**Antiplasmodial natural products: an update**

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**Abstract**  

**Background:** Malaria remains a significant public health challenge in regions of the world where it is endemic. An unprecedented decline in malaria incidences was recorded during the last decade due to the availability of effective control interventions, such as the deployment of artemisinin-based combination therapy and insecticide-treated nets. However, according to the World Health Organization, malaria is staging a comeback, in part due to the development of drug resistance. Therefore, there is an urgent need to discover new anti-malarial drugs. This article reviews the literature on natural products with antimalarial activity that was reported between 2010 and 2017.

**Methods:** Relevant literature was sourced by searching the major scientific databases, including Web of Science, ScienceDirect, Scopus, SciFinder, Pubmed, and Google Scholar, using appropriate keyword combinations.

**Results and Discussion:** A total of 1524 compounds from 397 relevant references, assayed against at least one strain of *Plasmodium*, were reported in the period under review. Out of these, 39% were described as new natural products, and 29% of the compounds had IC_{50} ≤ 3.0 µM against at least one strain of *Plasmodium*. Several of these compounds have the potential to be developed into viable anti-malarial drugs. Also, some of these compounds could play a role in malaria eradication by targeting gametocytes. However, the research into natural products with potential for blocking the transmission of malaria is still in its infancy stage and needs to be vigorously pursued.

**Keywords:** Malaria, *Plasmodium*, Antiplasmodial, Natural products, Plant metabolites, Marine natural products

**Background**  
Malaria remains a serious parasitic disease in the world, with 219 million infections and 435,000 deaths cited for 2017 in the latest World Malaria Report [1]. An assessment of older and more recent malaria maps shows that the disease has been geographically restricted during the twentieth century, and has remained endemic in the poor regions of the world where the climate is suitable for transmission [2–5]. In Africa, where the disease burden is the highest, there has been a general decline in the trend of *Plasmodium falciparum* malaria, from a prevalence of 40% in 1910–1929 to about 24% in 2010–2015 [6]. However, in the high transmission belt covering large parts of West and Central Africa, there is little change. This shrinkage of the malaria map has been interrupted by periods of rapid increase and decline in transmission [6]. The significant decline in malaria prevalence between 1945 and 1949 and again between 2005 and 2009 correlates with deliberate intervention programs. Each of these declines was preceded by a rise in malaria prevalence. The introduction of chloroquine (1) (Fig. 1) and dichlorodiphenyltrichloroethane (DDT) in 1945 and widespread use of insecticide-treated bed nets and artemisinin-based combination therapy (ACT) between 2005 and 2009 are partly credited for these declines. The rapid spread of resistance to chloroquine and emerging resistance to ACT in Africa, coupled with an increase in cases of vector-borne diseases in places like the USA, poses a threat to the gains that have been achieved in malaria control [6–9]. A World Health Organization (WHO) malaria report already shows a rise in malaria incidences in 2016 compared to 2015 [1]. Also, the sustained decline in mortality due to malaria since 2010 has stalled in some regions between 2015 and 2016 and has increased in other regions [1]. Therefore, the continued search for new anti-malarial agents remains an urgent priority.

Malaria chemotherapy has a strong historical link to natural products. The most successful anti-malarial...
agents have their origins in plant metabolites. The first successful anti-malarial drug was quinine (2), isolated from the bark of the South American *Cinchona* tree. This compound served as a lead structure in the development of the successful synthetic anti-malarial chloroquine (1), which, in recent years, has fallen out of favour as a result of the development of drug resistance by the parasite. Likewise, artemisinin (3) was isolated from the leaves of a Chinese medicinal plant, *Artemisia annua*. *Cinchona* bark and *Artemisia annua* were historically used to treat fever. Sophisticated target identification strategies following the sequencing of the *P. falciparum* genome in addition to the application of combinatorial chemistry hit identification strategies, did not lead to the expected increase in the number of new successful anti-malarial agents, and it is plausible that the next anti-malarial agents will be identified from a natural source again [10]. Due to structural characteristics such as multiple stereocenters, flexible conformations, presence of heteroatoms, natural products are more likely than synthetic compounds to have multiple targets and/or new targets. Researchers investigating natural products as potential anti-malarial drugs need to incorporate the screening of the compounds for the interaction with newly identified druggable targets, such as PfATP4 and DHODH, in order to identify hits/leads. Therefore, the continued exploration of natural products as antiplasmodial agents is of great scientific interest. Equally important is the need to review the literature in the field of malaria chemotherapy to provide a perspective for future research.

Plant-derived antiplasmodial compounds organized according to plant families covering the literature from 1990 to 2000 have been reviewed [11]. Similarly, reviews categorizing antiplasmodial compounds isolated from plants according to phytochemical classes have been conducted by Bero et al. (2005–2011) [12, 13], Nogueira and Lopes (2009–2010) [14], and Wright (2000–2010) [15]. Finally, reviews covering antiplasmodial marine natural products up to 2009 have been published by Laurent and Pietra, and Fattorusso and Tagliatela-Scafati [16, 17]. However, several new antiplasmodial chemotypes have been reported in the literature since 2010, in addition to the recent increase in antiplasmodial chemical scaffolds emerging from non-vegetal sources. Against this background, this article reviews the literature on natural products with antiplasmodial activity from 2010 to the end of 2017 and is organized according to structural types of compounds.

A thorough search of the relevant scientific databases, including Web of Science, ScienceDirect, Scopus, SciFinder, Pubmed, and Google Scholar, was conducted. The keyword combinations of antiplasmodial, anti-malarial, *Plasmodium*, and malaria compounds together with plant, phytochemical, marine sponge, nudibranch, alga, cyanobacteria, mushroom, fungi, and *Streptomyces* were used in the search. Within the period under review, a total of 1524 compounds from 397 relevant references, assayed against at least one strain of *Plasmodium*, were reported. Of these compounds, 593 (39%) were described as new natural products. The number of compounds isolated from vegetal material was 1165 (76%), while 359 were from non-plant sources. Among the compounds isolated from non-plant sources, 192 (53%) were described as new, while 401 (34%) of the compounds isolated from plants were new. These numbers show that medicinal plants are still the most comprehensively explored source for antiplasmodial compounds, which may be related to ease of access. However, this review also shows the potential of non-plant material to furnish new chemotypes. Regarding the potency of these compounds, 857 (56%) had IC\(_{50}\) \(\leq\) 10 \(\mu\)M, 625 (41%) had IC\(_{50}\) \(\leq\) 5.0 \(\mu\)M, and 447 (29%) had IC\(_{50}\) \(\leq\) 3.0 \(\mu\)M against at least one strain of *Plasmodium*. The cut-off value for potency remains an issue of ongoing debate, but the industry standard for considering a pure compound to be active is generally accepted as IC\(_{50}\) \(\leq\) 10 \(\mu\)M [18].

The in vitro antiplasmodial activities described in this review were obtained with various *P. falciparum* strains with different drug sensitivities. The chloroquine-sensitive strains were 3D7, NF54, D6, HB3, F32, D10, TM4/8.2, and MRC-pf-20. Other strains used were the chloroquine-resistant strains Dd2, FcB1, PfND0, FcM29, MRC-pf-303, and the multidrug-resistant K1, TM90-C2A, TM93-C1088, W2, TM90-C2B, TM91-C235, NHP1337, FCR3, K1CB1, and W2mef strains. Different assays were used to determine the in vitro antiplasmodial activities of the compounds. The most commonly cited methods were the radioactive hypoxanthine-incorporation assay, the colourimetric
enzyme-linked immunosorbent assays (ELISA) that measure *P. falciparum* lactate dehydrogenase protein (pLDH) and histidine-rich protein 2 (HRP2), a DNA-based fluorometric method using the PicoGreen (SYBR) assay, and microscopy. These methods have different sensitivities and the advantages and disadvantages have been investigated and reviewed [19–21]. Regardless of the in vitro assay method, in this review, only compounds with IC50 \( \leq 3.0 \) µM were considered to be of interest for further studies. Compounds with higher IC50 values are listed in Additional file 1. Among the compounds that are discussed, 317 (70.9%) were isolated from 50 different plant families, while 130 were from non-plant sources comprising of different species of marine sponges, alga, fungi, ascidians, nudibranch, cyanobacteria and actinobacteria (Fig. 2).

The antiplasmodial natural products are organized in seven classes, i.e. endoperoxides, alkaloids, terpenes, polyphenols, quinones and polyketides, macrocycles, and cyclic phosphotriesters, with subclasses where applicable. The review concludes with a summary of the cellular targets in *Plasmodium* identified for natural products and natural products with transmission-blocking potential.

**Endoperoxides**

The profound success of artemisinin (3) and derivatives as drugs for the treatment of malaria prompted the selection of endoperoxides as the first class of compounds to be discussed in this review. Endoperoxide polyketides (Fig. 3) belonging to the 1,2-dioxane and 1,2-dioxolane structural class with proven antiplasmodial activity have been isolated from marine sponges. The structural variability includes different lengths of the ‘western’ side chain, different branching patterns, and a fully saturated or monounsaturated cyclohexane ring, all of which affect the bioactivity [22]. Plakortin (4), isolated from the marine sponge *Plakortis simplex*, is the archetype compound of this class. It demonstrated potent submicromolar antiplasmodial activity against chloroquine-sensitive and -resistant parasites [23, 24]. A plausible mechanism of action, inspired by results obtained with artemisinin and other trioxanes, was proposed for these structurally simpler molecules. It involves an initial reaction of the peroxidic bond with Fe(II) heme to form an O-centred radical, which is transformed into a C-centred radical following intramolecular rearrangement. The rearranged C-centred radical on the ‘western’ alkyl side-chain represents the toxic species that kills parasites. The minimum structural requirements for antiplasmodial activity of this class of compounds have been identified. The oxygen atoms of the endoperoxide bond must be accessible to Fe(II), and the molecule must adopt the appropriate conformation for the intramolecular rearrangement through a concerted intramolecular electron transfer [25]. The lower antiplasmodial activity of the per oxyketal derivative manadoperoxide C (5) and its analogues isolated from Indonesian-sourced *Plakortis cfr. simplex* was rationalized on the basis of these structural requirements. The 6-methoxy substituent of the manadoperoxides constitutes a hindrance for Fe(II) to the peroxide bond, leading to lower activity [23]. The isolation of endoperoxide analogues 6–8 with a 1,2-diox-4-ene ring from *Plakortis simplex* allowed an extension of the structure-activity
relationship (SAR). For structurally similar compounds, the unsaturated derivatives were more active due to stereochemical influence, although they were still less active than 4. The lower activity compared to 4 could also be explained by the relative inaccessibility of the peroxide oxygen due to steric hindrance [22]. These results indicate that structural changes affecting the conformational behaviour of this class of compounds, profoundly influence the antiparasitic activity, and this knowledge will be beneficial for the design of more active analogues [23].

Alkaloids
Among the 447 isolated natural products with IC$_{50} \leq 3.0$ μM reported in this review, 31.9% are alkaloids.

Naphthylisoquinolines
The naphthylisoquinolines are a unique class of polyketide-derived biaryls of natural origin. These compounds are found exclusively in the Ancistrocladaceae from Central Africa and Southeast Asia, and Dioncophyllaceae endemic to the coast of West Africa. The compounds are composed of naphthalene and isoquinoline moieties and are biosynthetically derived from the acetate-polymalonate pathway [29, 30]. The naphthalene and isoquinoline regions are coupled through a rotationally restricted C–C or C–N axes. This rotational hindrance gives rise to axial chirality, while the isoquinoline unit can have up to three stereocentres. Twelve of the monomeric naphthylisoquinolines (14–25) (Fig. 5) are discussed in this review. Dimeric naphthylisoquinolines have been described from species of the Ancistrocladus genus, and these dimers join four aryl units through three biaryl axes and thereby potentially doubling the number of stereocentres [31]. Seventeen of the dimeric naphthylisoquinolines (26–42) (Fig. 6) are mentioned in this report. The Ancistrocladaceae mostly produce C-6 oxygenated alkaloids with an $S$-configuration at C-3, and these are called the Ancistrocladaceae-type, while the alkaloids of Dioncophyllaceae exclusively have an $R$-configuration at C-3 and lack oxygenation at C-6 and are called the Dioncophyllaceae-type [30]. Several of these compounds displayed nanomolar selective inhibition of the Plasmodium parasite viability.

Ancistectorines A$_1$ (14), N-methyl A$_1$ (15), A$_2$ (16), 5-epi-A$_2$ (17), A$_3$ (20), and C$_1$ (22) were isolated from the twigs of Chinese Ancistrioradus tectorius [32]. The six alkaloids potently inhibited the K1 strain of P. falciparum without cytotoxicity against rat skeletal myoblast (L6) cells. The 5,1$\prime$-coupled compounds 15, 16, and 17 were 3–7 times more active than chloroquine with 17 having an SI > 3000 [32]. The known N-methylated 5,1$\prime$-coupled ancistrocline (18) from the same plant also showed encouraging antiparasitic activity against the K1 and NF54 strains. In addition to low cytotoxicity against L6 cells, compound 18 was 2–3 times more active against chloroquine-resistant K1 than the chloroquine-sensitive NF54 strain [33]. However, the additional methoxy group on the naphthalene unit of 18 led to >30 fold decrease in activity compared to 15. The new dioncophyllines C$_2$ (19) and F (21), and the known ancistrocladisine A (25) and 5$\prime$-O-methyl dioncophylline D (23) were isolated from the...
root bark of Congolese Ancistrocladus ileboensis [30]. The total synthesis of 21, which was the first reported natural 5,8′-coupled dioncophyllaceous alkaloid, was achieved by palladium-catalyzed Suzuki–Miyaura cross-coupling of the two aryl moieties. Furthermore, the leaves of Ancistrocladus ileboensis yielded the 7,8′-coupled dioncophylline D2 (24), which was also previously unreported. Compounds 19, 21, 23, 24, and 25 were found to be active against the NF54 strain, with 21 displaying double the activity against the K1 over the NF54 strain. Furthermore, the new compounds were non-toxic to L6 cells with SI values ranging from 61 to 586 [30]. It is worthy to note that axial chirality influences the antiplasmodial activity of the naphthylisoquinolines when they exist as atropo-diastereomers. The M-configured analogues such as 17 generally showed superior selective antiplasmodial activity compared to the P-configured counterparts such as 16.

Dimerization of the naphthylisoquinoline core resulted in the rotationally-hindered 1,1′- or 3,3′-inked shuangcistrotectorines A–E (26–30) from the twigs of the Chinese Ancistrocladus tectorius. This was the first report of a natural product featuring three consecutive stereo axes, which in addition to the tetrahydroquinoline stereocentres, confers up to seven stereogenic units [34]. Biological assessment of these compounds revealed submicromolar antiplasmodial activity against the K1 strain coupled to low toxicity against L6 cells (SI = 99.8–610.6), with compounds 26, 27, and 30, in particular, displaying antiplasmodial activity superior to that of chloroquine [34]. Similarly, jozimine A2 (31), the first reported dioncophyllaceae-type sterically-hindered 3,3′-coupled dimeric naphthylisoquinoline isolated from a Congolese Ancistrocladus sp., displayed sub-nanomolar inhibitory activity, superior to that of chloroquine against the NF54 strain coupled to low cytotoxicity against L6 cells (SI > 11,400) [35]. Mbandakamines A (32) and B (33), the first dimeric naphthylisoquinolines featuring the unsymmetrical 6′,1″-coupling of the naphthalene units were isolated from the leaf of another uncharacterized Congolese Ancistrocladus sp. The diacetate salts of these highly sterically-hindered compounds were more active against the
Fig. 6 Structures of dimeric naphthylisoquinolines
NF54 strain than the free bases, possibly due to increased solubility [36]. Another unidentified Congolese Ancistrocladus sp. yielded the unsymmetrically 6,1′′-coupled mbbandakamine B2 (34), together with two other unique dimers named spirombandakamines A1 (35) and A2 (36). Compounds 35 and 36, which incorporate both a five-membered ketone ring alongside seven- and five-membered oxygenated heterocyclic rings into the dimeric structure, exhibited nanomolar antiplasmodial activity against both the K1 and NF54 parasite strains. The open-chain 34 was proposed as the biosynthetic precursor to the spiro-fused 35, but the higher antiplasmodial activity of 34 as compared to 35 and 36 implies that cyclization is not beneficial to activity [37]. Jozilebomines A (37) and B (38), two unsymmetrical 3,6′-coupled dimers isolated from the root extract of the Congolese Ancistrocladus ileboensis, exhibited selective antiplasmodial activity against NF54 P. falciparum strain, with weak toxicity towards L6 cells (SI = 160 and 52.3, respectively). However, this activity was lower than the related symmetrically coupled jozimine A2 (31) [38]. Three structurally unique heterodimeric naphthylisoquinolines, elalapasamines A–C (39–41), were isolated from the leaf of Ancistrocladus ealensis. The elalapasamines are the first reported unsymmetrical dimers in which the constituent monomeric naphthylisoquinoline units are linked at different positions, i.e. one 5,8′-coupled monomer links to another 7,8′-coupled unit at the 6′ position of the respective naphthanyl subunits. This subsequently results in three different biaryl linkages, with the inter-naphthanyl biaryl axis being configurationally unstable. Compounds 39–41 were active against P. falciparum (K1 and NF54) with low nanomolar IC50 values and low toxicity to L6 cells [39].

