



“A review study on alkaloids extraction from plants and their antimicrobial significant”

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Abstract

It is hoped that the reports of the review work will spur further research into the structural modification of the interesting compounds as novel antimalarial drugs. Malaria is one of the major health problems in developing countries. The disease kills a large number of people every year and also affects financial status of many countries. Resistance of the plasmodium parasite, the causative agent, to the existing drugs, including chloroquine, mefloquine, and artemisinin based combination therapy (ACT), is a serious global issue in malaria treatment and control. This warrants an urgent quest for novel compounds, particularly from natural sources such as medicinal plants. Alkaloids have over the years been recognized as important phytoconstituents with interesting biological properties. To possess antimalarial activity are presented. Several classes of alkaloids, including terpenoidal, indole, bisindole, quinolone, and isoquinoline alkaloids, were identified with a promising antimalarial activity.

Key words: artemisinin, malaria, antimalarial drug, chloroquine, mefloquine.

1. Introduction

Malaria is an extremely dangerous parasitic disease with ravaging effects in several parts of the world. The World Health Organization (WHO) estimate shows that approximately 3.3 billion people are living at risk places of malaria. Nearly 80% of cases and 90% of deaths are reported from sub-Saharan Africa and children under the age of 5 years and pregnant women are severely affected. In 2016, it was estimated that there were 216 million cases of malaria globally and 445,000 deaths due to malaria [3]. Five protozoan species of the genus *Plasmodium* (*Plasmodium falciparum*, *Plasmodium malariae*, *Plasmodium ovale*, *Plasmodium vivax*, and *P. knowlesi*) are responsible for human malaria, although the majority of malarial infections are caused by *P. falciparum* and *P. vivax*. While *P. vivax* is less dangerous but more widespread, *P. falciparum* is fatal and is predominant in Africa [1, 4]. Malaria has been treated with quinine, chloroquine, amodiaquine, mefloquine, and artemisinin derivatives (Figure 1), among other drugs. The alkaloidal drug, quinine, is the

first antimalarial drug isolated from Cinchona bark. The drug is still quite useful in the treatment of multidrug-resistant malaria. Chloroquine, a 4-aminoquinoline, was developed in the 1940s as a synthetic derivative from quinine. It was effective, cheap, and less toxic and was the drug of choice for malarial treatment for decades; however, its use has been restricted in modern malaria therapy due to parasite resistance to the drug [5, 6]. Mefloquine is structurally related to quinine and has been introduced to treat chloroquine-resistant malaria, though its use is limited because of resistance and neuropsychiatric side effects [7]. Artemisinin is a natural endoperoxide isolated from sweet worm wood plant *Artemisia annua*. Artemisinin and its semisynthetic analogs artemether, artether, and artesunate are potent antimalarial agents especially used in the regions where the resistance has developed to other antimalarial agents. The WHO recommends the use of artemisinin analogs in combination with other drugs (ACT) for the treatment of malaria in order to control resistance. Unfortunately, there have been reports of parasite resistance to the ACT [8].

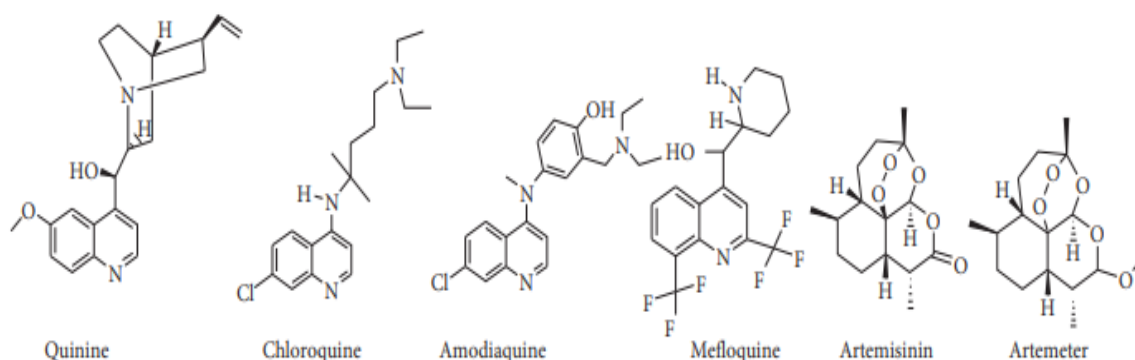


FIGURE 1: Structures of some antimalarial drugs.

