* (D-6)	33
(–)-Capaurine (**38**)	*Stephania pierrei* (T)		1910** (W-2) 4340* (D-6)	33
(–)-Thaicanine (**39**)	*Stephania pierrei* (T)		550** (W-2) 1610* (D-6)	33
(–)-Corydalmine (**40**)	*Stephania pierrei* (T)		840** (W-2) 2840* (D-6)	33
(–)-Tetrahydrostephabine (**41**)	*Stephania pierrei* (T)		1940** (W-2) 2230 (D-6)	33
(+)-Tetrandrine (**42**)	*Cyclea barbata* (Rt)		160** (W-2) 179* (D-6)	28
(–)-Cycleapeltine (**43**)	*Cyclea barbata* (Rt)		40.6** (W-2) 29.0 (D-6)	28
Dehatrine (**44**)	*Beilschmiedia madang* (W)	IC 50 µM	0.17** (K-1)	34
Bruceacanthinoside (**45**)	*Brucea javanica* (St)	IC 50 µM	25** (K-1)	35
Thalifaberidine (**46**)	*Thalictrum faberi* (Rt)	ED 50 ng/ml	122** (W-2) 880* (D-6)	36
Thalifaberine (**47**)	*Thalictrum faberi* (Rt)		441** (W-2) 5090* (D-6)	36
Thalifasine (**48**)	*Thalictrum faberi* (Rt)		49.3** (W-2) 238* (D-6)	36
Strychnobrasiline* (**49**)	*Strychnos myrtoides* (Stbk)			37
Malagashanine* (**50**)	*Strychnos myrtoides* (Stbk)			37
Korupensamine-A (**51**)	*Ancistroclacdus korupensis* (L, T)	IC 50 µg/ml	0.31 0.56$^{\varphi}$	38
Korupensamine-B (**52**)	*Ancistroclacdus korupensis* (L, T)		0.18 0.41$^{\varphi}$	38
Cryptolepine (**53**)	*Cryptolepis sanguinolenta* (Rt)		0.031** (K-1)	39
Tubulosine (**54**)	*Pogonopus tubulosus* (Bk)		0.011** (Indo) 0.006* (2087)	40
Psychotrine (**55**)	*Pogonopus tubulosus* (Bk)		0.39** (Indo) 0.14* (2087)	40
Cephaeline (**56**)	*Pogonopus tubulosus* (Bk)		0.011** (Indo) 0.027* (2087)	40
Isocryptolepine (**57**)	*Cryptolepis sanguinolenta* (Rt)	IC 50 µM	0.8*	41
Ancistroheynine A (**58**)	*Ancistrocladus heyneanus*	IC µg/ml	2.1	42
Korupensamine E (**59**)	*Ancistrocladus korupensis*		2.0	31
1,2-Di-*O*-acetyl-lycorine (**60**)	*Brunsvigia littoralis* (B)		1.0** (FAC-8) 1.0* (D-10)	43
Korundamine A (**61**)	*Ancistrocladus korupensis*		1.1	44
Febrifugine (**62**)	*Dichroafebrifuga* (Rt)	EC 50 M	7.0×10^{-10}* (FCR-3) 1.2×10^{-9}** (K-1)	45
Isofebrifugine (**63**)	*Dichroafebrifuga* (Rt)		3.4×10^{-9}* (FCR-3) 1.8×10^{-9}** (K-1)	45
10′-Hydroxyusambarensine (**64**)	*Strychnos usambarensis* (Rt)	IC µg/ml	0.480* (FCA-20) 0.160** (W2)	46
Hadranthine A (**65**)	*Duguetia hadrantha* (Stbk)	IC ng/ml	120* (D6) 120** (W2)	47
Sampangine (**66**)	*Duguetia hadrantha* (Stbk)		420* (D6) 68** (W2)	47
3-Methoxysampangine (**67**)	*Duguetia hadrantha* (Stbk)		280* (D6) 95** (W2)	47
Ancistrolikokine A (**68**)	*Ancistrocladus likoko* (Rtbk)	IC ng/ml	191* (NF 54) 140** (K1)	48
Ancistrolikokine B (**69**)	*Ancistrocladus likoko* (L)		538* (NF 54) 208** (K1)	48

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Table 1. (*Contd…*)

Compound (Structure no.)	Plant (plant parts)	Activity *In vitro* (strain)		Reference
Ancistrolikokine C (**70**)	*Ancistrocladus likoko* (L)		6232* (NF 54) 924** (K1)	48
Korupensamine A (**71**)	*Ancistrocladus likoko* (Rtbk)		24* (NF 54) 72** (K1)	48
(–) Roemrefidine (**72**)	*Sparattanthelium amazonum* (Stbk)	IC 50 µM	0.71* (2087) 0.58** (INDO)	49
Talcarpine (**73**)	*Alstonia macrophylla* (Stbk, Rtbk)	IC 50 µM	40.3** (K1)	50
Pleiocarpamine (**74**)	*Alstonia macrophylla* (Stbk, Rtbk)		6.44** (K1)	50
Alstoumerine (**75**)	*Alstonia macrophylla* (Stbk, Rtbk)		13.1** (K1)	50
20-*epi*-Antirhine (**76**)	*Alstonia macrophylla* (Stbk, Rtbk)		7.51** (K1)	50
Alstonerine (**77**)	*Alstonia macrophylla* (Stbk, Rtbk)		9.67** (K1)	50
Alstophylline (**78**)	*Alstonia macrophylla* (Stbk, Rtbk)		12.7** (K1)	50
Macralstonine (**79**)	*Alstonia macrophylla* (Stbk, Rtbk)		8.92** (K1)	50
O-Methylmacralstonine (**80**)	*Alstonia macrophylla* (Stbk, Rtbk)		0.85** (K1)	50
Alstomacrophylline (**81**)	*Alstonia macrophylla* (Stbk, Rtbk)		1.10** (K1)	50
Villalstonine (**82**)	*Alstonia macrophylla* (Stbk, Rtbk)		0.27** (K1) 0.94* (T9-96)	50
Villastonine N_b-oxide (**83**)	*Alstonia macrophylla* (Stbk, Rtbk)		10.7** (K1)	50
Alstomacroline (**84**)	*Alstonia macrophylla* (Stbk, Rtbk)		1.12** (K1) 10.2* (T9-96)	50
Macrocarpamine (**85**)	*Alstonia macrophylla* (Stbk, Rtbk)		0.36** (K1) 32.6* (T9-96)	50
Corynanthine (**86**)	*Corynanthe pachyceras* (Stbk)	IC 50 µM	> 200* (3D7)	51
α-Yohimbine (**87**)	*Corynanthe pachyceras* (Stbk)		> 200* (3D7)	51
Dihydrocorynantheine (**88**)	*Corynanthe pachyceras* (Stbk)		66.4* (3D7)	51
Corynantheine (**89**)	*Corynanthe pachyceras* (Stbk)		81.1* (3D7)	51
Corynantheidine (**90**)	*Corynanthe pachyceras* (Stbk)		41.1* (3D7)	51
(–) Curine (**91**)	*Isolona guesquiereina* (Stbk)	IC 50 µM	353** (FCM 29)	52
Isochondodendrine (**92**)	*Isolona guesquiereina* (Stbk)		892** (FCM 29)	52
N_b-Methylaffinisine (**93**)	*Peschiera fuchsiaefolia* (Stbk, Rtbk, S)	IC 50 ng/ml	> 5000* (D6) > 5000** (W2)	53
12-methoxy-N_b-methylvoachalotine (**94**)	*Peschiera fuchsiaefolia* (Stbk, Rtbk, S)		> 5000* (D6) > 5000** (W2)	53
16-*epi*-Affinine (**95**)	*Peschiera fuchsiaefolia* (Stbk, Rtbk, S)		2157* (D6) 1502** (W2)	53
Affinisine (**96**)	*Peschiera fuchsiaefolia* (Stbk, Rtbk, S)		1135* (D6) 960** (W2)	53
Vobasine (**97**)	*Peschiera fuchsiaefolia* (Stbk, Rtbk, S)		471* (D6) 816** (W2)	53
Voachalotine (**98**)	*Peschiera fuchsiaefolia* (Stbk, Rtbk, S)		2589* (D6) > 5000** (W2)	53
Voacamine (**99**)	*Peschiera fuchsiaefolia* (Stbk, Rtbk, S)		238* (D6) 290** (W2)	53
Conopharyngine (**100**)	*Peschiera fuchsiaefolia* (Stbk, Rtbk, S)		2214* (D6) 1337** (W2)	53
Coronaridine (**101**)	*Peschiera fuchsiaefolia* (Stbk, Rtbk, S)		498* (D6) 276** (W2)	53
Voacangine (**102**)	*Peschiera fuchsiaefolia* (Stbk, Rtbk, S)		1810* (D6) 1323** (W2)	53
Icajine (**103**)	*Strychnos icaja* (Rt)	IC 50 µM	Inactive at 80* (FCA 20) 95** (W2)	54
Vomicine (**104**)	*Strychnos icaja* (Rt)		Inactive at 30* (FCA 20)	54
Isostrychnine (**105**)	*Strychnos icaja* (Rt)		Inactive at 20* (FCA 20) 14** (W2)	54
Bisnordihydrotoxiferine (**106**)	*Strychnos icaja* (Rt)		3.826* (FCA 20) 4.480** (W2)	54
Sungucine (**107**)	*Strychnos icaja* (Rt)		7.816* (FCA 20) 10.139** (W2)	54
Isosungucine (**108**)	*Strychnos icaja* (Rt)		1.315* (FCA 20) 0.265** (W2)	54
18-Hydroxysungucine (**109**)	*Strychnos icaja* (Rt)		3.985* (FCA 20) 1.003** (W2)	54
18-Hydroxyisosungucine (**110**)	*Strychnos icaja* (Rt)		0.847* (FCA 20) 0.140** (W2)	54