The bioactivity of the dimeric naphthylisoquinolines, as with the monomers, is influenced by axial chirality as, for example, seen in the superior activity of jozimine A2 over the atropo-diastereomer, 3′-epi-jozimine A2 (42) [29, 35]. So far, jozimine A2 demonstrated the best antiplasmodial activity (IC50 = 1.4 nM) against the chloroquine-sensitive NF54 strain, while mbbandakamine B2 is the most active dimer against the chloroquine-resistant K1 strain (IC50 = 4.0 nM). With potent in vitro activities and high selectivity for the parasites over mammalian cell lines, the dimeric naphthylisoquinolines can be considered as viable anti-malarial hits. It will be worthwhile to study the mechanism of action as well as in vitro and in vivo potency against a comprehensive panel of drug-sensitive and -resistant parasites. Equally important for an anti-malarial drug is the need for oral bioavailability, and hence pharmacokinetic studies are highly desirable. The synthesis of some dimeric naphthylisoquinolines has been reported, and since only small amounts of these potent compounds are present in plant material, the syntheses of these compounds will be essential for further developments [40].

**Benzylisoquinolines and other isoquinolines**

Three new tricyclic isoquinoline alkaloids (Fig. 7) were isolated from the leaf extract of Cassia siamea (Fabaceae), a plant traditionally used to treat periodic fever and malaria in Indonesia. Among the isolated compounds, cassiarin J (43) and the first halogenated cassiarin congeners, cassiarin K (44), inhibited the in vitro growth of 3D7 P. falciparum [41]. However, both compounds 43 and 44 were less active than chemically simpler and the potent cassiarin A (45), suggesting that the role of the pyran ring of the cassiarins in antiplasmodial activity should be further explored in structure–activity relationship (SAR) investigations [42].

The L-tyrosine-derived benzylisoquinoline alkaloids form a structurally diverse group of plant-derived compounds, many of which are associated with potent biological activities, and antiplasmodial activity is no exception. During the review period, the activity of one morphinanedienone alkaloid (46) (Fig. 8), six aporphines (47–52), six berberine-type compounds (53–58), and seven bisbenzyltetrahydroisoquinoline alkaloids (59–65) (Fig. 9) were reported. The morphinanedienone alkaloid, (−)-milonine (46) from the bark of Dehaasia longipedi-cellata (Lauraceae), exhibited sub-micromolar selective antiplasmodial activity against K1 parasites [43]. Carraz et al. reported that a derivative of a related morphinan, tazopsine, is active against the liver stages of the parasite and that this class of compounds may have potential as anti-malarial leads [44].
Following the screening of crude extracts of Malaysian medicinal plants, the extract of Dehaasia longipedicellata was identified as a promising antiplasmodial starting point. Chemical investigation of the bark extract afforded boldine (47) and \((-\)-O,O-dimethylgrisabine (59) as the most active constituents, both of which were active against the K1 strain of P. falciparum, with 59, in particular, outperforming chloroquine in this assay. The compounds were not cytotoxic to a pancreatic cancer cell line (hTERT-HPNE) at 200 µM, indicating selective toxicity to the parasite [43]. Based on the antiplasmodial screening of 794 plant extracts from Papua New Guinea and Australia, four species were selected for further investigation, one of which was Stephania zippeliana (Menispermaceae) [45]. Stephania zippeliana yielded xylopine (48), which selectively inhibited the 3D7, FCR3, HB3, and K1, in addition to the D6 and W2 P. falciparum strains [46, 47]. Bioassay-guided fractionation of Stephania venosa tubers yielded the aporphine alkaloids stephanine (49), crebanine (50), and O-methylbulbocapnine (51) as antiplasmodial principles. Unfortunately, the most active alkaloid against 3D7 and W2 parasites, stephanine (49), was also the most cytotoxic to cancerous and non-cancerous cell lines [48]. Chemical interrogation of the root of Thalictrum flavum (Ranunculaceae) yielded the aporphine alkaloid, precocetine (52), the protoberberines, pseudoberberin (54) and berberin (55), and the bisbenzylisoquinoline thaligosidine (60). The compounds exhibited antiplasmodial activity against the FcB1 strain. However, the activity of the quaternary protoberberines was not selective towards the parasite [49]. The tetrahydroprotoberberine alkaloid cheilanthifoline (53), isolated from Corydalis calliantha (Papaveraceae), an annual herb used in Bhutanese traditional medicine to treat malaria, also displayed activity against the TM4 strain of P. falciparum [50].

Three bisbenzylisoquinoline alkaloids, 2-norcephanthine (61), cepharanoline (62), and fangchinoline (63), which were isolated from Stephania rotunda tuber as minor constituents, all showed potent antiplasmodial activity against the W2 strain with SI ≥ 40 [53]. Encouragingly, these compounds were twice as active as the major alkaloid of Stephania rotunda, cepharanthine (64), which was previously reported to inhibit parasites in vitro and in vivo [54]. Further investigation found that the Stephania rotunda alkaloid 64 and the protoberberine-type benzylisoquinolines palmatine (57) and pseudopalmatine (58) also inhibited the in vitro viability of P. falciparum W2. However, while 64 was found to be cytotoxic against K562 cells, this was not the case for 58 at the highest tested concentration (IC<sub>50</sub> < 25 µM). These findings supported the use of Stephania rotunda in malaria treatment by traditional healers in Cambodia [55]. Desgrouas et al. concluded that cepharanthine (64) affected the ring stage of the parasite [56, 57]. Furthermore, in in vitro studies, 64 had a synergistic antiplasmodial effect with the anti-malarial drugs chloroquine, atovaquone, and piperaquine, but had an antagonistic effect with dihydroartemisinin and mefloquine [56, 57]. In in vivo experiments, combinations of 64 and chloroquine, and 64 and amodiaquine were assayed in mice. Both combinations delayed parasitic growth and extended the life expectancies of the mice compared to the drugs alone [57]. Fangchinoline (63) and the methyl ether tetrandrin (65), both produced by Stephania tetrandra, are not only cytotoxic against cancer cell lines, but also reverse resistance of multidrug-resistant human cancer cells by inhibiting P-glycoprotein activity, thereby increasing drug concentration in the cells [58]. The resistance-reversal effect was also observed with Plasmodium; Ye and Van Dyke reported that 65 in combination with chloroquine resulted in a 44-fold potentiation of parasite killings [59]. These authors also reported on the structure–activity relationship of bisbenzylisoquinoline [59]. For activity, the configuration of C-1’ of the ‘right-hand’ ring should be S. The configuration of C-1 of the ‘left-hand’ ring has little influence on the antiplasmodial activity. Furthermore, the position of the bridges connecting the two monomeric benzylisoquinolines also plays a role and compounds with ether bridges between C-8 to C-7’, and between 11 and 12’...
(head–head and tail–tail dimer) have the highest anti-plasmodial activity.

**Phenanthrene derivatives: phenanthridine, phenanthroindolizidine, and phenanthrene alkaloids**

The dichloromethane bark extract of *Cryptocarya nigra* (Lauraceae) afforded the phenanthrene alkaloid 2-hydroxyatherosperminine (66) (Fig. 10), which was
found to be active against the \( P. falciparum \) K1 strain. The significantly improved activity of 66 over the C-2 deoxy analogue atherosperminine indicates a possible important region of the pharmacophore [60].

The methanol extract of \( Ficus septica \) (Moraceae) twigs exhibited in vitro antiplasmodial activity against the 3D7 strain \((IC_{50} = 2.0 \ \mu g/mL)\). Bioassay-guided fractionation of the chloroform fraction of the active methanol extract led to the isolation of the known compounds, dehydrotylophorine (67), dehydroantofine (68) and tylophoridine (69) (Fig. 10). The three phenanthroindolizidine alkaloids inhibited the 3D7 strain with sub-micromolar \( IC_{50} \) and had low cytotoxicity. The selective antiplasmodial activity of these alkaloids indicates that other alkaloids of this class should be further explored [61].

The benzophasenanthridine alkaloid nitidine (70) (Fig. 11) was isolated as the main antiplasmodial compound from \( Zanthoxylum chalybeum \) (Rutaceae) and \( Zanthoxylum rhoifolium \) [62, 63]. Compound 70 displayed rapid activity against chloroquine-sensitive and -resistant parasites with little evidence of cross-resistance, consistent with previous reports [64]. Treatment of \( Plasmodium berghei \)-infected mice with 70 gave an ED\(_{50}\) value of 18.9 mg/kg/day without mice mortality. Nitidine (70) did not interfere with parasite DNA replication and was found to localize in the parasite cytoplasm. The mechanism of action of 70 might be similar to that of chloroquine since it formed a complex with heme and inhibited the formation of \( \beta \)-haematin in vitro [62]. In contrast to the rapid activity of 70, dihydronitidine (71), isolated from \( Zanthoxylum heitzii \) bark, displayed a slow-acting drug effect against 3D7 parasites. This slow-acting effect, coupled with the fact that 71 will not carry a charge at the digestive vacuole pH, which is purportedly necessary for drug accumulation, suggests that the compound might act via a different mechanism of action [65]. The poor water solubility of 71 might also limit its viability as an anti-malarial lead.

**Terpenylindoles**

The monoterpenoid indole alkaloid uleine (72) (Fig. 12) was isolated as the major antiplasmodial alkaloid from the trunk bark of the Brasilian tree \( Aspidosperma parvifolium \) (Apocynaceae) and was more active against the W2 than the 3D7 strain, with low cytotoxicity against the Hep G2A16 and Vero cell lines [66]. Compound 72 was found to localize in the parasite digestive vacuole as a result of the presence of a basic aliphatic amino group, which undergoes protonation in the acidic digestive vacuole and accumulates in suitable concentrations to inhibit heme polymerization [67]. Uleine has also been isolated from \( Aspidosperma olivaceum \) [68]. Traditionally, the Nkundo people in the DR Congo use various parts of \( Greenwayodendron suaveolens \) (Annonaceae) to treat malaria. Some species of monkeys chew the bitter

![Fig. 10 Structures of phenanthrene alkaloids](image)

![Fig. 11 Structures of nitidine (70) and dihydronitidine (71)](image)

![Fig. 12 Structures of terpenyl alkaloids](image)
leaves, presumably for zoopharmacognostic purposes [69]. Two sesquiterpenyl indole alkaloids, N-acetylpolylyveline (73) and polyalthenol (74) (Fig. 12), isolated from the root bark of Greenwayodendron suaveolens, are active against the K1 strain. While polyalthenol was found to be cytotoxic against MRC-5 cells, 73 was more selective (SI = 10.6) [69].

**Bisindoles and related indoles**

Flinderole A (75) and isoborreverine (78) were isolated from the bark of the Australian tree Flindersia acuminata (Rutaceae) and flinderoles B (76) and C (77), and dimethylsoborreverine (79) from *Flindersia amboinensis* from Papua New Guinea [56]. These indole alkaloids (Fig. 13) exhibited selective antiparasitic activity against a wide panel of drug-sensitive and -resistant parasites. In a further investigation to ascertain which stage of the development cycle of the parasite is affected by the most active compound 79, it was observed that 79 was more active against *P. falciparum* trophozoites, with treated parasites showing changes in digestive vacuole morphology and a reduced formation of haemozoin [46, 70].

A different *Flindersia* species, *Flindersia pimenteliana*, was the source of the new pimentelamine C (80), the known borreverine (81), and 4-methylborreverine (82), which were reported to be active against *P. falciparum* 3D7 and Dd2 with low toxicity to HEK-293 cells [71]. Compound 80, which was isolated as the trifluoracetate salt from the plant leaves, is one of three new indole alkaloids incorporating an ascorbic acid moiety. Interestingly, the other two analogues without a polar N-oxide moiety on the ethylamine unit attached to the indoleskeleton, were inactive [71]. This suggests a SAR role for the ethylamine unit that could be further explored.

Two bisindole alkaloids with a vobasinyl-iboga skeleton tabernaegantiane B (83) and D (84) (Fig. 14), isolated from *Muntafara sessilifolia* (Apocynaceae) stem bark, inhibited the FcB1 plasmodial strain but these compounds were also cytotoxic against L6 and MRC-5 cells [72]. However, the C-3’ oxidized analogues 85 and 86, in particular, showed better selectivity towards the parasite suggesting the position of the linkage between the monomeric units might influence the bioactivities of these compounds [72]. This observation is supported by the
nanomolar antiplasmodial activity of another vobasinylboga alkaloid, voacamine, which also has a C-3/C-11' linkage [73]. A reinvestigation of Geissospermum laeve (Apocynaceae) using a dereplication strategy led to the isolation of new bisindole alkaloids, 3',4',5',6'-tetradehydrogeissospermine (87) and geissolosimine (88), from the bark of the tree [74]. Compound 88 has also been isolated from the bark of Geissospermum vellosii [75].
The compounds exhibited non-selective antiplasmodial activity against FcB1 parasites [74]. Moreover, 88 was also active against the D10 strain with low toxicity to Chinese hamster ovarian cells [75]. Divarine (89), longicaudatine (90), longicaudatine F (91), and longicaudatine Y (92) from the stem bark of *Strychnos malacoclados* (Loganiaceae) inhibited the growth of the 3D7 and W2 parasite strains. A cytotoxicity assay on WI-38 human fibroblasts with the most active 90 showed that the antiplasmodial activity is not specific. However, the structurally similar longicaudatine F (91), possessing an open ring in place of the six-membered oxygen heterocycle in 90, was 40 times more selective against the parasite, despite the slightly lower antiplasmodial activity [76]. A phytochemical investigation of *Strychnos icaja* root provided a new bisindole, strychnobaillonine (93), and the known strychnohexamine (94) (Fig. 14). The alkaloids were active against the 3D7 strain of *P. falciparum*, and the trisindole 94 was also cytotoxic against WI-38 cells (SI < 10), whereas 93 was not cytotoxic at the highest tested concentration (10 µg/mL) [77]. Interestingly, while monomers of *Strychnos* alkaloids do not have antiplasmodial activity, polymerization increases the basic nature of the monomers and confers antiplasmodial potency. This suggests that some degree of basicity is essential for antiparasitic activity of the *Strychnos* alkaloids and that compounds might localize in the parasite acidic digestive vacuole [78].

It was previously reported that ellipticine (95) (Fig. 15), isolated from *Aspidosperma vargasii* (Apocynaceae) bark, has in vitro and in vivo anti-malarial activity [79]. In search of more active analogues, semi-synthetic derivatives of 95 were prepared. 9-Nitroellipticine (96), in which ring A was modified, was more active than 95, while the 7-nitro derivative was the least active [80]. The indole-quinazoline alkaloid tryptoquivaline (97), obtained from the culture broth of *Neosartorya spinosa* KKU-1NK1 (sexual state of *Aspergillus* fungus species), was active against K1 parasites. The compound was slightly cytotoxic to Vero cells (SI = 25) but was inactive against a panel of cancer cell lines [81].

**β-Carbolines**

The β-carboline-indole alkaloid hyrtiosulawesine (98) (Fig. 16), isolated from the root of *Aristolochia cordigera* (Aristolochiaceae), inhibited the in vitro viability of *P. falciparum* (3D7) without any toxicity to Hep G2 cells. Similar inhibition of the FcB1 strain was observed with synthetic 98 [82]. However, the glucoside derivative of 98 was only half as active as 98 [83]. Marinacarboline A (99) isolated from *Marinactinospora thermotolerans* SCSIO 00652, an actinomycetes species from South China Sea marine sediments, was 18 times more active against the multi-drug resistant Dd2 strain than against the chloroquine-sensitive 3D7. The compound was not significantly cytotoxic to a panel of tumour cell lines (IC50 > 50 µM) [84]. The New Zealand ascidian *Pseudodistoma opacum* was the source of a new antiplasmodial alkylguanidine-substituted β-carboline alkaloid, opacalin A (100). The poor cytotoxicity of 100 against L6 cells indicates a selective antiparasitic activity against the K1 strain [85]. β-Carboline-1-propionic acid (101) was isolated from the root of *Eurycoma longifolia* (Simaroubaceae), a popular southeast Asian medicinal plant. It exhibited antiplasmodial activity against the 3D7 strain, but the cytotoxicity was not reported [86].
Piperidine, pyridone, and pyrimidine alkaloids

The leaf decoction of *Carica papaya* (Caricaceae), which is traditionally used to treat malaria in Indonesian Papua and Maluku islands, displayed in vitro antiplasmodial activity (51% inhibition at 4.8 µg/mL) [87]. Purification of an alkaloid-enriched fraction of the plant leaves yielded the dimeric piperidine alkaloids 102–104 (Fig. 17) as the antiplasmodial principles, while the monomeric carpanic acid and methyl carpamate were inactive. Carpine (102), with the best activity, was the major alkaloid, but it was inactive in vivo (11.9% suppression of *P. berghei* parasite at 5 mg/kg). The in vivo activity of a hydroalcoholic extract of papaya leaves suggests that other metabolites in the extracts might potentiate the antiplasmodial activity of the active compounds [87]. The observed lack of in vivo efficacy of 102 highlights the complex relationship between metabolites in natural extracts and emphasizes the need to validate in vitro potencies in animal models. Nevertheless, potent and selective activity of compounds can be exploited by medicinal chemistry methods in designing improved analogues. Cassine (105) and spectaline (106) from *Senna spectabilis* leaf were active against 3D7 *P. falciparum* in vitro. However, the 3-O-acetyl semi-synthetic derivatives were less active than the natural piperidine parents [88]. Ingamine A (107), together with two new ingamine-type piperidine alkaloids, (22S)-hydroxyingamine A (108) and dihydroingenamine D (109), were isolated from the marine sponge *Petrosid Ng5 Sp5*. Compounds 107–109 showed sub-micromolar antiplasmodial activity against D6 and W2 parasites without cytotoxicity against cancerous and noncancerous cells at 10 µg/mL [89]. An antiplasmodial high-throughput screen of the ethanolic extract of marine sponges from the Solomon Islands identified the active *Heliclona* sp. with an in vitro activity of < 1 µg/mL. Bioassay-guided fractionation of the extract from this sponge led to the isolation of haliclonacyclamine A (110). The bis-piperidine 110 was more active against chloroquine-resistant FcB1 than chloroquine-sensitive 3D7 parasites, with low cytotoxicity against MCF7 cancer cells. It suppressed...
parasitaemia in *Plasmodium vinckei petteri*-infected mice by 45% after 4 days of treatment with 10 mg/kg/day [90]. Most of the antiplasmodial piperidine alkaloids mentioned here are cyclic dimers. The potent, selective activity of these compounds makes them attractive as lead templates in anti-malarial drug design.

