Review

Antimalarial Activity of Plant Metabolites

Wen-Hui Pan 1, Xin-Ya Xu 1,2, Ni Shi 1, Siu Wai Tsang 1 and Hong-Jie Zhang 1,*

1 School of Chinese Medicine, Hong Kong Baptist University, 7 Baptist University Road, Kowloon Tong, Kowloon, Hong Kong SAR, China; 13480448@life.hkbu.edu.hk (W.-H.P.); xuxinya@scsio.ac.cn (X.-Y.X.); 14252252@life.hkbu.edu.hk (N.S.); tsang@hkbu.edu.hk (S.W.T.);
2 CAS Key Laboratory of Tropical Marine Bio-resources and Ecology, Guangdong Provincial Key Laboratory of Applied Marine Biology, South China Sea Institute of Oceanology, Chinese Academy of Science, Guangzhou 510070, China

* Correspondence: zhanghj@hkbu.edu.hk; Tel.: +852-3411-2956; Fax: +852-3411-2461

Received: 13 April 2018; Accepted: 2 May 2018; Published: 6 May 2018

Abstract: Malaria, as a major global health problem, continues to affect a large number of people each year, especially those in developing countries. Effective drug discovery is still one of the main efforts to control malaria. As natural products are still considered as a key source for discovery and development of therapeutic agents, we have evaluated more than 2000 plant extracts against Plasmodium falciparum. As a result, we discovered dozens of plant leads that displayed antimalarial activity. Our phytochemical study of some of these plant extracts led to the identification of several potent antimalarial compounds. The prior comprehensive review article entitled “Antimalarial activity of plant metabolites” by Schwikkard and Van Heerden (2002) reported structures of plant-derived compounds with antiplasmodial activity and covered literature up to the year 2000. As a continuation of this effort, the present review covers the antimalarial compounds isolated from plants, including marine plants, reported in the literature from 2001 to the end of 2017. During the span of the last 17 years, 175 antiplasmodial compounds were discovered from plants. These active compounds are organized in our review article according to their plant families. In addition, we also include ethnobotanical information of the antimalarial plants discussed.

Keywords: anti-malaria activity; plants; natural products; ethnopharmacology; Plasmodium parasites

1. Introduction

Malaria is still considered as a major global health problem, affecting a large population of the world. According to World Health Organization (WHO), there were about 216 million malaria cases globally and 445,000 deaths in 2016. Most of the cases and the deaths occurred in the WHO African region and affected primarily children and pregnant women [1].

P. falciparum, P. vivax, P. ovale, P. malariae and P. knowlesi are the five Plasmodium species that cause malaria disease in humans. P. falciparum is the deadliest strain that causes malaria and this form of parasite predominates in Africa [2,3]. Humans get infected with malaria parasites through the bites of female anopheline mosquitoes [4]. The Plasmodium parasites travel through blood and become mature and reproduce in the liver, leading to malaria disease. The common symptoms of malaria are fever and headache, and in severe cases, malaria causes death [5].

Currently, there is no commercially available malaria vaccine, though efforts to develop vaccines are still ongoing. The most promising vaccine candidate is RTS, S/AS01, which is in clinical trials for treatment of malaria caused by P. falciparum [1]. Several medications are available to prevent malaria for travellers in malaria-endemic countries, and a number of drugs are available for treatment of those who have the disease [6].
In 1820, French scientists Pelletier and Caventou discovered quinine (I) as the first antimalarial drug, which was originally isolated from the barks of *Cinchona* species (Rubiaceae) (Figure 1). *Cinchona* plants are used as folk medicines in South America by Peruvian Indians, and they were introduced to Europe in the 1700s [7]. Quinine is commercially obtained by solvent extraction from wild-growing *Cinchona* species in South America, or the plants cultivated in Indonesia [8].

Chloroquine (II) and its derivative 4- aminoquinoline were developed in the 1940s. They are widely used as antimalarial drugs, even today. The effectiveness of the drugs, however, has declined rapidly since the 1960s, which was due to the development of drug resistance by *P. falciparum* strains, leading to a significant malaria-associated death rate [9]. Mefloquine (III), is a 4-quinolinemethanol derivative obtained via total synthesis. It was introduced as a new antimalarial drug in 1985. The drug can be used to treat mild or moderate malaria but should not be used to treat severe malaria [10].

![Antimalarial drugs developed from plants.](image)

The current antimalarial drug of choice is artemisinin (Qinghaosu, IV), which was originally obtained from the leaves of Qinghao [*Artemisia annua* L. (Asteraceae)] in the 1970s. The compound is clinically effective against chloroquine-resistant malaria strains [11]. The plant Qinghao has been used as a traditional medicine in China for the treatment of fever of malaria origin for about 2000 years [12]. A large number of artemisinin analogs have also been synthesized. The best known among these derivatives are artemether, arteether (artemotil), artesunate and arteminol (β-dihydroartemisinin, DHA) [13]. Artemisinin and its semi-synthetic derivatives have shown better efficacy than quinine for both children and adults patients [14].

Although the anti-parasitic mechanism of action of artemisinin is still in question [15], the endoperoxide bridge is regarded as the key functional group responsible for eliciting free radical-mediated parasite killing mechanisms. According to one school of thought, *Plasmodium* parasites live and reproduce in the host by ingesting red blood cell hemoglobin. This results in an accumulation of heme Fe$^{2+}$ in the parasite. Fe$^{2+}$ firstly interacts and cleaves the peroxide bridge of artemisinin to form highly reactive free radicals, which in turn cause a series of parasite molecular events and eventually kill the parasites [16]. The most used artemisinin derivative today is the prodrug, dihydroartemisinin (V), which is metabolized into the pharmacologically active artemisinin (IV) in the body [17]. Artesunate was investigated as a potential inhibitor of the essential *P. falciparum* exported protein 1 (EXP1), a membrane glutathione S-transferase [18].

Clinically, it is unwise to use artemisinin as the lone therapy due to the potential risk of the parasites to develop resistance to this drug. Indeed, artemisinin drug resistance has been already detected in some Southern Asian countries: Lao People’s Democratic Republic, Cambodia, Thailand, Myanmar and Viet Nam [1]. This risk has led to the withdrawal of artemisinin monotherapy from clinical applications.

At present, the use of artemisinins in combination with other drugs, known as artemisinin-based combination therapy (ACT), is the most effective to treat malarial disease caused by *P. falciparum* infection. Five currently available ACTs are artemether in combination with lumefantrine, and four other forms based on artesunate in combination with amodiaquine (two formulations), mefloquine and sulfadoxine+pyrimethamine [1]. Unfortunately, resistance has already been detected to both
artemisinin and artesunate components of the multiple ACTs, as well as the non-artemisinin-based combination comprising atovaquone and proguanil. The current available antimalarial drugs are listed in Table 1 [1,19,20].

Table 1. Available antimalarial drugs.

| Chemical Class         | Generic Names                      | Chemical Class         | Generic Names                      |
|------------------------|------------------------------------|------------------------|------------------------------------|
| 4-Aminoquinolines      | chloroquine                         | Antibiotics            | azithromycin                        |
|                        | amodiaquine                         |                        | clindamycin                         |
|                        | piperaquine                         |                        | doxycycline                         |
| 8-Aminoquinolines      | primaquine                          | Artemisin-based combination therapy (ACT) |
|                        | quinine                             |                        | artesunate/sulfadoxine              |
|                        | quinidine                           |                        | pyrimethamine                       |
|                        | mefloquine                          |                        | primaquine                          |
|                        | halofantrine                        |                        | artesunate/sulfadoxine/pyrimethamine/pyrimethamine |
|                        | lumefantrine                        |                        | primaquine                          |
| Arylamino-alcohols     | proguanil                           | Antibiotics-antimalarial drug combination |
|                        | chlorproguanil                      |                        | doxycyclin/quinine                  |
| Biguanides             |                                    |                        | doxycycline/artesunate              |
|                        |                                    |                        | clindamycin/artesunate              |
| Glycosylamines         | pyrimethamine                       |                        | clindamycin/mefloquine              |
|                        | proguanil                           |                        |                                    |
|                        | cycloguanil                         |                        |                                    |
|                        | chlorproguanil                      |                        |                                    |
|                        | chlorcycloguanil                    |                        |                                    |
| Naphthoquinone         | atovaquone                          | Other combination therapy |
| Sesquiterpene lactones| artemisinin                         |                        | sulfadoxine/pyrimethamine/bulaquine/chloroquine |
|                        | arteether                           |                        | dapsone/chloroquine                 |
|                        | artemether                          |                        | dapsone/proguanil                   |
|                        | arteunate                          |                        | atovaquone/proguanil                |
|                        | dihydroartemisinin                  |                        |                                    |
| Sulfonamides/Sulfones  | sulfadoxine                         |                        |                                    |
|                        | sulfalene                           |                        |                                    |
|                        | dapsone                             |                        |                                    |

In the search for drug candidates, the initial step is the employment of appropriate bioassays to evaluate the antiplasmodial activity of a candidate. Several strains of *P. falciparum* have been used for this purpose in the past. The strains of *P. falciparum* that are sensitive and resistant to chloroquine are frequently used for antimalarial drug discovery programs. D6, D10, 3D7, TM4 and PoW are chloroquine-sensitive strains, whereas, W2, FCR-3, FcB1 and Dd2 represent chloroquine-resistant strains, and K1 is a multidrug resistant strain.

The need to discover effective and non-drug resistant antimalarial drugs is urgent as *Plasmodium* strains have already developed resistance to all of today’s available drugs including artemisinin. In that regard, it should be noted that natural products have proven to be a valuable source for the discovery of novel antimalarial therapeutic agents since the discovery of the first antimalarial drug in 1800s [20]. We, thus, pursued this approach in the search for new antimalarial potential drug leads.

In our antimalarial drug discovery program, we have evaluated more than 2000 plant extracts against D6 and W2 strains of *P. falciparum*. Dozens of these plants displayed antimalarial activity. Several of these plant leads were investigated further to uncover their antimalarial constituents. Phytochemical separation of these plant leads guided by bioassays led to the identification of ten new and 13 known active compounds [21]. Some of these compounds demonstrated potent antimalarial activity [22–29]. For example, polysyphorin (1) and raphidecurperoxin (2), isolated from *Raphidophora decursiva* (Araceae), showed antimalarial activities of 1.5 and 1.4 µM against the W2 clones of *P. falciparum*, respectively (Figure 2) [22]. Two trichotheccenes, roridin E (3) from *R. decursiva* (Araceae) and verrucarin L acetate (4) from *Ficus fistulosa* (Moraceae), were found to potently inhibit the parasite growth with IC$_{50}$ values in the sub-nano molar range [24].
De-replication to avoid duplication of previous efforts is an essential step in drug discovery protocols. To that end, we conducted a thorough review of the published literature on natural products possessing antimalarial activity. Previously, a literature review by Schwikkard and Van Heerden [30], covered plant-derived antiplasmodial active natural compounds up to the year 2000. The compounds were organized according to the origins of their corresponding plant families. The current review seeks to supplement the review of Schwikkard and Van Heerden. Compounds with antimalarial activity will also be organized according to their plant family of origin (Table 2). Literature published between 2001 and 2017 have been covered. In addition, we also included the ethnobotanic information of plants that have been used as folk medicines for the treatment of malarial disease (Table 3).

Figure 2. Compounds from *R. decursiva* and *F. fitulosa*. 
### Table 2. Antiplasmodial activities and toxicities of compounds isolated from terrestrial plants.