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Table 1. (*Contd…*)

Compound (Structure no.)	Plant (plant parts)	Activity *In vitro* (strain)		Reference
Cryptolepinoic acid (**111**)	*Cryptolepis sanguinolenta* (Rt)	IC 50 μM	>181** (K1) >181* (T9-96)	55
Ethyl cryptolepinoate (**112**)	*Cryptolepis sanguinolenta* (Rt)		3.76** (K1)	55
Cryptolepine (**113**)	*Cryptolepis sanguinolenta* (Rt)		0.23** (K1) 0.059* (T9-96)	55
Hydroxycryptolepine (**114**)	*Cryptolepis sanguinolenta* (Rt)		102** (K1) 76.6* (T9-96)	55
Quindoline (**115**)	*Cryptolepis sanguinolenta* (Rt)		>229** (K1) >229* (T9-96)	55
Cryptoheptine (**116**)	*Cryptolepis sanguinolenta* (Rt)		0.801** (K1) 1.18* (T9-96)	55
Cryptoquindoline (**117**)	*Cryptolepis sanguinolenta* (Rt)		34.6** (K1) 9.05* (T9-96)	55
1-*O*-acetylnorpluviine (**118**)	*Brunsvigia radulosa* (B)	IC 50 μg/ml	34.2** (FAC-8) 28.3* (D-10)	32
Anhydrolycorin-6-one (**119**)	*Brunsvigia radulosa* (B)		6.4** (FAC-8) 6.1* (D-10)	32
3-Hydroxy-6′-desmethyl-9-*O*-methylthalifaboramine (**120**)	*Thalictrum faberi* (Rt)	IC 50 ng/ml	112* (D6) 24.2** (W2)	56
3-Hydroxythalifaboramine (**121**)	*Thalictrum faberi* (Rt)		176* (D6) 10.2** (W2)	56
6′-Desmethylthalifaboramine (**122**)	*Thalictrum faberi* (Rt)		152* (D6) 11.2** (W2)	56
Ancistrobrevine B (**123**)	*Ancistrocladus robertsoniorum* (St, L)	IC 50 μM	4.7* (NF 54) 2.0** (K1)	57
Ancistrobertsonine A (**124**)	*Ancistrocladus robertsoniorum* (St, L)		>23.7* (NF 54) 15.9** (K1)	57
Ancistrobertsonine B (**125**)	*Ancistrocladus robertsoniorum* (St, L)		>23.0* (NF 54) 9.0** (K1)	57
Ancistrobertsonine C (**126**)	*Ancistrocladus robertsoniorum* (St, L)		10.1* (NF 54) 4.5** (K1)	57
Ancistrobertsonine D (**127**)	*Ancistrocladus robertsoniorum* (St, L)		4.8* (NF 54)	57

Rt, Roots; Bk, Bark; St, Stem; Stbk, Stem bark; W, Wood; T, Tuber; L, Leaves; Rtbk, Root bark; S, Seeds; B, Bulb; 22□, Strain susceptible to chloroquine; **, Strain resistant to chloroquine; 22. □, Showed significant chloroquine-potentiating action; 22. □, Tested *in vitro* against *P. berghei*. Note: Structures (**1–127**) are available from the authors on request.

configuration and also lacking oxirane ring showed moderate antimalarial activity. Therefore, it was concluded that epoxide functionality is not an essential requirement, other elements of the structure may come into play[30].

A bisbenzylisoquinoline alkaloid dehatrine (**44**) isolated from the wood of *Beilschmiedia madang* (Lauraceae), exhibited potent inhibitory activity (IC50 0.017 μM) against the proliferation of malaria pathogen *P. falciparum*, which was comparable to quinine[34].

Cryptolepine (**53**) 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. It was shown that the alkaloid might interact with DNA, and it appeared that two nitrogen atoms N and N-CH_3 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[39].

Another interesting antimalarial compound tubulosine (**54**) was found active *in vitro* against both sensitive and resistant strains of *P. falciparum*. The structure of this compound may be regarded as a mixed isoquinoline–indol analogue of the emetine group. Studies on molecular modelling showed that this type of alkaloid could not take the planar conformation as proposed previously. The indol moiety in tubulosine enhances the affinity for protozoan receptor, when compared with psychotrine (**55**) and cephaeline (**56**). The relative *in vitro* inactivity of (**55**) in comparison with (**56**) can be explained by its double bond in ring C, which enhances the coplanar conformation and electron environment[40].

Quassinoids

The quassinoids are heavily oxygenated lactones with majority of C_{20} basic skeleton named as picrasane. However, C_{18}, C_{19} and C_{25} quassinoids are also known. They have varying numbers of different oxygen-containing groups. With the exception of carbons C-5, C-9 and the methyl groups at C-4 and C-10, these oxygenated functions have been found on all the other carbon atoms. A wide spectrum of biological properties was reported for this class of compounds, of which antineoplastic and antimalarial have equal and parallel importance[58]. Plant-

Table 2. Antimalarial activity of quassinoids against *P. falciparum*

Compound (structure no.)	Plant (plant part)	Activity *In vitro* (strain)		Reference
Bruceine A (**128**)	*Brucea javanica* (Ft)	ED 50 μg/ml	0.011** (K-1)	59, 60
Bruceine B (**129**)	*Brucea javanica* (Ft)		0.011** (K-1)	59, 60
Bruceine C (**130**)	*Brucea javanica* (Ft)		0.005** (K-1)	59, 60
Bruceantin (**131**)	*Brucea javanica* (Ft)		0.0008** (K-1)	59, 60
Bruceolide (**132**)	*Brucea javanica* (Ft)		0.451** (K-1)	59, 60
Brusatol (**133**)	*Brucea javanica* (Ft)		0.003** (K-1)	59, 60
Bruceine D (**134**)	*Brucea javanica* (Ft)		0.015** (K-1)	59, 60
Eurycomanone (**135**)	*Erycoma longifolia* (Rt)	EC 50 ng/ml	48.1** (W-2) 47.7* (D-6)	25
Gutolactone (**136**)	*Simaba guianensis* (Bk)	IC 50 ng/ml	4.0** (W-2) 4.1* (D-6)	61
Simalikalactone-D (**137**)	*Simaba guianensis* (Bk)		1.6** (W-2) 1.5* (D-6)	61
Cedronin (**138**)	*Simaba cedron* (St, Bk)	IC 50 μg/ml	0.25** (FZR-8) 0.23* (FCC-2)	62
Eurycomanol (**139**)	*Eurycoma longifolia* (Rt)	IC 50 μM	1.231–4.897**	63
Eurycomanol-2-*O*-*β*-D-glucopyranoside (**140**)	*Eurycoma longifolia* (Rt)		0.389–3.498**	63
13-*β*,18-Dihydroeurycomanol (**141**)	*Eurycoma longifolia* (Rt)		0.504–2.343**	63
Samaderines X (**142**)	*Quassia indica* (St)		0.015 (K-1)	64
Samaderines Z (**143**)	*Quassia indica* (St)		0.071** (K-1)	64
Samaderines B (**144**)	*Quassia indica* (St)		0.071** (K-1)	64
Samaderines E (**145**)	*Quassia indica* (St)		0.21** (K-1)	64

Rt, Roots; Ft, Fruit; Bk, Bark; St, Stem; 22. □, Strain susceptible to chloroquine; **, Strain resistant to chloroquine.

Table 3. Antimalarial activity of sesquiterpenes against *P. falciparum*

Compound (structure no.)	Plant (plant parts)	Activity *In vitro* (strain)		Reference
Artemisinin (**146**)	*Artemisia annua*	EC 50 μg/ml	0.01 (FCH-5)	65
α-Peroxyachifolid (**147**)	*Achillea millefolium*		1.0 (FCH-5)	65
(**148**)	*Anthemis nobilis*		5.0 (FCH-5)	65
(**149**)	*Anthemis nobilis*		5.0 (FCH-5)	65
1*β*-Hydroperoxyisobilin (**150**)	*Anthemis nobilis*		1.0 (FCH-5)	65
trans-Pinocarveyl-hydroperoxide (**151**)	*Anthemis nobilis*		5–10 (FCH-5)	65
Arteinculton (**152**)	*Artemisia martima* *A. Pontica* *A. abrotanum*		5–10 (FCH-5)	65
(**153**)	*A. abrotanum*		5-10 (FCH-5)	65
(**154**)	*A. abrotanum* (L)		> 1 (FCH-5)	65
(**155**)	*A. absinthium* (L)		1.0 (FCH-5)	65
(**156**)	*Heterothalamus psiadioides*		<1 (FCH-5)	65
Nardosinon (**157**)	*Nardostachys chinensis*		1.4 (FCH-5)	65
Rugosal A (**158**)	*Rosa rugosa*		1.0 (FCH-5)	65
10,12-Peroxycalamenene (**159**)	*Cyperus rotundus* (T)	EC 50 M	2.33×10^{-6}** (K-1)	69
Patchoulenone (**160**)	*Cyperus rotundus* (T)		1.08×10^{-4}** (K-1)	69
Caryophyllene-16-*α*-oxide (**161**)	*Cyperus rotundus* (T)		3.45×10^{-4}** (K-1)	69
Neurolenin A (**162**)	*Neurolaena lobata* (Wp)	IC 50 μM	0.92 (NF-54)	70
Neurolenin B (**163**)	*Neurolaena lobata* (Wp)		0.62 (NF-54)	70
Neurolenin C/D (8 : 2) (**164/165**)	*Neurolaena lobata* (Wp)		0.62 (NF-54)	70
Nardoperoxide (**166**)	*Nardostachys chinensis* (Rt)	EC 50 M	1.5×10^{-6}	71
Isonardoperoxide (**167**)	*Nardostachys chinensis* (Rt)		6.0×10^{-7}	71
Sipandinolide (**168**)	*Siparuna andina* (L)	IC 50 μg/ml	46.2* (poW)	72

Rt, Roots; T, Tuber; L, Leaves; Wp, Whole plant.
*, Strain susceptible to chloroquine; **, Strain resistant to chloroquine.

derived antimalarial quassinoids are presented in Table 2 (refs 59–64).