The new pyridone alkaloid 111 (Fig. 17), with a 1,4-dihydroxy-5-phenyl-2-pyridinone skeleton, was isolated from the Ascomycetes fungus, *Septoria pistaciarum*. Compound 111 was active against *P. falciparum* D6 and W2 strains, but it was also cytotoxic against Vero cells. Three other analogues without a free N-hydroxy group on the pyridone heterocycle were inactive, suggesting a SAR role for substituents on the ring nitrogen [91].

The extract of *Biemna laboutei*, a marine sponge collected at Salary Bay in Madagascar, showed antiplasmodial activity with IC$_{50}$ of 3.2 µg/mL. Chemical investigation of the active extract yielded new tricyclic pyrimidine alkaloids named netamines. Among the isolated alkaloids, netamine K (112), with a $\Delta^{8,8a}$-double bond in the tricyclic skeleton, exhibited activity against *P. falciparum* without toxicity to KB cells at the highest tested concentration of 1 µM [92].

**Pyrroles**

A series of 14 structurally related bromopyrrole alkaloids (Fig. 18) derived from sponges of the *Agelas* and *Axinella* genera were assayed for antiplasmodial activity against the K1 strain. Dibromopalau’amine (113) had the highest activity against the parasite, although it was also cytotoxic against L6 cells. The slightly less potent spongadiacin B (114) and dispacamidine B (115) were more selective against the parasite (SI = 32.7 and > 67.2, respectively). Preliminary SAR observations in this series indicated that the aminimidazole ring and the level of oxidation are important for antiplasmodial activity. Analogs lacking the imidazole ring were inactive while those in which the ring is not oxidized were less active. Some bromopyrrole alkaloids inhibited *Plasmodium* type II fatty acid synthase (FAS II) enzyme, suggesting that this might be part of the mechanism of action [93].

The new bispyrroloiminoquinone tsitsikammamine C (116), with nanomolar antiplasmodial activity against 3D7 and Dd2 *P. falciparum* strains, together with the equally active makaluvamines G (117), J–L (118–120), were isolated from the marine sponge *Zyzzya* sp. [94]. Compounds 116 and 118 were equally active against both parasite schizonts and trophozoites. Subcutaneous
treatment of *P. berghei* infected mice with 117 at 8 mg/kg/day for 4 days suppressed parasitaemia by 48% with no apparent toxicity to mice. Damirone A (121), with a benzoquinone group in place of the iminoquinone moiety of the makaluvamines, was less active, suggesting that the iminoquinone group is crucial for activity. Methylation of the iminium nitrogen led to an increase in activity [94]. Bioassay- and LC–MS-guided fractionation of an active extract from the Alaskan-sourced *Latrunculia* sp. sponge yielded discorhabdins A (122), and C (123), and dihydrodiscorhabdin C (124) [95]. The most potent pyrroloiminoquinones, 122 and 124, with nanomolar antimalarial activity against D6 and W2 strains, were also the most selective (SI = 130 and 75, respectively). In an in vivo experiment, *P. berghei*-infected mice were treated with 122 and 124 at 10 mg/kg/day and although 50% suppression of parasitaemia was observed with 122 after 2 days of treatment, both compounds resulted in symptoms of severe toxicity [95].

**Other alkaloids**

Concoctions prepared from *Buxus* plant species are used for the treatment of malaria in various traditional medicine systems [96, 97]. An alkaloid-enriched fraction from the leaves of *Buxus sempervirens* (Buxaceae), which exhibited selective antimalarial activity (IC$_{50}$ = 0.36 µg/mL, SI = 20.3), was subjected to bioassay-guided fractionation and yielded the cycloartane alkaloid, O-tigloylcyclovirobuxeine B (125) (Fig. 19), as the major antimalarial compound. The antimalarial activity of 125 against the NF54 strain was slightly less than that of the crude alkaloid fraction, but the compound was not significantly cytotoxic against L6 cells. Compound 125 was also detected in significant quantities in a leaf decoction of *Buxus sempervirens* that was prepared in accordance with ethnobotanical protocols [98]. Purification of the chloroform fraction of an extract from the combined twigs, leaves, and fruits of *Buxus cochinchnensis* yielded a number of bioactive triterpenoids, including the cycloartane alkaloid, N-benzoyldihydrocycloartane B (126). This compound inhibited both Dd2 *P. falciparum* and HT-29 human colon cancer cells, suggesting non-selective activity [99]. Two pregnane-type steroidal alkaloids, mokluangin A (127) and irehline (128), isolated from the root of *Holarrhena pubescens* (Apocynaceae), were active against K1 *P. falciparum* with low cytotoxicity against NCI-H187 lung cancer cells (IC$_{50}$ = 30.6 and 27.7 µM, respectively) [100]. Two new cassane diterpene alkaloids, caesalminines A (129) and B (130) (Fig. 19), possessing a tetracyclic furanoditerpenoid skeleton were isolated from the seeds of *Caesalpinia minax* (Fabaceae). The compounds, which were proposed to be biosynthetically derived from the aminolysis of the geranylgeranyl pyrophosphate precursor, inhibited K1 *P. falciparum* [101].

A new Amaryllidaceae alkaloid, (+)-5,6-dehydrolycorine (131) (Fig. 20), isolated from the bulbs of *Lycoris radiata* (Amaryllidaceae), inhibited the in vitro viability of *P. falciparum* (D6 and W2), albeit with associated cytotoxicity against eight human tumour cell lines, indicating non-specific antiparasitic activity [102]. Similarly, the macrocyclic lactams cripowellin A–D (132–135) (Fig. 20), which were isolated from the alkaloid-enriched extract of *Crinum erubescens* (Amaryllidaceae), inhibited the Dd2 strain with nanomolar IC$_{50}$ values but were also cytotoxic against cancerous A2780 cells. Importantly, the presence of the 1,3,5-trioxepane-ring in 132 and 134 correlated with improved activity [103]. Another bioassay-guided purification, this time of *Crinum firmifolium* leaf extract, led to the isolation of the new 2-alkylquinolinones 136 and the known 137, which were both active against the 3D7 and Dd2 strains with mild cytotoxicity against A2780 mammalian ovarian cancer cells [104]. Incorporation of a branched alkyl into 137 to form 138...
improved antiplasmodial activity, suggesting that branching of the alkyl side chain is beneficial to potency [104].

The bromotyrosine alkaloid psammaplysin H (139) was isolated from a marine Pseudoceratina sponge together with the known psammaplysin F (140), previously isolated from a Hyattella sponge, and both exhibited antiplasmodial activity against the 3D7 strain (Fig. 21) [105]. Psammaplysin H (139), which has a trimethylated quaternary terminal nitrogen, was not toxic to HEK293 and HepG2 mammalian cells, while 140 suffered from reduced activity coupled with significant cytotoxicity [106]. Preliminary SAR studies indicated that substitution on the terminal nitrogen influences the selective antiplasmodial activity. Four other antiplasmodial bromotyrosine derivatives, aplysinone D (141), homoaeorothonin (142), 11,19-dideoxyfistularin 3 (143), and 11-hydroxyfistularin (144), were isolated from Suberea ianthelliformis, a marine sponge from the Solomon Islands. Unfortunately, these compounds were also cytotoxic against Vero cells [107].

Interrogation of the marine sponge Monanchora unguiculata, collected at the Mitsio islands of Madagascar, yielded four new guanidine alkaloids ptlimycalins E–H (145–148), along with the known crambscisidin 800 (149) and fromiamycalin (150) (Fig. 22). The compounds exhibited sub-micromolar antiplasmodial activity against the 3D7 strain but were also cytotoxic against KB cells [108]. Similarly, four new antiplasmodial tricyclic thiazine alkaloids thiaplakortones A–D (151–154) (Fig. 22), isolated from the Australian marine sponge Plakortis lita, showed nanomolar inhibition against the 3D7 and Dd2 parasites, with low toxicity to human HEK293 cells (SI = > 62 – > 500) [109]. The decalin-tetramic acid metabolite phomasetin (155) was obtained following the culturing of the Pyrenochaetopsis sp. RK10-F058 fungus. Biological assessment revealed that 155 was active against P. falciparum 3D7 with moderate cytotoxicity against cancerous HeLa, HL-60, and srcts-NRK cells. The same culture broth yielded two more decalin metabolites, possessing a cyclopentanone-fused decalin skeleton and a serine-derived N-methylated amino acid instead of the tetramic acid moiety. However, they were > 21 times less active than 155, indicating that the cyclized tetramic acid group might be crucial for potent activity [110]. Apidiopsamine A (156) (Fig. 22), with a rare pyrrolo-quinoline conjugated to an adenine nucleobase, was isolated from the Australian ascidian Apidiopsis confluata. The new metabolite was active against the 3D7 and Dd2 strains without significant toxicity against HEK-293 cells [111].

An extract from the leaves of Prosopis glandulosa (Fabaceae), collected in Nevada, yielded a new tertiary indolizidine alkaloid Δ1,6-juliprosopine (157) (Fig. 23). Interestingly, the leaf extract of the same plant collected in Texas produced the known quaternary alkaloid juliprosine (158) but not 157. The two compounds inhibited the D6 and W2 strains without any toxicity to Vero cells at the highest tested concentration of 23.8 µg/mL [112]. Allnorsecurinine (159), previously reported as a synthetic compound, was isolated with ent-norsecurinine (160) from the antiplasmodial plant Phyllanthus fraternus (Phyllanthaceae) (methanol extract IC₅₀ = 0.44 µg/mL against 3D7) [113]. The two securinega alkaloids were more active against chloroquine-resistant W2 than against chloroquine-sensitive 3D7 parasites. No cytotoxicity was observed against human umbilical vein endothelial cells at the highest concentration of 100 µM [114]. The root bark extract of the Ugandan anti-malarial medicinal plant Citropsis articulata (Rutaceae) displayed
77% inhibition of FcB1 *P. falciparum* at 10 µg/mL with low cytotoxicity against Vero cells. A pyranoacridone alkaloid, 5-hydroxynoracronycine (161), was isolated as the most active constituent against the same parasite strain. However, the compound was also moderately cytotoxic against Vero cells (SI = 10) [115].

The polyamine diamide orthidine F (162) (Fig. 23) from the New Zealand-sourced ascidian *Aplidium orthium* was active against K1 *P. falciparum* without cytotoxicity against L6 cells. A synthetic 2-hydroxyphenylacamide derivative 163 was > 100 times more active while retaining selectivity. Preliminary SAR indicated that the two arylamide terminals and the spermine fragment are essential for antimalarial activity. Similarly, the hydroxy group at C-2 of the aromatic rings is important for improved antimalarial activity [116].

**Terpenes**

Among the 447 isolated natural products with IC₅₀ ≤ 3.0 µM reported in this review, 30.8% are terpenoids.

**Monoterpenes**

The iridoid specicoside (164) (Fig. 24), isolated from an antimalarial ethyl acetate extract of *Kigelia africana* (Bignoniaceae), was active against the *P. falciparum* W2, CAM10 and SHF4 strains without cytotoxicity against LLC/MK-2 cells. Specicoside (164) acted in synergy with artemether in inhibiting the W2mef strain but had an antagonistic effect with p-hydroxycinnamic acid, which is also present in *Kigelia africana* [117, 118].

**Sesquiterpenes**

A phytochemical investigation of the active chloroform extract of *Drimys brasiliensis* (Winteraceae) stem bark (*P. falciparum* FcR3, IC₅₀ 3.0 µg/mL) led to the isolation of drimane sesquiterpenes but the most active compound was 1β-(*p*-coumaroyloxy)polygodial (165) (Fig. 25) [119]. Preliminary antimalarial screening of *Salacia longipes* var. camerunensis (Celastraceae) seed extract showed that it was active against the W2 strain with an IC₅₀ of 2.28 µg/mL. Extensive purification of the active extract afforded the β-agarofuran sesquiterpenoids salaterpenes A–D (166–169) (Fig. 25), which were also active against W2 parasites [120]. The root extract of *Ferula pseudalpina* (Apiaceae) yielded an antimalarial metabolite
sanandajin (170), the first isolated disesquiterpene-coumarin. This compound, a cadinanyl ester of the sesquiterpene coumarin glabanic acid, inhibited the K1 parasite and had moderate cytotoxicity against L6 cells [121].

The eremophilane sesquiterpenoid sporogen-AO1 (171), produced by the soil fungus *Penicillium copticola* PSURSPG138, inhibited K1 parasites but was also cytotoxic against human oral epidermoid carcinoma (KB) and Vero cells [122]. The endophytic fungus *Phomopsis archeri*, isolated from *Vanilla albidia* cortex stem, yielded an extract with antiplasmodial activity (IC$_{50}$ = 5.0 μg/mL) from which an aromatic sesquiterpene phomoarcherin B (172) (Fig. 25), with antiplasmodial activity but also moderate cytotoxicity against cholangiocarcinoma and KB cells, was isolated [123]. The Australian nudibranch *Phyllidia ocellata* has produced three new isonitrile sesquiterpenes, 2-isocyanoclovene (173), 2-isocyanoclovanene (174) and 4,5-epi-10-isocyanoisodauc-6-ene (175), with selective antiplasmodial activity against the 3D7 and Dd2 strains. The isothiocyanate and formamide analogues were significantly less active, further reinforcing the argument that the isonitrile functionality is crucial.

![Fig. 22](https://example.com/fig22.jpg)

**Fig. 22** Structures of guanidines 145–150, thiazines 151–154, phomasetin 155 and aplidiopsamine A 156
for the potent activity of isonitrile terpenes \[124\]. Young et al. adapted a β-haematin inhibition assay to allow for the assaying of small amounts of marine natural products and was able to prove that six terpenoid isonitriles inhibit heme crystallization at different levels \[125\]. The sesquiterpene-derived spiro heterocycle 3,4-dehydrotheteaspirone (176) (Fig. 25) has been isolated from Laumoniera bruceadelpha (Simaroubaceae) bark extract and was found to inhibit 3D7 parasites selectively \[126\].

**Sesquiterpene lactones**

Many species in the genus *Chloranthus* (Chloranthaceae), known in traditional Chinese medicine as “Sikuaiwa”, have been documented as a treatment for malaria. A library of 44 lindenane-type sesquiterpenoid monomers and dimers isolated from different *Chloranthus* species and *Sarcandra glabra* (Chloranthaceae) were assayed for antiplasmodial activity. Potent activity was observed for twenty-six of the compounds (177–202) (Fig. 26). Compounds with IC\(_{50} \leq 100\) nM were also assessed for cytotoxicity on embryonic lung tissue (WI-38) cells, and some compounds, e.g. fortunilide A (177), sarglabolide J (186), and chlorajaponilide C (191) had potencies comparable to that of artemisinin and were not cytotoxic. Preliminary SAR observations indicated that all the active compounds were dimers, had a Δ4 double bond and a hydroxy group at C-4′, and contain a (Z)-5-hydroxy-4-oxopent-2-enoate ester. The presence and nature of the ester groups at C-13′ and C-15′ affected the antiplasmodial activity, suggesting that these ester groups could be manipulated to optimize potency \[127\]. The potent and selective antiplasmodial activity warrants further exploration of this group of compounds.