| Family         | Species                        | Extract Solvent | Compound                                                                 | Antiplasmodial IC<sub>50</sub> (µM) | Cytotoxicity, ED<sub>50</sub> (µM) | References |
|----------------|--------------------------------|-----------------|--------------------------------------------------------------------------|--------------------------------------|------------------------------------|------------|
| **Annonaceae** | *Friesodielsia discolor*      | EtOAc           | 30-formyl-20,40-dihydroxy-60-methoxychalcone (5)                          | 9.2 (K1)                             | 21.8 (KB); 13.9 (MCF-7)            | [31]       |
|                |                                |                 | 8-formyl-7-hydroxy-5-methoxyflavanone (6)                               | 9.3 (K1)                             | 41.9 (KB); 34.5 (MCF-7)            |            |
|                |                                |                 | tectochrysin (7)                                                         | 7.8 (K1)                             | 59.1 (KB); 16.8 (MCF-7)            |            |
| **Meliaceae**  | *Mitraphana diversifolia*     | CH<sub>2</sub>Cl<sub>2</sub>/MeOH | 5-hydroxy-6-methoxyonychine (8)                                          | 9.9 (3D7); 11.4 (IEx2)               | 120.0 (HEK293)                     | [32]       |
|                | *Mililusa cuneata*            | Acetone         | mililusacunines A (9)                                                   | 19.3 (TM4)                           | –                                  | [33]       |
|                |                                |                 | mililusacunines B (10)                                                  | 10.8 (K1)                            | –                                  |            |
| **Araceae**    | *Rhaphidophora decursiva*     | MeOH            | polypsyrhin (1)                                                          | 1.7 (D6); 1.5 (W2)                   | 8.3 (KB)                           | [22,23]    |
|                |                                |                 | rhaphidecurperoxin (2)                                                  | 1.8 (D6); 1.4 (W2)                   | 13.1 (KB)                          |            |
|                |                                |                 | rhaphidecurperoxinol A (11)                                             | 7.2 (D6); 4.2 (W2)                   | 28.7 (KB)                          |            |
|                |                                |                 | rhaphidecurperoxinol B (12)                                             | 12.9 (D6); 11.2 (W2)                 | 23.9 (KB)                          |            |
|                |                                |                 | grandisin (13)                                                          | 3.5 (D6); 3.4 (W2)                   | 32.4 (KB)                          |            |
|                |                                |                 | epigrandisin (14)                                                       | >23 (D6); 7.7 (W2)                   | 37.0 (KB)                          |            |
|                |                                |                 | decursivine (15)                                                        | 11.2 (D6); 12.6 (W2)                 | –                                  | [22,23]    |
|                |                                |                 | Roridin E (3)                                                           | 0.0004 (D6); 0.003 (W2)              | 0.0004 (KB)                        | [24]       |
| **Asclepiadaceae** | *Gongronema napalense*           | EtOH           | gongroneside A (16)                                                     | 1.6 (D6); 1.4 (W2)                   | >13.7 (KB)                         | [25]       |
| **Asteraceae** | *Achillea millefolium*       | MeOH            | apigenin 7-O-glucoside (17)                                             | 25.3 (D10); 15.3 (W2)                | –                                  | [34]       |
|                |                                |                 | luteolin 7-O-glucoside (18)                                             | 61.1 (D10); 62.5 (W2)                | –                                  |            |
| **Asclepiadaceae** | *Carpesium drossa*            | MeOH            | 2-isopropenyl-6-acetyl-8-methoxy-1,3-benzodioxin-4-one (19)              | 2.5 (D10)                           | 63.2 (SK-OV-3)                     | [35]       |
|                |                                | Petroleum ether-EtOAc (1:1, v/v)                                      | E-phytol (20)                         | 8.5 (PoW); 11.5 (Dd2)               | –                                  | [36]       |
|                |                                |                 | 6E-geranylgeraniol-19-oic acid (21)                                      | 12.9 (PoW); 15.6 (Dd2)               | –                                  |            |
| **Buxaceae**   | *Buxus sempervirens*          | MeOH            | 5-(penta-1,3-diynyl)-2-(3,4-dihydroxybut-1-ynyl)-thiophene (22)          | 50.2% (100 mg/kg)                    | –                                  | [37]       |
|                |                                |                 | 5-(penta-1,3-diynyl)-2-(3-chloro-4-acetoxy-but-1-ynyl)-thiophene (23)     | 32.7% (100 mg/kg)                    | –                                  |            |
| **Buxaceae**   | *Buxus sempervirens*          | MeOH            | compound (24)                                                           | 0.5–3.0 (HB9)                        | 7.0 (Hela)                         | [38]       |
|                |                                |                 | compound (25)                                                           | 0.5–3.0 (HB9)                        | >20 (Hela)                         |            |
|                |                                |                 | 25-O-(trans)-feruloyl-23-hydroxybetulin (26)                             | 0.5–3.0 (HB9)                        | >20 (Hela)                         |            |
| **Cecropiaceae** | *Cecropia pachystachya*        | EtOH            | β-sitosterol (32)                                                        | >120 (W2)                            | –                                  | [39]       |
|                |                                |                 | tormentic acid (33)                                                     | 19.0-25.2 (W2)                       | –                                  |            |
Table 2. Cont.

| Family                      | Species                      | Extract Solvent | Compound                          | Antiplasmodial IC₅₀ (µM) * | Cytotoxicity, ED₅₀ (µM) b (Cell Line) | References |
|-----------------------------|------------------------------|-----------------|-----------------------------------|---------------------------|--------------------------------------|------------|
|                             |                              |                 | fortunilide A (34)                | 0.005 (Dd2)               | 8.8 (WI-38)                          |            |
|                             |                              |                 | fortunilide B (35)                | 0.02 (Dd2)                | 3.1 (WI-38)                          |            |
|                             |                              |                 | fortunilide C (36)                | 0.2 (Dd2)                 | -                                    |            |
|                             |                              | EtOH            | fortunilide D (37)                | 0.03 (Dd2)                | 0.5 (WI-38)                          |            |
|                             |                              |                 | fortunilide E (38)                | 0.04 (Dd2)                | >100 (WI-38)                         |            |
|                             |                              |                 | fortunilide F (39)                | 5.3 (Dd2)                 | -                                    |            |
|                             |                              |                 | fortunilide G (40)                | 0.05 (Dd2)                | 1.2 (WI-38)                          |            |
|                             |                              |                 | fortunilide H (41)                | 0.2 (Dd2)                 | -                                    |            |
|                             |                              |                 | fortunilide I (42)                | 0.09 (Dd2)                | -                                    |            |
|                             |                              |                 | fortunilide J (43)                | 9.9 (Dd2)                 | -                                    |            |
|                             |                              |                 | fortunilide K (44)                | 4.7 (Dd2)                 | -                                    |            |
|                             |                              |                 | fortunilide L (45)                | 0.1 (Dd2)                 | 15.5 (WI-38)                         |            |
|                             |                              |                 | sarglabolide I (46)               | 4.6 (Dd2)                 | -                                    |            |
|                             |                              |                 | sarglabolide J (47)               | 0.007 (Dd2)               | 4.0 (WI-38)                          |            |
|                             |                              |                 | shizukaol K (48)                  | 0.9 (Dd2)                 | -                                    |            |
|                             |                              |                 | shizukaol L (49)                  | 0.1 (Dd2)                 | -                                    |            |
|                             |                              |                 | shizukaol C (50)                  | 0.02 (Dd2)                | 0.8 (WI-38)                          |            |
|                             |                              |                 | shizukaol M (51)                  | 0.10 (Dd2)                | 4.5 (WI-38)                          |            |
|                             |                              |                 | chlorahololide D (53)             | 0.01 (Dd2)                | 0.2 (WI-38)                          |            |
| C. multisachys               | -                            |                 | chloramultilide B (65)            | 7.1 (Dd2)                 | -                                    |            |
|                             |                              |                 | chlorajaponilide C (65)           | 10.1 (Dd2)                | 5.4 (WI-38)                          |            |
|                             |                              |                 | shizukaol N (54)                  | 0.1 (Dd2)                 | 10.0 (WI-38)                         |            |
|                             |                              |                 | shizukaol E (56)                  | 1.8 (Dd2)                 | -                                    |            |
|                             |                              |                 | shizukaol F (59)                  | 0.6 (Dd2)                 | -                                    |            |
|                             |                              |                 | shizukaol G (60)                  | 0.01 (Dd2)                | 0.2 (WI-38)                          |            |
|                             |                              |                 | shizukaol H (61)                  | 0.01 (Dd2)                | 1.7 (WI-38)                          |            |
|                             |                              |                 | shizukaol I (62)                  | 0.03 (Dd2)                | 16.7 (WI-38)                         |            |
| C. serratus and C. spicatus | -                            |                 | spicachlorantin D (63)            | 0.5 (Dd2)                 | -                                    |            |
|                             |                              |                 | shizukaol A (64)                  | 1.5 (Dd2)                 | -                                    |            |
| Sarcandra glabra            | -                            |                 | sarcandrolide B (55)              | 0.27 (Dd2)                | -                                    |            |
|                             |                              |                 | sarcandrolide A (86)              | 0.3 (Dd2)                 | -                                    |            |
|                             |                              |                 | sarcandrolide J (57)              | 11.4 (Dd2)                | -                                    |            |
| Family          | Species                      | Extract Solvent | Compound                                                                 | IC₅₀ (µM) * (P. falciparum) | Cytotoxicity, ED₅₀ (µM) b (Cell Line) | References |
|-----------------|------------------------------|-----------------|--------------------------------------------------------------------------|----------------------------|---------------------------------------|------------|
| Chrysobalanaceae| Parinari capensis            | Petroleum ether and CH₂Cl₂ | 10,13-dihydroxy-9-methyl-15-o xo-20-norkaur-16-en-18-oic acid γ-lactone (66) | 1.7 (FCR-3)               | 5.5 (Graham)                          | [41]       |
|                 |                              |                 | 10-hydroxy-13-methoxy-9-methyl-15-oxo-20-norkaur-16-en-18-oic acid γ-lactone (37) | 1.9 (FCR-3)               | 3.2 (Graham)                          |            |
|                 |                              |                 | 10-hydroxy-9-methyl-15-oxo-20-norkaur-16-en-18-oic acid γ-lactone (68) | 5.0 (FCR-3)               | 9.6 (Graham)                          |            |
| Clusiaceae      | Garcinia mckeaniana          | Acetone         | mckeanianones A (69)                                                    | 6.2 (TM4)                 | –                                     | [42]       |
|                 |                              |                 | mckeanianones B (70)                                                   | 6.7 (TM4)                 | 12.9 (Vero)                           |            |
|                 |                              |                 | mckeanianones C (71)                                                   | 6.0 (TM4)                 | 29.5 (Vero)                           |            |
|                 |                              |                 | barnaxanthones I (72)                                                  | 8.5 (TM4)                 | –                                     |            |
|                 |                              |                 | barnaxanthones E (73)                                                  | 8.3 (TM4)                 | –                                     |            |
| Connaraceae     | Rouea minor (Gaertn.) Aubl.  | CHCl₃           | nouri noside (74)                                                       | 3.7 (D6); 2.1 (W2)        | KB: ED₅₀ >35.1                        | [26]       |
|                 |                              |                 | rouremin (75)                                                          | 5.1 (D6); 4.5 (W2)        | KB: ED₅₀ >25.5                        |            |
|                 |                              |                 | 1-(26-hydroxyhexanoxy)-glycerol (76)                                    | 9.5 (D6); 12.7 (W2)       | KB: ED₅₀ >41.2                        |            |
| Cornaceae       | Cornus florida L.           | EtOH            | ergosta-4,6,8,22-tetraene-3-one (77)                                     | 61.0 (D10)                | 27.0 (L6)                            | [43]       |
|                 |                              |                 | 3-epideoxyfindissol (78)                                                | 128.0 (D10)               | 14.7 (L6)                            |            |
|                 |                              |                 | 3β-O-cis-coumaryl betulinic acid (79)                                    | 10.4 (D10)                | 5.6 (L6)                             |            |
|                 |                              |                 | 3β-O-trans-coumaryl betulinic acid (80)                                  | 15.3 (D10)                | 9.3 (L6)                             |            |
| Cucurbitaceae   | Cogniauxia podolena Baill.   | CHCl₂           | cucurbitacin B (81)                                                     | 2.9 (Fm29 strain)         | 94% inhibition of KB at 1.8 µM       | [44]       |
|                 |                              |                 | cucurbitacin D (82)                                                    | 7.8 (Fm29 strain)         | 95% inhibition of KB at 1.9 µM       |            |
|                 |                              |                 | 20-epibryonolic acid (83)                                               | 4.4 (Fm29 strain)         | 20% inhibition of KB at 2.2 µM       |            |
| Ebenaceae       | Diospyros quezita Thw.       | CHCl₃           | betulinic acid 3-cafate (84)                                            | 1.4 (D6); 1.0 (W2)        | 4.0 (KB)                             | [27]       |
| Euphorbiaceae   | Jatropha isatelli            | -               | compound 85                                                             | –                         | –                                     | [45]       |
|                 |                              |                 | compound 86                                                             | –                         | –                                     |            |
| Stropholobia fonbicalyx | MeOH              |                 | 9-O-demethyltrigonostere (87)                                           | 8.7 (K1)                 | 2.6 (KB)                             | [46]       |
|                 |                              |                 | 3,6,9-trimethoxyphenanthroline (88)                                     | 9.9 (K1)                 | 12.3 (KB)                            |            |
| Fabaceae        | Cajanus cajan L.            | EtOAc           | (+)-catechin 3-gallate (70)                                             | 12.0 (Fv-B1)              | >75 (MRC-5)                          | [48]       |
|                 |                              |                 | (+)-catechin 3-gallate (91)                                             | 1.0 (Fv-B1)               | >75 (MRC-5)                          |            |
|                 |                              |                 | prosopiolignin (92)                                                    | 0.1 (D6); 0.3 (W2)        | 20.2 (KB)                            | [49]       |
|                 |                              |                 | isorosopinolignin (93)                                                  | 0.1 (D6); 0.3 (W2)        | 18.8 (KB)                            |            |
| Fagaceae        | Quercuslaceyi               | MeOH            | kaempferol 3-O-glucosides (94-97)                                       | 0.6-2.3 (HB3)             | <3.0 (Hela)                          | [38]       |
| Hypericaceae    | Vismia orientalis           | -               | vismonone D (98)                                                       | 2.4 (K1)                 | 10.0 (L6 cell)                       | [50]       |
|                 |                              |                 | acetylvismonone D (100)                                                 | 0.1 (W2)                 | –                                     | [51]       |
|                 |                              |                 | 3-geranyloxyemodin anthrone (99)                                        | 1.7 (W2)                 | –                                     |            |
| Family         | Species                          | Extract Solvent          | Compound                        | Antiplasmodial IC$_{50}$ (µM) *  | Cytotoxicity, ED$_{50}$ (µM) b | References |
|----------------|----------------------------------|--------------------------|---------------------------------|----------------------------------|---------------------------------|------------|
| Lamiaceae      | Ocimum sanctum                   | EtOAc compound 101       | 0.1 (D07)                       | –                                | [52]                             |
|                | Phlomis brunnosegia              | MeOH                     | lutokalin 7-O-β-D-glucopyranoside (102) | 5.4 (K1)                         | >200                             |
|                |                                  |                          | chrysoert 7-O-β-D-glucopyranoside (103) | 12.7 (K1)                        | >194                             |
|                | Salvia radula                    | MeOH:CHCl$_3$ = 1:1      | betulafoliol oxide (104)         | 10.4 (FCR-3)                     | –                               |
|                |                                  |                          | salvigenin (105)                | 75.0 (FCR-3)                     | 207 (MCF-7)                      |
| Loganiaceae    | Styrchnos icaja                  | EtOAc:EtOH-NH$_4$OH (96:3:1) | 15-hydroxystyrycine (106)       | 101.0 (W2)                       | –                               |
|                |                                  |                          | N-methyl-sec-iso-pseudostrychnine (107) | 110.6 (W2)                  | –                               |
| Lythraceae     | Ammannia multiflora, A. bacifera | MeOH                     | 4-hydroxyn-α-tetralone (108)     | 194.0 (NF-54)                    | –                               |
|                |                                  |                          | tetralone-4-O-β-D-glucopyranoside (109) | 124.0 (NF-54)                    | –                               |
|                |                                  |                          | ammaniol (110)                  | 88.3 (NF-54)                     | –                               |
| Malvaceae      | Theoeis damis                     | Acetone–water (7:3)      | (R)-(-)-gossypol (111)           | 4.5 (D07)                        | –                               |
| Moronmiaceae   | Duryphora saasfus                 | CH$_3$Cl$_2$/MeOH         | 1-(4-hydroxybenzyl) 6,7-methylenedioxy-2-methylisoquolium 3-trifluoracetate (112) | 3.0 (D07); 4.4 (D02) | 120.0 (HEK293)                  |
|                | Gloeoscylos brevipes Benth.      | CHCl$_3$/MeOH (1/1)      | methyl 2-(1’β-geranyl-3’β-hydroxy-2’-oxyhex-3’-enyl) acetate (113) | 2.2 (D06), 6.6 (W2) | –                               |
|                |                                  |                          | 2-(1’β-geranyl-3’β-hydroxy-2’-oxyhex-3’-enyl) acetic acid (114) | 4.8 (D06), 8.3 (W2) | –                               |
| Moraceae       | Ficus fistulosa                  | -                        | verrucarin I, acetate (4)        | 0.001 (D06), 0.001 (W2)         | 0.2 (KB)                        |
|                | F. septica                      | MeOH                     | dehydroryllopine (115)           | 0.4 (D07)                       | 8.2 (L929)                      |
|                |                                  |                          | dehydrortofoine (116)           | 0.03 (D07)                      | >55 (L929)                      |
|                |                                  |                          | tylaphoridine D (117)           | 0.06 (D07)                      | >56 (L929)                      |
| Myristicaceae  | Kema glauca                     | EtOAc                    | malabaricine A (118)            | 8.5 (K1)                        | >61 (KB), 55.4 (NCI-H187)       |
| Piperaceae     | Piper sarmentosum                | Hexane-MeOH              | sarmentine (119)                | 85.5 (K1)                       | –                               |
|                | P. tricuspe                      | Petroleum ether          | 1-piperetyl pyrrolidine (120)    | 21.9 (K1)                       | –                               |
|                |                                  |                          | dictyochromol (121)             | 9.6 (FcB1)                      | 7.7 (L-6)                       |
|                |                                  |                          | 3-farnesyl-p-hydroxy benzoic acid (122) | 29.8 (FcB1)                    | 40.9 (L-6)                      |
|                |                                  |                          | 2’E,6’E,2-farnesyl hydroquinone (123) | 1.4 (FcB1)                      | 1.1 (L-6)                       |
| Platanaceae    | Platanus occidentalis            | MeOH                     | kaempferol 3-O-rhamnosides (124-127) | 0.5–1.8 (HB3)                  | 9.3–20.0 (Hela)                 |
|                |                                  |                          | n-auclaurine (128)              | 6.9 (D06), 8.0 (W2)             | 38.0 (KB)                       |
|                |                                  |                          | epimeroxynauclaurine (129)      | 12.4 (D06), 13.2 (W2)           | >37.9 (KB)                      |
|                |                                  |                          | 3α,23-dihydroxyurs-12-en-28-oic acid (130) | 9.7 (D06), 12.7 (W2)            | >42.2 (KB)                      |
|                |                                  |                          | oleanolic acid (131)            | 4.6 (D06), 5.1 (W2)             | 46.0 (KB)                       |
| Family          | Species                                  | Extract Solvent | Compound                                      | Antiplasmodial IC₅₀ (µM)ᵃ | Cytotoxicity, ED₅₀ (µM)ᵇ | References |
|----------------|------------------------------------------|-----------------|-----------------------------------------------|---------------------------|---------------------------|------------|
| Rutaceae       | Citropsis articulata                     | MeOH            | 5-hydroxynoracronycine (132)                  | 2.8 (FcB1)                | 28.8 (Vero)               | [64]       |
|                |                                          |                 | 1,5-dihydroxy-2,3-dimethoxy-10-methyl-9-acridone (133) | 10.0 (FcB1)              | 101 (Vero)                |            |
|                |                                          |                 | trans-avicenol (134)                          | 7.8 (K1); 1.5 (F32); 3.5 (PFB); 6.4 (FcB1) | 12.8 (MCR5)               |            |
|                | Zanthoxylum chiloperone var. angustifolium Engl. | CH₂Cl₂          | canthin-6-one (135)                           | 24.1 (K1); 9.1 (F32); 14.6 (PFB); 16.2 (FcB1) | 42.7 (MCR5)               | [65]       |
| Simaroubaceae  | Eurycoma longifolia                      | CH₂Cl₂          | eryviconone (137)                             | 0.08 (D6); 0.04 (W2)      | 0.02 (A-549); <0.006 (MCF-7) | [66,67]   |
|                | Picrodendron sprucei                     | Hexane/H₂O      | pasakbumin B (138)                            | 0.05 (D6); 0.05 (W2)      | 0.02 (A-549); <0.006 (MCF-7) |            |
| Apocynaceae    | Aspidosperma thyrsi                      | EtOH            | ellipticine (140)                             | 0.07 (K1)                 | –                         |            |
|                | A. desmanthum                            | EtOH            | aspidocarpine (141)                           | 0.02 (K1)                 | –                         |            |
| Piperaceae     | Pothomorphe peltata                      | CHCl₃/EtOH      | 4-nerolidylcatechol (142)                     | 0.7 (K1)                  | –                         |            |
| Theaceae       | Camellia sinensis                        | MeOH            | neflouquine (143)                             | –                         | –                         | [68]       |
|                |                                          |                 | galcatecin (144)                              | –                         | –                         |            |
| Tiliaceae      | Corisia bilamellata                      | MeOH            | 3α,20-lupandiol (145)                         | 19.8 (D6); 19.1 (W2)      | >90 (KB)                  | [29]       |
|                |                                          |                 | grewin (146)                                  | 11.2 (D6); 5.5 (W2)       | >107.5 (KB)               |            |
|                |                                          |                 | nitidanin (147)                               | 21.2 (D6); 18.4 (W2)      | >90 (KB)                  |            |
|                |                                          |                 | 2α,3β-dihydroxysalacen-12-en-28-oc acid (148) | 21.1 (D6); 8.6 (W2)       | 51.5 (KB)                 |            |
|                |                                          |                 | 2,6-dimethoxy-1-acetyloquinol (149)           | 42.2 (D6); 23.0 (W2)      | 169 (KB)                  |            |
| Verbenaceae    | Lippia javanica                          | EtOAc (aerial parts) | lippialactone (150)                          | 23.8 (D10)                | –                         | [70]       |