The quassinoids brusatol (**133**), bruceantin (**131**) and brucein A, B and C (**128–130**) differ only in the nature of the ester moiety. The 3-,15-ester was supposed to be responsible for antimalarial activity. Bruceantin (**131**) showed most potent activity, while (**128**) and (**129**) were the least potent. The introduction of rigid alkyl groups

such as gem-dimethyl, gem-methyl and isopropyl at C-23 also contributed to the enhancement of antimalarial activity, as seen in (**131**) and (**133**)[59,60].

Cedronin (**138**) belongs to the few quassinoids with a C_{19} skeleton. Its IC50 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, as an A-ring with unsaturated ketol at position 1 and 2, *d*-lactone, and an oxide bridge between C-8 and C-15. The results also suggested that C_{19} quassinoid cedronin exhibits lower selective toxicity against *Plasmodium* than against mammalian cells. The compound also exhibited *in vivo* activity against *P. vinkei petteri* with ED50 value of 1.8 mg/kg/day[62].

Sesquiterpenes

The discovery of Qinghaosu (**146**) (artemisinin), a novel sesquiterpene lactone endoperoxide antimalarial cons-

Table 4. Antimalarial activity of triterpenoids against *P. falciparum*

Compound (structure no.)	Plant (plant parts)	Activity *In vitro* (strain)		Reference
Gedunin (**169**)	*Azadirachta indica* (L), *Cedrela odorata*,	IC 50 µg/ml	0.72** (K-1)	73
	Guarea multiflora, *Khaya grandifoliola* (Bk, Sd)		1.25** (W-2)	74
Nimbinin (**170**)	*Azadirachta indica* (L)			
	Cedrela odorata		0.77** (K-1)	73
	Guarea multiflora			
11-*b*-Acetoxygedunin (**171**)	-do-		3.11** (K-1)	73
Nimbolide (**172**)	-do-		1.74** (K-1)	73
Dihydrogedunin (**173**)	-do-		2.63** (K-1)	73
Bruceajavanin A (**174**)	*Brucea javanica* (St)		1.1** (K-1)	35
Dihydrobruceajavanin A (**175**)	*Brucea javanica* (St)		2.5** (K-1)	35
Ursolic acid* (**176**)	*Spathodea campanulata* (St, Bk)		34–97% sup. at dose of 15–16 mg/kg/day	75
Tomentosolic acid* (**177**)	*Spathodea campanulata* (St, Bk)		0–82% sup. dose 5–40 mg/kg/day	75
3*b*,20*b*-Dihydroxyurs-12-en-28-oic acid* (**178**)	*Spathodea campanulata* (St, Bk)		11–53% sup. dose 20–80 mg/kg/day	75
Betulinic acid (**179**)	*Triphyophyllum peltatum* (Rt, Bk)	IC 50 µg/ml	10.46 (NF-54)	76
	Ancistrocladus heyneanus		19.6** (K-1)	
	Uapaca nitida (Rt, Bk)		25.9** (T9-96)	
Lupeol (**180**)	*Vernonia brasiliana* (L)		45% at conc. 25 µg/ml	77
28-*nor*-Isoiguesterin-17-carbaldehyde (**181**)	*Salacia kraussii* (Rt)	IC 50 ng/ml	94.0** (K-1) 79.9* (NF-54)	78
17-(methoxycarbonyl)-28-*nor*-Isoiguesterin (**182**)	*Salacia kraussii* (Rt)		27.6** (K-1) 37.1* (NF-54)	78
28-Hydroxyisoiguesterin (**183**)	*Salacia kraussii* (Rt)		114.4** (K-1) 140.2* (NF-54)	78
Isoiguesterol (**184**)	*Salacia kraussii* (Rt)		22.9** (K-1) 54.1* (NF-54)	78
Pristimerin (**185**)	*Salacia kraussii* (Rt)		190.4** (K-1) 270* (NF-54)	78
Celastrol (**186**)	*Salacia kraussii*		180.9** (K-1) 254.2 (NF-54)	78
Meldenin (**187**)	*Azadirachta indica* (L)	IC 50 µg/ml	5.23** (K-1)	79
Isomeldenin (**188**)	*Azadirachta indica* (L)		50.0** (K-1)	79
Nimocinol (**189**)	*Azadirachta indica* (L)		50.0** (K-1)	79
Nimbandiol (**190**)	*Azadirachta indica* (L)		50.0** (K-1)	79
Methylangolensate (**191**)	*Khaya grandifoliola* (Bk, Sd)		5.39** (W-2)	74
7-Deacetylkhivorin (**192**)	*Khaya grandifoliola* (Bk, Sd)		5.08** (W-2)	74
1-Deacetylkhivorin (**193**)	*Khaya grandifoliola* (Bk, Sd)		9.63** (W-2)	74
6-Acetylswietenolide (**194**)	*Khaya grandifoliola* (Bk, Sd)		7.46** (W-2)	74
16-*O*-(*b*-arabinopyranosyl)-3-oxo-12, 16*b*,21*b*,22-tetrahydroxyhopane (Glinoside A) (**195**)	*Glinus oppositifolius* (Ap)	IC 50 µg/ml	42, 30* (3D7) 39, 42** (W2)	74

Rt, Roots; Bk, Bark; St, Stem; T, Tuber; L, Leaves; Sd, Seed.
*, Strain susceptible to chloroquine; **, Strain resistant to chloroquine; *, Compounds (**109–111**) tested *in vivo* against *P. berghei*.

tituent from the Chinese plant 'Qinghao' (*Artemisia annua*), prompted the investigation of some other naturally occurring peroxides for their schizonticidal activity[10]. Table 3 (refs 65–72) gives a brief account of various sesquiterpenoids reported for their antimalarial activity.

Artemisinin is a new class of antimalarials, where the endoperoxide moiety plays an important role. Its 1,2,4 trioxane ring is unique in nature and is essential for the activity. 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[66]. 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[67]. 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*[68].

The endoperoxide sesquiterpene: 10,12-peroxycalamenene (**159**) exhibited strongest effect of EC50 2.33×10^{-6} M (ref. 69). It was demonstrated in neurolenin B (**163**), that α,β-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[70].

The two guaiane-type endoperoxides: nardoperoxide (**166**) and isonardoperoxide (**167**) isolated from the roots of *Nardostachys chinensis*, showed strongest antimalarial effects. It is noteworthy that activity and selectivity of isonardoperoxide (**167**) was comparable to those of quinine, a clinically used drug. Nardoperoxide and isonardoperoxide seem to be the promising lead compounds for antimalarial drugs[71].

Table 5. Antimalarial activity of flavonoids and xanthones against *P. falciparum*

Compound (structure no.)	Plant (plant parts)	Activity *In vitro* (strain)		Reference
7-Hydroxy-3′-4′-(methylenedioxy) flavan (**196**)	*Terminalia bellerica* (Ft rind)	IC 50 μM	>50* (3D-7)	82
Exiguaflavone A (**197**)	*Artemisia indica* (St)	IC 50 M	1.08×10^{-5}** (K-1)	83
Exiguaflavone B (**198**)	*Artemisia indica* (St)		1.60×10^{-5}** (K-1)	83
7-*O*-Methylgarcinone E (**199**)	*Garcinia cowa* (Bk)	IC 50 μg/ml	2.50	84
Cowanin (**200**)	*Garcinia cowa* (Bk)		3.00	84
Cowanol (**201**)	*Garcinia cowa* (Bk)		1.60	84
Cowaxanthone (**202**)	*Garcinia cowa* (Bk)		1.50	84
β-Mangostin (**203**)	*Garcinia cowa* (Bk)		3.00	84
1,7-Dihydroxyxanthone (**204**)	*Garcinia dulcis* (Bk)		3.88	83
12β-Hydroxy-des-D-garcigerrin-A (**205**)	*Garcinia dulcis* (Bk)		2.08	85
1-*O*-Methylsymphoxanthone (**206**)	*Garcinia dulcis* (Bk)		3.71	85
Symphoxanthone (**207**)	*Garcinia dulcis* (Bk)		3.75	85
Garciniaxanthone (**208**)	*Garcinia dulcis* (Bk)		0.96	85
(–)-*cis*-3-acetoxy-4′,5,7-trihydroxy-flavanone (**209**)	*Siparuna andina* (L)	IC 50 μg/ml	24.3* (poW)	72
6-Hydroxyluteolin-7-*O*-(1″-α-rhamnoside) (**210**)	*Vriesea sanguinolenta* (L)	IC 50 μM	2.13** (K-1) 3.32* (NF-54)	86
Formononetin (**211**)	*Andira inermis* (St, L)	IC 50 μg/ml	>50* (poW) >50** (Dd2)	87
Prunetin (**212**)	*Andira inermis* (St, L)		27.8* (poW) >50** (Dd2)	87
Biochanin A (**213**)	*Andira inermis* (St, L)		46.8* (poW) >50** (Dd2)	87
Calycosin (**214**)	*Andira inermis* (St, L)		4.2* (poW) 9.8** (Dd2)	87
Genistein (**215**)	*Andira inermis* (St, L)		2.0* (poW) 4.1** (Dd2)	87
Pratensein (**216**)	*Andira inermis* (St, L)		45* (poW) >50** (Dd2)	87

Ft, Fruit; Bk, Bark; St, Stem; L, Leaves.
*, Strain susceptible to chloroquine; **, Strain resistant to chloroquine.