Thirteen plants used in Burkina Faso to treat malaria were investigated, and due to the promising in vitro and in vivo anti-malarial activity, *Dicoma tomentosa* (Asteraceae) was selected for further studies \[128\]. Bioassay-guided purification of the whole plant extract yielded the known germacranoide sesquiterpene lactone, urospermal A 15-O-acetate (203) (Fig. 27) as the major antiplasmodial compounds. The compound exhibited antiplasmodial activity against the 3D7 and W2 strains without evidence of haemolysis, indicating a direct action
on the parasite. However, 203 was cytotoxic against WI38 human fibroblasts SI = 3.3, suggesting non-selective activity [129]. The root of an antiplasmodial Dicoma species from South Africa, Dicoma anomala subsp. ger-rardii was the source of a eudesmanolide-type sesquiterpene lactone, dehydrobrachylaenolide (204), which inhibited D10 P. falciparum but was less active against the K1 strain and moderately cytotoxic against CHO cells (SI = 9). Semi-synthetic derivatives of 204, in which the α-methylene ketone and lactone were reduced, were less active. This indicates that the exocyclic methylene group is essential for activity [130]. The dichloromethane extract of Trichospira verticillata (Asteraceae) exhibited antiplasmodial activity against Dd2 P. falciparum with an IC₅₀ of approximately 5 µg/mL. Fractionation of the extract afforded the new germacranolide trichospirolide A (205) (Fig. 27) as the most active constituent. However, it was also toxic to A2780 ovarian cancer and HEK293 cells [131]. Another antiplasmodial germacranolide, 15-O-methylgoyazensolide (206), was isolated from the leaf and twig extract of Piptocoma antillana (Asteraceae). It was equally active against the Dd2 strain and A2780 human ovarian cancer cells, indicating a non-selective antiplasmodial activity [132]. Antiplasmodial screening of 12 plants used in traditional medicine against malaria in Benin resulted in an extract of the aerial parts of Acanthospermum hispidum (Asteraceae) with potent activity against 3D7 and W2 parasites (IC₅₀ = 7.5 and 4.8 µg/mL, respectively) [133]. Two acanthospermolide-type sesquiterpene lactones (207 and 208) were subsequently isolated as the major antiplasmodial compounds without haemolytic activity [134]. Compound 208 was less cytotoxic against WI38 human fibroblasts than 207, indicating that 208 was more selective in the toxicity to 3D7 parasites [134]. Two other sesquiterpene lactones, vernpicrin (209) and vernomelitensin (210), from Vernonia guineensis (Asteraceae) leaves were also active against Dd2 and Hb3 parasite strains without haemolysis [135]. The dichloromethane extract of Eupatorium perfoliatum (Asteraceae) aerial parts inhibited P. falciparum with low cytotoxicity (IC₅₀ = 2.7 µg/mL and SI = 27). The new dimeric guaianolide, diguaiaiperfolin (211), was isolated as the main antiplasmodial compound from the active extract, but the compound was moderately cytotoxic against L6 cells (SI = 8) [136].

All the different classes of sesquiterpene lactones reported so far exhibited non-selective antiplasmodial activity. The bioactivities of sesquiterpene lactones have been ascribed to the presence of an α-methylene-γ-lactone moiety in the structures. The conjugate Michael acceptor property of this highly reactive functionality allows it to react with the thiol group of crucial cell proteins hence the unselective activity. SAR studies around this enigmatic functionality to make sesquiterpene lactones more selective are essential if these compounds are to enjoy further development as anti-malarial scaffolds.

![Fig. 25 Structures of sesquiterpenes 165–176](image-url)
Three new cassane diterpenes (Fig. 28) from an active chloroform extract of *Caesalpinia sappan* (Fabaceae) seeds (IC$_{50}$ = 0.38 µg/mL against K1), caesalspanins G–I (212–214), inhibited K1 *P. falciparum* [137]. Cytotoxicity studies against a panel of cancer cell lines showed moderate selectivity for the parasite (SI = 10.5–17.6). The three active compounds have a hydroxy group at C-12,
Fig. 27 Structures of sesquiterpene lactones 203–211

Fig. 28 Structures of cassane diterpenes 212–215
whereas compounds lacking the C-12 hydroxy were less active [137]. The dichloromethane extract of *Caesalpinia bonducella* root showed in vivo dose-dependent antiplasmodial activity [138]. A phytochemical investigation of the root afforded norcaesalpin D (215) as the antiplasmodial component. This cassane diterpenoid was active against 3D7, Dd2, and artemisinin-resistant (IPC 5202 Battambang, IPC 4912 Mondolkiri-Cambodia) strains. No cytotoxicity was observed against mammalian LLC-MK2 cells at the highest concentration (200 µg/mL) tested [139].

The leaf extract of *Aphanamixis grandifolia* (Meliaceae) produced the diterpenoid lactones amphadilactones A–F and H–I (216–223) (Fig. 29) [140, 141]. The structures of amphadilactones E and F feature a novel carbon skeleton with a 1,1,2,2-tetrasubstituted cyclobutane moiety. Compounds 216–223 inhibited the Dd2 strain with sub-micromolar IC₅₀ values. The interesting structures and antiplasmodial activity of 216–219 have motivated the total synthesis of the compounds [142]. Furthermore, compounds 216–219 showed potent inhibition of diacylglycerol O-acyltransferase-1 (DGAT-1) isozyme. *P. falciparum* encodes only one DGAT enzyme, PfDGAT, and it is necessary for parasite proliferation during the intraerythrocytic stage [143]. With the unprecedented carbon frameworks, it is worthwhile to investigate whether the new amphadilactones exert antiplasmodial activity by inhibiting PfDGAT [140, 141]. The hexane and dichloromethane bark extracts of *Cupania cinerea* (Sapindaceae), an Ecuadorian ethnobotanical plant, were active against *P. falciparum* K1 strain (IC₅₀ = 2.9 and 3.1 µg/mL, respectively) [144]. Subsequent bioassay-guided purification of the extracts yielded the new linear diterpenoid glycosides cupacinoside (224) and 6′-de-O-acetylcupacinoside (225), both displaying antiplasmodial activity against K1 parasites but also cytotoxicity against L6 cells [145].

The serrulatane diterpenoid 226, which was isolated from the aerial parts of *Eremophila microtheca* (Scrophulariaceae), was not active at 10 µM against *P. falciparum*. However, a semi-synthetic amide derivative 227 exhibited antiplasmodial activity against the 3D7 and Dd2 strains without being cytotoxic to HEK293 cells at 80 µM [146]. Two new pre-segetane and jatrophone diterpenoids euphorbesulins A (228) and G (229) (Fig. 30), from the twigs of *Euphorbia esula* (Euphorbiaceae), have also

![Fig. 29 Structures of diterpenes 216–225](image_url)
shown activity against the \textit{P. falciparum} Dd2 strain \cite{147}. Antiplasmodial screening of 150 Iranian ethnomedicinal plants identified \textit{Salvia sahendica} (Lamiaceae) hexane root extract with potent activity against the K1 strain (70\% inhibition at 0.85 \(\mu\)g/mL) \cite{148}. A subsequent phytochemical investigation led to the isolation of abietane diterpenoids as the bioactive constituents and ferruginol (230), \(\Delta^9\)-ferruginol (231), and 7\(\alpha\)-acetoxyroleanone (232) inhibited K1 parasites. However, 232 was also toxic to L6 cells, indicating a non-selective antiplasmodial activity. Chemical modifications, which included deacetylation and dehydrogenation of ring B, and hydroxylation of the benzoquinone ring of 232, led to a reduction in activity without improving selectivity \cite{148}. However, the semi-synthetic phthalimide derivative 233 of ferruginol had an improved selective antiplasmodial activity. Preliminary SAR studies of a library of semi-synthetic derivatives of ferruginol indicated that a hydroxy group at C-12 is beneficial for activity while an acetate group at C-12 reduced the activity against the K1 strain, but improved the activity against the 3D7 strain. Chlorination of the phthalimide group was detrimental to activity \cite{149}.

A marine sponge from Thailand, \textit{Stylorella cf. massa}, has produced some bifunctionalized amphilectane diterpenoids. The most active metabolite, 8-isocyano-15-formamidoamphilect-11(20)-ene (234) (Fig. 31), exhibited antiplasmodial activity against the K1 strain and was not cytotoxic against MCF-7 breast cancer cells. Analogues bearing an isocyanate and isothiocyanate functionalities were up to ten times less active, indicating that the isonitrile group improved activity. Also, an analogue with only the formamide functional group but lacking an isonitrile group, was not active against \textit{P. falciparum}, suggesting that the formamide group does not contribute to antiplasmodial activity \cite{150}. Two more isonitrile amphilectanes, monamphilectines B (235) and C (236), were isolated from the Caribbean marine sponge \textit{Svenzea flava} collected off the coast of Puerto Rico \cite{151}. The new metabolites were described as the first marine natural products with an \(\alpha\)-substituted monocyclic \(\beta\)-lactam ring. The compounds were active against the 3D7 parasites with nanomolar IC_{50} values. Interestingly, 8,15-diisocyanato-11(20)-amphilectene (237), which differs from the new compound by the absence of the substituted \(\beta\)-lactam moiety, was also active, which suggests that the \(\beta\)-lactam moiety does not contribute to antiplasmodial potency and further confirms the crucial role of the isocyanide (isonitrile) functionality \cite{151}. Potent antiplasmodial activity against W2 parasites was also reported for monamphilectine A (238), with an unsubstituted \(\beta\)-lactam ring \cite{152}. Pustulosaisonitrile-1 (239), which was isolated from the Australian nudibranch \textit{Phyllidiella pustulosa}, exhibited antiplasmodial activity against 3D7 and Dd2 \textit{P. falciparum} strains \cite{153}. Diastereoisomers of 239, obtained by enantio- and stereoselective total synthesis, were as active as the natural compound, but also showed cross-resistance \cite{153}. The

![Fig. 30 Structures of diterpenes 226–233](image)

antiplasmodial activity of isonitrile terpenoids has been demonstrated to be due to inhibition of haemozoin formation [125, 154]. Therefore, further development of this class of compound will depend on the ability to avoid cross-resistance. A new linear diterpenoid, bifurcatriol (240), featuring two stereogenic centres, was isolated from the Irish brown alga *Bifurcaria bifurcata* and was active against *K1 P. falciparum* with negligible cytotoxicity against L6 cells [155].

The stem extract of *Drypetes gerrardii* var *gerrardii* (Putranjivaceae) exhibited potent antiplasmodial activity against *P. falciparum* (IC$_{50}$ = 0.5 µg/mL). Two new metabolites, the diterpene-derived phenanthrenone drypetenone D (241) and phenanthrenone heterodimer drypetenone E (242) (Fig. 32), were subsequently isolated from this extract. These compounds were active against the NF54 strain with low cytotoxicity against L6 cells (SI = 71 and 31, respectively). However, the more active and selective monomer 241 did not show in vivo activity in *P. berghei*-infected mice [156]. The phenanthrenone derivatives fimbricalyx A (243) and B (244), isolated from *Strophioblachia fimbricalyx* (Euphorbiaceae) root, also inhibited *P. falciparum* K1. Interestingly, the new fimbricalyx B exhibited nanomolar antiplasmodial activity, better than mefloquine, without being cytotoxic against Vero and human cancerous cells at 10 µM [157].

**Triterpenes**

The chloroform extract of a combination of *Buxus cochinchenensis* (Buxaceae) leaves, twigs, and fruits yielded five betulin coumaroyl esters (245–249) (Fig. 33) [99]. The lupane esters 245, 248, and 249 were also isolated from the methanolic supercritical fluid extract of *B. sempervirens* together with five other new coumaroyl and feruloyl esters of betulin (250–254) [158]. The coumaroyl and feruloyl esters have either a Z- or E-configuration and are attached to betulin at either C-3 or C-23. The esters were active against *P. falciparum* Dd2, HB3, and NHP1337 strains without cytotoxicity against HeLa cells. Ester 250, with an E-feruloyl group attached at C-23, was the most active with sub-micromolar IC$_{50}$ values, whereas analogues with E or Z coumaroyl or Z-feruloyl
at C-23 were slightly less active. Also, C-3 modified analogues were less active than the C-23 modified counterparts. These observations identify the importance of the E-feruloyl moiety and suggest that modification at C-23 is more advantageous for activity. Importantly, the esterified betulin derivatives were more active than betulin and 23-hydroxybetulin, and the diacetate ester was inactive [99, 158]. Betulone (255), isolated from the bark of *Cupania cinerea* (Sapindaceae), inhibited *P. falciparum* K1 and had moderate cytotoxicity against L6 cells [145].

Happi et al. investigated the chemical constituents of *Entandrophragma congoense* (Meliaceae) bark, a plant used in Cameroonian traditional medicine against malaria. They isolated the apotirucallane triterpenoids prototiamins A–G (256–262) and the known 263 as the major constituents, and gladoral A (264) was obtained as a minor metabolite (Fig. 34) [159]. The compounds displayed antiplasmodial activity against NF54 *P. falciparum* strain with varying levels of toxicity to L6 cells (SI = 4–107). Triterpenoid 256, with a sub-micromolar IC$_{50}$ value, was the most selective against the parasite [160, 161]. Comparing the activities of the compounds allowed some preliminary SAR assumptions. Compounds 256 and 257 differ only in the orientation of the

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| Compound | R$^1$ | R$^2$ | IC$_{50}$ Value | SI |
|----------|-------|-------|-----------------|----|
| DD2 IC$_{50}$ | 0.65 µM | SI = >31 |
| HB3 IC$_{50}$ | 1.9 µM | SI = >11 |
| NHP1337 IC$_{50}$ | 1.4 µM | SI = >14 |
| 246 R$^1$ | α- (E)-p-coum | R$^2$ = OH | |
| DD2 IC$_{50}$ | 1.28 µM | SI = >16 |
| HB3 IC$_{50}$ | 1.02 µM | SI = >20 |
| 247 R$^1$ | β- (Z)-p-coum | R$^2$ = OH | |
| DD2 IC$_{50}$ | 0.63 µM | SI = >32 |
| HB3 IC$_{50}$ | 0.8 µM | SI = 8.8 |
| NHP1337 IC$_{50}$ | 1.53 µM | SI = 4.6 |

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![Fig. 33 Structures of betulin derivatives](image-url)
hydroxy group at C-24 and presence or absence of acetylation at C-7 of ring B. Analogue 256, with an α-oriented OH group and acetylation of the OH at C-7, was twice as active and four times more selective than 257. Compound 258, which has a similar structure to 256 but with an epoxide ring between C-24 and C-25 instead of the free α-OH in 256, was 8 times less selective. These observations suggest a SAR role for these positions that could be exploited further to optimize potency and selectivity. Another tirucallane triterpenoid, isoflindissone lactone (265), was isolated from the dichloromethane extract of *Boswellia serrata* (Burseraceae) oleo-gum resin by bioassay-guided purification of an extract that inhibited *P. falciparum* with IC_{50} = 2.6 µg/mL. Compound 265 was active against the NF54 parasite strain with low toxicity against L6 cells (IC_{50} = 40 µM) [162]. The ethyl acetate stem bark extract of *Kigelia africana* (Bignoniaceae) inhibited *P. falciparum* W2 strain and two field isolates, CAM10 and SHF4 (IC_{50} = 11.15, 4.74 and 3.91 µg/mL, respectively). Phytochemical investigations of this active extract yielded the known triterpenoid 266 alongside other metabolites. Compound 266 was active against the W2 and CAM10 strains, with moderate cytotoxic against monkey kidney (LLC-MK2) cells (IC_{50} = 9.4 µg/mL) [117]. A synergistic effect was observed with a combination of 266 and artemether on the W2mef parasite strain, but the compound had an antagonistic effect with quinine [118].

Bioassay-guided fractionation of the methanol extract of the aerial parts of *Momordica balsamina* (Cucurbitaceae) afforded the new curcurbitacin balsaminol F (267), the glycoside balsaminoside B (268), and the known kuguaglycoside A (269) (Fig. 35). Glycosides 268 and 269 displayed antiplasmodial activity against the 3D7 and Dd2 strains, while the aglycone 267 was much less active. This suggests that the sugar unit is beneficial to the antiplasmodial activity. However, the compounds were not selective when the cytotoxicity against MCF-7 breast cancer cells is compared to the antiplasmodial activity. Interestingly, the triacetyl semi-synthetic derivative 270 of balsaminol F was 22 and 50 times (for 3D7 and Dd2, respectively) more active than the parent compound without cytotoxicity against MCF-7 cells. However, the activity was lost with the corresponding tribenzoyl ester derivative of balsaminol F [163]. Similar improvement in potency and selectivity was observed when karavilagenin C (271), which was isolated from *Momordica balsamina*, and was esterified at C-3 and/or C-23 to give different alkanoyl and benzoyl/cinnamoyl derivatives. For the alkanoyl analogues, the diacetyl and

![Fig. 34 Structures of triterpenes 256-266](image-url)
dipropanoyl derivatives were more active than the mono analogues, while the monobutanoyl compound was more active than the dibutanoyl counterpart. Moreover, all the mono-aryl/cinnamoyl derivatives were superior compared to the diaryl/cinnamoyl counterparts [164]. These observations allow the conclusion that for bulky groups, mono-esterification is optimal for activity, while di-esterification is favoured for the smaller groups. It will be worthwhile to study the preferred point of esterification for the monoesters.

The root bark of *Greenwayodendron suaveolens* (Annonaceae) afforded polycarpol (272) as one of the active metabolites against K1 *P. falciparum*, but it was also cytotoxic against MRC-5 cells (SI = <1) [69]. Antiplasmodial assay of 14 Kenyan medicinal plants identified the methanol root bark extract of *Turraea robusta* (Meliaceae) as the most active against NF54 and K1 parasites (IC50 = 2.4 and 3.5 µg/mL, respectively) [165]. Azadironolide (273) was subsequently isolated as the most active antiplasmodial compound from the plant stem bark with moderate cytotoxicity against Vero cells [166].