ᵃ IC₅₀: Concentration that resulted in 50% death of *Plasmodium falciparum*. ᵇ ED₅₀: Concentration that resulted in 50% cell death.
| Family     | Ethnologic Plant            | Country | Plant Part | Antiplasmodial Activity (IC_{50}) (µg/mL, Unless Indicated) \(^a\) | Cytotoxicity (CC_{50} for Cells, LD_{50} for Brine Shrimp) (µg/mL, Unless Indicated) \(^b,c\) | References |
|------------|-----------------------------|---------|------------|-------------------------------------------------|-------------------------------------------------|-----------|
| Acanthaceae| Justilia schimperand (Hochst ex Nees) T. Alnder | Nigeria | Roots     | –                                                | –                                                | [71]      |
| Anacardiaceae | Mangifera indica L. | Nigeria | Leaves | % parasitaemia reduced from 8.9 at 60 mg/kg to 7.2 at 240 mg/kg (mice) | 208.3 mg/kg (mice) | [72] |
|             |                            | Nigeria | Leaves   | –                                                | 3079.1 (brine shrimp)                             | [73]      |
|             |                            | Nigeria | Stem barks | –                                                | 2456.0 (brine shrimp)                             | [73,74]  |
|             | Pseudoprotorhus longifolius H. Perr. | Madagascar | Leaves | –                                                | –                                                | [75]      |
|             | Rhus taratana (Bak.) H. Perr. | Madagascar | Leaves | –                                                | –                                                | [75]      |
|             | Sclerocarya birrea (A. Rich) Hochst. | South Africa | Stem bark (MeOH) | 5.91 (D6)                                        | –                                                | [76]      |
|             | S. caffra Sond.             | Madagascar | Leaves | –                                                | –                                                | [75]      |
| Annonaceae  | Annona senegalensis Rolyns & Gh | Nigeria | Leaves   | –                                                | 6811.0 (brine shrimp)                             | [73]      |
|             | Ensertia chlomotha Oliv.    | Nigeria | Stem barks | –                                                | 214.3 (brine shrimp)                              | [73,74]  |
| Apocynaceae | Alstonia boonei DeWild    | Nigeria | Leaves, stem barks | % parasitaemia reduced from 19.4% (negative control) to 5.5% at 240 mg/kg (mice) | 78.77 mg/kg (mice)                              | [72,74]  |
|             | A. parvifolium A. DC.      | Brazil  | Trunk woods (EtOH) | 44.0 (W2), 39.0 (3D7)                           | >500 (Vero)                                     | [7]       |
|             |                            | Brazil  | Trunk barks (EtOH) | 32.8 (W2), 20.5 (3D7)                           | >500 (Vero)                                     | [7]       |
|             |                            | Brazil  | Leaves (CH_{2}Cl_{2}) | 7.0 (W2), 25.5 (3D7)                           | >500 (Vero)                                     | [7]       |
|             |                            | Brazil  | Leaves (EtOH) | 7.0 (W2), 5.0 (3D7)                           | –                                                |          |
|             |                            | Brazil  | Trunk wood (CH_{2}Cl_{2}) | <6 (W2), <6 (3D7)                           | >500 (Vero)                                     | [7]       |
|             |                            | Brazil  | Trunk bark (CH_{2}Cl_{2}) | <6 (W2), <6 (3D7)                           | –                                                |          |
|             |                            | Brazil  | Trunk bark (EtOH) | 5.0 (W2), 7.0 (3D7)                           | >500 (Vero)                                     | [7]       |
|             |                            | Brazil  | Leaves (EtOH) | 32.8 (W2), 20.5 (3D7)                           | –                                                | [7]       |
|             |                            | Brazil  | Leaves (CH_{2}Cl_{2}) | <6 (W2), <6 (3D7)                           | –                                                |          |
|             |                            | Brazil  | Trunk woods (EtOH) | 36.5 (W2), 48.0 (3D7)                           | –                                                |          |
|             |                            | Brazil  | Trunk woods (CH_{2}Cl_{2}) | 9.5 (3D7)                                   | >500 (Vero)                                     | [7]       |
|             |                            | Brazil  | Trunk woods (EtOH) | 19.8 (W2), 1.0 (3D7)                           | –                                                | [7]       |
|             |                            | Brazil  | Trunk barks (CH_{2}Cl_{2}) | <6 (W2), <6 (3D7)                           | >500 (Vero))                                    | [7]       |
Table 3. Cont.