Triterpenoids

Twenty-six triterpenoids isolated from different medicinal plants exhibiting antimalarial property are compiled in Table 4 (refs 73–80).

Gedunin (**169**) possessed activity about three times higher than chloroquine, but twenty-times lower than quinine. Comparison of activities of gedunin (**169**) and dihydrogedunin (**173**) suggested that the reduction of the double bond in *a,b*-unsaturated keto function lead to a

Table 6. Antimalarial activity of quinones against *P. falciparum*

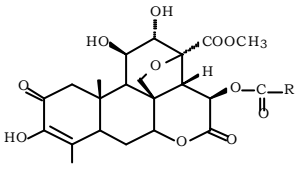
Compound (structure no.)	Plant (plant parts)	Activity *In vitro* (strain)		Reference
Digitolutein (**217**)	*Morinda lucida* (Stbk, Rtbk)	IC 50 µg/ml	12.92	90
Rubiadin-1-methylether (**218**)	*Morinda lucida* (Stbk, Rtbk)		8.10	90
Damnacanthal (**219**)	*Morinda lucida* (Stbk, Rtbk)		9.20	90
1-Hydroxybenzoisochroman (**220**)	*Psychotria camponutans* (Wd)		2.66** (K-1)	91
Benz-(*g*)-isoquinoline-5,10-dione (**221**)	*Psychotria camponutans* (Wd)		0.84** (K-1)	91
5 and 8-Hydroxy-2-(1′-hydroxy)-ethyl-naphtho-(2,3-*b*)-furan-4,9-dione (**222/223** mix)	*Tabebuia ochracea* (inner Stbk)	IC 50 M	1.67×10^{-7} [j] 6.77×10^{-7}** (FcB2)	92
Plumbagin (**224**)	*Nepenthes thorelii* (Rt)	IC 50 µM	0.27	93
2-Methylnaphthazarin (**225**)	*Nepenthes thorelii* (Rt)		5.79	93

Rtbk, Root bark; Stbk, Stem bark; Wd, Wood; Rt, Roots.
*, Strain susceptible to chloroquine; **, Strain resistant to chloroquine; [j], Tested *in vitro* against *P. berghei*.
Note: Structures (**217–225**) are available from the authors on request.

Table 7. Antimalarial activity of miscellaneous compounds against *P. falciparum*

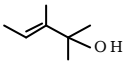
Compound (structure no.)	Plant (plant parts)	Activity *In vitro* (strain)		Reference
a-Cyperone (**226**)	*Cyperus rotundus* (T)	IC 50 µg/ml	5.5** (K-1)	81
N-Isobutyldeca-2,4-dienamide (**227**)	*Zanthoxylum gilletii* (Rt)		5.37** (K-1)	81
Securinine (**228**)	*Margaritaria discoidea* (Rtbk)		5.35** (K-1)	81
Phloroglucinol derivative (**229**)	*Hypericum calycinum* (Ap)		0.88** (K-1)	94
Hazaleamide (**230**)	*Fagara rhetza* (Bk)	IC 50 µM	43.0** (K-1)	95
3-*O*-Benzoylhosloppone (**231**)	*Hoslundia opposita* (Rtbk)	IC 50 µg/ml	0.4** (K-1)	96
4,7-Dimethyl-1-tetralone (**232**)	*Cyperus rotundus* (T)	EC 50 M	8.62×10^{-5}** (K-1)	69
Diterpeneperoxide (**233**)	*Amomum krervanh* (St)	EC 50 µM	0.017	97
Myrtenal (**234**)	*Amomum krervanh* (Ft)		5–50	97
Myrtenol (**235**)	*Amomum krervanh* (Ft)		5–50	97
trans-Pinocarveol (**236**)	*Amomum krervanh* (Ft)		5–50	97
Termilignan (**237**)	*Terminalia bellerica* (Ft rind)	IC 50 µM	9–6* (3D7)	82
Thannilignan (**238**)	*Terminalia bellerica* (Ft rind)		>50* (3D7)	82
Anolignan B (**239**)	*Terminalia bellerica* (Ft rind)		20.5* (3D7)	82
Tomentosrin (**240**)	*Xanthium strumarium* (Ap)	IC 50 µg/ml	7.8** (K-1)	98
8-*epi*-Xanthatin-1*b*-5*b*-epoxide (**241**)	*Xanthium strumarium* (Ap)		7.8** (K-1)	98
Xanthumin (**242**)	*Xanthium strumarium* (Ap)		31** (K-1)	98
8-*epi*-Xanthin (**243**)	*Xanthium strumarium* (Ap)		125** (K-1)	98
Muzanzagenin (**244**)	*Asparagus africanus* (Rt)	IC 50 µM	61* (K-39) 23* (3D7) 163** (V1/Sd) 16** (Dd2)	99
(+)-Nyasol (**245**)	*Asparagus africanus* (Rt)		12** (Dd2) 12* (3D7)	99
5,7-Dimethoxy-8-(3′-hydroxy-3′-methyl-1-butene)-coumarin (**246**)	*Toddalia asiatica* (Rt)	IC 50 µg/ml	8.8** (VI/S) 16.2* (K39)	100
Heptaphylline (**247**)	*Clausena harmandiana* (Rt)	IC 50 µg/ml	3.2–6.4** (K-1)	101
Dentatin (**248**)	*Clausena harmandiana* (Rt)		8.5–12.3** (K-1)	101
Clausarin (**249**)	*Clausena harmandiana* (Rt)		0.1–0.7** (K-1)	101
Ophiobolin A (**250**)	*Cochliobolus heterostrophus* (Cul Fl)	IC 50 ng/ml	<528.8* (D6) 580** (W2)	102

Glinus oppositifolius (Ap).
Rt, Roots; Bk, Bark; St, Stem; T, Tuber; Rtbk, Root bark; Ap, Aerial parts; Cul fl, Cultural filterates; L, Leaves.
*, Strain susceptible to chloroquine; **, Strain resistant to chloroquine.
Note: Structures (**226–250**) are available from the authors on request.



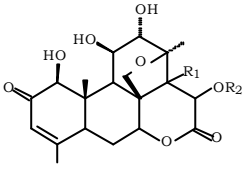
[**128**] R = 

[**129**] R = Me

[**130**] R = 

[**131**] R = 

[**133**] R = C-15 *b*-OH

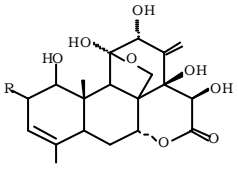


[**134**] R_1 = OH, R_2 = H

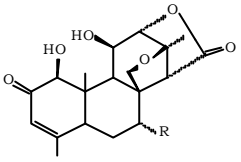
[**136**] R_1 = H, R_2 = 

[**137**] R_1 = H, R_2 = 

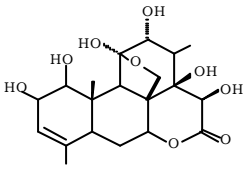
[**132**] R = 



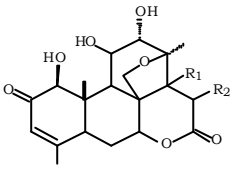
[**135**] R = (= O)
[**139**] R = OH
[**140**] R = OGlc



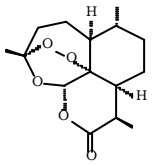
[**138**] R = OH
[**144**] R = (= O)



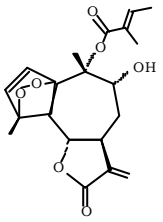
[**141**]



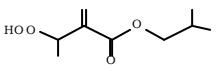
[**142**] R_1 = H, R_2 = OAc
[**143**] R_1 = H, R_2 = OH
[**145**] R_1 = OH, R_2 = H



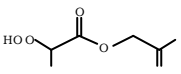
[**146**]



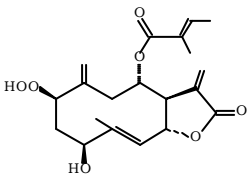
[**147**]



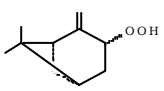
[**148**]



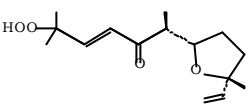
[**149**]