An ethnomedicinal survey of plant use in the Northern sector of Kibale National Park in western Uganda indicated that *Neoboutonia macrocalyx* (Euphorbiaceae) is used to treat malaria [167]. Chemical investigation of the plant leaf afforded the new cycloartane triterpenoids neomacrolactone (274), 22α-acetoxyneomacrolactone (275), 6-hydroxyneomacrolactone (276), 22α-acetoxy-6-hydroxyneomacrolactone (277), and 4-methylene-neomacrolactone (278), and the previously reported 22-de-O-acetyl-26-deoxyneoboutomellerone (279) (Fig. 35). These compounds exhibited antiplasmodial activity against FcB1 *P. falciparum*, but were generally cytotoxic against KB and MRC-5 cells. Interestingly, neomacroin (280) with an open ring A, thus lacking an α,β-unsaturated carbonyl conjugated to the cyclopropane ring, showed low cytotoxicity but was slightly less potent (IC50 = 3.2 µM) [168]. Two novel triterpenoids, salvadiolone C (281) and perovskone B (282) (Fig. 36), with rare carbon skeletons, were isolated from an antiplasmodial hexane extract of *Salvia hydrangea* (Lamiaceae). The antiplasmodial activity against K1 parasites was selective when compared to cytotoxicity against L6 cells. The rare carbon scaffolds can be rationalized by a Diels–Alder-type addition of an acyclic monoterpene to a diterpenoid. The monoterpene in the case of 281 is myrcene and trans-β-ocimene for 282, and the additional oxepane ring in 281 confers structural rigidity. These structural types were only previously reported in salvadiol from *Salvia bucharica* and perovskone from *Perovskia abrotanoides*.
(Lamiaceae) [169]. Three new triterpenoid saponins, maesargentoside I, III, IV (283–285) from the leaf extract of *Maesa argentea* (Myrsinaceae) have displayed non-selective antiplasmodial activity against K1 *P. falciparum* [170]. The medicinal mushroom *Ganoderma boninense* produced a new nortriterpenoid with a 3,4-seco-27-norlanostane rearranged skeleton. The metabolite gano- boninketal C (286) inhibited *P. falciparum* 3D7 strain with low cytotoxicity against A549 cells [171]. The antiplasmodial activity of squalene (287), isolated from *Uapaca paludosa* (Euphorbiaceae) trunk bark extract, was reported for the first time. However, it was also cytotoxic against KB and Vero cells [172].

The ethyl acetate extract of the soil fungus *Neosartorya tatenoi* KKU-2NK23 exhibited antiplasmodial activity (IC$_{50}$ = 3.09 µg/mL). A chemical investigation of the fungal material yielded the known meroterpenoid azsonapyrone A (288) (Fig. 36). The compound was active against the K1 strain with low cytotoxicity against KB cells (IC$_{50}$ = 48.18 µg/mL). However, the compound was cytotoxic against cancerous NCI-H187 cells, suggesting some level of selectivity in the toxicity to cells. An analogue of 288, which had a free hydroxy group at C-3 instead of the acetoxy in 288, was inactive, suggesting a SAR role at this position and indicating that acetylation of the free hydroxy is beneficial to activity [173].

**Steroids**

An analysis of 65,000 small molecules using the in silico similarity ensemble approach (SEA), predicted antiplasmodial activity for selected physalins. Physalins B, D, F, and G were then isolated from *Physalis angulata* (Solanaceae) and evaluated for in vitro and in vivo anti-malarial activity. Physalins B (289) and F (290) (Fig. 37) had in vitro activity against W2 parasite but were also cytotoxic (SI = 12 and 6, respectively). Interestingly, all the mice treated with 290 died from an exacerbated infection due to the increase in parasitaemia that was attributed to an immunosuppressive effect of the compound. However, physalin D (291), without the immunosuppressive effect, decreased parasitaemia in *P. berghei* infected mice by 65% at 100 mg/kg [174]. The n-butanol fraction of *Caesalpinia volkensii* (Fabaceae) methanol stem bark extract inhibited *P. falciparum* D6 and W2 strains (IC$_{50}$ = 4.5 and 1.3 µg/mL, respectively) better than the less polar fractions. Bioassay-guided purification led to the isolation of the new steroid glycoside 3-O-[(β-glucopyranosyl-(1→2)-O-β-xylopyranosyl]stigmasterol (292) with antiplasmodial activity against the D6 and W2 strains. Crucially, the aglycone, which was isolated from the chloroform fraction, was inactive, suggesting that the two sugars potentiate antiplasmodial activity [175]. The marine red alga *Halymenia floresii* has produced a new steroid, halyme- niaol (293), which inhibited 3D7 *P. falciparum* and was
not cytotoxic [176]. Chemical re-investigation of the Caribbean sponge *Pandaros acanthifolium* has yielded two new steroid glycosides, pandaroside G (294) and pandaroside G methyl ester (295). The two compounds were active against the K1 strain as well as cytotoxic against L6 cells, indicating non-selective toxicity. The compounds did not inhibit recombinant *P. falciparum* fatty acid biosynthesis enzymes at the highest tested concentration (20 µg/mL) [177].

**Limonoids**

African great apes such as Chimpanzees have been observed to ingest the non-nutritional bitter bark and sap of *Khaya anthotheca* (Meliaceae) in the wild, and it has been proposed that this unusual feeding is for medicinal purposes [178, 179]. In an effort to identify bioactive constituents from this plant, the seed petroleum ether extract was tested against *P. falciparum* and showed good activity (IC$_{50}$ = 0.96 µg/mL). Bioassay-guided purification of the extract yielded the known limonoids grandifolione (296) and 7-deacetylkhivorin (297) (Fig. 38) as the active antiplasmoidal constituents. The compounds inhibited the K1 strain, and 296 was less toxic towards L6 cells than 297, SI = 64 and 11, respectively [180]. Two new antiplasmoidal limonoids, kostchiyienones A (298) and B (299), were isolated from the root extract of *Pseudocedrela kostchyi* (Meliaceae). Previous investigations indicated that the extract inhibited *P. falciparum* schizont development [181]. Antiplasmoidal activity of the new compounds against 3D7 and PfINDO strains was selective, and the compounds were not toxic to HEK239T cells (IC$_{50}$ > 200 µg/mL). The antiplasmoidal activity of limonoids has been attributed to the presence of the α, β-unsaturated carbonyl moiety in the structures, which may be involved in Michael-type addition reactions [182].

**Quassinoids**

The leaf of the tropical Amazonian medicinal plant *Quassia amara* (Simaroubaceae) is used traditionally by people in French Guinea for the preparation of popular anti-malarial remedies, alone or in combination with other plants [183]. The plant leaf extract was prepared according to traditional instructions and found to be active against *P. falciparum* in vitro and in vivo, without signs of general toxicity [184]. The known quassinoid simalikalactone D (300) (Fig. 39), identified as the main antiplasmoidal component of *Quassia amara*, had an IC$_{50}$ of 10 nM against the FcB1 parasite and showed in vivo efficacy (oral) [185]. The known cytotoxicity of quassinoids prompted investigations into the toxicity of 300. The compound displayed antiproliferative activity against cancerous KB cells (IC$_{50}$ = 6.3 nM) but was less cytotoxic against HeLa and noncancerous Vero cells (IC$_{50}$ = 2 and 10 µM, respectively). Similarly, Raji B cells mitotic activity was inhibited at concentrations larger than 45 nM, but no apoptosis or necrosis was observed at a concentration of up to 200 µM of 300. The compound did not inhibit heme crystallization or parasite-induced host erythrocyte membrane permeability. Moreover, 300 showed a stage-specific activity by inhibiting DNA replication in mature trophozoites. An additive effect was observed in combination studies with 300 and the traditional anti-malarials chloroquine, artemisinin, and analogues. Interestingly, a synergistic effect was observed with atovaquone, opening the possibility of combination therapy to combat drug resistance and mitigate toxicity [186].

Two

**Fig. 37** Structures of steroids
more quassinoid metabolites of *Quassia amara*, quassin (301) and neo-quassin (302), isolated from the stem bark, inhibited the MRC-pf-20 and MRC-pf-303 strains. However, the two compounds and the control (artesunate) were less active than the crude stem bark extract \( (IC_{50} = 0.0025 \, \mu g/mL) \), and the extract was not toxic to mice. A combination treatment with artesunate and 301 or 302 showed synergism at a ratio of 1:2 and additive interaction at a 2:1 ratio; a similar result was obtained when 301 and 302 were combined [187]. These findings suggest that other metabolites in the stem bark extract might potentiate the antimalarial activity of these two compounds. The frequent ethnomedicinal usage, superior activity, and general lack of toxicity of *Quassia amara* extract make it an attractive herbal anti-malarial remedy worthy of further development. The acetone stem extract of *Bracea javanica* (Simaroubaceae) produced the antimalarial quassinoids bruceine D (303), and H (304) (Fig. 39). Bruceine D (303) was also isolated from the roots of the plant. Both compounds inhibited *P. falciparum* K1 strain, but 303 was also cytotoxic against cancerous human KB and NCI-H187 cells [188, 189]. *Eurycoma longifolia* (Simaroubaceae) root extract yielded the new 18-dehydro-6α-hydroxyeurycomalactone (305), alongside known eurycomanone (306) and eurycomanol (307), with nanomolar antiplasmodial activity [86]. The bioactivity of quassinoids has been correlated with the presence of an α,β-unsaturated ketone in ring A. Quassinoids possessing an oxymethylene bridge joining C-8 and C-13 have also shown pronounced activity [188]. These
two structural features are considered essential for potent antimalarial activity but might also be responsible for the cytotoxicity of the compounds. Furthermore, hydroxy groups at C-11 and C-12 have been implicated in the cytotoxicity of quassinoids [189]. Thus, medicinal chemistry approaches could be employed to optimize the antimalarial activity and reduce cytotoxicity of this class of compounds, especially since there might be a different mechanism of action from the traditional anti-malarials.

**Polyphenols**

Among the 447 isolated natural products with \(\text{IC}_{50} \leq 3.0 \, \text{µM}\) reported in this review, 17.4% are polyphenols.

**Biflavonoids**

Traditional healers in Congo-Kinshasa claim that the chewing of *Garcinia kola* (Clusiaceae) nuts in small quantities daily can ward off malaria. This ethnomedical use was validated by the activity of seed extracts against *P. falciparum* in vitro and *P. berghei* in vivo [190, 191]. Moreover, 5 µg/mL of a 70% ethanolic extract of the seed inhibited *P. falciparum* by 87%. Subsequent bioassay-guided fractionation led to the isolation of three biflavonones GB1a (308), GB1 (309), and GB2 (310) (Fig. 40), as the antiplasmodial principles. All three compounds exhibited sub-micromolar antiplasmodial activity against the FCR3 strain with low cytotoxicity against cancerous KB3-1 cells (SI = 77 to 900). In vivo treatment of *P. berghei*-infected mice with 100 mg/kg of the principal and most active constituent, 309, led to 52% suppression of parasites. The compound was orally active, which is crucial for an anti-malarial lead, and no visible signs of toxicity were observed in the treated mice [192]. Another biflavonoid, volkensiflavone (311), with antiplasmodial activity against the F32 and FcM29 *P. falciparum* strains, was isolated from *Allanblackia floribunda* (Clusiaceae). Two structural analogues of 311 with an additional hydroxy at C-3‘ on the lower flavone unit were >10 times less active, suggesting a SAR that could be further exploited [193].

**Prenylated flavonoids**

The ethyl acetate extract of *Artocarpus styracifolius* (Moraceae) stem bark (10 µg/mL) inhibited FcB1 *P. falciparum* by 87%. A phytochemical investigation of this extract yielded prenylated flavonoids, the new styracifolin B (312), together with known artonin B (313), artonin F (314), heterophyllin (315) and artheterophyllin B (316) (Fig. 41) [194]. The compounds displayed antiplasmodial activity against FcB1 parasites with varying degrees of cytotoxicity against KB and MRC-5 cells (IC\(_{50}\) = 4.7–97 µM). An assessment of the structural features of the flavonoids shows that the two most cytotoxic compounds 312 and 315 had a prenyl chain at C-3. The C-3 prenyl side chain was transformed into a furan ring that was fused to flavonoid ring B in the most selective analogue (314) [194]. A crude extract from *Macaranga triloba* (Euphorbiaceae) inflorescence showed antiplasmodial activity against the 3D7 strain with an IC\(_{50}\) of 2.01 µg/mL [195]. The prenylated flavonoids nymphaeol C (317) and 6-farnesyl-3’,4’,5,7-tetrahydroxyflavanone (318) were isolated from this extract and inhibited the 3D7 parasites. The compounds also displayed varying levels of cytotoxicity to cancerous HL-60, MCF-7, and HeLa cells (IC\(_{50}\) = 1.3–23 µg/mL), suggesting some degree of selectivity in the toxicity to cellular components [195].

The antiplasmodial activity of *Tephrosia purpurea* (Fabaceae), a widely distributed medicinal plant, was validated in vitro against the D6 and W2 strains [196, 197]. A phytochemical investigation of *Tephrosia purpurea* subsp. *leptostachya* afforded a new antiplasmodial prenylflavone, (E)-5-hydroxytephrostachin (319) (Fig. 41). It was not cytotoxic to cancerous HepG2 cells at 100 µM while being moderately cytotoxic against non-cancerous human cells, indicating selectivity against D6 parasites [198]. The aerial parts of the related *Tephrosia subtriflora* were also active against *P. falciparum* 3D7, D6, and KSM 009 field isolate (IC\(_{50}\) = 4.5–11.4 µg/mL [199]. The prenylated flavonoid MS-II (320) was subsequently isolated from the active extract and inhibited the 3D7, KSM 009, and artemisinin-sensitive F32-TEM strains. The compound was not cytotoxic against Hep2 and Vero...
cells at 247.5 µM, suggesting a selective antiplasmodial activity [199]. Furthermore, the root extract of Tephrosia aequilata, which inhibited 3D7 P. falciparum by 100% at 10 µg/mL, produced the new aequichalcone C (321). It inhibited the 3D7 strain without being cytotoxic against HEK-293 cells up to 40 µM, indicating selectivity [200].

Another prenylated flavonoid, carpachromene (322), was isolated from Flindersia pimenteliana (Rutaceae) as one of the antiplasmodial principles, and it was not cytotoxic against HEK-293 cells at 40 µM [71].

Although many prenylated flavonoids are active against the malaria parasite, many of these compounds are also cytotoxic, and selectivity is a problem. Fröhlich et al. reported that prenylated chalcones isolated from hops (Humulus lupulus, Cannabaceae) interfere with haem degradation in P. falciparum, suggesting a possible mechanism of action [201].

Other flavonoids

Methanol supercritical fluid extraction yielded four kaempferol 3-O-rhamnosides (323–326) from Platanus occidentalis (Platanaceae) and three kaempferol 3-O-glucosides (327–330) from Quercus laceyi (Fagaceae) (Fig. 42) [158]. The glycoside esters exhibited activity against HB3 parasites but were 2–11 times less active against a multidrug-resistant NHP1337 clone. The glucosides 327–330 were also cytotoxic against HeLa cells, while rhamnosides 323–326 were more selective against HB3 parasites (SI = 6–34) [158]. An ethnobotanical survey of medicinal plants used by the people in the Comoros Islands indicated that a decoction of Flacourtia indica (Salicaceae) stem and leaves is used against malaria. But, extracts prepared from the aerial parts of this plant displayed only weak activity against K1 parasites (IC50 = 49 µg/mL) for dichloromethane and > 50 µg/mL for polar extracts [202]. However, in support of the ethnomedical use of the plant, a 95% ethanol extract of Flacourtia indica inhibited the 3D7 strain (IC50 = 0.5 µg/
mL), but was inactive against K1 at the highest tested concentration (10 µg/mL). Chemical investigation of the active extract afforded six phenolic compounds (Fig. 42) of which the flavonolignans, mururin A (331), and catechin-[5,6-e]-4β-(3,4-dihydroxyphenyl)dihydro-2(3H)-pyranone (332) exhibited selective antiplasmodial activity. Compound 331 inhibited 3D7 and K1 P. falciparum, while 332 was active only against the 3D7 strain. Both compounds also inhibited β-haematin formation similar to chloroquine and H2O2-mediated heme degradation, suggesting a possible mechanism of action [203]. The known flavonoid, 3',4',7-trihydroxyflavone (333), isolated from Albizia zygia (Fabaceae) extract, inhibited K1 P. falciparum but was also cytotoxic against L6 cells [204]. (-)-Epigallocatechin-3-gallate (EGCG) (334), the major polyphenol in green tea (Camellia sinensis, Theaceae), displayed antiplasmodial activity against 3D7 P. falciparum. EGCG also inhibited chaperone and ATPase functions by targeting PfHsp70-1 and PfHsp70-2 [205]. A previous study had shown that EGCG did not interfere with the parasite folate pathway. Moreover, the antiplasmodial activity of green tea and 334 was demonstrated previously, and EGCG was shown to have an additive effect in combination with artemisinin [206]. However, a higher IC50 value (37.2 µM) for EGCG against 3D7 parasites was reported in that study, even though comparable assay methods were used to evaluate the activity. The availability, low cost, and lack of toxicity of green tea coupled with the potentiating effect on the antiplasmodial activity of artemisinin could be exploited to design new artemisinin combination therapies [206].