Given the development of resistance of the malarial parasites against many of the current treatment regimens, there has been urgent quest to identify new antimalarial chemotherapeutic agents from natural sources, particularly medicinal plants, in order to possibly avoid problems related to drug resistance [9–14]. This is due to the widespread use of plant materials in the treatment of malaria in many traditional medical practices together with the fact that plants were the sources of the two prominent antimalarial lead compounds, quinine and artemisinin.

Several classes of phytoconstituents are responsible for the antimalarial activity of plants including alkaloids, terpenes, steroids, and flavonoids. Alkaloids are considered as an important group exhibiting diverse biological activities, particularly antimalarial activity. They constitute an important class of structurally diversified compounds that are having the nitrogen atom in the heterocyclic ring and are derived from the amino acids [15]. Large numbers of alkaloids have been isolated from different plant sources and reported for their potent antimalarial activity, some of which have been previously reviewed up till the year 2012 [1, 13, 16–20]. However, more updates on the current research on alkaloids as potential antimalarial agents are needed. In the present review work, alkaloids from medicinal plants with antimalarial property which are reported recently from 2013 to 2019 are summarized. They are discussed in subclasses of alkaloids and the chemical structures of the newly reported compounds and those with antiplasmodial activity are shown in the figures according to their subclasses.

Terpenoidal and Steroidal Alkaloids.

Several alkaloids having varying terpenoidal backbone, including the cassane-type diterpenes, indoloterpene, and bisindolomonoterpenic alkaloids, have been isolated recently from medicinal plants (*Caesalpinia minax*, *Polyalthia oliveri*, and *Strychnos nux-vomica*) and shown to possess good antiplasmodial activity. Ma et al. [21] isolated two new diterpene alkaloids, caesalminines A (**1**) and B (**2**), possessing a tetracyclic cassane-type diterpenoid skeleton with *c*-lactam ring from the seeds of *Caesalpinia minax* (Fabaceae). Compounds **1** and **2** exhibit antiplasmodial activity with IC₅₀ values of 0.42 and 0.79 μM, respectively. Substitution of the amino hydrogen of the diterpenoid (in compound **1**) with the alcoholic group (C₂H₅OH) produced a compound (**2**) with slightly reduced antiplasmodial activity. In another study, three new indolosesquiterpene alkaloids, 8α-polyveolinone (**3**), *N*-acetyl-8α-polyveolinone (**4**), and *N*-acetyl-polyveoline (**5**), together with three known compounds, were isolated from the stem bark of *Polyalthia oliveri* (Annonaceae) by Kouam et al. [22]. Compounds **4** and **5** exhibit moderate antiplasmodial activity against *P. falciparum* NF54 strain with low cytotoxicity on L6 myoblast (L6) cell line. In a related study of another plant in the same family, three bisindolomonoterpenic alkaloids, together with the known compound, strychnochrysin (**6**), were isolated from the stem bark of *Strychnos nux-vomica* L. (Loganiaceae). These longicaudatine-type alkaloids display antiplasmodial activity against both the chloroquine-resistant and chloroquine-sensitive strains. The most interesting was compound **6** with an IC₅₀ value at around 10 μM [23]. Muganza et al. [24] reported the isolation of two known indolosesquiterpene alkaloids, polyalthenol (**7**) and *N*-acetyl-polyveoline (**5**), from various parts of the tree *Greenwayodendron suaveolens* (Engl. & Diels) Verdc. (syn. *Polyalthia suaveolens* Engl. & Diels) (Annonaceae). The highest selectivity was observed for compound **5** against *P. falciparum* K1 (IC₅₀ 2.8 μM, selectivity index 10.9).