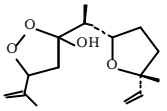
[**150**]



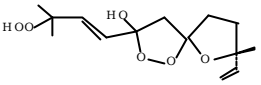
[**151**]



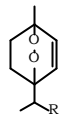
[**152**]

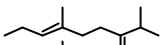


[**153**]

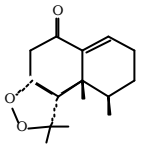


[**154**]

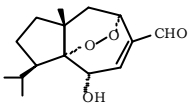


(155) R= 

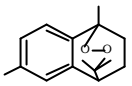
(156) R= 



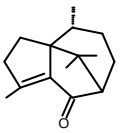
[**157**]



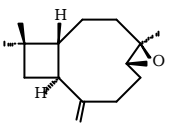
[**158**]



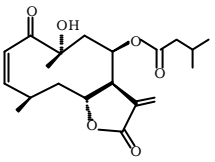
[**159**]



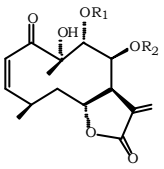
[**160**]



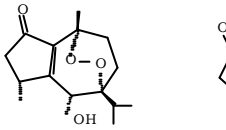
[**161**]



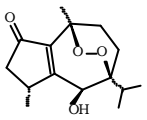
[**162**]



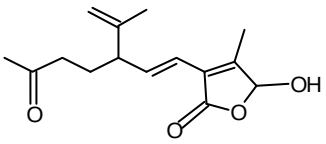
[**163**] R_1 = Ac, R_2 = ival
[**164**] R_1 = ival, R_2 = H
[**165**] R_1 = H, R_2 = ival
Ac = Acetate
Ival = isovalerianyloxy



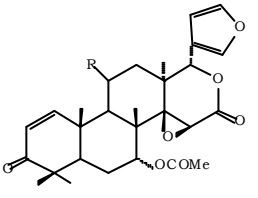
[**166**]



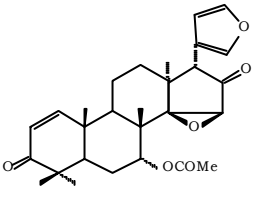
[**167**]



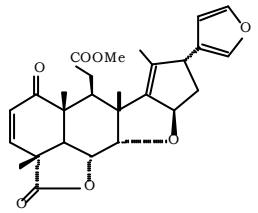
[**168**]



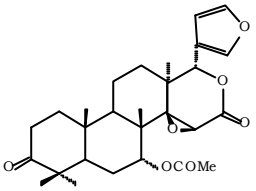
[**169**] R = H
[**171**] R = OCOMe



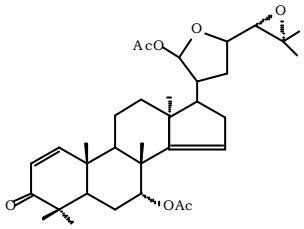
[**170**]



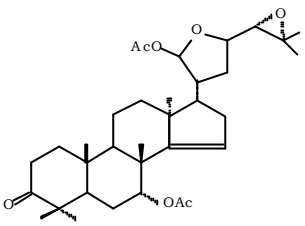
[**172**]



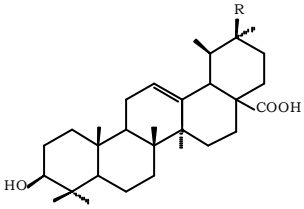
[**173**]



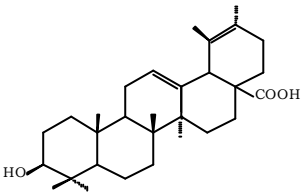
[**174**]



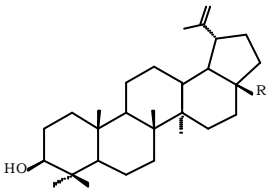
[**175**]



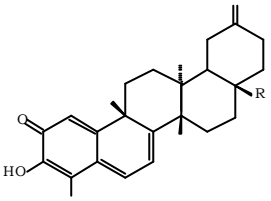
[**176**] R = H
[**178**] R = OH



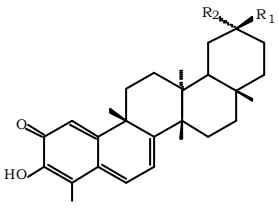
[**177**]



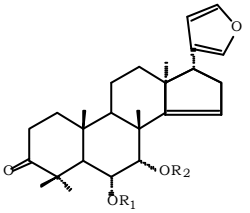
[**179**] R = COOH
[**180**] R = Me



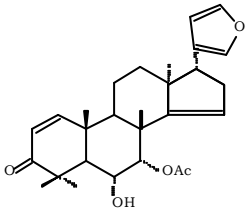
[**181**] R = CHO
[**182**] R = COOMe
[**183**] R = CH_2OH



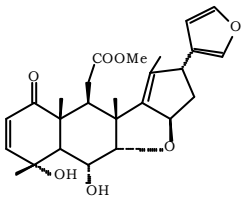
[**184**] R_1 = H, R_2 = CH_2OH
[**185**] R_1 = Me, R_2 = COOMe
[**186**] R_1 = Me, R_2 = COOH



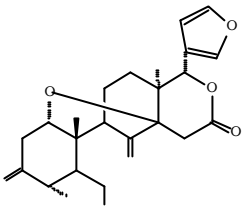
[**187**] R_1 = Ac, R_2 = H
[**188**] R_1 = H, R_2 = Ac



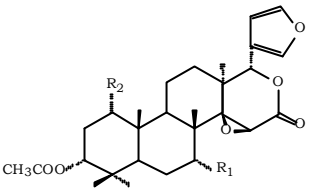
[**189**]



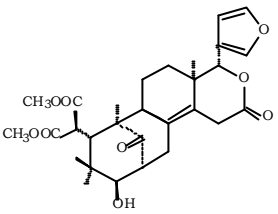
[**190**]



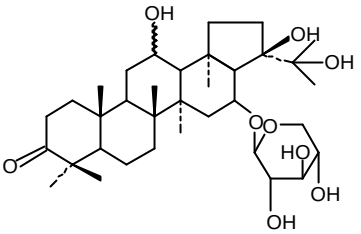
[**191**]



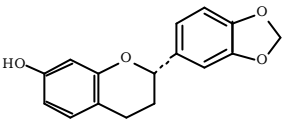
[**192**] R_1 = OH, R_2 = $COOCH_3$
[**193**] R_1 = $COOCH_3$, R_2 = OH



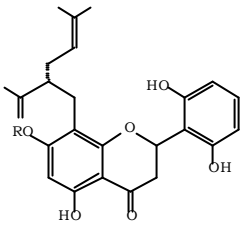
[**194**]



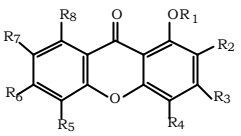
[**195**]

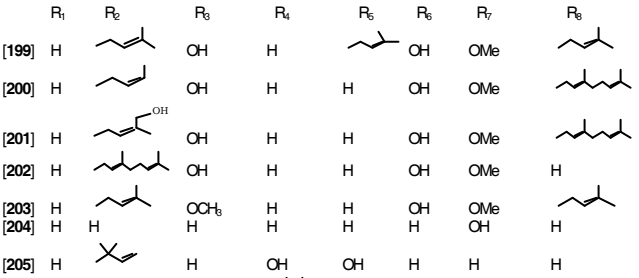


[**196**]
[**198**] R = CH_3

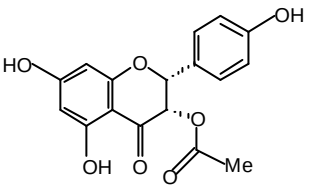


[**197**] R = H

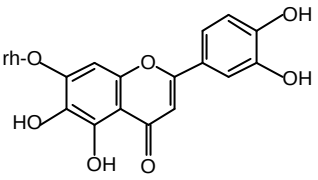




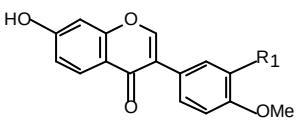
[**199**] H, OH, H, OH, OMe
[**200**] H, OH, H, H, OH, OMe
[**201**] H, OH, H, OH, H, H, OH, OMe
[**202**] H, OH, H, H, OH, OMe, H
[**203**] H, OCH_3, H, H, OH, OMe
[**204**] H, H, H, H, H, H, OH, H
[**205**] H, H, OH, OH, H, H, H
[**206**] Me, OH, H, OH, OH, H, H
[**207**] H, OH, H, OH, OH, H, H
[**208**] H, H, OH, H, OH, OH



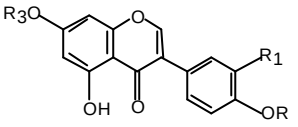
[**209**]



[**210**] rh = rhamnose



[**211**] R_1 = H
[**214**] R_1 = OH



[**212**] R_1 = H, R_2 = H, R_3 = Me
[**213**] R_1 = H, R_2 = Me, R_3 = H
[**215**] R_1 = H, R_2 = H, R_3 = H
[**216**] R_1 = OH, R_2 = Me, R_3 = H

decrease of antimalarial activity and increase in toxicity. It was already established that α,β-unsaturated keto function is an important feature for antimalarial activity in quassinoids. Gedunin is a limonoid, an oxidized triterpene closely related to the quassinoids. It has also been reported that treatment of gedunin with alkali results in the formation of quassinoid-like structures[73]. Gedunin was also shown to exhibit an additive effect when combined with chloroquine[74,81].