**Coumarins and lactones**

Bioassay-guided fractionation of the rhizome extract of the Korean medicinal plant, Angelica purpuraeefolia (Apiaceae) led to the isolation of the pyranocoumarins 3′-decanoyl-cis-khellactone (335) and 4′-decanoyl-cis-khellactone (336) as the main antiplasmodial compounds (Fig. 43). Both compounds inhibited D10 parasite strains without cytotoxicity against cancerous SK-OV-3 cells, suggesting selectivity towards the parasite [207]. The known metabolite 6-acetyl-2-isopropenyl-8-methoxy-1,3-benzodioxin-4-one (337), with an additional oxygen atom in the lactone ring, was also isolated as the main antiplasmodial constituent from a Carpesium divaricatum (Asteraceae) extract [208]. The dichloromethane
extract of *Malleastrum* sp. (Meliaceae) showed antimalarial activity against the Dd2 strain with IC$_{50}=1.3$ µg/mL. A new butanolid lactone, malleastrumolide A (338), was subsequently isolated from the active extract and was found to inhibit Dd2 parasites, but it was also cytotoxic against A2780 cancer cells [209].

**Phenolic acids, phenylethanoids, phenylpropanoids, and other shikimic acid-derived metabolites**

The leaf extract of *Dacryodes edulis* (Burseraceae), a West African traditional medicinal plant, exhibited antimalarial activity against 3D7 and Dd2 parasites (IC$_{50}=6.45$ and 8.62 µg/mL, respectively) [210]. Antiplasmodial screening of the stem bark extract showed that it was also active with an IC$_{50}$ of 4.34 and 6.43 µg/mL against 3D7 and Dd2 strains, respectively. Chemical investigations of the stem bark extract afforded methyl gallate (339) (Fig. 44) as the most active compound against the same parasite strains without cytotoxicity against LLC-MK2 cells. Preliminary investigations showed that 339 acts on late-stage parasite trophozoites and schizonts. Compound 339 also acts in synergism with quinine but had an additive effect with artemether [211]. A new gallic acid ester, 2,3,4-trihydroxy-2-methylbutyl gallate (340), with activity against D6 and W2 *P. falciparum*, was isolated from the aerial parts of *Limonium leptophyllum* (Plumbaginaceae). The compound was almost twice as active against the chloroquine-resistant W2 strain as against the chloroquine-sensitive D6 strain [212]. Likewise, a galloylated norbegenin derivative, 4′-O-(3′-methylgalloyl)norbegenin (341), was obtained as the most active antimalarial constituent of *Diospyros sanza-minika* (Ebenaceae) stem bark extract. Norbegenin, which was also isolated from the same extract, was 32 times less active (40.15 µM), indicating that the additional galloyl group is beneficial to the antimalarial activity [213]. Antiplasmodial activity was demonstrated for *Anogeissus leiocarpus* (Combretaceae) methanol bark extract (IC$_{50}=18.8$ µg/mL), and ellagic acid (342) was isolated as the most active antimalarial metabolite of the extract against 3D7 *P. falciparum* [214].

The leaf extract of South American folkloric medicinal plant *Jacaranda glabra* (Bignoniaceae) exhibited antimalarial activity against the K1 strain. Bioassay-guided purification was subsequently used to isolate the phenylethanoid glucosides jacaglabrosides A–D (343–346) (Fig. 45). All four jacaranone-based glucosides (343–346) inhibited *P. falciparum* K1 strain. Compounds 344–346 were not cytotoxic, but 343 showed cytotoxicity against L6 cells [216].

The ethyl acetate fraction of *Magnolia grandiflora* (Magnoliaceae) fruit and twig extracts inhibited Dd2 *P. falciparum* (IC$_{50}=10$ µg/mL). The known 4′-O-methyl honokiol (347) was the most active among the isolated bioactive neolignans against the Dd2 strain. The position and number of substituents on the neolignan aromatic rings affected the bioactivity. Honokiol, which is structurally similar to 347 but is not methoxylated, was six times less active (IC$_{50}=16.5$ µM). However, magnolol, which is isomeric to honokiol, was only slightly less active (IC$_{50}=3.4$ µM) than 347, while an additional methoxy group on magnolol (3-methoxymagnolol) resulted in a 30 fold decrease in activity [217]. More SAR studies are needed to fully understand the effect of substituents on the antimalarial activity of simple neolignans. A new dihydrobenzofuranoid neolignan, ococymosin (348), was obtained from the antimalarial hexane stem extract (IC$_{50}=1.25$ µg/mL) of *Ocotea cymosa* (Lauraceae) as the most active metabolite against the Dd2 strain [218]. The antimalarial screening of a
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library of marine- and plant-derived extracts showed that *Grevillea* (Poorinda Queen, Proteaceae) leaf and twigs extract displayed antiplasmodial activity. Subsequent bioassay-guided purification of the active extract yielded the hemiquinone-containing phenylpropanoid glycosides robustasides D (349) and G (350) (Fig. 45) as the main antiplasmodial constituents. Both compounds were more active against chloroquine-resistant *P. falciparum* than to chloroquine-sensitive strains. Compound 350 was more active against the Dd2 and K1 strains, whereas 349 was more active against the multidrug-resistant TM93-C1088 and TM90-C2B strains. Treatment of *P. berghei*-infected mice with 32 mg/kg dose of 350 twice a day for 4 days suppressed parasitaemia by 95% without evidence of toxicity [219]. The phenylpropanoid glycoside vanicoside F (351), isolated as a major constituent of *Polygonum hydropiper* (Polygonaceae) aerial parts, also inhibited *P. falciparum* D6 and W2 strains without cytotoxicity against Vero cells [220].

The culture broth of the *Penicillium* sp. FKI-4410 (*Penicillium viticola* sp. nov) fungus afforded some tropolones, among which puberulic acid (352) and a new derivative viticolin B (353) (Fig. 46) showed activity. Compound 352 showed potent nM activity against K1 and FCR3 parasites and was not cytotoxic against MCR-5 cells, whereas 353 was less active and selective. Treatment of *P. berghei*-infected mice with 2 mg/kg of 352 for 3 days suppressed parasitaemia by 69%, comparable to chloroquine and artesunate. A preliminary SAR of the tropone compounds suggests that a hydroxy group at C-7 and a methoxy group at C-2 are important for activity while a carboxylic acid function at C-4 improves selectivity [221].
A phytochemical reinvestigation of *Cleistochlamys kirkii* (Annonaceae) leaf extract led to the isolation of new polyoxygenated cyclohexenones cleistodienediol (354), cleistodienol B (355), and the known cleistodienol A (356) (Fig. 47). The configuration of the exocyclic double bond in 356 was revised based on the similarity of the nuclear magnetic resonance spectroscopic and specific rotation data with those of 354. The absolute configuration of 356 was established by X-ray diffraction analysis, which showed that it adopts a half-chair conformation. All three compounds inhibited 3D7 and Dd2 *P. falciparum* strains but were also cytotoxic against noncancerous HEK-293 and cancerous MDA-MB-231 cells. The additional acetylation of compound 356 led to a decrease in activity and selectivity, suggesting a SAR role that could be further explored [222].

The strobilurins are used commercially in agriculture as fungicides. An investigation of the extracts from the fungus *Favolaschia tonkinensis* led to the isolation of the β-methoxyacrylate derivatives, 9-methoxystrobilurins A, B, and G (357–359), and oudemansin B (360) (Fig. 48). The compounds were active against K1 *P. falciparum* strain and weakly cytotoxic against Vero cells [223].

Xanthones
The extract from fruit pericarp of *Pentadesma butyracea* (Clusiaceae) exhibited antiplasmodial activity against W2 parasites with IC₅₀ = 1.8 µg/mL. Bioassay-guided purification of the extract yielded the new prenylxanthone pentadexanthone (361), together with the known cratoxylone (362), garcinone E (363) and α-mangostin (364) (Fig. 49). All four xanthones were active against K1 *P. falciparum* strain and weakly cytotoxic against Vero cells [224]. The antiparasmodial activity of 363 from the same plant against FcB1 was previously reported, but it was also cytotoxic against MCF-7 cells [225]. Xanthone 364 was isolated from *Garcinia mangostana* (mangosteen, Clusiaceae) husk and it inhibited FCR3 *P. falciparum* but, surprisingly, it was much less active against the 3D7 strain. Intrapitoneal treatment of *P. berghei* infected mice with 364 at 100 mg/kg suppressed parasitaemia by 80%. Oral treatment produced only 27% suppression. The compound was not cytotoxic to U-937 cells (LC₅₀ = 130.6 µM), but caused haemolysis of red blood cells at 69.7 µM [226]. Another prenylated xanthone, makuraxanthone (365), was isolated from an antiplasmodial extract of *Allanblackia floribunda* (Clusiaceae) and had activity against the F32 and FcM29 parasites [193]. *Hypericum lanceolatum* (Hypericaceae) is a multipurpose medicinal plant that is used by the people in the southwest province of Cameroon to treat fever [227]. In an effort to rationalize this ethnomedicinal use scientifically, the stem bark ethyl acetate fraction was assayed and antiplasmodial activity was observed against the W2mef parasite, IC₅₀ = 5.02 µg/mL. A bioassay-guided purification of the extract afforded 5-hydroxy-3-methoxyxanthone (366) as the most active compound. It inhibited *P. falciparum* SHF4 field isolate but was slightly less active against the W2mef strain. The compound was not cytotoxic against LLC-MK2 cells at the highest concentration tested (100 µg/mL). Interestingly, the 3-hydroxy-5-methoxy isomer of 366 was inactive, suggesting that substitution pattern of the xanthone skeleton play a crucial role in the bioactivity [228]. *Garcinia* species produce a unique group of metabolites called caged *Garcinia* xanthones (CGXs) in which the C-ring of the xanthone skeleton has a prenyl substituent that has been transformed to form a tricyclic ring. It was observed that these compounds with interesting bioactivities tend to localize in cell mitochondria and cause damage to it [229]. Gambogic acid (367) (Fig. 49), the representative CGX, was isolated from *Garcinia*.
(Gamboge) resin and exhibited antiplasmodial activity against Dd2 parasites with a sub-micromolar IC50 value. Chemically modified analogues 368 and 369 that incorporated a triphenylphosphonium group into the CGX skeleton displayed low nanomolar activity against parasite trophozoites and schizonts, whereas replacement of the CGX scaffold with a planar xanthone structure led to a reduction in activity. These observations indicate
the beneficial effect of conjugating a triphenylphosphonium moiety to the CGXs and the vital role of the CGX scaffold in the activity of these compounds. The CGXs caused mitochondrial fragmentation and morphological changes within the parasite but did not affect the mitochondrial electron transport chain. This suggests a different mechanism of action from other anti-malarial drugs, such as atovaquone, that target parasite mitochondria. The cytotoxicity of the compounds against HEK293 cells was in the µM range, making them selectively toxic to the parasite at the active concentration (SI > 100) [230]. A tetrahydroxanthone dimer, dicerandrol D (370), from the endophytic fungus Diaporthe sp. (CY-5188) also inhibited P. falciparum with a sub-micromolar IC_{50} value and moderate cytotoxicity. The bioactivity is influenced by the configuration, and the C-12 epimer, dicerandrol B, was inactive [231].

**Phloroglucinol derivatives**

Two new dimeric phloroglucinols, mallotojaponins B (371) and C (372) (Fig. 50), were obtained from Mallotus oppositifolius (Euphorbiaceae) leaf and inflorescence ethanol extract. Both compounds were active against the Dd2 parasite and cytotoxic against cancerous A2780 cells. Also, the compounds displayed cytoidal activity against the HB3 (LD_{50} 14.6 and 0.81 µM for 371 and 372, respectively) and Dd2 strains (LD_{50} = 6.7 and 0.8 µM for 371 and 372, respectively). Mallotophenone, isolated from the same plant, lacked the prenyl chain of the mallotojaponins and was inactive. Also, 372, with two prenyl chains, was more active than the monoprenylated 371, suggesting that prenylation is essential for the antimalarial activity of these compounds [232]. The synthesis of mallotojaponin C (372) was demonstrated in a three-step procedure [233]. Seven new polycyclic poly-prenylated acylphloroglucinols (PPAPs), symphonones A (373), C–E (374–376), G (377), H (378), and 14-deoxy-7-epi-isogarcinol (379) have been isolated from Symphonia globulifera (Clusiaceae) root bark extract. It was previously observed that the extract inhibited P. falciparum by 97% at a concentration of 10 µg/mL. These benzophenone derivatives were active against FcB1 P. falciparum but were also cytotoxic against MRC-5 cells [234].

**β-Triketones**

This interesting antiplasmodial scaffold is present in compounds isolated from plants of the Myrtaceae. These compounds have been isolated as adducts of phloroglucinol and terpenes, as well as simple acylated syncarpic acid derivatives. A new phloroglucinol β-triketone rhodomyrtosone F (380) (Fig. 51) from Syncarpia glomulifera (Myrtaceae) stem bark extract, displayed sub-micromolar inhibition of Dd2 P. falciparum and only inhibited HEK293 cells by 58% at 50 µM, suggesting selective toxicity to parasites [235]. Likewise, rhodomyrtone (381), from the flower extract of Angophora woodsiana (Myrtaceae), was active against 3D7 and Dd2 parasites but moderately cytotoxic [236]. Tomentosone A (382), with a novel hexacyclic ring system that features a bisfurano moiety, was isolated from the dichloromethane extract of Rhodomyrtus tomentosa leaves (Myrtaceae). The compound inhibited 3D7 and Dd2 parasites without being cytotoxic against HEK293 cells at 40 µM [237]. Watsonianones B (383) and C (384), from the flowers of Corymbia watsoniana (Myrtaceae), have also shown antimalarial activity [238]. Watsonianone C is the first 4,4a,9a-tetrahydro-2H-xanthene-1,3,5,7(6H,8H)-tetraone to be reported while watsonianone B possesses the rare bisfurano moiety present in 382 and is only the fourth fused bisfurano-β-triketone to be reported. Compounds 383 and 384 exerted antimalarial activity on the parasite ring stage, with 383 acting predominantly on early ring stage trophozoites. Tomentosone A (382), with an additional syncarpic acid moiety and an isobutyl instead of the ethylphenyl group, was less active than 383. The beneficial role of the ethylphenyl over the isobutyl chain was further demonstrated by the activity of rhodomyrtosone A, which was 50 times less than that of 383 [238]. Woodsianone B (385), a simple acetylated syncarpic acid derivative with an epoxide-containing isopentyl side chain, was also obtained from Angophora woodsiana and inhibited the 3D7 and Dd2 parasites [236]. Unfortunately, the terpene-β-triketone adducts demonstrated only weak antimalarial activity, and this was attributed to poor water solubility of the compounds. Indeed, the more water-soluble analogues have shown better activity. It is plausible that improving the water solubility might lead to more active compounds. The β-triketone pharmacophore can be considered as a novel antimalarial scaffold [236].

**Other polyphenols**

Atrinorin (386) (Fig. 52) was isolated from the antimalarial Kigelia africana (Bignoniaceae) bark extract and inhibited the CAM10, SHF4, and W2 parasite strains. The polyphenolic depside 386 also inhibited W2mef parasites and showed synergism in combination with artemether [117, 118].

**Quinones and polyketides**

**Anthraquinones**

An antimalarial screening of 6900 extracts identified Kniphofia ensifolia (Asphodelaceae) dichloromethane extract as active against Dd2 parasites (IC_{50} = 6 µg/mL) [239]. Bioassay-guided fractionation afforded the
bisanthraquinones chryslandicin (387) and 10-(chrysophanol-7-yl)-10-hydroxy-chrysophanol anthrone (388), and the phenylanthraquinone, knipholone (389) as active principles (Fig. 53). The compounds displayed activity against Dd2 *P. falciparum* but were also moderately cytotoxic to cancerous A2780 cells [239]. Inhibition of the 3D7 strain was previously reported for all the three compounds, but 387 and 388 were not cytotoxic against KB cells [240]. Aloe-emodin, which was also isolated from *Kniphofia ensifolia*, was less active against the Dd2 parasites (IC$_{50}$ = 58 µM) and did not exhibit antiproliferative activity against A2780 cells. However, a semi-synthetic derivative of aloe-emodin, the 3,4-di-O-methylcaffeoyl ester 390, potently inhibited *P. falciparum* without being cytotoxic [239]. The crude extract of *Kniphofia foliosa* root also inhibited *P. falciparum* W2 and D6 strains with IC$_{50}$ = 11.29 and 8.92 µg/mL, respectively. A reinvestigation of the extract yielded a new bisanthraquinone, 10-(chrysophanol-7-yl)-10-methoxy-chrysophanol anthrone (391), and the compound was more active against the chloroquine-resistant W2 strain than against the D6 strain [241]. The leafhopper pathogenic fungus *Torrubiella sp.* BCC 28517 also produced a dimeric anthraquinone, torrubiellin B (392), with activity
against K1 *P. falciparum*. The new compound, which had rare C-4–C-5′ and C-11–C-10α′ linkages, was cytotoxic against cancerous human KB, NCI-H187, and MCF-7 cells. The structural analogue torrubiellin A, with two less hydroxy groups (C-6 and C-7), was ten times less active against parasites [242]. Antiplasmodial screening of crude extracts of marine actinomycetes from Thailand identified *Streptomyces sp.* BCC45596 to have potent activity with IC₅₀ = 1.45–3.56 µg/mL. Bioassay-guided purification of the extracts led to the isolation of two new C-glycosylated benz[a]anthraquinones, urdamycinone E (393) and G (394), and the known urdamycin E (395). Sub-micromolar antiplasmodial activity was obtained for these compounds against the K1 strain. However, the compounds also showed antiproliferative activity against cancerous KB, MCF-7, and NCI-H187 cells, but were less cytotoxic against non-cancerous Vero cells [243]. The antiplasmodial activity of four more anthraquinones (396–399) from an active root extract of *Rennellia elliptica* (Rubiaceae) was demonstrated [244].
Naphthoquinones
The leaf extract of *Pentas longiflora* (Rubiaceae), which is used in Kenyan folk medicine to treat malaria, was active against *P. falciparum* [245]. Antiplasmodial investigation of the root extract showed a better activity against the W2 and D6 parasites than the leaf extract (IC\(_{50}\) = 0.93 and 0.99 µg/mL, respectively). Phytochemical investigation yielded the pyranonaphthoquinones pentalongin (400) and psychorubrin (401) (Fig. 54) with antiplasmodial activity against W2 and D6 strains. However, both compounds were also cytotoxic [246]. The ethyl acetate extract of *Markhamia tomentosa* (Bignoniaceae) stem bark showed activity against the W2 and K1 strains (IC\(_{50}\) = 1.46 and 2.81 µg/mL, respectively). Two furanonaphthoquinones (402 and 403) were isolated from the extract and inhibited the W2 and K1 parasites. However, 402 and 403 were also cytotoxic against L6 cells [247]. Plumbagin (404) is the major phytochemical in the extracts of several *Plumbago* species (Plumbaginaceae), including *Plumbago indica* and *Plumbago zeylanica*, with anti-malarial activity [248, 249]. Plumbagin (404) inhibited 3D7 and K1 *P. falciparum* strains and suppressed parasitaemia in *P. berghei*-infected mice by 41% after treatment (25 mg/kg body weight). Acute and subacute toxicity was observed in mice after oral administration of 404 above 100 and 25 mg/kg body weight, respectively. The relatively poor in vivo anti-malarial activity of 404 might be due to low bioavailability in living cells [250].