| Family                  | Ethnologic Plant | Country | Plant Part                  | Antiplasmodial Activity (IC$_{50}$) (µg/mL, Unless Indicated) | Cytotoxicity (CC$_{50}$ for Cells, LD$_{50}$ for Brine Shrimp) (µg/mL, Unless Indicated) | References |
|-------------------------|------------------|---------|-----------------------------|---------------------------------------------------------------|------------------------------------------------------------------------------------------|------------|
|                         |                  |         |                             | (µg/mL, Unless Indicated)                                      | (µg/mL, Unless Indicated)                                                                 |            |
| A. spruceanum Benth. ex Müll. Arg. | Brazil           |         | Leaves (EtOH)               | 65.0 (W2); >100 (3D7)                                         | –                                                                                       | [7]        |
|                         |                  |         | Leaves (CH$_2$Cl$_2$)       | 23.25 (W2); 47.0 (3D7)                                        | –                                                                                       |            |
|                         |                  |         | Trunk woods (EtOH)          | 29.5 (W2); 41.5 (3D7)                                         | –                                                                                       |            |
|                         |                  |         | Trunk woods (CH$_2$Cl$_2$)  | <6 (W2); <6 (3D7)                                              | 109.6 (Vero))                                                                            |            |
|                         |                  |         | Trunk woods (CHCl$_3$)      | 37.0 (W2); >100 (3D7)                                         | –                                                                                       |            |
|                         |                  |         | Trunk barks (EtOH)          | 26.3 (W2); 14.0 (3D7)                                         | –                                                                                       |            |
|                         |                  |         | Trunk barks (CH$_2$Cl$_2$)  | <6 (W2); <6 (3D7)                                              | –                                                                                       |            |
|                         |                  |         | Trunk barks (CHCl$_3$)      | 37.0 (W2); >100 (3D7)                                         | –                                                                                       |            |
| A. tomentosum Mart.     | Brazil           |         | Trunk woods (EtOH)          | 26.5 (W2); 25.0 (3D7)                                         | –                                                                                       | [7]        |
|                         |                  |         | Leaves (EtOH)               | 23.8 (W2); 27.0 (3D7)                                         | –                                                                                       |            |
|                         |                  |         | Fruits (EtOH)               | 20.5 (W2); 38.6 (3D7)                                         | –                                                                                       |            |
|                         |                  |         | Seeds (EtOH)                | 24.5 (W2); 3.0 (3D7)                                          | >500 (Vero))                                                                             |            |
| Aristolochiaceae        | Aristolochia asperata Lamk. | Madagascar | Roots, stems, leaves       | –                                                              | –                                                                                       | [75]       |
| Asteraceae              | Artemisia annua L. | China   | Whole plants                | –                                                              | –                                                                                       | [77]       |
|                         | Tithonia diversifolia A. Gray | Nigeria | Leaves                     | –                                                              | 2304 (brine shrimp)                                                                    | [73]       |
|                         | Vernonia angulata Del. |         | Leaves                     | –                                                              | –                                                                                       | [71]       |
| Araliaceae              | Arctiaceae       |         | Aerial parts                | –                                                              | –                                                                                       | [78]       |
|                         | A. basilicar L.   | Madagascar | Aerial parts                | –                                                              | –                                                                                       | [75]       |
| Bignoniaceae            | Fernandoa sp.     | Madagascar | Aerial parts                | –                                                              | –                                                                                       | [75]       |
|                         | Egelia madagascariensis | Sprague var. hidebrandt | Leaves                     | –                                                              | –                                                                                       | [78]       |
| Brassicaceae            | Brassica nigra (L.) Koch. | Madagascar | Seeds                      | –                                                              | –                                                                                       | [71]       |
| Cactaceae               | Cereus perlette L. |         | Leaves, fruits, roots      | –                                                              | –                                                                                       | [71,73]    |
| Celastraceae            | Magnemia zinnii (L.) Loes | Kenya | leaves, root barks         | 36.6–41.5%                                                     | –                                                                                       | [90]       |
| Combretaceae            | Combretum yunnanum Hechel | Madagascar | Leaves                     | –                                                              | –                                                                                       | [71]       |
|                         | Terminalia catappa | Nigeria | Leaves (EtOH)              | 3.1 (K1)                                                       | 159.9 µg/L (L6)                                                                        | [91]       |
|                         | T. latifolia Engl. | Nigeria | leaves                     | –                                                              | 272.9 (brine shrimp)                                                                   | [73]       |
| Commelinaceae           | Commelina benghalensis L. | Madagascar | Aerial parts                | –                                                              | –                                                                                       | [73]       |
| Family         | Ethnologic Plant                     | Country          | Plant Part     | Antiplasmodial Activity (IC₅₀) (µg/mL, Unless Indicated) | Cytotoxicity (CC₅₀ for Cells, LD₅₀ for Brine Shrimp) (µg/mL, Unless Indicated) | References |
|----------------|--------------------------------------|------------------|----------------|----------------------------------------------------------|--------------------------------------------------------------------------------|------------|
|                |                                      |                  |                | (P. falciparum)                                          | (Cell Line)                                                                        |            |
| Compositae     | Brachylaena ramiiflora (DC.) H. Humb | Madagascar       | Aerial parts   | –                                                        | –                                                                                 | [75]       |
|                | Conyza aegyptiaca Ait. Var lineoloba | Madagascar       | Aerial parts   | –                                                        | –                                                                                 | [75]       |
|                | Inula perrieri H. Humb.              | Madagascar       | Leaves         | –                                                        | –                                                                                 | [75]       |
|                | Parthenium hysterophorus L.          | Madagascar       | Aerial parts   | –                                                        | –                                                                                 | [75]       |
|                | Seneo amygdalifolius (ex DC.) H. Humb| Madagascar       | Aerial parts   | –                                                        | –                                                                                 | [75]       |
|                | Senecio inuloides DC.                | Madagascar       | Leaves         | –                                                        | –                                                                                 | [75]       |
|                | Tagetes erecta L.                    | Madagascar       | Leaves         | –                                                        | –                                                                                 | [75]       |
|                | T. patula L.                         | Madagascar       | Leaves         | –                                                        | –                                                                                 | [75]       |
|                | Vernonia laiopus O. Hoffm.           | Kenya            | Root barks     | –                                                        | –                                                                                 | [75]       |
|                | V. pectoralis Bak.                   | Madagascar       | Aerial parts   | –                                                        | –                                                                                 | [75]       |
|                | V. irichiadon Bak.                   | Madagascar       | Leaves         | –                                                        | –                                                                                 | [75]       |
|                | V. chapordi Drak.                    | Madagascar       | Aerial parts   | –                                                        | –                                                                                 | [75]       |
|                | V. sp. (Dr. Hely)                    | Madagascar       | Aerial parts   | –                                                        | –                                                                                 | [75]       |
|                | V. amprandrandensisii Bak.           | Madagascar       | Aerial parts   | –                                                        | –                                                                                 | [75]       |
| Cucurbitaceae  | Momordica charantia L.               | Madagascar       | Aerial parts   | –                                                        | –                                                                                 | [75]       |
|                | Zehneria sabra (L.f.) Sond.          |                  | Roots          | –                                                        | –                                                                                 | [71]       |
|                | Bridelia micrantha Benth.            | Nigeria          | Leaves         | –                                                        | >90,000 (brine shrimp)                                                           | [73]       |
|                | Croton goodyi H. Bn.                 | Madagascar       | Leaves         | –                                                        | –                                                                                 | [75]       |
|                | C. nucrosochus Hochst. Ex Del.       |                  | Leaves/barks/roots | –                                                        | –                                                                                 | [71]       |
|                | Euphorbia hirta                      | Nigeria          | Whole plants (Hexane) | 4.3 (K1)  | 14.2 (L6)                                           | [81,82]    |
|                | Flueggea microcarpa Blume            | Madagascar       | Aerial parts   | –                                                        | –                                                                                 | [75]       |
| Euphorbiaceae  | Jatropha curcas L.                   | Nigeria          | Leaves (EtOAc) | 2.4 (K1)  | 126.5 (L6)                                           | [75,81,82] |
|                | Manihot utilisma Pohl.               | Madagascar       | Leaves, roots  | –                                                        | –                                                                                 | [75]       |
| Phyllanthus ananus Schum. & Thonn. | Brazil, Cuba, Haiti, Nigeria, Elsewhere | Whole plants (MeOH) | 5.0 (3D7)  | –                                                        | –                                                                                 | [83,84]    |
|                | India                                | Whole plants     | –              | 14.5 (3D7)                                              | –                                                                                 | [85]       |
|                | Nigeria                               | Leaves (EtOAc)   | 5.6 (K1)  | 77.7 (L6)                                           | [81,82]    |
|                | Ghana                                | Whole plants     | –              | –                                                        | –                                                                                 | [85]       |
|                | West Africa                           | Aerial parts     | –              | –                                                        | –                                                                                 | [85]       |
|                | Phyllanthus sp.                       | Madagascar       | Aerial parts   | –                                                        | –                                                                                 | [75]       |
Table 3. Cont.

| Family         | Ethnologic Plant                  | Country      | Plant Part            | Antiplasmodial Activity (IC$_{50}$) (µg/mL, Unless Indicated) a | Cytotoxicity (CC$_{50}$ for Cells, LD$_{50}$ for Brine Shrimp) (µg/mL, Unless Indicated) b,c | References |
|----------------|-----------------------------------|--------------|-----------------------|-----------------------------------------------------------------|-----------------------------------------------------------------------------------------------|------------|
| Fabaceae       | *Acacia nilotica* L.               | Pakistan     | Leaves (EtOH)         | 1.3 (SD)                                                         | -                                                                                              | [86]       |
|                | *Caesalpinia benthanniana*         | Ghana        | Leaves (MeOH)         | 4.0 (Ghana)                                                     | 32.0 (MRC-5)                                                                                   | [79]       |
|                | *Cajanus cajan* Mill sp.          | Nigeria      | Leaves                | -                                                                | 988.5 (brine shrimp)                                                                           | [73,74]    |
|                | *Calliandra haematocarpa* Hassk.   | Nigeria      | Roots                 | -                                                                | -                                                                                              | -          |
|                | *Calpurnia ovata* (Ait.) Benth.    |              | Leaves                | -                                                                | -                                                                                              | [71]       |
|                | *Cassia siamea*                    | Nigeria      | Stem barks (EtOAc)    | 2.70 (K1)                                                       | 988.5 (stem bark), 8232.2 (brine shrimp)                                                      | [73]       |
|                |                                   |              | leaves                | -                                                                | -                                                                                              |           |
|                | *Piliostigma thonningii* Schum     | Nigeria      | Leaves                | -                                                                | 7958.0 (brine shrimp)                                                                          | [73]       |
| Flacourtiaceae | *Homalium* sp.                     | Madagascar   | Aerial parts          | -                                                                | -                                                                                              | [75]       |
| Gramineae      | *Phragmites muelleriana* Kurth.    | Madagascar   | Aerial parts          | -                                                                | -                                                                                              | [75]       |
| Hydrengeaceae  | *Dichroa febrifuga*                | China        | Roots                 | -                                                                | -                                                                                              | [67]       |
| Icacinaceae    | *Cassinopsis madagascariensis* (Basil.) H. Bn. | Madagascar | Leaves, stem barks    | -                                                                | -                                                                                              | [75]       |
| Lamiaceae      | *Hyptispratensis* Pott.            | Madagascar   | Leaves                | -                                                                | -                                                                                              | [75]       |
|                | *Ocimum carum* Sims.               | Nigeria      | Leaves (EtOAc)        | 1.8 (K1)                                                        | 60.1 (L6)                                                                                     | [75,81]    |
|                | *O. lamifolium* Hochst. ex Benth.  | Madagascar   | Stems, seeds          | -                                                                | -                                                                                              |           |
|                | *Caspephyl fikoumens L.*           | Nigeria      | Vines                 | -                                                                | -                                                                                              | [74]       |
| Leguminosae    | *Cinnamomum camphora* (L.) Sieb.   | Madagascar   | Leaves                | -                                                                | -                                                                                              | [75]       |
|                | *Abrus precatorius* L.             | Madagascar   | Leaves                | -                                                                | -                                                                                              | [75]       |
|                | *Albizia lebbeck* Benth.           | Madagascar   | Aerial parts          | -                                                                | -                                                                                              | [75]       |
|                | *Casalynina bonducella* Fleming.    | Madagascar   | Seeds, roots          | -                                                                | -                                                                                              | [75]       |
|                | *Cassia occidentalis* L.           | Madagascar   | Aerial parts          | -                                                                | -                                                                                              | [75]       |
|                | *Crotalaria spinosa* Hochst.       | Madagascar   | Leaves                | -                                                                | -                                                                                              | [75]       |
|                | *Erythrina indica* Lamk.           | Madagascar   | Aerial parts          | -                                                                | -                                                                                              | [75]       |
|                | *Piliostigma thonningii*           | Nigeria      | Leaves (EtOAc)        | 3.6 (K1)                                                        | 56.1 (L6)                                                                                     | [81]       |
| Lilliaceae     | *Pongamia pinnata* L.              | India        | Barks (MeOH)          | 11.7 (CQ-sensitive)                                             | >200 (THP-1)                                                                                  | [86]       |
|                | *Allium sativum* L.                |              | Bulbs                 | -                                                                | -                                                                                              | [71]       |
| Loganiaceae    | *Antlachys amplexicaulis* Bak.      | Madagascar   | Aerial parts          | -                                                                | -                                                                                              | [75]       |
|                | *A. rhizophoroides* Bak.           | Madagascar   | Roots, leaves         | -                                                                | -                                                                                              | [75]       |
|                | *Strychnus moxtuolides* Leeuwenberg | Madagascar | Aerial parts          | -                                                                | -                                                                                              | [75]       |
Table 3. Cont.