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. Some recent reports of antimalarial activity from these classes of compounds are presented in Table 5 (refs 82–87).

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[88].

The ethanol extract of the bark of *Garcinia dulcis* (Guttiferae) furnished five xanthones (**204**–**208**); garciniaxanthone (**208**) showed inhibitory effects on the growth of *P. falciparum* with IC 50 value of 0.96 μg/ml[85].

Quinones

Chemically, quinones are compounds with a 1,4-diketocyclohexa-2,5-dienoid or a 1,2-diketocyclohexa-3,5-dienoid moiety. 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*[89]. Some of the naturally occurring quinones tested for antimalarial activity are presented in Table 6 (refs 90–93).

Roots of *Nepenthes thorelii* yielded plumbagin (**224**) and 2-methylnaphthazarin (**225**) both of which were evaluated against *P. falciparum*. The quinone structure was regarded essential for the activity of naphthoquinones like plumbagin (**224**)[93].

Miscellaneous compounds

Various compounds with different chemical structures possessing antimalarial activity are presented in Table 7 (refs 81, 94–102).

The most active constituents isolated from the tubers of *Cyperus rotundus* (Cyperaceae), the root bark of *Zanthoxylum gilletii* (Rutaceae) and the root bark of *Margaritaria discoidea* (Euphorbiaceae) were α-cyperone (**226**), N-isobutyldeca-2,4-dienamide (**227**) and securinine (**228**), respectively. All these compounds were shown to possess significant antimalarial activity due to the presence of α,β-unsaturated carbonyl moiety. The α,β-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*[81,96].

Conclusion

Several plants are used in traditional medicine for the treatment of malaria and fever in many parts of world. These require further detailed investigation with ethnopharmacological approach. It therefore seems worthwhile to study such plants, which have been used over the centuries for medicinal purposes. The ethnopharmacological approach used in the search for new antimalarial compounds from plants appears to be predictive compared to the random screening approach. The recently developed new isolation and characterization techniques together with development of new pharmacological testing have led to interest in plants as a source of new drugs. However, a promising approach is needed to use these agents as templates for designing new derivatives with improved properties. The search for additional antimalarials from higher plants must continue to fight the disease.

1. Global malaria control bulletin. *Bull. WHO*, 1993, **71**, 281–284.
2. Ekthawatchai, S. *et al*., Synthetic and naturally occurring antimalarials. *J. Heterocyclic Chem*., 1999, **36**, 1599–1605.
3. Kumar, S., Malaria runs amok in India. *New Sci.*, 1994, 9.
4. Beckmann, H., In *Antimalarial Drugs: Their Nature, Action and Use*, 1958, pp. 529–533.
5. Bharel, S., Gulati, A., Abdin, M. Z., Srivastava, P. S. and Jain, S. K., Structure, biosynthesis and functions of artemisinin. *Fitoterapia*, 1996, **67**, 387–399.
6. Mukherjee, T., Antimalarial herbal drugs. A review. *Fitoterapia*, 1991, **62**, 197–204.
7. Luo, X-De and Shen, C-C., The chemistry, pharmacology, and clinical application of Qinghaosu (Artemisinin) and its derivatives. *Med. Res. Rev.*, 1987, **7**, 29–52.
8. Carvalho, L. H., Brandao, M. G. L., Santos-Filho, D., Lopes, J. L. H. and Krettli, A. U., Antimalarial activity of crude extracts from Brazilian plants studied *in vivo* in *Plasmodium berghei*-infected mice and *in vitro* against *Plasmodium falciparum* in culture. *Braz. J. Med. Biol. Res*., 1991, **24**, 1113–1123.

9. Sharma, P. and Sharma J. D., Plants showing antiplasmodial activity – from crude extracts to isolated compounds. *Indian J. Malariol.*, 1998, **35**, 57–110.
10. Klayman, D. L., Quinghaosu (artemisinin): An antimalarial drug from China. *Science*, 1985, **228**, 1049–1055.
11. Kirby, G. C., Khumalo-Ngwenya, N. B., Grawehr, B. A., Fison, T. W., Warhurst, D. C. and Phillipson, J. D., Antimalarial activity from 'Mhekara' (*Uapaca nitida* Mull-Arg.), a Tanzanian tree. *J. Ethnopharmacol.*, 1993, **40**, 47–51.
12. Ratsimamanga, V. S. *et al.*, *In vitro* antimalarial activity, chloroquine potentiating effect and cytotoxicity of alkaloids of *Hernandia voyronii* Jum. (Hernandiaceae). *Phytother. Res.*, 1994, **8**, 18–21.
13. Valsaraj, R., Pushpangadan, P., Nyman, U., Smitt, U. V., Adsersen, A. and Guditsen, L., New antimalarial drugs from Indian medicinal plants. International Seminar on Recent Trends in Pharmaceutical Sciences, Oatacamund Abstract, No. 2A, 18–20 February 1995.
14. Francois, G., Assi, L. A., Holenz, J. and Bringmann, G., Constituents of *Picralima nitida* display pronounced inhibitory activities against asexual erythrocytic forms of *Plasmodium falciparum in vitro. J. Ethnopharmacol.*, 1996, **54**, 113–117.
15. Gantier, J. C., Fournet, A., Munos, M. H. and Hocquemiller, R., The effect of some 2-substituted quinolines isolated from *Galipealongfolia* on *Plasmodium vinckei petteri* infected mice. *Planta Med.*, 1996, **62**, 285–286.
16. Francois, G. *et al.*, Growth inhibition of asexual erythrocytic forms of *Plasmodium falciparum* and *P. berghei in vitro by* naphthylisoquinoline alkaloid-containing extracts of *Ancistrocladus* and *Triphyophyllum* species. *Int. J. Pharmacognosy.*, 1997, **35**, 55–59.
17. Agbedahunsi, J. M., Elujoba, A. A., Makinde, J. M. and Oduda, A. M. J., Antimalarial activity of *Khaya grandifoliola* stem bark. *Pharm. Biol.*, 1998, **36**, 8–12.
18. Awe, S. O., Olajide, O. A., Oladiran, O. O. and Makinde, J. M., Antiplasmodial and antipyretic screening of *Mangifera indica* extract. *Phytother. Res.*, 1998, **12**, 437–440.
19. Awe, S. O. and Makinde, J. M., Effect of petsolum ether fractions of *Morinda lacida* on *Plasmodium berghei* in mice. *Pharm. Biol.*, 1998, **36**, 301–304.
20. Benoit-Vical, F., Valentin, A., Caurnae, V., Pelissier, Y., Mallie, M. and Bastide, J. M., *In vitro* antiplasmodial activity of stem and root extracts of *Nauclea latefolia* S.M. (Rubiaceae). *J. Ethnopharmacol.*, 1998, **61**, 173–178.
21. Rahman, N. N. N. A., Furuta, T., Kojima, S., Tabane, K. and Ali-Mohd., M., *In vitro* and *in vivo* study revealed that malarias medicinal plants, *Piper sarmentosum, Andrographis paniculata* and *Tinospora crispa* produce considerable antimalarial effect. *J. Ethnopharmacol.*, 1999, **64**, 249–254.
22. Campbell, W. E., Gammon, D. W., Smith, P., Abrahams, M. and Purves T. D., Composition and antimalarial activity *in vitro* of the essential oil of *Tetradenia riparia. Planta Med.*, 1997, **63**, 270–272.
23. Milhan, G., Valentin, A., Benoit, F., Mallie, M., Bastide, J. M., Pelissier, Y. and Bessiere, J. M., *In vitro* antimalarial activity of eight essential oils. *J. Essential Oil Res.*, 1997, **9**, 329–333.
24. Said, I. M., Latiff, A., Partridge, S. J. and Phillipson, J. D., Alkaloids from *Dehaasia incrassata. Planta Med.*, 1991, **57**, 389.
25. Kardono, L. B. S., Angerhofer, C. K., Tsauri, S., Padmawinata, K., Pezzuto, J. M. and Kinghorn, A. D., Cytotoxic and antimalarial constituents of the roots of *Eurycoma longifolia. J. Nat. Prod.*, 1991, **54**, 1360–1367.
26. Wright, C. W., Allen, D., Cai, Ya., Phillipson, J. D., Said, I. M., Kirby, G. C. and Warhurst, D. C., *In vitro* anti of amoebic and antiplasmodial activities of alkaloids isolated from *Alstonia angustifolia* roots. *Phytother. Res.*, 1992, **6**, 121–124.
27. Ratsimamanga-Urverg, S. *et al.*, *In vitro* antimalarial activity and chloroquine potentiating action of two bisbenzylisoquinoline enantiomer alkaloids isolated from *Strychnopsis thouarsii* and *Spirospermum penduliflorum. Planta Med.*, 1992, **58**, 540–543.
28. Lin, L-Z. *et al.*, Cytotoxic and antimalarial bisbenzylisoquinoline alkaloids from *Cyclea barbata. J. Nat. Prod.*, 1993, **56**, 22–29.
29. Likhitwitayawuid, K., Angerhofer, C. K., Cordell, G. A. and Pezzuto, J. M., Cytotoxic and antimalarial bisbenzylisoquinoline alkaloids from *Stephania erects. J. Nat. Prod.*, 1993, **56**, 30–38.
30. Likhitwitayawuid, K., Angerhofer, C. K., Chai, H., Pezzuto, J. M. and Cordell G. A., Cytotoxic and antimalarial alkaloids from the bulbs of *Crium amabile. J. Nat. Prod.*, 1993, **56**, 1331–1338.
31. Hallock, Y. F. *et al.*, Michellamines D-F, new HIV-inhibitory dimiric naphthylisoquinoline alkaloids and korupensamine E, a new antimalarial monomer, from *Anchistrocladus korupensis. J. Nat. Prod.*, 1997, **60**, 677–683.
32. Campbell, W. E. *et al.*, Bioactive alkaloids from *Brunsvigia radulosa. Phytochemistry*, 2000, **53**, 587–591.
33. Likhitwitayawuid, K., Angerhofer, C. K., Chai, H., Pezzuto, J. M. and Cordell, G. A., Cytotoxic and antimalarial alkaloids from the tubers of *Stephania pierrei. J. Nat. Prod.*, 1993, **56**, 1468–1478.
34. Kitagawa, I. *et al.*, Dehatrine, an antimalarial bisbenzylisoquinoline alkaloid from the Indonesian medicinal plant *Belischmiedia madang*, isolated as a mixture of two rotational isomers. *Chem. Pharm. Bull.*, 1993, **41**, 997–999.
35. Kitagawa, I., Mahmud, T., Simanjuntak, P., Hori, K., Uji, T. and Shibuya, H., Indonesian medicinal plants. VIII. Chemical structures of three new triterpenoids, bruceajavanin A, dihydrobruceajavanin A, and bruceajavanin B, and a new alkaloidal glycoside, bruceacanthinoside, from the stems of *Brucea javanica* (Simaroubaceae). *Chem. Pharm. Bull.*, 1994, **42**, 1416–1421.
36. Lin, L-Z. *et al.*, Thalifaberidine, a cytotoxic aporphine-benzylisoquinoline alkaloid from *Thalictrum faberi. J. Nat. Prod.*, 1994, **57**, 1430–1436.
37. Rasoanaivo, P., Ratsimamanga-Urverg, S., Milijaona, R., Rafatro, H., Rakoto-Ratsimamanga, A., Galeffi, C. and Nicoletti, M., *In vitro* and *in vivo* chloroquine-potentiating action of *Strychnos myrtoides* alkaloids against chloroquine-resistant strains of *Plasmodium* malaria. *Planta Med.*, 1994, **60**, 13–16.
38. Hallock, Y. F. *et al.*, Korupensamines A–D, novel antimalarial alkaloids from *Ancistrocladus korupensis. J. Org. Chem.*, 1994, **59**, 6349–6355.
39. Kirby, G. C., Paine, A., Warhurst, D. C., Noamese, B. K. and Phillipson, J. D., *In vitro* and *in vivo* antimalarial activity of cryptolepine, a plant-derived indoloquinoline. *Phytother. Res.*, 1995, **9**, 359–363.
40. Sauvain, M. *et al.*, Antimalarial activity of alkaloids from *Pogonopus tubulosus. Phytother. Res.*, 1996, **10**, 198–201.
41. Grellier, P. *et al.*, Antimalarial activity of cryptolepine and isocryptolepine, alkaloids isolated from *Cryptolepis sanguinolenta. Phytother. Res.*, 1996, **10**, 317–321.
42. Bringmann, G. *et al.*, Ancistroheynine A, the first 7,8′-coupled naphthylisoquinoline alkaloids from *Ancistrocladus heyneanus. Phytochemistry*, 1996, **43**, 1405–1410.
43. Campbell, W. E. *et al.*, Cytotoxic and antimalarial alkaloids from *Brunsvigia littoralis. Planta Med.*, 1998, **64**, 91–93.
44. Hallock, Y. F., Cordellina, J. H., Schaffer, M., Bringmann, G., Francois, G. and Boyd, M. R., Korundamine A, a novel HIV-inhibitory and antimalarial 'hybrid' naphthylisoquinoline alkaloid heterodime from *Ancistrocladus korupensis. Bioorg. Med. Chem. Lett.*, 1998, **8**, 1729–1734.
45. Takaya, T. *et al.*, New type of Febrifugine analogues, bearing a quinolizidine moiety, show antimalarial activity against *Plasmodium* malaria parasite. *J. Med. Chem.*, 1999, **42**, 3163–3166.