Perylenequinones
The perylenequinones cercosporin (405), 14-O-acetyl-cercosporin (406), and di-O-acetylcercosporin (407) (Fig. 54) were isolated from the culture medium of the plant pathogenic fungus, *Septoria pistaciarum*. Compound 405 was also obtained from an extract of the endophytic fungus *Mycosphaerella* sp. F2140. The phytotoxins 405–407 inhibited *P. falciparum* D6 and W2 strain but were also cytotoxic against MCF-7 and Vero cells. Interestingly, a new cercosporin analogue with a hydroxy and a methoxy group instead of the methylenedioxy bridge in 405–407 was inactive. This suggests a SAR role at these two positions that could be exploited for optimized antiparasitic activity [251, 252].

Other polyketides
The Solomon Island-sourced marine sponge *Xestospongia testudinaria* produced a halenaquinone-type polyketide 3-ketoadoiaquinone A (408) (Fig. 55), which selectively inhibited the FcB1 and 3D7 strains. Halenaquinone, which differs from 408 only in the absence of the dioxothiazine ring, was inactive, indicating that a dioxothiazine ring is necessary for the antiplasmodial activity.
The crude extract of terrestrial Streptomyces sp. BCC71188 from Thailand inhibited P. falciparum (IC$_{50}$ = 0.19 µg/mL). Two benzoquinone polyketides, geldanamycin (409) and 17-demethoxyreblastatin (410), were isolated from the extract and showed antiplasmodial activity against the K1 strain. The quinone moiety in 409 appears to contribute to the cytotoxicity since the structural analogue 410 with a phenol group instead of the quinone was more selective against the parasite [254]. Two new antiplasmodial azaphilones, longirostrerone A (411) and C (412), were isolated from the ethyl acetate extract of the Thailand soil fungus Chaetomium longirostre. Both compounds inhibited K1 P. falciparum but were also cytotoxic against cancerous KB cells. Compound 411 was also cytotoxic against NCI-H187 and MCF-7 cancer cells, whereas 412 was inactive, indicating selective cytotoxicity [255]. Longirostrerone D, which differs from 411 in the configuration of the isochromeno-lactone ring junction and a double bond in the butyrolactone ring, was inactive. Likewise, longirostrerone B, which lacks the lactone moiety, was less active. These observations suggest that the nature of the six-membered ring attached to isochromene, the lactone ring, and the configuration of the compounds play a role in the activity, and further modifications might produce analogues that are more selective.

Three other new cyclohexenones, poupartones A–C (413–415) were isolated from the ethyl acetate leaf extract of Poupartia borbonica (Anacardiaceae) by bio-assay-guided fractionation [256]. The extract was previously shown to inhibit the 3D7 strain of P. falciparum with IC$_{50}$ = 3.28 µg/mL. The compounds were active against W2 and 3D7 parasites but were also cytotoxic against HeLa and WI38 cells. No haemolytic activity was observed with the compounds, indicating that the antiplasmodial activity was due to direct action on the parasites. Treatment of P. berghei-infected mice with 413 (15 mg/kg/day for 4 days) led to 69.5% parasite suppression, but it was also toxic to the mice. A toxicity assay of 413 using the zebrafish embryo model indicated that the compound might be cardiotoxic [256].

The Senegalese marine sponge Axinysa diffei produced an antiplasmodial mixture containing three glycosphingolipids axidjiferosides A–C (416–418) (Fig. 55). The mixture represented 2.16% of the dried sponge lipid content, while axidjiferoside A (416) constituted 60% of the mixture. The compounds were identified as homologs of β-galactopyranosylceramide, containing a 2-amino-1,3,4-trihydroxy-octadecene sphingoid base. Moreover, the fatty acid methyl ester of the major compound (416) was identified as 2-hydroxytetradecanoic acid. The mixture exhibited antiplasmodial activity against the FcB1 strain (IC$_{50}$ = 0.53 µM) and was not cytotoxic against a panel of cancerous cells. The activity also appeared to be parasite selective because Leishmania donovani and Trypanosoma brucei were not susceptible to the mixture [257]. The endophytic fungus Diaporthe miceliae produced epoxycytochalasin H (419) with potent antiplasmodial activity against D6 and W2 parasite strains. The compound was not cytotoxic against Vero cells, indicating that the toxicity to the parasite is selective [258].

Macrocycles

Macrolides

The bromophycolides are diterpene-benzoate macrolides that were isolated from the Fijian marine red alga Callophycus serratus and had antiplasmodial activity [259]. A reinvestigation of Callophycus serratus afforded bromophycochlorides R (420), S (421), and U (422) (Fig. 56) with antiplasmodial activity and moderate cytotoxicity against cancerous cells [260]. Bromophycolides with 15- and 16-membered rings have shown potent antiplasmodial activity. No significant influence of the lactone ring size on activity was observed between 15- and 16-membered lactone rings. The macrolide ring appears to improve
bioactivity, considering that non-macrocyclic diterpene-
benzoic acids and diterpene-phenols were less active.
Furthermore, isolation of the less active 14-membered
ring callophycolide A (IC$_{50}$ = 5.4 µM), which lacked the
bromine atoms and a cyclohexane ring, showed that
these features are not essential but improve the potency
[259, 261]. Some bromophycolides target haem crystalli-
zation, suggesting that the mechanism of action involves
the inhibition of haemoglobin formation [262]. Bastimolide
A (423), a 40-membered ring polyhydroxy macrolide
with 10 stereocentres and a rare tert-butyl terminus, was
isolated from marine cyanobacterium, Okeania hirsuta
(PAB-19MAY11-4) [242]. The planar structure and abso-
lute configuration of the macrocyclic lactone, which con-
sist of a 1,3-diol, one 1,3,5-triol, and six 1,5-diols, were
established by X-ray crystallography. It was hypothesized
that the rare tert-butyl group near the lactone ester in the
bastimolide structure protects the lactone ring
against hydrolysis. The compound inhibited multidrug-
resistant strains TM90-C2A, TM90-C2A, TM91-C235,
and W2 with nanomolar IC$_{50}$ values. Surprisingly, the
chloroquine-sensitive HB3 strain was less susceptible to
423 (IC$_{50}$ in µM). Additionally, the semi-synthetic (2E)-
isomer was more active against the HB3 strain than the
(2Z) natural product. Further investigation of Okeania
hirsuta yielded bastimolide B, in which lactonization
produced a 24-membered ring and a highly oxidized side
chain that terminated in a tert-butyl group. Bastimolide
B was not as active as 423, suggesting that the lactone
ring size affects the potency [263, 264]. The Thailand
marine sponge Pachastrissa nux exhibited antiplasmo-
dial activity against K1 P. falciparum (IC$_{50}$ = 0.7 µg/mL).
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The Thailand marine sponge Pachastrissa nux exhibited antiplasmo-
dial activity against K1 P. falciparum (IC$_{50}$ = 0.7 µg/mL).
(430), and 11,11′-O-dimethylelaipophylin (431) as active metabolite against the K1 strain, but these compounds were also cytotoxic against cancerous and Vero cells [254]. *Streptomyces* sp. BCC72023, isolated from rice stems, produced the macrolide efomycin G (432) and 29-O-methylabierixin (433), with activity against K1 *P. falciparum* [267].
Resorcylic acid lactones

The mycelial culture of the filamentous fungus, *Paecilomyces* sp. SC0924 produced the new 14-membered ring β-resorcylic acid lactones (RALs, Fig. 57) paecilomycins A (434), E (435), F (436), together with aigialomycin B (437) and aigialomycin F (438), all with potent antiplasmodial activity. Paecilomycin E (435) and aigialomycin F (438) showed sub-micromolar inhibition of 3D7 parasites, with all the compounds more potent against the 3D7 than the Dd2 strain, suggesting resistance by the Dd2 strain. The compounds were not cytotoxic against Vero cells at 50 µM [268]. Cochliomycins A–F are structural analogues of the paecilomycins and were initially isolated from the culture broth of *Cochliobolus lunatus* in trace quantities [269, 270]. Two cochliomycin analogues were subsequently isolated in larger amounts from an optimized fermentation broth, and the natural cochliomycins and some derivatives were obtained by semi-synthesis. In contrast to the paecilomycins, the cochliomycins generally showed poor antiplasmodial activity. However, semi-synthetic acetonide derivative 439 inhibited *P. falciparum* (SI = 184) selectively, whereas the hydroxylated parent was inactive. Also, cochliomycin C, the chlorinated derivative of paecilomycin F (436), was inactive. SAR deductions from the RAL structures indicate that the presence of acetyl and acetonide groups on the lactone ring hydroxy groups improve activity, with the acetonide derivative having a superior activity. A chlorine atom on the aromatic C-5 decreases activity, while the C-2 phenolic group is important for selective activity. The presence of an enone moiety in the lactone macrocycle contributes to cytotoxicity, whereas the configuration of the 1,2,3-triol or 1,2-diol stereocentres had a negligible effect on the activity [271].

Cyclodepsipeptides and other peptides

The cyclodepsipeptides lagunamides A–C (440–442) (Fig. 58) were obtained from the marine cyanobacterium, *Lyngbya majuscula*. The planar lagunamide macrocyclic scaffold consists of peptide and polyketide substructures, and the main differences are in the polyketide part. Lagunamides A and B are 26-membered macrocycles, whereas lagunamide C has an additional methylene carbon in the polyketide structure. The compounds exhibited potent antiplasmodial activity against NF54 *P. falciparum* strain and were also cytotoxic against cancerous cells [272, 273]. The double bond in the side chain of 441 might be responsible for the lower activity. Mollemycin A (443), a glyco-hexadepsipeptide with a polyketide residue, was isolated from an Australian *Streptomyces* sp. CMBM0244 and had a potent nanomolar antiplasmodial activity. It was equally active against the 3D7 and Dd2 strains and only slightly cytotoxic against human fibroblast cells (SI > 20), suggesting selectivity against the parasites [274]. Two other antiplasmodial octacyclodepsipeptides, octaminomycins A (444) and B (445), were isolated from Indonesian soil *Streptomyces* sp. RK85-270. The octaminomycin amino acid sequence was established as cyclo-(Pro-N-MeTyr-Leu-Pro-Val-Leu-Phe-Thr). Furthermore, the only structural difference is the presence of propionyl and acetyl chains on the threonine nitrogen in 444 and 445, respectively. Both compounds were active against 3D7, Dd2, and K1 strains, and were not cytotoxic at 30 µM [275]. A new cyclodepsipeptide incorporating a 3-hydroxy-4-methylpentadecanoic acid moiety, fusaripeptide A (446), was obtained from *Mentha longifolia* (Lamiaceae) root endophytic fungus, *Fusarium* sp. from Saudi Arabia. The amino acid sequence was established as cyclo-(Ala-Ala-Thr-Ile-Tyr-Glu). Compound 446 exhibited antiplasmodial activity against D6 *P. falciparum* and was moderately cytotoxic against cancerous L5178Y and PC12 cells [276].

Carmaphycin B (447) (Fig. 59), with an amino acid sequence of l-Val-l-Met sulfone-l-Leu, was isolated from the cyanobacterium, *Symphloca* sp. The tripeptide with hexanoyl and an α,β-epoxyketone groups on the N
and carboxyl ends, respectively, had potent nM in vitro and in vivo antiplasmodial activity, but it was also cytotoxic against HepG2 cells. The synthetically modified analogue 448 with a d-Val-L-Nle-L-Leu amino acid sequence showed improved antiplasmodial activity and selectivity (SI = 379). The peptides act in synergy with artemisinin and kill the parasite by targeting the β5 subunit of Plasmodium proteasome [277]. A marine actinobacteria from Papua New Guinea, Streptomyces bangulaensis, produced the antiplasmodial tetrapeptide, actinoramide A (449).
The compound displayed sub-micromolar antiplasmodial activity against *P. falciparum* Dd2, HB3, 7G8, GB4, and cp250 strains, and no cytotoxicity. The 25-epimer of 449, 25-epi-actinoramide A was about 20-fold less active, suggesting an influence of the configuration on activity. Actinoramide F, which is structurally similar to 449 but has a 5-amino-5,6-dihydrouracil terminus instead of the cyclic 2-amino-4-ureidobutanonic acid of 449, was inactive. This suggests that the terminal substructure of the actinoramides is crucial for antiplasmodial activity [278]. A new antiplasmodial cyclic tetrapeptide, apicidin F (450), was isolated from the rice fungus pathogen, *Fusarium fujikuroi*, and the amino acid composition was established to be L-tryptophan, D-pipecolic acid, L-phenylalanine, and L-2-amino-octanedioic acid [279].

Cyclopeptide alkaloids are 13, 14, or 15-membered ring polyamides with a styrilamine unit, a β-hydroxy amino acid and other common amino acid forming the macrocycle. The macrocyclic polyamide has an attached side chain, which could be basic or neutral. Spinanine B (451) (Fig. 59), a cyclopeptide alkaloid from the stem bark of *Ziziphus spina-christi* (Rhamnaceae), inhibited the K1 strain of *P. falciparum* without cytotoxicity to MRC-5 cells at 64 µM [280]. Evaluation of the antiplasmodial activity of 19 cyclopeptide alkaloids facilitated some SAR conclusions. Preliminary SAR studies indicated that the 13-membered ring cyclopeptide alkaloids were generally more active than the 14 and 15 membered analogues. Also, a methoxy group on the styrilamine moiety was more favourable for antiplasmodial activity than a hydroxy group [281, 282].

**Cyclic phosphotriesters**

A marine actinobacterium, *Salinospora* sp., produced a new class of antiplasmodial scaffold based on a bicyclic phosphotriester core, substituted with alkyl chains. Among the new compounds, salinipostins A-D, F-G, and I (452–458) (Fig. 60) potently inhibited W2 *P. falciparum* without cytotoxicity. Preliminary SAR findings indicated that an increase in alkyl chain length attached to the phosphoester oxygen (R²) and vinyl carbon (R¹) led to increased activity while branching of the R¹ alkyl causes a slight reduction in activity. The most active 452 had sub-micromolar IC₅₀ values and stage-specific activity on early stage parasite ring forms, but parasite trophozoites were less susceptible. The compound did not affect parasite schizonts, indicating that it acts by disrupting the processes required for the establishment or growth of intracellular parasites. Salinipostin A (452) did not inhibit haemozoin formation but appears to cause cellular disorganization and disintegration of internal structures. Moreover, experiments for resistance selection
under three different conditions failed to identify mutant resistant strains, suggesting that the compound may be less susceptible to resistance development. These compounds represent a new class of antiplasmodial agents, and further biological studies on them are warranted [283].

**Mechanism of action of antiplasmodial natural products: Plasmodium cellular targets identified for natural products**

Understanding the mechanism of action of bioactive molecules facilitates the development of leads into improved therapeutic compounds and aids in the understanding of resistance evolution. Natural products have proven to be a prolific source of drug leads, but limited knowledge about the mechanism of action often impedes further development [284]. In order to understand the mechanism of action of anti-malarial natural products, it is necessary to identify the molecular targets in the parasite. The anti-malarial drugs in current use are based on pharmacophores acting on a small number of targets as their mechanism of action. The use of these compounds as monotherapy resulted in the emergence of multidrug-resistant parasites [285, 286]. Many of the candidates currently in the anti-malarial drug pipeline are based on chemical modifications to overcome the handicaps of the traditional anti-malarials [287]. Eventual development of resistance to these new therapies when they become clinically useful is inevitable. Therefore, it is imperative to discover new therapeutics with novel targets and mechanisms of action. The increased understanding of the *Plasmodium* parasite biology following the sequencing of its genome has led to the identification of novel potential drug targets that are thought to be essential for parasite survival [288].