Alkaloids having steroidal nucleus have also been isolated and shown to possess antimalarial activity. Dua et al. [25] investigated the *in vitro* antimalarial and cytotoxic effects of the known compound, conessin (**8**), which was isolated from the plant *Holarrhena antidysenterica*. The four-day *in vivo* test was also used to test for the antimalarial activity against a chloroquine-sensitive *P. berghei* NK65 strain in BALB/c mice. Compound (**8**) shows *in vitro* antiplasmodial activity with its IC₅₀ values of 1.9 μg/ml and 1.3 μg/ml in the schizont maturation and pLDH assays, respectively, and cytotoxicity IC₅₀ of 14 μg/ml. The compound also significantly reduces parasitaemia (88.95% parasite inhibition) in *P. berghei*-infected mice. In addition, the phytochemical investigation of an alkaloidal extract of the related plant *Holarrhena pubescens* roots led to the isolation of a new pregnene-type alkaloid, mokluangin D (**9**), together with nine known steroidal alkaloids. Two of the known compounds, irehline (**10**) and mokluangin A (**11**), show most potent antimalarial activity against *P. falciparum* K1 strain (a multidrug-resistant strain) with IC₅₀ values of 2.0 μM, respectively, and weak cytotoxic activity (27.7 and 30.6 μM, respectively) against the NCI-H187 cell line. Five other compounds show moderate activity. Compound **9** was not tested. A study of the structure activity relationships in these compounds (illustrated with compound **11**) indicates that the C-3 amino group, the nature of the E ring, and the carbonyl group at C-18 are important for the activity against the *P. falciparum* K1 strain [26]. Furthermore, Pan et al. [27] reported the isolation of a known buxus alkaloid, *N*-3-benzoyldihydrocyclomicrophylline F (**12**), together with other compounds from *Buxus cochinchinensis*

Pierre ex Gagnep. (Buxaceae). The buxus alkaloid (**12**) was found to show significant *in vitro* antimalarial activity against the drug-resistant Dd2 strain of *P. falciparum* with IC₅₀ value of 2.07 μ M (cytotoxicity against HT-29 human carcinoma is 1.9 μ M and against NF-KB is >20).

Indole Alkaloids. A number of indole alkaloids (Figure 3) have been isolated recently and shown to possess potent antiplasmodial activity. Chemical investigation of *Alstonia macrophylla* bark led to the isolation of two new nitrogenous derivatives, alstoniaphyllines A (**13**) and B (**14**), a new indole alkaloid, alstoniaphylline C (**15**), and eight known alkaloids including alstonisine (**16**). Compound **16** exhibits antiplasmodial activity against *P. falciparum*, with an IC₅₀ value of 7.6 μ M [28]. Another new indole alkaloid, 12-hydroxy-*N*-acetyl-21(*N*)-dehydroplumeran-18-oic acid (**17**), and 11 known indole alkaloids including 20-*epi*-dasycarpidone (**18**) were isolated from *Aspidosperma ulei* Markgr. (Apocynaceae). Only compound **18** is active against multidrug-resistant K1 strain of *P. falciparum* with IC₅₀ value of 16.7 μ M. None of these compounds exhibited toxicity to fibroblasts (IC₅₀ > 50 μ g/mL) [29]. Also, Tchinda et al. [30] reported the isolation of a new bisindole alkaloid, strychnobaillonine (**19**), with original C-17-N-1' and C-23-C-17' junctions, in addition to three other known compounds from the roots of *Strychnos icaja*. Compound **19** shows potent activity against the chloroquine-sensitive 3D7 strain of *P. falciparum* with an IC₅₀ value of 1.1 μ M. More recently, two new sarpagine-type indole alkaloids together with five known alkaloids, including 16-demethoxycarbonylvoacamine (**20**), were isolated from the bark of *Tabernaemontana macrocarpa* Jack. Compound **20** shows antiplasmodial activity against *P. falciparum* 3D7 and cytotoxic activity against human cell line, HepG2 cells [31].

Phenanthroindolizine Alkaloids. The structures of some phenanthroindolizine alkaloids with promising antiplasmodial activity are shown in Figure 3. Kubo et al. [32] isolated a new seco-phenanthroindolizine alkaloid, 4a,b-*seco*-dehydroantofine (**21**), and three known phenanthroindolizine alkaloids, dehydrotylophorine (**22**), dehydroantofine (**23**), and tylophoridine D (**24**), from the twigs of *Ficus septica*. While compound **21** exhibits a moderate antimalarial activity against the 3D7 strain of *P. falciparum* with IC₅₀ value 4.0 μ M, the known alkaloids (**22–24**) display strong activity with IC₅₀ values of 0.42, 0.028, and 0.058 μ M, respectively. The cytotoxicities of the compounds (**21–24**) against mouse fibroblast cells L929 are >56 (SI \geq 14), 8.2 (SI \geq 19.5), >55 (SI \geq 1964), and >56 μ M (SI \geq 966), respectively. Compounds **23** and **24** (particularly **23**) exhibit the highest selectivity against the malaria parasite. From the structure activity relationship, opening of ring A (present in compound **21**) possibly reduces antiplasmodial activity, while the four methoxy substituents at rings D and E (present in compound **23**) could be essential for activity.