| Family          | Ethnologic Plant | Country | Plant Part | Antiplasmodial Activity (IC₅₀) (µg/mL, Unless Indicated) | Cytotoxicity (CC₅₀ for Cells, LD₅₀ for Brine Shrimp) (µg/mL, Unless Indicated) | References |
|-----------------|------------------|---------|------------|--------------------------------------------------------|--------------------------------------------------------------------------------|------------|
| Malvaceae       | Gossypium arboreum L. | Nigeria | Leaves     | –                                                      | 94.1 (brine shrimp)                                                            | [73]       |
|                 | G. barbadense L.  | Nigeria | Leaves     | –                                                      | 3585.0 (brine shrimp)                                                          | [73]       |
|                 | G. hirsutum L.    | Nigeria | Leaves     | 257.2 (brine shrimp)                                   |                                                                                | [73]       |
| Meliaceae       | Azadirachta indica A. Juss | Africa | leaves     | The percentage parasitaemia reduced from 15.7% to 4.8% at 240 mg/kg (in vivo) | 140.0 mg/kg (mice)                                                             | [72]       |
| Melianthaceae   | Sterculia macrophylla King | Indonesia | Seeds | –                                                      | 78% inhibition at 100 (Indo)                                                   | [89]       |
|                 |                  |         | Barks      | –                                                      | –                                                                               | [89]       |
| Menispermaceae  | Burassia australis Sc. Elliot | Madagascar | Leaves, root barks and stems | –                                                      | –                                                                               | [71]       |
|                 | B. congesta Deene | Madagascar | Root barks | –                                                      | –                                                                               | [71]       |
|                 | B. gracilis Deene | Madagascar | Root barks | –                                                      | –                                                                               | [71]       |
|                 | Burassia macrocarpa Thou. | Madagascar | Root barks | –                                                      | –                                                                               | [71]       |
|                 | B. nigrescens R. Cap. | Madagascar | Root barks | –                                                      | –                                                                               | [71]       |
|                 | Chiruethera urinaforms Baill. | Madagascar | Stem barks | –                                                      | –                                                                               | [71]       |
|                 | Cissampelos pareni L. | Madagascar | Roots | –                                                      | –                                                                               | [71]       |
|                 | C. nigrescens R. Cap. | Madagascar | Roots | –                                                      | –                                                                               | [71]       |
|                 | Spirosernum penduliflorum Thou. | Madagascar | Roots, stem barks | –                                                      | –                                                                               | [71]       |
|                 | Strylemyrs thoasaei Baill. | Madagascar | Leaves, root barks | –                                                      | –                                                                               | [71]       |
|                 | Triclisia macarca (Bail.) Deels. | Madagascar | Root barks, stem barks | –                                                      | –                                                                               | [71]       |
| Mimosaceae      | Acacia cotecho (L.f.) Willd. | Cameroon | Leaves | –                                                      | –                                                                               | [71]       |
|                 | Moraceae          | Ficus elastica Roxb. ex Hornem. | Cameroon | Roots (MeOH) | 9.5 | – | [91] |
|                 | F. sur Fousk. | Kenya | Leaves, stem barks, root barks | 34.1–48.4% Inhibition | – | [89] |
|                 | F. humnfingi Blume | Nigeria | Leaves (Hexane) | 2.7 (NF54); 10.4 (K1) | >20 (KB) | [90] |
| Myrtaceae       | Pidium guajava L. | Nigeria | Stem barks | –                                                      | 707.2 (brine shrimp)                                                            | [72]       |
| Ochnaceae       | Lophira alata Banks | Nigeria | Leaves (Hexane) | 2.5 (NF54); 2.5 (K1) | >20 (KB) | [90] |
| Papilionaceae   | Pericopsis elata Harms | Nigeria | leaves | –                                                      | 601.8 (brine shrimp)                                                            | [73]       |
|                 | Pterocarpus osun Craib | Nigeria | Stem barks | –                                                      | –                                                                               | [74]       |
| Periplocaceae   | Cryptoleptus angulatus | West Africa | Roots | –                                                      | 13.9 (MCF7)                                                                    | [92]       |
|                 | Parquetina negrescens (Alt.) Bullock | Nigeria | Root barks | –                                                      | –                                                                               | [74]       |
| Family           | Ethnologic Plant                   | Country          | Plant Part       | Antiplasmodial Activity (IC$_{50}$) (µg/mL, Unless Indicated) | Cytotoxicity (CC$_{50}$ for Cells, LD$_{50}$ for Brine Shrimp) (µg/mL, Unless Indicated) | References |
|------------------|-----------------------------------|------------------|------------------|---------------------------------------------------------------|-----------------------------------------------------------------|------------|
| Phytoleacaceae   | Phytolacca dioecandra L'Hèr.      | Madagascar       | Leaves           | –                                                             | –                                                              | [71]       |
| Polygonaceae     | Rumex alpinus subsp. jacq.        | Madagascar       | Leaves and stems | –                                                             | –                                                              | [71]       |
| Potamogetonaceae | Potamogeton jassicus Hass.Karl    | Madagascar       | Aerial parts     | –                                                             | –                                                              | [71]       |
| Ranunculaceae    | Clematis mauritiana Lamk. var. normalis | Madagascar  | Aerial parts     | –                                                             | –                                                              | [71]       |
| Rhamnaceae       | Rhamnus primades L'Herit          | Kenya            | Leaves, root barks | 34.1–43.9% inhibition                                         | –                                                              | [80]       |
| R. stadio A. Rich. |                                       | Kenya            | Root barks       | 11.1% inhibition                                              | –                                                              | [80]       |
| Cinchona ledgeriana Müens | Madagascar       | Madagascar       | Stem barks       | –                                                             | –                                                              | [75]       |
| C. officinalis L. |                                       | Madagascar       | Stem barks       | –                                                             | –                                                              | [75]       |
| C. succulenta Pauon et Kuntzsch | Madagascar | Madagascar       | Stem barks       | –                                                             | –                                                              | [75]       |
| Cephalanthusspathelliferus Bak. | Madagascar | Madagascar       | Leaves           | –                                                             | –                                                              | [75]       |
| Dimai fragrans Gaertn. | Madagascar | Madagascar       | Roots            | –                                                             | –                                                              | [75]       |
| D. gerraldii Bak. | Madagascar                      | Madagascar       | Roots            | –                                                             | –                                                              | [75]       |
| D. verticillate Bak. | Madagascar                   | Madagascar       | Roots            | –                                                             | –                                                              | [75]       |
| D. breviflora Bak. | Madagascar                      | Madagascar       | Roots            | –                                                             | –                                                              | [75]       |
| D. cunea Bak.    | Madagascar                      | Madagascar       | Roots            | –                                                             | –                                                              | [75]       |
| Rubiaceae        | Morinda lucida Benth.            | Africa           | Leaves           | The percentage parasitaemia reduced from 14.0 % to 5.8 % at 240 mg/kg (in vivo) | 134.5 mg/kg (mice)                                              | [72]       |
|                  |                                    | Nigeria          | Stem barks       | P. berghei                                                   | 2.6 (brine shrimp)                                              | [73]       |
|                  |                                    | Nigeria          | Leaves           | –                                                             | 383.9 (brine shrimp)                                            | [73]       |
|                  | Morinda latifolia S.M.           | Nigeria          | Stem barks       | –                                                             | 9368.0 (brine shrimp)                                           | [73]       |
|                  | Salvia sp. (andrombavifoliv)      | Madagascar       | Aerial part      | –                                                             | –                                                              | [75]       |
|                  | Sarcocephalus latifolius (J. E. Smith) E. A. Bruce | Nigeria          | Root barks       | –                                                             | –                                                              | [74]       |
|                  | Schima trifolium concinum Bak.   | Madagascar       | Root barks       | –                                                             | –                                                              | [75]       |
|                  | S. farinipennis Bak.             | Madagascar       | Root barks       | –                                                             | –                                                              | [75]       |
|                  | S. rubrifolius Bak.              | Madagascar       | Root barks       | –                                                             | –                                                              | [75]       |
|                  | Citropsis articulata (Willd. ex Spreng.) Swingle & Kellerman | Uganda           | Roots            | 77% inhibition at 10 (FcB1)                                   | 12% inhibition at 10 (Vero)                                     | [64]       |
|                  |                                    | Nigeria          | Stem barks       | 24.7                                                      | >50% inhibition at 16.7 (Vero)                                  | [75]       |
|                  |                                    | Nigeria          | Leaves           | 0.9                                                        | 9.3% inhibition at 0.9 (Vero)                                   | [75]       |
|                  |                                    | Nigeria          | Stem barks       | 1.5-dihydroxy-2,3-dimethoxy-10-methyl-9-acridone3.0         | 30.5% inhibition at 3.0 (Vero)                                  | [75]       |
|                  |                                    | Nigeria          | Leaves           | 7α-obacunyl acetate                                          | >50% inhibition at 9.3 (Vero)                                   | [75]       |
Table 3. Cont.

| Family         | Ethnologic Plant            | Country     | Plant Part                        | Antiplasmodial Activity (IC<sub>50</sub>) (µg/mL, Unless Indicated) | Cytotoxicity (CC<sub>50</sub> for Cells, LD<sub>50</sub> for Brine Shrimp) (µg/mL, Unless Indicated) | References |
|----------------|-----------------------------|-------------|-----------------------------------|---------------------------------------------------------------------|-----------------------------------------------------------------------------------|------------|
| **Rutaceae**   |                             |             |                                   |                                                                     |                                                                                  |            |
|                | *Evodia fujiana* H. Perr.   | Madagascar  | Root barks, stem barks            | -                                                                   | -                                                                              | [75]       |
|                | *Toddalia asiatica* (L.) Lam. | Kenya; Madagascar | Root barks, root barks, stem barks | -                                                                   | -                                                                              | [75,80]    |
|                | *Zanthoxylum tsimangosse H. Perr.* | Madagascar | Stem barks                        | -                                                                   | -                                                                              | [75]       |
| **Santalaceae**| *Okurubaka auriculata* Phellog & Nomand | Nigeria     | Stem barks                        | -                                                                   | -                                                                              | [75]       |
| **Sapindaceae**| *Dodonaea viscosa* Jacq.    | Madagascar  | Leaves                            | -                                                                   | -                                                                              | [75]       |
|                | *D. madagascariensis* Rdlk. | Madagascar  | Leaves                            | -                                                                   | -                                                                              | [75]       |
| **Selaginellaceae** | *Salaginella vogelli* Cameroun    | Cameroon    | Leaves (MeOH)                     | 32.2                                                               | -                                                                              | [91]       |
| **Schizaceae**  | *Mohria caffrorum* (L.) Desv. | Madagascar  | Aerial parts                       | -                                                                   | -                                                                              | [75]       |
| **Simaroubaceae** | *Brucea antidysenterica* J.F. Mill. |             | Stems, barks, seeds               | -                                                                   | -                                                                              | [71]       |
| **Ulmaceae**   | *Tremia commersonii* Boj.   | Madagascar  | Aerial part                        | -                                                                   | -                                                                              | [75]       |
|                | *T. orientalis* Blume       | Madagascar  | Root barks                         | 2.0 (K1)                                                           | 32.5 (L6)                                                                      | [75]       |
| **Verbanaceae**| *Lippia multiflora* Moldenke | Nigeria     | Aerial part                        | -                                                                   | 1.1 (brine shrimp)                                                            | [75]       |
|                | *Clerodendrum myricoides* (Hochst.) Vatke | Kenya    | Root barks                         | 9.8% (*Plasmodium berghei* NK65)                                   | -                                                                              | [71,80]    |
|                | *Vitex doniana*             | Nigeria     | Leaves (Hexane)                    | 3.6 (K1)                                                           | 431.4                                                                         | [81,82]    |
|                | *Stem barks* (Hexane)       |             |                                   | 6.8 (K1)                                                           | ND                                                                             | [81]       |
| **Zingiberaeae** | *Curcuma longa* L.         | Madagascar  | Leaves                            | -                                                                   | -                                                                              | [75]       |
|                | *Zingiber officinale* Roscoe |             | Rhizome                           | -                                                                   | -                                                                              | [71]       |

<sup>a</sup> IC<sub>50</sub>: Concentration that resulted in 50% death of *Plasmodium falciparum*.  
<sup>b</sup> LD<sub>50</sub>: Concentration that was lethal to 50% of test animals.  
<sup>c</sup> CC<sub>50</sub>: Concentration that resulted in 50% cell death.
2. Plant-derived Antimalarial Compounds

2.1. Annonaceae–Asteraceae Families

2.1.1. Annonaceae Family

Annonaceae is a family of flowering plants consisting of about 2400 species. Two plants in this family have been phytochemically investigated for their antiplasmodial and cytotoxic activities. From the leaves of *Friesodielia discolor*, Prawat et al. isolated two new flavonoids, 3′-formyl-2′,4′-dihydroxy-6′-methoxychalcone (5), 8-formyl-7-hydroxy-5-methoxyflavone (6), and the known tectochrysin (7) (Figure 3) [31]. They displayed antiplasmodial activity against the K1 multidrug resistant strain of *P. falciparum* with IC$_{50}$ values of 9.2, 9.3 and 7.8 µM, respectively. However, these compounds also exhibited cytotoxicity against the cancer cell lines KB and MCF-7, with the IC$_{50}$ values ranging from 13.9–34.5 µM.

According to Mueller et al. [32], 5-hydroxy-6-methoxyonychene (8), an alkaloid obtained from the roots of the Australian tree plant *Mitrephora diversifolia*, showed IC$_{50}$ values of 9.9 and 11.4 µM against the 3D7 and Dd2 clones of *P. falciparum*, respectively.

Miliusacunines A (9) and B (10) were identified from an acetone extract of the leaves and twigs of *Miliusa cuneatas* [33]. Compound 9 demonstrated inhibitory activity against the TM4 malarial strain (IC$_{50}$ 19.3 µM), and compound 10 displayed activity against the K1 malarial strain (IC$_{50}$ 10.8 µM). Both isolates showed no toxicity to the Vero cells at the elevated concentrations.

2.1.2. Araceae Family

Zhang et al. [22,23] performed extensive research on *Rhaphidophora decursiva*, a vine growing in Vietnam. The MeOH extract of the plant leaves and stems showed antimalarial activity against both D6 and W2 clones with no apparent cytotoxicity at a concentration of 20 µg/mL. Seven compounds were identified from the stems and leaves of the plant through a bioassay-guided separation (Figure 4). Polysyphorin (1) and raphidecursperoxin (2) were among the most active compounds, which demonstrated antimalarial activity with IC$_{50}$ values of 1.4–1.8 µM against the D6 and W2 strains and cytotoxicity with ED$_{50}$ values of 8.3–13.1 µM against KB cells (Figure 2). Raphidecursinol A (11) and B (12), grandisin (13), epigrandisin (14) and decursivine (15) also showed activities against *P. falciparum* (D6 and W2) with IC$_{50}$ values of 3.4–12.9 µM and cytotoxicity of ED$_{50}$ values of 23.9–37.0 µM against KB cells with an exception of compound 14, which showed no antimalarial activity against D6 strain at 23 µM.
According to the further investigation of Zhang et al. [24], a potent but toxic trichothecene compound, roridin E (3), was identified from the same plant extract (Figure 2). The investigators determined that the compound was able to inhibit parasite growth with IC$_{50}$ values in the sub-nano molar range. However, roridin E was also very cytotoxic against KB cells. Interestingly, these researchers reported another trichothecene compound (4) from a plant in a different family, and the compound showed equally potent antimalarial activities as that of roridin E, but with much less cytotoxicity (see Section 2.8.3).

2.1.3. Asclepiadaceae Family

Libman et al. reported the antimalarial bioassay-directed separation of Gongronema napalense, leading to the identification of a new steroidal glycoside, gongroneside A (16) (Figure 5) [25]. The compound showed inhibitory activity against the D6 and W2 clones with IC$_{50}$ values of 1.6 and 1.4 µM, respectively. Gongroneside A showed no cytotoxicity against KB cells at a concentration of 13.7 µM.

Figure 5. Compound from an Asclepiadaceae plant.
2.1.4. Asteraceae Family

Apigenin 7-O-glucoside (17) and luteolin 7-O-glucoside (18), two flavonoid glycosides obtained from the aerial parts of *Achillea millefolium*, showed antiplasmodial activities against D10 and W2 strains with IC$_{50}$ values in the range of 15.3–62.5 µM [34] (Figure 6).

![Compounds from Asteraceae plants.](image)

2-Isopropenyl-6-acetyl-8-methoxy-1,3-benzodioxin-4-one (19), isolated from the whole plants of the Korean folk medicine *Carpesium divaricatum*, was reported to show antimalarial activity [35,93] (Figure 6). The compound exhibited activity against D10 with an IC$_{50}$ value of 2.3 µM.