Crucial enzymes and macromolecules in the parasite fatty acid, haemoglobin, protein, Ca$^{2+}$ metabolism, glyoxalase detoxification system, and protein folding pathways have been inhibited by natural products. Reports on natural products as inhibitors of potential and proven antiplasmodial targets together with the mechanism of action are summarized in Table 1. Natural products have also modulated their parasite killing effect by disrupting the haem detoxification systems as well as induction of oxidative stress and lipid peroxidation in the parasite (Table 1). Some natural products have also been reported to mediate antiplasmodial activity by inducing morphological and ultrastructural changes that are detrimental to parasite viability [230, 289].

**Natural products with transmission-blocking potentials**

Malaria chemotherapy has focused mainly on controlling the disease. Thus, most anti-malarial drugs act on asexual blood stage parasites that are responsible for the clinical manifestations of the disease. However, there has been a shift in focus towards malaria elimination strategies. In this regard, compounds with activity against asymptomatic gametocytes and liver stage parasites, including hypnozoites (prophylaxis), are crucial to the eradication agenda. As yet, artesunate, artemether, methylene blue, and primaquine are the known gametocidal agents, with primaquine being the only approved prophylactic and gametocytocidal drug [309]. Some natural products have shown transmission blocking potential by exhibiting activity against one or more of these parasite life cycle stages. These natural products are summarized in Table 2. Similarly, extracts from *Zanthoxylum heitzii*, *Vernonia amygdalina*, *Artemisia afra*, *Trichilia emetica*, *Turraea floribunda*, and *Leonotis leonurus* have shown gametocidal activity [65, 310, 311]. The standardized commercial preparation NeemAzal®, an azadirachtin-enriched neem extract, has also demonstrated potent transmission-blocking activity ex vivo and in vivo [312, 313]. The targeting of gametocytes is indeed of great importance in the fight against malaria. The limited information available in the literature on drugs with this activity may be a reflection of the difficulty of assaying gametocidal activity.

**Conclusions**

The present review covered the antiplasmodial natural products reported between 2010 and 2017. A breakdown of the statistics of compounds and the biological source reported per year is given in Fig. 61. A total of 447 compounds derived from plant, microorganisms, and marine organisms were found to have IC$_{50}$ ≤ 3.0 µM against at least one strain of asexual blood-stage *P. falciparum*. Some of these compounds showed potent selective activity against parasites. However,
Table 1  Mechanism of action of antiplasmodial natural products

| Pathway                          | Mechanism of action                  | Target                                                                                       | Compound                     | Compound class               | References |
|----------------------------------|--------------------------------------|------------------------------------------------------------------------------------------------|------------------------------|------------------------------|------------|
| Fatty acid metabolism            | Inhibition of type II fatty acid synthase (FAS II) enzymes | Plasmodium falciparum enoyl-ACP reductase (PfFabI)                                          | Oroidin                      | Bromopyrrole alkaloid         | [290]      |
|                                  |                                      |                                                                                                | Luteolin 7-O-β-D-glucopyranoside | Flavonoid glycoside          | [291]      |
|                                  |                                      |                                                                                                | Anthecularin                 | Sesquiterpene lactone        | [292]      |
|                                  |                                      |                                                                                                | 4-Hydroxyanthecotulide       | Sesquiterpene lactone        | [293]      |
|                                  |                                      |                                                                                                | 4-Acetoxyanthecotulide       | Sesquiterpene lactone        | [293]      |
|                                  |                                      |                                                                                                | Mucusisoflavone C            | Flavonoid                    | [294]      |
|                                  |                                      |                                                                                                | 3-O-Methylquercetin          | Flavonoid                    | [294]      |
|                                  |                                      |                                                                                                | Isowightone                  | Flavonoid                    | [294]      |
|                                  |                                      |                                                                                                | Evernic acid                 | Phenolic acid                | [295]      |
|                                  |                                      |                                                                                                | Psoromic acid                | Phenolic acid                | [295]      |
|                                  |                                      |                                                                                                | Methylenebissindinin         | Flavonoid                    | [296]      |
|                                  |                                      | Plasmodium falciparum β-ketoacyl-ACP reductase (PfFabG)                                       | Anthecularin                 | Sesquiterpene lactone        | [292]      |
|                                  |                                      |                                                                                                | 4-Hydroxyanthecotulide       | Sesquiterpene lactone        | [293]      |
|                                  |                                      |                                                                                                | 4-Acetoxyanthecotulide       | Sesquiterpene lactone        | [293]      |
|                                  |                                      |                                                                                                | Psoromic acid                | Phenolic acid                | [295]      |
|                                  |                                      | Plasmodium falciparum β-hydroxyacyl-ACP dehydratase (PfFabZ)                                  | Evernic acid                 | Phenolic acid                | [295]      |
|                                  |                                      |                                                                                                | Vulpic acid                  | Phenolic acid                | [295]      |
|                                  |                                      |                                                                                                | Psoromic acid                | Phenolic acid                | [295]      |
|                                  |                                      |                                                                                                | Catechin gallate             | Catechin                     | [297]      |
|                                  |                                      |                                                                                                | Bromopyrrolothromarginin     | Bromopyrrole alkaloid        | [93]       |
|                                  |                                      | Plasmodium falciparum β-hydroxycyclopentyl-ACP dehydratase (PfFabZ)                          | Bromophylolide A             | Macrocyclic meroditerpene    | [262]      |
|                                  |                                      |                                                                                                | Bergenin                     | Phenolic glycoside           | [298]      |
|                                  |                                      |                                                                                                | Fraxetin                     | Coumarin                     | [299]      |
|                                  |                                      |                                                                                                | 1,3,6-Trihydroxy-2-(3-methyl butadienyl-7-methoxy-8-(3-methyl but-2-enyl)xanthene-9-one | Xanthone                     | [300]      |
|                                  |                                      |                                                                                                | 2,4-6-O-Benzoyl-β-D-glucopyranosyloxy)-7-(1α, 2a, 6α-trihydroxy-3-oxocyclohex-4-enyl)-5-hydroxybenzyl alcohol | Phenolic glycoside           | [301]      |
|                                  |                                      | Detoxification of haem                                                                      | Dimethylisoborreverine       | Indole alkaloid               | [46]       |
|                                  |                                      |                                                                                                | Nitidine                     | Benzopanthenidine alkaloid    | [62]       |
| Pathway                          | Mechanism of action                                                                 | Target                                      | Compound                     | Compound class          | References |
|---------------------------------|------------------------------------------------------------------------------------|---------------------------------------------|------------------------------|-------------------------|-------------|
|                                  | Inhibition of β-haematin formation, inhibition of H2O2 and glutathione mediated hemin degradation | Axisonitrile-3                             | Axisonitrile-3               | Sesquiterpene isonitrile | [154]       |
|                                  | Inhibition of β-haematin formation, inhibition of H2O2 mediated haemin degradation | Diiisocyanoadociane                        | Diiisocyanoadociane          | Diterpene isonitrile    | [154]       |
|                                  |                                                                                     | Catechin-[5,6-e]-4β-(3,4-dihydroxyphenyl) dihydro-2(3H)-pyranone | Catechin-[5,6-e]-4β-(3,4-dihydroxyphenyl) dihydro-2(3H)-pyranone | Phenylpropanoid catechin | [203]       |
|                                  |                                                                                     | Mururin A                                  | Mururin A                   | Phenylpropanoid catechin | [203]       |
|                                  |                                                                                     | JB42C                                       | JB42C                       | Sesquiterpene lactone   | [302]       |
| Oxidative stress                | Production of ROS and lipid peroxidation product                                   | Trafficking, transmembrane and vesicular transport parasite proteins | Plakortin                    | Coumarin lactone        | [302]       |
| Haemoglobin degradation         | Inhibition of food vacuole falcipains                                              | Falcipain 2                                | 2,3,6-Trihydroxy benzoic acid | Phenolic acid            | [304]       |
|                                  |                                                                                     |                                             | 2,3,6-Trihydroxy methyl benzoate | Phenolic ester           | [304]       |
|                                  |                                                                                     |                                             | Symplastatin 4              | Depsipeptide            | [284]       |
|                                  |                                                                                     |                                             | Symplastatin 4              | Depsipeptide            | [284]       |
| Glyoxalase detoxification system | Inhibition of Plasmodium falciparum glyoxalase I (PfGLO1)                         | Falcipain 2' and 3                        | Puberulic acid              | Tropone                 | [305]       |
|                                  |                                                                                     |                                             | Hinokitiol                  | Tropone                 | [305]       |
|                                  |                                                                                     |                                             | Tropolone                   | Tropone                 | [305]       |
| Protein folding                 | Inhibition of Plasmodium falciparum Hsp70-1 (PfHsp70-1) chaperone function          | (PfHsp70-1)                                | Malonganenone A             | Purine alkaloid         | [306]       |
|                                  |                                                                                     |                                             | Malonganenone C             | Alkaloid                | [306]       |
|                                  |                                                                                     |                                             | Lapachol                    | Naphthoquinone          | [306]       |
|                                  | Inhibition of chaperone and ATPase functions                                        | PfHsp70-1, PfHsp70-2                      | Epigallocatechin 3-gallate   | Catechin                | [205]       |
| Protein degradation             | inhibition of Pf20S proteasome                                                      | β5 subunit                                 | Carmaphycin B               | Tripeptide              | [277]       |
| Ca2+ metabolism                 | Inhibition of SERCA-type Ca2+-ATPase                                               | PIATP6                                     | Artemisinins                | Sesquiterpene endoperoxide | [307]       |
| Protein biosynthesis            | Inhibition of cytoplasmic lysyl-tRNA synthetase                                     | PfLysyl-tRNA synthetase                    | Cladosporin                 | Isocoumarin             | [308]       |
others were equally cytotoxic against cancerous and/or noncancerous cells. Notwithstanding the cytotoxicity, we have considered these compounds to be promising anti-malarial hits of which the cytotoxicity could be mitigated by medicinal chemistry approaches, as was demonstrated, for example, with ferruginol (230) and caramaphycin B (447) [149, 277]. Also, some of these compounds could serve as templates for designing novel antiplasmodial pharmacophores using the strategy of diversity-oriented synthesis. More than half of the compounds belong to three major chemical classes comprising alkaloids (31.9%), terpenoids (30.8%), and polyphenols (17.4%). This is consistent with the phytochemical distribution of antiplasmodial compounds from earlier reviews [12, 13]. This review also discussed compounds with potent selective antiplasmodial activities that belong to classes from which antiplasmodial activity has not been previously reported. Such novel antiplasmodial scaffolds, e.g. the tropolones and cyclic phosphotriesters, are important in the battle against malaria because these compounds might possess a novel

### Table 2 Natural products with transmission-blocking potential

| Compound           | Parasite          | Active on                  | Activity                                                                 | IC<sub>50</sub>     | References |
|--------------------|-------------------|----------------------------|--------------------------------------------------------------------------|----------------------|------------|
| Dihydronitidine    | *Plasmodium berghei* | Early mosquito stage      | Inhibition of ookinete formation                                         | 1.7 µM               | [65]       |
| Heitziquinone      | P. berghei        | Early mosquito stage      | Inhibition of ookinete formation                                         | 17 µM                | [65]       |
| Mallojaponin C     | *P. falciparum NF54* | Stage V gametocytes      | Gametocytocidal                                                         | 3.6 µM               | [232]      |
| Carmaphycin B      | *P. falciparum NF54* | Stage V gametocytes      | Gametocytocidal                                                         | 160 nM               | [277]      |
| Carmaphycin B      | *P. berghei*      | Liver stage               | Gametocytocidal. Inhibition of microgamete exflagellation. Prevent oocysts development in mosquito at 3.84 µM | 61.6 nM              |            |
| Parthenine         | *P. falciparum NF54* | Stage V gametocytes      | Early mosquito stage Inhibition of ookinete formation 100% inhibition at 191 µM | [314]                |
| Parthenolide       | *P. falciparum NF54* | stage V gametocytes      | Gametocytocidal. Inhibition of microgamete exflagellation. Prevent oocysts development in mosquito at 4 µM | [314]                |
| Deacetylnimbim     | *P. berghei*      | Early mosquito stage      | Inhibition of ookinete formation                                         | 100% inhibition at 100 µM | [315]      |
| Azadirachtin       | *P. falciparum NF54* | Stage V gametocytes      | 100% inhibition of microgamete exflagellation                            | [316]                |
| Vernodalol         | *P. berghei*      | Early mosquito stage      | Inhibition of early sporogenic stages development                       | 18.7 µM              | [310]      |
| Vernolide          | *P. berghei*      | Early mosquito stage      | 9–33% inhibition of early sporogenic stages development at 50 µM         | [310]                |
| Usnic acid         | *P. berghei*      | Liver stage               | Inhibition of intracellular development                                 | 2.3 µM               | [295]      |
| Vulpic acid        | *P. berghei*      | Liver stage               | Inhibition of intracellular development                                 | 10.2 µM              | [295]      |
| Psoromic acid      | *P. berghei*      | Liver stage               | Inhibition of intracellular development                                 | 31.6 µM              | [295]      |
| Evernic acid       | *P. berghei*      | Liver stage               | Inhibition of intracellular development                                 | 77.3 µM              | [295]      |
| Balsaminol F       | *P. berghei*      | Liver stage               | Inhibition of intracellular development                                 | >95% inhibition at 15 µM | [163]      |
| Balsaminside B     | *P. berghei*      | Liver stage               | Inhibition of intracellular development                                 | >95% inhibition at 15 µM | [163]      |
| Triacetyl balsaminol F | *P. berghei* | Liver stage               | Inhibition of intracellular development                                 | >95% inhibition at 15 µM | [163]      |
| 6-Deoxy-8-O-methylrabelomycin | *P. berghei* | Liver stage               | Inhibition of intracellular development                                 | 18.5 µM              | [317]      |
| X-14881 E          | *P. berghei*      | Liver stage               | Inhibition of intracellular development                                 | 3.0 µM               | [317]      |
| Marilone A         | *P. berghei*      | Liver stage               | Inhibition of liver cell infection                                       | 12.1 µM              | [318]      |
mechanism of action and expand the therapeutic arsenal against the disease.

Many of the plants were investigated based on the ethnobotanical history of use against malaria, while the non-plant materials were mostly investigated because of their chemical profiles. This underscores the need to employ the dual approach of ethnobotanical reputation and chemical profiling in the search for anti-malarial natural products. Although fewer marine and microorganisms have been screened for antiplasmodial compounds compared to plants, the diverse nature of metabolites produced by these alternative sources presents a compelling case for intensive exploration. Only a small number of in vivo studies to validate the in vitro efficacy of these compounds have been conducted. This is not surprising considering that natural products are usually isolated in small amounts, which is barely sufficient for in vitro testing. Nevertheless, the need for in vivo confirmation of observed in vitro potency could not be overemphasized. Therefore, efficient total synthesis of the most promising compounds identified in this review should be prioritized.

It is now accepted that the *Plasmodium* parasite transmission from an infected host to uninfected mosquitoes should be blocked to curtail the spread of malaria. Compounds with activity against sexual and liver stage parasites are therefore crucial to the malaria eradication agenda. Sadly, only a few chemical compounds have a proven ability to kill liver and sexual stage parasites. In spite of the fruitful relationship between malaria chemotherapy and natural products, only a few natural products have been evaluated for activity against the parasite gametocytes and liver forms. As this review has shown, the few investigated natural products have shown promise. Therefore, the exploration of natural products in this regard cannot be overemphasized. The compounds covered in this review will be a good starting point, since natural products, unlike the synthetic counterparts, might have multi-stage activity. Priority should be given to compounds of which the mode of action does not involve the inhibition of haemozoin formation since stage V gametes, which are the transmissible form of the parasite, do not digest haemoglobin. Standardized assay methods for evaluating late stage gametocidal and liver stage activities have been developed that will aid in the high-throughput screening of natural products [319, 320].

**Supplementary information**

*Supplementary information* accompanies this paper at https://doi.org/10.1186/s12936-019-3026-1.

*Additional file 1.* Antiplasmodial activity reported (2010–2017) for all natural products, irrespective of level of activity (no cutoff value for activity).
Abbreviations
ACT: artemisinin-based combination therapy; ATPase: adenosine triphosphatase; CGX: Garcinia xanthones; DDT: dichlorodiphenyltrichloroethane; DGAT: diacylglycerol O-acyltransferase; DNA: deoxyribonucleic acid; EGGC: epigallocatechin-3-gallate; ELISA: enzyme-linked immunosorbent assays; Glu: glutamic acid; HRP: histidine-rich protein 2; Ile: isoleucine; LC-MS: liquid chromatography-mass spectrometry; Leu: leucine; Met: methionine; MeTyr: methyl tyrosine; Nle: norleucine; µM: micromolar; nM: nanomolar; NMR: nuclear magnetic resonance spectroscopy; PDDGAT: Plasmodium falciparum diacylglycerol O-acyltransferase; PfHsp: Plasmodium falciparum heat shock protein; Phe: phenylalanine; pLDH: Plasmodium lactate dehydrogenase protein; PPAP: polyphenylated acylphloroglucinol; Pro: proline; ROS: reactive-oxygen species; SAR: structure–activity relationship; St: selectivity index; Thr: threonine; USA: United States of America; Val: valine; WHO: World Health Organization.

Authors' contributions
The two authors have equally contributed to the concept and writing of the review. Both authors read and approved the final manuscript.

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