Alkaloids.

Isoquinoline and related alkaloids with antiplasmodial activity have also been isolated. Fadaeinasab et al. [33] isolated seven isoquinoline alkaloids from the bark of *Actinodaphne macrophylla*. They display *in vitro* antiplasmodial activity against *P. falciparum* 3D7 with IC₅₀ values ranging from 0.05 to 3.11 μ M for cycleanine (**25**), 10-demethylxylopinine (**26**), reticuline (**27**), laurotetanine (**28**), bicuculine (**29**), α -hydrastine (**30**), and anolobine (**31**), respectively. Compound **26** was found to be the most active. Possibly, the fusion of the two isoquinoline rings (in compound **26**) enhances antiplasmodial activity. In another study, compound **35** was not tested. The *N,N*-dimethyl groups of the ethylamine side chain (in compounds **33** and **34**) are,

perhaps, essential for antiplasmodial activity. Malebo et al. [35] also isolated four pure alkaloids including palmatine (**36**) and mixtures of alkaloids from the leaves of *Annickia kummeriae*. The alkaloids exhibit low cytotoxicity (IC_{50} 30–90 $\mu\text{g/ml}$) and strong-to-moderate anti-plasmodial activity (IC_{50} 0.08 ± 0.001 – 2.4 ± 0.642 $\mu\text{g/ml}$, SI 1.5–1154). Compound **36** exhibits the highest activity against *P. falciparum* K1 (IC_{50} 0.080 ± 0.001 $\mu\text{g/ml}$, selectivity index (SI) 1154). Further, three known compounds, dihydronitidine (**37**), pellitorine (**38**), and heitzi-quinone (**39**), with antiparasitic activity were identified in *Zanthoxylum heitzii* (Rutaceae) bark extract. Compound **37** is the most active compound with an IC_{50} value of 0.0089 $\mu\text{g/ml}$ (25 nM), though it is slower in action, while compounds **38** and **39** are less potent, with IC_{50} values of 9.7 ± 1.6 μM and 8.8 ± 0.5 μM , but they are fast-acting [36].