*Microglossa pyrifolia*, a medicinal plant used against malaria in Ghana, was tested against both PoW and Dd2 strains of *Plasmodium berghei* by Köhler et al. [36]. Two diterpenes, *E*-phytol (20) (IC$_{50}$: 8.5 µM (PoW); 11.5 µM (Dd2)), and 6*E*-geranylgeraniol-19-oic acid (21) (IC$_{50}$: 12.9 µM (PoW); 16.6 µM (Dd2)) were shown to be the most active compounds in their test system (Figure 6).

A *Plasmodium berghei*-infected mouse model was used to evaluate the antimalarial activity of the 80% methanol extract of the roots of the traditionally used antimalarial plant *Echinops hoehnelii*. The methanol extract could suppress the parasite growth by 68.5% at a dose of 200mg/kg. No acute oral toxicity was observed in the animal study, indicating the safety use of the plant extract. Further phytochemical separation of the plant led to the isolation of two acetylenicthiophenes, 5-(penta-1,3-diynyl)-2-(3,4-dihydroxybut-1-ynyl)-thiophene (22) and 5-(penta-1,3-diynyl)-2-(3-chloro-4-acetoxy-but-1-yn)-thiophene (23), which displayed significant growth suppression of the *Plasmodium* parasite by 50.2% and 32.7% at 100 mg/kg, respectively [37] (Figure 6).

2.2. Buxaceae Family

Cai et al. identified several new antimalarial compounds from *Buxus sempervirens* [38], the native and introduced plant species in the United States. The traditionally used plants have received scant attention as potential source materials for drug discovery research as compared to the botanical materials from tropical and semitropical areas of the world. The eight lupane triterpenes (24–31), isolated from the *Buxus* plant (Figure 7), were evaluated for their activity against multi-drug-resistant malaria parasites (HB3, IC$_{50}$ 0.5–3.0 µM) and counterscreened against HeLa cells (IC$_{50}$ 7 µM for 24; >20 µM for 25–31). Strikingly, 23-*O*-(trans)-feruloyl-23-hydroxybetulin (26) displayed antimalarial
activity at a concentration that was 75-fold more selective to the drug-resistant parasite strain than to HeLa cells.

2.3. Cecropiaceae–Cucurbitaceae Families

2.3.1. Cecropiaceae Family

*Cecropia pachystachya* is a medicinal plant, which has been used in Brazil. The ethanol extracts of the different parts of the plants were evaluated for their activity against *P. falciparum* in vitro and *P. berghei* in vivo [39]. The parasitemia of malaria-infected mice was reduced by 35–66% with treatment of the ethanol extracts of the wood, root, and leaf materials in comparison with the non-treated control group. The plant root extracts were further analyzed and fractionated to provide subfractions, which were also active in an in vivo study. Two compounds, β-sitosterol (32) and tormentic acid (33), were identified from the subfractions (Figure 8). Both compounds showed plasmodial inhibitory activity. However, only tormentic acid (33) demonstrated inhibitory activity against *P. falciparum* chloroquine-resistant parasites (W2) (IC$_{50}$ 19.0–25.2 µM).

2.3.2. Chloranthaceae Family

Yue et al. [40] recently reported the isolation of 32 antimalarial lindenane-type sesquiterpenoids (34–65) from several plants in Chloranthaceae family with IC$_{50}$ values lower than 11.4 µM against *P. falciparum* strain Dd2. The 12 new sesquiterpenoid dimers fortunilides A–L (34–45), along with 7 known isolates (46–51 and 53) were isolated from *C. fortune*. Compounds 52, 54, 58, 59 and 60–64...
were obtained from *C. serratus* and *C. spicatus*, and compounds 55–57 were separated from *Sarcandra glabra*. Compound 65 was originated from *C. multisachys*. Among these isolates, fortunilide A (34), sarglabolide J (47) and chlorajaponilide C (52) exhibited low nanomolar activities with IC\textsubscript{50} values of 5.2, 7.2 and 1.1 nM, respectively, and their selectivity index values toward mammalian cells were greater than 500 (Figure 9).

![Compounds from Chloranthaceae plants.](image-url)

**Figure 9.** Compounds from Chloranthaceae plants.
2.3.3. Chrysobalanaceae Family

From the Petroleum ether/CH$_2$Cl$_2$ extracts of the stems of *Parinari capensis*, three kaurene diterpene lactones, 10, 13-dihydroxy-9-methyl-15-oxo-20-norkaur-16-en-18-0ic acid γ-lactone (66), 10-hydroxy-13-methoxy-9-methyl-15-oxo-20-norkaur-16-en-18-0ic acid γ-lactone (67) and 10-hydroxy-9-methyl-15-oxo-20-norkaur-16-en-18-0ic acid γ-lactone (68) were isolated (Figure 10) [41]. They possess antimalarial activity against FCR-3 with IC$_{50}$ values of 1.7, 1.9 and 5.0 µM, respectively.

![Figure 10. Compounds from a Chrysobalanaceae plant.](image)

The three compounds (66–68) also displayed cytotoxicity against Graham cells with ED$_{50}$ values in the range of 3.2–9.2 µM, which preclude them from further biological investigation. They could, however, be used effectively as lead compounds for drug optimization through synthesis.

2.3.4. Clusiaceae Family

Phytochemical separation of the concentrated acetone extract of the dried leaves and branches of *Garcinia mckeaniana* has led to the identification of three new xanthones, mckeanianones A-C (69–71), and two known ones, bannaxanthones I (73) and E (73) (Figure 11). These compounds all contain two isoprene units. They were evaluated for their activity against the TM4 and K1 strains of *P. falciparum* with IC$_{50}$ values in the range of 6.0–8.5 and 3.6–7.3 µM, respectively, and compounds 70, 71 and 73 showed cytotoxicity against Vero cells with the IC$_{50}$ values in the range of 12.6–29.5 µM [42].

![Figure 11. Compounds from a Clusiaceae plant.](image)

2.3.5. Connaraceae Family

From the work of He et al. [26], bioassay-guided separation of the chloroform extract of the stems of *Rourea minor* (Gaertn.) Aubl. led to the identification of three active compounds including two new neolignan glycosides, rourinose (74) and rouremin (75), and the known 1-(26-hydroxyhexacosanoyl)-glycerol (76) (Figure 12). The three compounds showed weak to moderate in vitro activities against the D6 and W2 clones of *P. falciparum*. Compound 74 demonstrated IC$_{50}$ values at 3.7 (D6) and 2.1 (W2) µM; 75 at IC$_{50}$ values of 5.1 (D6) and 4.5 (W2) µM, and 76 at IC$_{50}$ values of 9.5 (D6) and 12.7 (W2) µM. These compounds exhibited no cytotoxicity against KB cells at 20 µg/mL.
2.3.6. Cornaceae Family

In vitro IC\textsubscript{50} values against the \textit{P. falciparum} D10 strain were determined for ergosta-4,6,8,22-tetraene-3-one (77) (61.0 μM), 3-epideoxyflindissol (78) (128.0 μM), 3\(\beta\)-\textit{O}-\textit{cis}-coumaroyl betulinic acid (79) (10.4 μM) and 3\(\beta\)-\textit{O}-\textit{trans}-coumaroyl betulinic acid (80) (15.3 μM) (Figure 13), which were separated from the leaves of \textit{Cornus florida} L. by Graziose et al. for the first time [43].

![Figure 12. Compounds from a Connaraceae plant.](image)

![Figure 13. Compounds from a Cornaceae plant.](image)

2.3.7. Cucurbitaceae Family

\textit{Cogniauxia podolaena} Baill. is a folk medicine that has been traditionally used to treat malaria in Congo Brazzaville. Banzouzi et al. [44] identified cucurbitacins B (81) and D (82), and 20-epibryonolic acid (83), the three triterpenes from the stems of this plant (Figure 14). These compounds exhibited inhibitory activity against FcM29 strain with IC\textsubscript{50} values of 2.9, 7.8 and 4.4 μM, respectively. Both cucurbitacins B and D showed a high cytotoxicity with approximately 95% inhibition against KB cells at 1 μg/mL, while 20-epibryonolic acid displayed a better selectivity index (20% inhibition of KB cells at 1 μg/mL).

![Figure 14. Compounds from a Cucurbitaceae plant.](image)
2.4. Ebenaceae–Euphorbiaceae Families

2.4.1. Ebenaceae Family

Ma et al. [27] investigated the plant Diospyros quaesita Thw., known as “Muang Kout” in Laos. Of the isolates from the up parts of this plant, betulinic acid 3-caffeate (84) demonstrated antiplasmodial activity against the D6 and W2 clones with IC\textsubscript{50} values of 1.40 and 0.98 µM, respectively (Figure 15). The compound was cytotoxic to KB cells with an ED\textsubscript{50} value of 4.0 µM.

![Figure 15. Compounds from an Ebenaceae plant.](image)

Through the screening of a natural product-based synthetic compound library, Hadi et al. [45] discovered that jatrophones (the natural products from Jatropha isabelli) possess significant antiplasmodial activity. The jatrophone diterpene derivatives 85 and 86 displayed antiplasmodial activities against strains 3D7 and K1 of P. falciparum with IC\textsubscript{50} values of 5.7/5.9 and 6.1/5.9 µM, respectively (Figure 16). The two compounds showed low cytotoxicities against the human HepG2, RAJI, BJ and HEK293 cells with EC\textsubscript{50} values at around 26 µM.

![Figure 16. Compounds from Euphorbiaceae plants.](image)

Seephonkai et al. [46] studied the Thai traditional medicinal plant Strophioblachia fimbricalyx, and isolated 9-O-demethyltrigonostemone (87) and a new phenanthropolone, 3,6,9-trimethoxyphenanthropolone (88), which exhibited antimalarial activity against the multiresistant K1 strain of P. falciparum with IC\textsubscript{50} values of 8.7 and 9.9 µM, respectively (Figure 16).

2.5. Fabaceae–Fagaceae Families

2.5.1. Fabaceae Family

According to Nigerian ethnobotany, the plant Cajanus cajan L. (Fabaceae) can be used for treatment of malaria. From the methanol extract of the leaves of this plant, 2’,6’-dihydroxy-4-methoxy chalcone (89), a cajachalcone, was isolated through bioassay-guided fractionation, which used the parasite lactate dehydrogenase assay by targeting the K1 strain of P. falciparum (Figure 17). The cajachalcone showed an IC\textsubscript{50} value of 7.4 µM [47].
were evaluated for their antimalarial activity against the W2 clone of *P. falciparum* var. *glaberrimum* with an IC$_{50}$ value of 2.4 µM (Figure 18). However, the compound also showed cytotoxicity against KB cells with an IC$_{50}$ value of 10.0 µM. 

According to the work of Samoylenko et al. [49], prosopilosidine (92) and isoprosopilosidine (93), isolated from the leaves of *Prosopis glandulosa* var. *glandulosa*, showed potent antimalarial activity against the D6 and W2 strains of *P. falciparum* with high selectivity index (SI) values (Figure 17). Compound 92 exhibited IC$_{50}$ values of 0.1 (D6) and 0.3 (W2) µM, while 93 demonstrated IC$_{50}$ values of 0.1 (D6) and 0.3 (W2) µM. Compounds 92 and 93 showed much lower cytotoxicity to KB cells with ED$_{50}$ values of 20.2 and 18.8 µM, respectively.

### 2.5.2. Fabaceae Family

Subsequent bioassay-guided fractionation work by Cai et al. [38] yielded four kaempferol 3-O-glucosides (94–97) from *Quercus laceyi* (Figure 18). The IC$_{50}$ values for these compounds against multi-drug-resistant malaria parasites HB3 are 0.6–2.1 µM, and the IC$_{50}$ value against HeLa cells was <3 µM.

### 2.6. Hypericaceae Family

*Visnia orientalis*, a traditional medicine used in Tanzania, was studied by Mbwanbo et al. [50]. Vismione D (98), isolated from the stem barks of this plant, exhibited activity against the K1 strain with an IC$_{50}$ value of 2.4 µM (Figure 18). However, the compound also showed cytotoxicity against human L6 cells with an IC$_{50}$ value of 10.0 µM.

Pure isolates from the hexane extract of the stem barks of the African plant *Psorospermum glaberrimum* were evaluated for their antimalarial activity against the W2 clone of *P. falciparum* by Ndjakou Lenta et al. [51]. The isolates 3-geranyloxyemodin anthrone (99) and acetylvismione...
D (100) displayed inhibition activity against the W2 strain with IC₅₀ values of 1.7 and 0.1 µM, respectively (Figure 19).

![Figure 19. Compounds from Hypericaceae plants.](image)

2.7. Lamiaceae–Lythraceae Families

2.7.1. Lamiaceae Family

An EtOH extract of the dried root barks of Ocimum sanctum exhibited considerable in vitro antimalarial activity. Bioactivity-directed separation of the EtOH extract resulted in the isolation of a new antimalarial natural compound (101) (Figure 20). The compound showed comparable activity to the positive controls, chloroquine and amodiaquine, against the *P. falciparum* 3D7 strains with an IC₅₀ value of 0.1 µM [52].

![Figure 20. Compounds from Lamiaceae plants.](image)

From the study of Kirmizibekmez et al. [53], luteolin 7-O-β-D-glucopyranoside (102) and chrysoeriol 7-O-β-D-glucopyranoside (103), two flavonoid glycosides isolated as the major antimalarial constituents from Phlomis brunneogaleata through an activity-directed separation (Figure 20), showed activity with IC₅₀ values of 5.4 and 12.7 µM against the K1 clones, respectively.

The extracts of 17 *Salvia* species, which are used as folk medicines in South Africa, were subjected to biological testing by Kamatou et al. [54]. The potential activity of the *Salvia* plant extracts against the FCR strain of *P. falciparum* and their cytotoxic effects against MCF-7 cells were investigated. These extracts showed antiplasmodial activity with IC₅₀ values in the range of 3.9–26.0 µg/mL. The extracts from *S. radula* demonstrated the most potent activities. Two compounds, betulafolientriol oxide (104) and salvigenin (105), were subsequently isolated (Figure 20), and they showed antimalarial activity with IC₅₀ values of 10.4 and 75.0 µM, respectively.