46. Frederich, M. *et al.*, 10′-Hydroxyusambarensine, a new antimalarial bisindole alkaloid from the roots of *Strychnos usambrensis*. *J. Nat. Prod.*, 1999, **62**, 619–621.
47. Muhammad, I., Dunbar, D. C., Takamatsu, S., Walker, L. A. and Clark, A. M., Antimalarial, cytotoxic, and antifungal alkaloids from *Duguetia hadrantha*. *J. Nat. Prod.*, 2001, **64**, 559–562.
48. Bringmann, G., Gunther, C., Saeb, W., Mies, J., Wickramasinghe, A., Mudogo, V. and Brun, R., Ancistrolikokines A–C: New 5,8′-coupled naphthylisoquinoline alkaloids from *Ancistrocladus likoko*. *J. Nat. Prod.*, 2000, **63**, 1333–1337.
49. Munoz, V. *et al.*, Antimalarial activity and cytotoxicity of (–)-roemrefidine isolated from the stem bark of *Sparattanthelium amazonum*. *Planta Med.*, 1999, **65**, 448–449.
50. Keawpradub, N., Kirby, G. C., Steele, J. C. P. and Houghton, P. J., Antiplasmodial activity of extracts and alkaloids of three *Alstonia* species from Thailand. *Planta Med.*, 1999, **65**, 690–694.
51. Staerk, D., Lemmich, E., Christensen, J., Kharazmi, A., Olsen, C. E. and Jaroszewski, J. W., Leishmanicidal, antiplasmodial and cytotoxic activity of indole alkaloids from *Corynanthe pachyceras*. *Planta Med.*, 2000, **66**, 531–536.
52. Mambu, L., Martin, M-T., Razafi-Mahefa, D., Ramanitrahasimbola, D., Rasoanaino, P. and Frappier, F., Spectral characterization and antiplasmodial activity of bisbenzylisoquinolines from *Isolona ghesquiereina*. *Planta Med.*, 2000, **66**, 537–540.
53. Federici, E., Palazzino, G., Nicoletti, M. and Galeffi, C., Antiplasmodial activity of the alkaloids of *Peschiera fuchsiaefolia*. *Planta Med.*, 2000, **66**, 93–95.
54. Frederich, M. *et al.*, New antimalarial and cytotoxic sungucine derivatives from *Strychnos icaja* roots. *Planta Med.*, 2000, **66**, 262–269.
55. Paulo, A., Gomes, E. T., Steele, J., Warhurst, D. C. and Houghton, P. J., Antiplasmodial activity of *Cryptolepis sanguinolenta* alkaloids from leaves and roots. *Planta Med.*, 2000, **66**, 30–34.
56. Lin, L-Z. *et al.*, Phenolic aporphine-benzylisoquinoline alkaloids from *Thalictrum faberi*. *Phytochemistry*, 1999, **50**, 829–834.
57. Bringmann, G. *et al.*, Ancistrobertsonines B, C, and D as well as 1,2-didehydroancistrobertsonine D from *Ancistrocladus robertsoniorum*. *Phytochemistry*, 1999, **52**, 321–332.
58. Polonsky, J., *Quassinoid Bitter Principles II* (eds Herz, W. *et al.*), In Progress in the Chemistry of Organic Natural Products, 1985, p. 222; 239.
59. Anderson, M. M., O'Neill, M. J., Phillipson, J. D. and Warhurst, D. C., *In vitro* cytotoxicity of a series of quassinoids from *Brucea javanica* fruits against KB cells. *Planta Med.*, 1991, **57**, 62–74.
60. Sharma, S. C. and Agarwal, V. K., *Brucea javanica* (Linn.) Merr.: A potent anticancer and antimalarial plant – a review. *Indian J. Pharm. Sci.*, 1993, **55**, 77–85.
61. Cabral, J. A., McChesney, J. D. and Milhous, W. K., A new antimalarial quassinoid from *Simaba guianensis*. *J. Nat. Prod.*, 1993, **56**, 1954–1961.
62. Moretti, C., Deharo, E., Sauvain, M., Jardel, C., David, P. T. and Gasquet, M., Antimalarial activity of Cedronin. *J. Ethnopharmacol.*, 1994, **43**, 57–61.
63. Ang, H. H., Chan, K. L. and Mak, J. W., *In vitro* antimalarial activity of quassinoids from *Eurycoma longifolia* against Malaysian chloroquine-resistant *Plasmodium falciparum* isolates. *Planta Med.*, 1995, **61**, 177–178.
64. Kitagawa, I., Mahmud, T., Yokota, Ko-ichi, Nakagawa, S., Mayumi, T., Kobayashi, M. and Shibuya, H., Indonesian medicinal plants XVIII characterization of quassinoids from the stem of *Quassia indica*. *Chem. Pharm. Bull.*, 1996, **41**, 2009–2014.
65. Rucker, G., Walter, R. D., Manns, D. and Mayer, R., Antimalarial activity of some natural peroxides. *Planta Med.*, 1991, **57**, 295–296.
66. Li, Z. L., Gu, H. M., Warhurst, D. C. and Peters, W., Effects of Qinghaosu and related compounds on incorporation of (G-3H) hypoxanthine by plants, *Plasmodium falciparum in vitro*. *Trans. R. Soc. Trop. Med. Hyg.*, 1983, **77**, 522–523.
67. Gu, H. M., Warhurst, D. C. and Peters, W., Rapid action of Qinghaosu and related drugs on incorporation of (^{3}H) isoleucine by *Plasmodium falciparum in vitro*. *Biochem. Pharmacol.*, 1983, **32**, 2463–2466.
68. Zhao, Y., Hanton, W. K. and Lee, K-H., Antimalarial agents: Artesunate, an inhibitor of cytochrome oxidase activity in *plasmodium berghei*. *J. Nat. Prod.*, 1986, **49**, 139–142.
69. Thebtaranonth, C., Thebtaranonth, Y., Wanauppathamkul, S. and Yuthavong, Y., Antimalarial sesquiterpenes from tubers of *Cyperus rotundus*: structure of 10,12-peroxycalamenene, a sesquiterpene endoperoxide. *Phytochemistry*, 1995, **40**, 125–128.
70. Francois, G., Passreiter, C. M., Woerdenbag, H. J. and Looveren, M. V., Antimalarial activities and cytotoxic effects of aqueous extracts and sesquiterpene lactones from *Neurolaena lobata*. *Planta Med.*, 1996, **62**, 126–129.
71. Takaya, Y. *et al.*, Novel antimalarial guaiane-type sesquiterpenoids from *Nardostachys chinensis* roots. *Tehtrahedron Lett.*, 1998, **39**, 1361–1364.
72. Jenett-Siems, K. *et al.*, Sipandinolide: A butenolide including a novel type of carbon skeleton from *Siparuna andina*. *Planta Med.*, 2000, **66**, 384–385.
73. Bray, D. H., Warhurst, D. C., Connolly, J. D., O'Neill, M. J. and Phillipson, J. D., Plants as source of antimalarial drug. Pt.7 activity of some species of Meliaceae plants and their constituent limoids. *Phytother. Res.*, 1990, **4**, 29–35.
74. Bickii, J., Nijifutie, N., Foyere, J. A., Basco, L. K. and Ringwald, P., *In vitro* antimalarial activity of limonoids from *Khaya grandifoliola* C.D.C (Meliaceae). *J. Ethnopharmacol.*, 2000, **69**, 27–33.
75. Amusan, O. O. G., Adesogan, E. K. and Makinde, J. M., Antimalarial active principles of *Spathodea companulata* stem bark. *Phytother. Res.*, 1996, **10**, 692–693.
76. Bringmann, G., Saeb, W., Assi, L. A., Francois, G., Narayanan, A. S. S., Peters, K. and Peters, E-M., Betulinic acid: Isolation from *Triphyophyllum peltatum* and *Ancistrocladus heyneanus*, antimalarial activity, and crystal structure of the benzyl ester. *Planta Med.*, 1997, **63**, 255–257.
77. De Almeida Alves, T. M., Nagem, T. J., De Carvalho, L. H., Krettli, A. U. and Zani, C. L., Antiplasmodial triterpene from *Vernonia brasiliana*. *Planta Med.*, 1997, **63**, 554–555.
78. Figueiredo, J. N., Raz, B. and Sequin, U., Novel quinone methides from *Salacia kraussii* with *in vitro* antimalarial activity. *J. Nat. Prod.*, 1998, **61**, 718–723.
79. Joshi, S. P., Rojatkar, S. R. and Nagasampagi, B. A., Antimalarial activity of neem (*Azadirachta indica*). *J.M.A.P.S.*, 1998, **20**, 1000–1002.
80. Traore, F. *et al.*, Structure and antiprotozoal activity of triterpenoid saponins from *Glinus oppositifolius*. *Planta Med.*, 2000, **66**, 368–371.
81. Weenen, H., Nkunya, M. H. H., Bray, D. H., Mwasumbi, L. B., Kinabo, L. S., Kilimali, V. A. E. B. and Wijnberg, J. B. P. A., Antimalarial compounds containing an α,β-unsaturated carbonyl moiety from Tanzanian medicinal plants. *Planta Med.*, 1990, **56**, 371–373.
82. Valsaraj, R., *et al.*, New anti-HIV-1, antimalarial, and antifungal compounds from *Terminalia bellerica*. *J. Nat. Prod.*, 1997, **60**, 739–742.
83. Chanphen, R., Thebtaranonth, Y., Wanauppathamkul, S. and Yuthavong, Y., Antimalarial principles from *Artemisia indica*. *J. Nat. Prod.*, 1998, **61**, 1146–1147.
84. Likhitwitayawuid, K., Phadungcharoen, T. and Krungkrai, J., Antimalarial xanthones from *Garcinia cowa*. *Planta Med.*, 1998, **64**, 70–72.
85. Likhitwitayawuid, K., Chanmahasathien, W., Ruangrungsi, N. and Krungkrai, J., Xanthones with antimalarial activity from *Garcinia dulcis*. *Planta Med.*, 1998, **64**, 281–282.