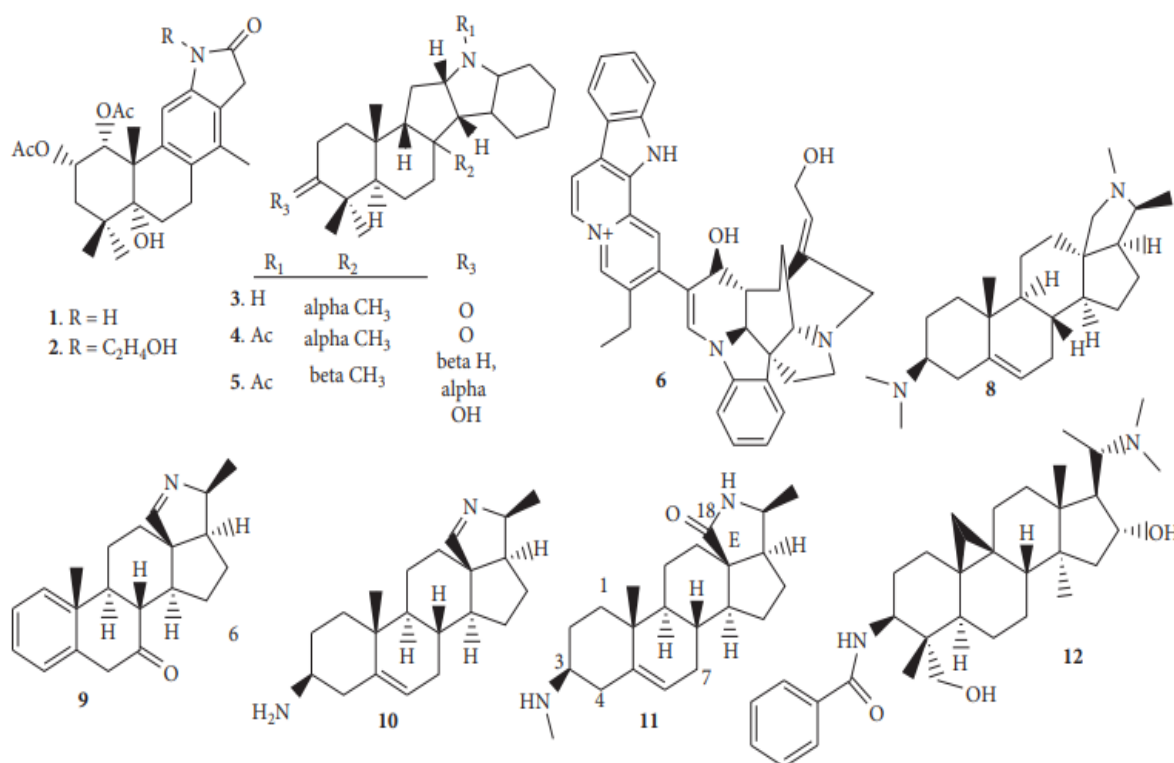


FIGURE 2: Structures of terpenoidal and steroidal alkaloids.

Naphthoisoquinoline Alkaloids. Naphthoisoquinoline alkaloids have also been reported recently, many of which are dimeric. Naphthoisoquinoline alkaloids are usually characterized by the C5/C8' linkage between the naphthalene and the isoquinoline portions of these alkaloids. Dionicophyllaceous alkaloids possess naphthoisoquinoline nucleus. Dioncophylline F (**45**), the first 5,8'-coupled dionicophyllaceous alkaloid (i.e., lacking an oxygen function at C-6 and possessing an *R*-configuration at C-3), was isolated from Congolese liana *Ancistrocladus ileboensis* with some other alkaloids. The alkaloids show high and specific activities against *P. falciparum* [39]. In addition, dimeric naphthoisoquinoline alkaloids were reported from the *Ancistrocladus* species. Mbandakamines A (**46**) and B (**47**) were isolated from the leaves of a Congolese *Ancistrocladus* species as the first dimeric naphthylisoquinoline alkaloids with an unsymmetrically coupled central biaryl axis (Figure 6). Mbandakamine A (**46**) exhibits good antimalarial activity [40].

In a related study on the root bark of the same plant, *Ancistrocladus* species from the Democratic Republic of Congo, a new dimeric naphthylisoquinoline alkaloid, jozimine A2 (**48**), was isolated. Compound **48** is one

of the as yet very rare naphthylisoquinoline dimers whose central biaryl axis is rotationally hindered. Moreover, it is the first natural dimer of a dioncophyllaceae-type alkaloid that is lacking oxygen functions at C6 and bearing *R* configurations at C3 initiates two isoquinoline portions. The new dimer (**48**) exhibits excellent, and specific, antiplasmodial activity [41].

Aporphine and Morphinandienone Alkaloids. Chemically, aporphine alkaloids possess a tetracyclic framework. They incorporate a tetrahydroisoquinoline substructure and belong to the isoquinoline class of alkaloids. Several aporphine alkaloids possessing antimalarial activity have been isolated recently (Figure 7).

A new aporphine alkaloid named vireakine (**49**) along with two known alkaloids, stephanine (**50**) and pseudo-palmatine (**51**), described for the first time in *Stephania rotunda*, together with five known alkaloids, was isolated and identified. The compounds were evaluated for their *in vitro* antiplasmodial and cytotoxic activities. All tested compounds show significant antiplasmodial activity with IC_{50} values ranging from 1.2 to 52.3 μM with a good selectivity index for compound **51** with IC_{50} value of 2.8 μM against W2 strain of *P. falciparum* and with $IC_{50} > 25 \mu\text{M}$ on K562S cells [42]. Further, from the twigs of *Dasymaschalon obtusipetalum*, one new p-quinonoid aporphine alkaloid, obtusipetadione (**52**), and eleven known compounds were isolated. Compound **52** shows significant *in vitro* antiplasmodial activity against the *P. falciparum* strains TM4 and K1 (multidrug-resistant strain) with IC_{50} values of 2.46 ± 0.12 and $1.38 \pm 0.99 \mu\text{g/mL}$, respectively, with no cytotoxicity [43]. In another report, six alkaloids were isolated from the bark of *Dehaasia longipedicellata*. All the compounds display potent-to-moderate activity against the growth of *P. falciparum* K1 isolate (resistant strain) with IC_{50} values ranging from 0.031 to 30.40 μM . Two of the compounds, a bisbenzylisoquinoline, (-)-*O, O'*-dimethyl-grisabine (**53**), and a morphinandienone, (-)-milonine (**54**), were the most potent compounds, with IC_{50} values of 0.031 and 0.097 μM , respectively, which are comparable to the standard, chloroquine (0.090 μM). All of the compounds showed no potency against lung (A549) cancer cells and weak cytotoxicity against skin (A375) cancer cells [44].