2.7.2. Loganiaceae Family

A phytochemical study was carried out for the stem barks of Strychnos icaja for the first time by Tchinda et al. [55], which led to the isolation of the monomers 15-hydroxyvomicine (106) and...
Among the isolated compounds, 4-hydroxy-\(\text{N}-\text{methyl-sec-iso-pseudostrychnine} (107).\) The isolates were evaluated against the \(P.\ falciparum\) 3D7 strain with IC\(_{50}\) values of 101.0 and 110.6 \(\mu\text{M},\) respectively (Figure 21).

![Image of compounds 106 and 107](image_url)

**Figure 21.** Compounds from a Loganiaceae plant.

2.7.3. Lythraceae Family

The plants in the genus of \(Ammannia\) are frequently used in China and India as folk medicines for treatment of various diseases. Upadhyay et al. [56] investigated the compounds in four species of this genus (\(Ammannia: A.\ multiflora, A.\ verticillata, A.\ Baccifera\) and \(A.\ coccinea\)) for their antimalarial activities. Among the isolated compounds, 4-hydroxy-\(\alpha\)-tetralone (108) and tetralone-4-\(\beta\)-\(D\)-glucopyranoside (109) from \(A.\ multiflora,\) and ammaniol (110) from \(A.\ baccifera\) displayed antimalarial activities against the \(P.\ falciparum\) NF-54 strain with IC\(_{50}\) values of 194.0, 124.0 and 88.3 \(\mu\text{M},\) respectively (Figure 22).

![Image of compounds 108, 109, and 110](image_url)

**Figure 22.** Compounds from Lythraceae plants.

2.8. Malvaceae–Myristicaceae Families

2.8.1. Malvaceae Family

LC-PDA-MS-SPE-NMR technique was used by Sprogøe et al. in combination with CD to detect (R)-(−)-gossypol [(R)-1] (111) in the twigs of \(Thespesia\ danis\) (Figure 23) [57]. (R)-1 demonstrated antimalarial activity with an IC\(_{50}\) value of 4.5 \(\mu\text{M}.\) However, its enantiomer was inactive up to a concentration of 20 \(\mu\text{M}.

![Image of compound 111](image_url)

**Figure 23.** Compounds from a Malvaceae plant.

2.8.2. Monimiaceae Family

The compound 1-(4-hydroxybenzyl)-6,7-methylenedioxy-2-methylisoquinolinium trifluoroacetate (112), a new benzylisoquinoline alkaloid isolated by mass-guided separation of the \(\text{CH}_2\text{Cl}_2/\text{MeOH}\)
extract of Doryphora sassafras (Figure 24) [58]. Compound 112 showed antiplasmodial activity against two different strains (3D7 and Dd2) of P. falciparum with IC\textsubscript{50} values of 3.0 and 4.4 µM, respectively. The compound did not exhibit inhibitory activity against the human embryonic kidney cell line (HEK293) at a concentration of 120 µM.

![Figure 24. Compounds from Monimiaceae plants.](image)

A phytochemical study of the leaves of Glossocalyx brevipes Benth. led to isolation of two new homogentisic acid derivatives of methyl 2-(1′β-geranyl-5′β-hydroxy-2′-oxocyclohex-3′-enyl) acetate (113) and 2-(1′β-geranyl-5′β-hydroxy-2′-oxocyclohex-3′-enyl) acetic acid (114), which displayed antiplasmodial activity against D6/W2 clones with IC\textsubscript{50} values of 2.2/6.6 and 4.8/8.3 µM, respectively (Figure 24) [59].

2.8.3. Moraceae Family

According to the investigation of Zhang et al. [24], an antimalarial trichothecene compound, verrucarin L acetate (4), was identified from Ficus fistulosa (Figure 2). The antimalarial potency of 4 was equivalent to that of roridin E (3) isolated from Rhaphidophora decursiva, a plant from a different family. However, 4 was observed to be much less cytotoxic to KB cells (ED\textsubscript{50} 0.2 µM) than 3.

Bioassay-directed separation of the MeOH extract of the twigs of Ficus septica afforded three known phenanthroindolizine alkaloids, dehydroantofine (115), dehydrotylophorine (116) and tylophoridicine D (117) by Kubo et al. (Figure 25) [60]. They showed antiplasmodial activity against the P. falciparum 3D7 strain with IC\textsubscript{50} values in the range of 0.03–0.4 µM. Compound 115 also displayed cytotoxicity against the mouse fibroblast cells L929 with an IC\textsubscript{50} value of 8.2 µM, while the other two compounds showed no toxicity at a concentration of 50 µM.

![Figure 25. Compounds from a Moraceae plant.](image)

2.8.4. Myristicaceae Family

Phytochemical investigation of the fruits of Knema glauca by Rangkaew et al. [61] led to the isolation of malabaricone A (118) as an active compound against the P. falciparum K1 strain with an IC\textsubscript{50} value of 8.5 µM (Figure 26). The compound was cytotoxic towards KB cell with an ED\textsubscript{50} value of >61 µM.
2.9. Piperaceae–Platanaceae Families

2.9.1. Piperaceae Family

The Piperaceae family consists of many plants that are used by the native populations in Thailand as traditional medicines for the treatment of various diseases. Sarmentine (119) and 1-piperettyl pyrrolidine (120) were isolated from the fruits of *Piper sarmentosum* by Rukachaisirikul et al. [62], and they exhibited antiplasmodial activity against the K1 strain with IC50 values of 85.5 and 21.9 µM, respectively (Figure 27).

From the whole plant of *Piper tricuspe*, dictyochromenol (121), 3-farnesyl-p-hydroxy benzoic acid (122) and 2′E,6′E-2-farnesyl hydroquinone (123) were isolated by Saez Vega et al. [63] (Figure 27). The compounds are active against several strains of *P. falciparum* with IC50 values ranging from 1.4 to 29.8 µM. Cytotoxic effects were also observed for the compounds with EC50 values in the range of 1.1–41.0 µM. The results suggest that the antimalarial activity of the compounds was most probably the direct result of their cytotoxicity.

2.9.2. Platanaceae Family

Bioactivity-guided fractionation of *Platanus occidentalis* by Cai et al. [38] yielded four kaempferol 3-O-rhamnosides (124–127) (Figure 28). The IC50 values for these compounds against multi-drug-resistant malaria parasites HB3 ranged from 0.5 to 1.8 µM. The IC50 values against HeLa cells were in the range of 9.3–20.0 µM.

![Figure 26. Compound from a Myristicaceae plant.](image1)

![Figure 27. Compounds from Piperaceae plants.](image2)

![Figure 28. Compounds from a Platanaceae plant.](image3)
2.10. Rubiaceae-Rutaceae Families

2.10.1. Rubiaceae Family

Naucleorine (128), epimethoxynaucleorine (129), 3α,23-dihydroxyurs-12-en-28-oic acid (130) and oleanolic acid (131) were identified from the stems of Nauclea orientalis by He et al. [28] (Figure 29). The compounds showed antiplasmodial activities against the P. falciparum D6(∗)/W2(∗) strains with the IC50 values shown as below: compound 128 (IC50 6.9*/6.0** µM); 129 (IC50 12.4*/13.2** µM); 130 (IC50 9.7*/12.7** µM) and 131 (IC50 4.6*/5.1** µM). Compounds 128–131 displayed cytotoxicity against KB cells with ED50 values of 38.0, >37.9, >42.2 and 46.0 µM, respectively.

![Figure 29. Compounds from a Rubiaceae plant.](image1)

2.10.2. Rutaceae Family

Based on an ethnomedicinal survey of the plants in Uganda, Citropsis articulata was selected for phytochemical study to investigate its antimalarial constituents [64]. From the ethyl acetate extract of the root barks of this plant, two known alkaloids, 5-hydroxynoracronycine (132) and 1,5-dihydroxy-2,3-dimethoxy-10-methyl-9-acridone (133), were identified as the best growth inhibitors of P. falciparum with IC50 values of 2.8 and 10.0 µM, respectively. The compounds were cytotoxic towards Vero cells at EC50 values of 28.8 and 101.0, respectively.

![Figure 30. Compounds from Rutaceae plants.](image2)

The roots and stem barks of Zanthoxylum chiloperone have been used as a folk medicine for the treatment of malaria and for its emmenagogue and antirheumatic properties. The pyranocoumarin trans-avicennel (134) and two canthinone alkaloids, canthin-6-one (135) and 5-methoxycanthin-6-one (136), were identified from the stem barks of this plant by Cebrián-Torrejón et al. [65] (Figure 30). These compounds possessed antiplasmodial IC50 values against chloroquine/mefloquine resistant and sensitive strains of P. falciparum (F32, K1, PFB and FcB1 cells) in the range of 1.4–41.6 µM. Compounds 134 and 135 were cytotoxic towards Vero cells with EC50 values of 12.8 and 42.7 µM, respectively.

2.11. Simaroubaceae Family

Kuo et al. [66] found that among the isolates from the roots of Eurycoma longifolia, eurycomanone (137) and pasakbumin B (138) [67] displayed potent antimalarial activity against the P. falciparum W2/D6 strains with IC50 values of 0.04/0.06 and 0.05/0.08 µM, respectively (Figure 31). The compounds also exhibited strong cytotoxicity toward human breast cancer (MCF-7) and lung cancer (A549) cells at low concentrations.
De Andrade-Neto et al. [68] studied a number of Simaroubaceous plants, resulting in the isolation of the following compounds: the quassinoid neosergeolide (139) from the roots and stems of Picrolemma spruce (Figure 31); the indole alkaloids ellipticine (140) and aspidocarpine (141) from the barks of Aspidosperma vargasii and A. desmanthum (Apocynaceae), respectively; and 4-nerolidylcatechol (142) from the roots of Pothomorphe peltata (Piperaceae). Compounds 139–141 presented significant inhibitory activity against the multi-drug resistant K1 strain with IC\textsubscript{50} values of 0.002, 0.07, 0.02 and 0.7 µM, respectively, and these compounds displayed antimalarial potency greater than those of quinine and chloroquine.

![Compounds from Simaroubaceae plants.](image1)

2.12. Theaceae–Tiliaceae Families

2.12.1. Theaceae Family

Gallocatecin (143) is a flavonoid contained in the tea leaf extract of Camellia sinensis (Figure 32). Based on molecular docking studies, Tegar et al. [69] found that gallocatecin has stronger antimalarial potency than mefloquine (144), a synthetic drug with antimalarial activity.

![Compound from Theaceae plants.](image2)

2.12.2. Tiliaceae Family

According to the study of Ma et al. [29], five isolates from the leaves, stems and twigs of Grewia bilamellata, 3a,20-lupandiol (145), grewin (146), nitidanin (147), 2α,3β-dihydroxoyolean-12-en-28-oic acid (148) and 2,6-dimethoxy-1-acetonylquinol (149), displayed antimalarial activity against the P. falciparum D6 and W2 clones with IC\textsubscript{50} values in the range of 5.5–42.2 µM (Figure 33). These compounds showed no cytotoxicity towards KB carcinoma cell line at a concentration of 50 µM.
Chromatographic separation of the ethyl acetate extract of the aerial parts of *Lippia javanica* yielded a new antimalarial α-pyrene, lippillactone (150) (Figure 34). This compound is active against the D10 strain with an IC$_{50}$ value of 23.8 µM. Compound 119 is also mildly cytotoxic [70].

3. Marine Plant-Derived Antimalarial Compounds

Marine organisms offer unique opportunity to discover lead compounds for the treatments of malaria.

Separation of the extracts of Fijian red alga *Callophycus serratus* by Lane et al. led to the isolation of bromophycolides J-Q (151–158) [94] (Figure 35), the macrolide diterpene-benzoate derivatives represented as two novel carbon skeletons. These diterpenes, together with the previously reported ten bromophycolides, bromophycolides A-I (159–167) and debromophycolide A (168) from this alga (Figure 36) [95], were evaluated for their antimalarial activity against *P. falciparum*. The IC$_{50}$ values of bromophycolides A, D, E, H and M (159, 162, 163, 164 and 154) were observed to be 0.9, 0.3, 0.8, 0.9 and 0.5 µM, respectively. Some of these compounds also exhibited strong cytotoxicity toward DU4475, a human breast cancer cell line. The ED$_{50}$ values of bromophycolides N and Q (155 and 158) were 1.5 and 2.0 µM, respectively.
4. Ethnologic Antimalarial Compounds

At present, more than 80% of the world’s population relies on ethnopharmacologic healing modalities and plants for their primary health care and wellness [97]. In Africa and many other developing countries, ethnomedicines are often regarded as their primary choice to treat diseases as they are obtained most affordable and accessible from locally available plants or other natural sources.

From the sponge *Diacarnus megaspinorhabdosa* collected in Xisha Islands, four new norterpenic cyclic peroxides, diacarnuperoxides M (169) and N (170), (+)-2, 3, 6-epihurghaperoxide (171) and (+)-2,3,6-epihurghaperoxide acid (172), together with the known norterpenic cyclic peroxides,
(−)-muqubilin A (173), nuapapuin A (174) and diacarperoxide A (175) were isolated by Yang et al. [96] (Figure 37). They exhibited inhibitory activity against W2 clones of the malaria parasite *P. falciparum* with IC$_{50}$ values of 4.2, 3.0, 1.6, 4.9, 5.6, 5.5 and 1.6 µM, respectively.

### 4. Ethnologic Antimalarial Compounds

At present, more than 80% of the world’s population relies on ethnopharmacologic healing modalities and plants for their primary health care and wellness [97]. In Africa and many other developing countries, ethnomedicines are often regarded as their primary choice to treat diseases as they are obtained most affordable and accessible from locally available plants or other natural sources [78]. Plants are the major resource for the treatment of malaria infections in sub-Saharan Africa, where health care facilities are limited [98]. Ethnomedicinal plants have played a pivotal role in the treatment of malarial for centuries [71,99].