86. Bringmann, G., Ochse, M., Zotz, G., Peters, K., Peters, E-M., Brun, R. and Schlauer, J., 6-Hydroxyluteolin-7-*O*-(1″-α-rhamnoside) from *Vriesea sanguinolenta* Cogn. and marchal (Bromeliaceae). *Phytochemistry*, 2000, **53**, 965–969.
87. Kraft, C., Jenett-Siems, K., Siems, K., Gupta, M. P., Bienzle, U. and Eich, E., Antiplasmodial activity of isoflavones from *Andira inermis*. *J. Ethanopharm*., 2000, **73**, 131–135.
88. Liu, K. C. C., Yang, S-L, Roberts, M. F., Elford, B. C. and Phillipson, J. D., Antimalarial activity of *Artemisia annua* flavonoids from whole plants and cell cultures. *Planta Cell Rep.*, 1992, **11**, 637–640.
89. Carvalho, L. H., Ferrari, W. M. S. and Krettli, A. U., A method for screening drugs against the liver stages of malaria using *Plasmodium gallinaceum* and *Aedes* mosquitoes. *Braz. J. Med. Biol. Res.*, 1992, **25**, 247–255.
90. Koumaglo, K., Gbeassor, M., Nikabu, O., De Souza, C. and Werner, W., Effects of three compounds extracted from *Morinda lucida* on *Plasmodium falciparum*. *Planta Med.*, 1992, **58**, 533–534.
91. Solis, P. N., Lang'at, C., Gupta, M. P., Kirby, G. C., Warhurst, D. C. and Phillipson, J. D., Bioactive compounds from *Psychotria camponutans*. *Planta Med.*, 1995, **61**, 62–65.
92. Perez, H., Diaz, F. and Medina, J. D., Chemical investigation and *in vitro* antimalarial activity of *Tabebuia ochracea* ssp. *Neochrysantha*. *Int. J. Pharmacognosy*, 1997, **35**, 227–231.
93. Likhitwitayawuid, K., Kaewamatawong, R., Ruangrungsi, N. and Krungkai, J., Antimalarial naphthoquinones from *Nepenthes thorelii*. *Planta Med.*, 1998, **64**, 237–241.
94. Decostered, L. A., Hoffmann, E., Kyburz, R., Bray, D. and Hostettmann, K., A new phloroglucinal derivative from *Hypericum calycimum* with antifungal and *in vitro* antimalarial activity. *Planta Med.*, 1991, **57**, 548–551.
95. Shibuya, H., Takeda, Y., Zhang, R., Tong, R-X. and Kitagawa, I., Indonesian medicinal plants. III. On the constituents of the bark of *Fagara rhetza* (Rutaceae). Alkaloids, phenylpropanoids, and acid amide. *Chem. Pharm. Bull.*, 1992, **40**, 2325–2330.
96. Achenbach, H., Waibel, R., Nkunya, M. H. H. and Weenen, H., Antimalarial compounds from *Hoslundia opposita*. *Phytochemistry*, 1992, **1992**, 3781–3784.
97. Kamchonwongpaisan, S. *et al.*, An antimalarial peroxide from *Amomum krervanh* Pierre. *Tetrahedron Lett.*, 1995, **36**, 1821–1824.
98. Joshi, S. P., Rojatkar, S. R. and Nagasampagi, B. A., Antimalarial activity of *Xanthium strumarium*. *J.M.A.P.S.*, 1997, **19**, 366–368.
99. Oketch-Rabah, H. A. and Dossaji, S. F., Antiprotozoal compounds from *Asparagus africanus*. *J. Nat. Prod.*, 1997, **60**, 1017–1022.
100. Oketch-Rabah, H.-A., Mwangi, J. W., Lisgarten, J. and Mberu, E. K., A new antiplasmodial coumarin from *Toddalia asiatica* roots. *Fitoterapia*, 2000, **71**, 636–640.
101. Yenjai, C., Sripontan, S., Sriprajun, P., Kittakoop, P., Jintasirikul, A., Tanticharoen, M. and Thebtaranonth, Y., Coumarins and carbazoles with antiplasmodial activity from *Clausena harmandiana*. *Planta Med*., 2000, **66**, 277–279.
102. Shen, X. *et al.*, Characterization of 6-*epi*-3-anhydroophiobolin B from *Cochliobolus heterostrophus*. *J. Nat. Prod*., 1999, **62**, 895–897.

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