Also, one new aporphine named tavoyanine A (**56**), along with four known aporphines, three of which are roemerine (**57**), laurolicsine (**58**), and boldine (**59**), and one morphinandienone type, sebiferine (**60**), were isolated from the leaves of *Phoebe tavoyana* (Meissn.) Hook f. (Lauraceae). Compounds **56–60** were found to exhibit potent inhibitory activity against the growth of *P. falciparum* 3D7 clone, with IC_{50} values of 0.89, 1.49, 1.65, and 2.76 $\mu\text{g/ml}$, respectively [46]. Compound **60** was previously isolated from *Dehaasia longipedicellata* but was found to have moderate activity against *P. falciparum* KI isolate (resistant strain) with IC_{50} value of 22.46 μM [44].

Protoberberine Alkaloids.

This class of compounds is mainly found in the plants of the Papaveraceae family. The alkaloids are characterized by a tetracyclic ring system that “hides” a substituted phenethylamine or vanillylamine, depending on the viewing “angle”.

Wangchuk et al. [47] carried out phytochemical studies of the aerial parts of *Meconopsis simplicifolia* (Don) Walpers (Papaveraceae), resulting in the isolation of one new protoberberine-type alkaloid, simplicifolianine (**61**), and five known alkaloids. Compound **61** displays the most potent antiplasmodial

activity against the *P. falciparum* strains, TM4/8.2 (chloroquine-antifolate-sensitive strain) and K1CB1 (multidrug-resistant strain) with IC_{50} values of

0.78 $\mu\text{g/mL}$ and 1.29 $\mu\text{g/mL}$, respectively. The compounds did not show any significant cytotoxic activity against carcinoma KB cells and normal Vero cells. In another study, coptisine (**62**), an alkaloid from *Coptidis rhizoma* (Ranunculaceae), was found to be a novel and potent inhibitor of *Plasmodium falciparum* dihydroorotate dehydrogenase (PfDHODH) with an IC_{50} value of $1.83 \pm 0.08 \mu\text{M}$ [48].

Compound **63** exhibits *in vitro* anti-malarial activity against the TM4 strain, with an IC_{50} value of $19.3 \pm 3.4 \mu\text{M}$, while compound **64** demonstrates significant activity against the K1 strain, with an IC_{50} value of $10.8 \pm 4.1 \mu\text{M}$. Both compounds show no discernible cytotoxicity to the Vero cell line at the concentration levels evaluated. In another study, a bioassay-guided fractionation of the tubers of *Stephania venosa* (Blume) Spreng (Menispermaceae) led to the isolation of four aporphine and one tetrahydroprotoberberine alkaloids including stephanine (**50**), which was observed to be the most active anti-plasmodial compound but is also the most cytotoxic with the lowest selectivity index [50]. Compound **50** was previously reported in *Stephania rotunda* with significant anti-plasmodial activity [42].

Amaryllidaceae Alkaloids

A particular characteristic of the family of Amaryllidaceae is a consistent presence of an exclusive group of alkaloids, which have been isolated from the plants of all the genera of this family. The Amaryllidaceae alkaloids represent a large and still expanding group of isoquinoline alkaloids, the majority of which are not known to occur in any other family of plants.

Phytochemical investigation of the bulbs of *Lycoris radiata* (Fam: Amaryllidaceae) resulted in the isolation of five new Amaryllidaceae alkaloids: (+)-5,6-dehydrolycorine (**68**), (+)-3 α ,6 β -diacetylbulbispermine (+)-3 α -hydroxy-6 β -acetylbulbispermine (+)-8,9-methyl-N-oxide (**71**), and 5,6-dihydro-5-methyl-2-hydroxyphenanthridine (**72**), together with two known compounds. Compound **68** exhibits antimalarial activity with IC_{50} values of 2.3 μM for D6 strain and 1.9 μM for W2 strain of *P. falciparum*. Compound **68** also shows potent cytotoxicity against astrocytoma and glioma cell lines (CCF-STTG1, CHG-5, SHG-44, and U251), as well as HL-60, SMMC-7721, and W480 cell lines with IC_{50} values of 9.4–11.6 μM [51]. Also, antimalarial bioassay-guided fractionation of the swamp lily *Crinum erubescens* (Amaryllidaceae) led to the isolation of four compounds with potent antiplasmodial activity. They include three known compounds, cripowellin A (**73**), cripowellin B (**74**), and hippadine (**75**), as well as the new compounds cripowellin C (**76**) and D (**77**). The antiplasmodial activities (IC_{50} values) of compounds **73**, **74**, **76**, and **77** were determined to be 30 ± 2 , 180 ± 20 , 26 ± 2 , and $260 \pm 20 \text{ nM}$, respectively, while compound **75** is inactive. Their antiproliferative IC_{50} values against the A2780 human ovarian cancer cell line were 11.1 ± 0.4 , 16.4 ± 0.1 , 25 ± 2 , and $28 \pm 1 \text{ nM}$, respectively. Presence of OH group in the cripowellin backbone (indicated by R in the structures of **73** and **74** or **76** and **77**) seems to enhance antiplasmodial activity [52].

Crinane alkaloids were also isolated from the Amaryllidaceae family. A chemical investigation of *Amaryllis belladonna* Steud. (Amaryllidaceae) bulbs resulted in the isolation of the new crinane alkaloid 1,4-dihydroxy-3-methoxy powellan (**78**), along with the three known crinane alkaloids, distichamine (**79**), 11-O-acetylambelline (**80**), and ambelline (**81**), as well as the two lycorane alkaloids, acetylcaranine (**82**)

and hippadine (**75**). Compound **82** shows the most potent inhibitory activity, with an IC_{50} value of $3.3 \pm 0.3 \mu M$, but compound **75** is inactive despite its structural similarity. Slight structural differences of conjugation and substituents in the tetrahydrophenanthridine moiety seem to greatly affect the inhibitory activity. The crinane-type alkaloid (**80**) exhibits weak inhibitory activity (IC_{50} , $35 \pm 1 \mu M$), whereas **81** shows stronger activity with an IC_{50} value of $7.3 \pm 0.3 \mu M$. The difference in the antiplasmodial activity of these two compounds could be explained by the placement of oxy-substitution at C-11, since acetylation of the oxygenated C-11 of the ethanol bridge slightly decreased the inhibitory activity. The new crinane-type alkaloid **78** showed weak inhibitory activity (IC_{50} , $37 \pm 3 \mu M$). Compound **79** has little inhibitory activity, despite its similarity to **80** and **81**. Only compound **82** shows inhibitory, though very weak, effect against A2780 ovarian cells with an IC_{50} value of $56 \pm 1 \mu M$ [53]. In a recent study, lycorine (**83**), along with 14 other alkaloids, was isolated from *Worsleya procera* roots. The compound (**83**) exhibits antiplasmodial activity against both sensitive (3D7) and resistant (K1) *P. falciparum* parasite strains with IC_{50} values of 2.5 and $3.1 \mu M$, respectively, and a low cytotoxic profile against human hepatocarcinoma cells (HepG2), with a selectivity index greater than 100 [54].

Four cyclopeptide alkaloids were isolated from the root bark of *Hymenocardia acida*. These include hymenocardinol (**84**) as well as hymenocardine *N*-oxide (**85**) and a new cyclopeptide alkaloid containing an unusual histidine moiety named hymenocardine-H (**86**). All the compounds show moderate antiplasmodial activity, with IC_{50} values ranging from 12.2 to $27.9 \mu M$, the most active one being compound **85**, with an IC_{50} value of $12.2 \pm 6.6 \mu M$. Compounds **84–86** were found not to be cytotoxic against MRC-5 cells ($IC_{50} > 64.0 \mu M$) [56]. In addition, nine cyclopeptide alkaloids were isolated from the roots of *Ziziphus oxyphylla*.

Quinoline Alkaloids.

Chemical investigation of the roots of the Australian desert plant *Eremophila microtheca* yielded a novel quinoline-serrula alkaloid, microthecaline A (**88**), which displays moderate antimalarial activity against *P. falciparum* (3D7 strain), with an IC_{50} value of $7.7 \mu M$ [58]. In another study, seven known furoquinoline alkaloids and two known methoxyflavones were isolated from *Melicope madagascariensis* (Rutaceae). One of the compounds, 6-methoxy-7-hydroxydictamnine (heliparvifoline) (**89**), exhibits weak antimalarial activity (IC_{50} $35 \mu M$) against the chloroquine-resistant strain Dd2 of *P. falciparum*.

Pyridocoumarin Alkaloids.

Chemical investigation of the aerial parts of *Goniothalamus australis* resulted in the isolation of two pyridocoumarin alkaloids, goniothalines A (**90**) and B (**91**), as well as eight known natural products, including sauristolactam (**92**), an aristolactam alkaloid, as well as (-)-anonaine (**55**). Compounds **92** and **55** are active against a chloroquine-sensitive *P. falciparum* line (3D7) with IC_{50} values of 9.0 and $7.0 \mu M$, respectively. The novel natural products (**90** and **91**) display no *in vitro* antiparasitic activity at $50 \mu M$. Data from the study suggested that 3-methoxy substituent moderately reduces biological function. Also methylation of the nitrogen and demethoxylation at C-8 in the aristolactam skeleton (compound **92**) are important for *P. falciparum* growth inhibition.

Acridone Alkaloids.

The root bark of *Zanthoxylum simullans* Hance afforded five known acridone alkaloids, together with other

compounds. Their antimalarial activity was tested against two different strains of the parasite *P. falciparum*, 3D7 and Dd2. Normelicopidine (**93**) is the most active against Dd2 with IC₅₀ value of 18.9 µg/mL.

Macrocyclic Alkaloids.

The macrocyclic dilactone alkaloid, carpaine (**94**), was isolated from *Carica papaya* L. leaf. The compound (**94**) was screened against *Plasmodium falciparum* 3D7 and Dd2 strains. The cytotoxicity was evaluated against NL20 cells. The compound exhibits good activity against both strains of *P. falciparum*, 3D7 and Dd2, with IC₅₀ values of 4.21 µM and 4.57 µM, respectively, and high selectivity for the parasite and was nontoxic to healthy uninfected human red blood cells [62]. The effects of **94** may be related to its macrocyclic dilactone structure, a possible cation chelating structure.

Conclusion

In the present review, they belong to a great structural diversity including terpenoids, steroid, indole, phenanthroindolizine, isoquinoline, benzyloisoquinoline, hasubanane, naphthoisoquinoline, aporphine, morphinandienone, protoberberine, Amygdalaceae, cyclopeptide, quinoline, pyridocoumarin, acridone, and macrocyclic alkaloids. Many of the compounds with interesting antimalarial property were reported for the first time within this period and they present an array of potential lead compounds towards development of novel antimalarial drugs. Their antiplasmodial and cytotoxicity data were presented. Structure activity relationships were discussed where possible.

Particularly, the most interesting of the newly isolated compounds include the cassane-type diterpene alkaloids, caesalminines A (**1**) and caesalminines B (**2**), and the bisindole alkaloid, strychnobailonine (**19**). Some other known compounds, including the isoquinolines, cycleanine (**25**), and 10-demethylxylopinine (**26**), were also reported to show strong antimalarial property with low IC₅₀ values. However, some of the compounds have relatively high cytotoxicity profile, while some have not been investigated for their toxicity profile. Another observation is that majority of the study of the antimalarial activity has been based on *in vitro* studies, while *in vivo* studies are quite rare.

The identified alkaloids with promising antimalarial activity should serve as lead compounds for drug design to obtain compounds with improved efficacy and lower toxicity. They should also be subjected to toxicity and *in vivo* efficacy studies. Additionally, the mode of action of the promising compounds should be explored. It is hoped that the outcome of the present review will spur further research into the structural modification and/or development of the promising compounds as novel antimalarial drugs.

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