Early writing of over 6000 years ago in Egypt and China, and those of the Vedic civilisation dated 1600 B.C. in India, indicate that malaria has afflicted humans since antiquity, and there is ample evidence that antimalarial traditional medicaments have been used in virtually all cultures as the mainstay for the treatment of this disease. In the 5th century B.C., Hippocrates rejected superstition as a cause for the fevers that afflicted ancient Greeks. He instead recognized the seasonality of fevers and described the early clinical manifestations and complication of malaria [71].

The widely used antimalarial drug, artemisinin, was isolated from the traditional Chinese herb *Artemisia annua* L. (Qinghao) [11], which has been used in China as an ethnomedicine for close to 2000 years. The treatment of malaria with Qinghao was first recorded in “Zhouhou Bei Ji Fang”, the handbook of prescriptions for emergencies in 243 A.D. [71,77].

The use of ethnomedicine such as herbs for the treatment of malaria varies by region, environment and population subgroups. It may be more preferred in some areas than in others. In order to explore the ethnologic basis of these antimalarial plants, several hundred species from 50 families are presently reviewed and listed in Table 3. These plants were collected from 13 countries and areas, exemplified by Madagascar, Nigeria, South Africa and India. The antimalarial activity and toxicity of these plants are also presented in the table [7,64,72–76,79–92,100].

### 5. Conclusions

It is imperative that the search for new antimalarial agents continues at an unabated pace in order to meet the challenges posed by the development of antimalarial drug resistance. During the last decade, numerous antimalarial compounds have been isolated from plants, and many of these compounds exhibit significant activity against *P. falciparum* in vitro. It is, therefore, evident that plant secondary metabolites continue to play an important role in pre-clinical antimalarial drug discovery.

We present in this comprehensive review, the structures of 175 plant-derived antiplasmodial compounds that have been published during the period of 2001–2017. The relevant plants are organized according to the geographical origins of their corresponding plant families.

Among the 175 plant-derived antiplasmodial compounds, several classes of compounds that showed nanomolar range of activity can be regarded as lead compounds to further explore their antimalarial potential. The trichothecene roridin E (3) from *Rhaphidophora decursiva* (Araceae family) showed potent inhibitory effects against the parasite growth with IC$_{50}$ values in the sub-nano molar range (IC$_{50}$: 0.4 nM (D6), 1 nM (W2)) with high cytotoxicity against KB cells (ED$_{50}$: 0.4 nM). However, its closely related structural analog, verrucarin L acetate (4), identified from *Ficus fistulosa* (Moraceae family), displayed much lower cytotoxicity to KB cells (ED$_{50}$ 200 nM) while retaining the same level of the antiplasmodial activity as 3. Identified from the plant (*Ficus septica*) in the same genus as that of 4, the phenanthroindolizine alkaloids dehydroantofine (116) and tylophoridicine D (117) demonstrated potent antiplasmodial activity against the *P. falciparum* 3D7 strain with IC$_{50}$ values of 30 and 60 nM, respectively, and the compounds showed no toxicity at a concentration of 50 µM. A recent study found that the lindenane-type sesquiterpenoids fortunilide A (34), sarglabolide J (47) and chlorajaponilide C
from the plant in Chloranthaceae family displayed potent antiplasmodial activity against Dd2 strain of with IC\textsubscript{50} values of 5.2, 7.2 and 1.1 nM, respectively, and these compounds also showed low cytotoxicity to the mammalian cells WI-38 with IC\textsubscript{50} values of 8.8, 4.0 and 5.4 \(\mu\)M, respectively. More prominently, fortunilide E (38) containing a peroxide group showed antiplasmodial activity of 43 nM with no cytotoxicity at 100 \(\mu\)M.

This review also describes 25 antimalarial compounds that were reported from marine plants during the time period covered. In addition, we included ethnologic information on antimalarial plants from 50 families that are used as folk medicines for the treatment of malaria. Taken together, all the information presented attests to the fact that the phytochemical investigation of terrestrial plants coupled with the biological validation of ethnomedicines constitute proven strategies for the discovery of potential lead compounds for antimalarial drug development.

**Author Contributions:** All authors contributed to surveying the literature, preparation and editing of the manuscript.

**Acknowledgments:** This work was supported by the Research Grants Council of the Hong Kong Special Administrative Region, China (Project No. HKBU 12103014) and the Hong Kong Baptist University (HKBU) Interdisciplinary Research Matching Scheme (RC-IRMS/15-16/02).

**Conflicts of Interest:** The authors declare no conflict of interest.

**References**

1. World Health Organization. *World Malaria Report 2017*; WHO Press: Geneva, Switzerland, 2017.
2. Mueller, I.; Zimmerman, P.A.; Reeder, J.C. *Plasmodium malariae* and *Plasmodium ovale*—The “bashful” malaria parasites. *Trends Parasitol.* 2007, 23, 278–283. [CrossRef] [PubMed]
3. Collins, W.E. *Plasmodium knowlesi*: A malaria parasite of monkeys and humans. *Annu. Rev. Entomol.* 2012, 57, 107–121. [CrossRef] [PubMed]
4. Kajfasz, P. Malaria prevention. *Int. Marit. Health* 2009, 60, 67–70. [PubMed]
5. Beare, N.A.; Taylor, T.E.; Harding, S.P.; Lewallen, S.; Molyneux, M.E. Malarial retinopathy: A newly established diagnostic sign in severe malaria. *Am. J. Trop. Med. Hyg.* 2006, 75, 790–797. [PubMed]
6. Mehlhorn, H. *Encyclopedia of Parasitology*, 3rd ed.; Springer: New York, NY, USA, 2008.
7. Dolabela, M.F.; Oliveira, S.G.; Peres, J.M.; Nascimento, J.M.; Póvoa, M.M.; Oliveira, A.B. In vitro antimalarial activity of six Aspidosperma species from the state of Minas Gerais (Brazil). *An. Acad. Bras. Ciênc.* 2012, 84, 899–910. [CrossRef] [PubMed]
8. Boulos, M.; Dutra, A.P.; DiSanti, S.M.; Shiroma, M.; Amato, N.V. The clinical evaluation of quinine for the treatment of *Plasmodium falciparum* malaria. *Rev. Soc. Bras. Med. Trop.* 1997, 30, 211–213. [CrossRef] [PubMed]
9. Guerin, P.J.; Olliario, P.; Nosten, F.; Druilhe, P.; Laxminarayan, R.; Binka, F.; Kilama, W.L.; Ford, N.; White, N.J. Malaria: Current status of control, diagnosis, treatment, and a proposed agenda for research and development. *Lancet Infect. Dis.* 2002, 2, 564–573. [CrossRef]
10. Fidock, D.A.; Rosenthal, P.J.; Croft, L.; Brun, R.; Nwaka, S. Antimalarial drug discovery: Efficacy models for compound screening. *Nat. Rev. Drug. Discov.* 2004, 3, 509–520. [CrossRef] [PubMed]
11. Tu, Y. The discovery of artemisinin (qinghaosu) and gifts from Chinese medicine. *Nat. Med.* 2011, 17, 1217–1220. [CrossRef] [PubMed]
12. Klayman, D. Qinghaosu (artemisinin): An antimalarial drug from China. *Science* 1985, 228, 1049. [CrossRef] [PubMed]
13. Sriram, D.; Rao, V.S.; Chandrasekharra, K.V.; Yogeeswari, P. Progress in the research of artemisinin and its analogues as antimalarials: An update. *Nat. Prod. Res.* 2004, 18, 503–527. [CrossRef] [PubMed]
14. Zhang, Y.K.; Ge, M.; Plattner, J.J. Recent Progress in the synthesis of antimalarial agents. *Org. Prep. Proced. Int.* 2012, 44, 340–374. [CrossRef]
15. Kappe, S.H.; Vaughan, A.M.; Boddey, J.A.; Cowman, A.F. That was then but this is now: Malaria research in the time of an eradication agenda. *Science* 2010, 328, 862–866. [CrossRef] [PubMed]
16. Ginsburg, H.; Atamina, H. The redox status of malaria-infected erythrocytes: An overview with an emphasis on unresolved problems. *Parasite* 1994, 1, 5–13. [CrossRef] [PubMed]
17. Zani, B.; Gathu, M.; Donegan, S.; Olliaro, P.L.; Sinclair, D. Dihydroartemisinin-piperine for treating uncomplicated Plasmodium falciparum malaria. Cochrane Database Syst. Rev. 2014, 1, 1–160. [CrossRef] [PubMed]
18. Lisewski, A.M.; Quiros, J.P.; Ng, C.L.; Adikesavan, A.K.; Miura, K.; Putluri, N.; Eastman, R.T.; Scanfeld, D.; Regenbogen, S.J.; Altenhofen, L.; et al. Supergenomic network compression and the discovery of EXP1 as a glutathione transferase inhibited by artesunate. Cell 2014, 158, 916–928. [CrossRef] [PubMed]
19. Schlüter, M. Antimalarial drugs—What is in use and what is in the pipeline. Arch. Pharm. Chem. Life Sci. 2008, 341, 149–163. [CrossRef] [PubMed]
20. Newman, D.J.; Cragg, G.M. Natural products as sources of new drugs from 1981 to 2014. Int. J. Mol. Sci. 2018, 19, 1382.
21. Zhang, H.J.; Li, W.F.; Fong, H.H.S.; Soejarto, D.D. Discovery of bioactive compounds by UIC-ICBG drug discovery program in the 18 years since 1998. Molecules 2016, 21, 1448. [CrossRef] [PubMed]
22. Zhang, H.J.; Tamez, P.A.; Vu, D.H.; Ghee, T.T.; Nguyen, V.H.; Le, T.X.; Le, M.H.; Nguyen, M.C.; Do, T.T.; Soejarto, D.D.; et al. Antimalarial compounds from Rhaphidophora decursiva. J. Nat. Prod. 2001, 64, 772–777. [CrossRef] [PubMed]
23. Zhang, H.J.; Qiu, S.; Tamez, P.; Tan, G.T.; Aydogmus, Z.; Nguyen, V.H.; Nguyen, M.C.; Angerhofer, C.; Soejarto, D.D.; Pezzuto, J.M.; et al. Antimalarial agents from plants II. Decurivine, a new antimalarial indole alkaloid from Rhaphidophora decursiva. Pharm. Biol. 2002, 40, 221–224. [CrossRef]
24. Zhang, H.J.; Tamez, P.A.; Aydogmus, Z.; Tan, G.T.; Saikawa, Y.; Hashimoto, K.; Nakata, M.; Hung, N.V.; Xuan, L.T.; Cuong, N.M.; et al. Antimalarial agents from plants. III. Trichoethecenes from Ficus fistulosa and Rhaphidophora decursiva. Planta Med. 2002, 68, 1088–1091. [CrossRef] [PubMed]
25. Libman, A.; Zhang, H.; Ma, C.; Southavong, B.; Sydara, K.; Bouamanivong, S.; Tan, G.T.; Fong, H.H.; Soejarto, D.D. A first new antimalarial pregnane glycoside from Gongronema napalense. Asian J. Tradit. Med. 2008, 3, 203–210. [PubMed]
26. He, Z.D.; Ma, C.Y.; Tan, G.T.; Sydara, K.; Tamez, P.; Southavong, B.; Bouamanivong, S.; Soejarto, D.D.; Pezzuto, J.M.; Fong, H.H.; et al. Rourinoside and rouremin, antimalarial constituents from Rourea minor. Phytochemistry 2006, 67, 1378–1384. [CrossRef] [PubMed]
27. Ma, C.Y.; Musoke, S.F.; Tan, G.T.; Sydara, K.; Bouamanivong, S.; Southavong, B.; Soejarto, D.D.; Fong, H.H.; Zhang, H.J. Study of antimalarial activity of chemical constituents from Diospyros quaesita. Chem. Biodivers. 2008, 5, 2442–2448. [CrossRef] [PubMed]
28. He, Z.D.; Ma, C.Y.; Zhang, H.J.; Tan, G.T.; Tamez, P.; Sydara, K.; Bouamanivong, S.; Southavong, B.; Soejarto, D.D.; Pezzuto, J.M.; et al. Antimalarial constituents from Nauclea orientalis (L.) L. Chem. Biodivers. 2005, 2, 1378–1386. [CrossRef] [PubMed]
29. Ma, C.; Zhang, H.J.; Tan, G.T.; Hung, N.V.; Cuong, N.M.; Soejarto, D.D.; Fong, H.H. Antimalarial compounds from Grewia bilamellata. J. Nat. Prod. 2006, 69, 346–350. [CrossRef] [PubMed]
30. Schwikkard, S.; van Heerden, F.R. Antimalarial activity of plant metabolites. Nat. Prod. Rep. 2002, 19, 675–692. [CrossRef] [PubMed]
31. Prawat, U.; Phupornprasert, D.; Butsuri, A.; Salae, A.W.; Boonsri, S.; Tuntiwachwuttikul, P. Flavonoids from Friesodielia discolor. Phytochem. Lett. 2012, 5, 809–813. [CrossRef]
32. Mueller, D.; Davis, R.A.; Duffy, S.; Avery, V.M.; Camp, D.; Quinn, R.J. Antimalarial activity of azafluorenone alkaloids from the Australian tree Mitrephora diversifolia. J. Nat. Prod. 2009, 72, 1538–1540. [CrossRef] [PubMed]
33. Promchaisri, T.; Jaidee, A.; Cheenpracha, S.; Trisuwan, K.; Rattanajak, R.; Kamchonwongpaisan, S.; Laphookhieo, S.; Pyne, S.G.; Rithwikgrom, T. Antimalarial Oxoprotoberberine Alkaloids from the Leaves of Milusia cuneata. J. Nat. Prod. 2016, 79, 978–983. [CrossRef] [PubMed]
34. Vitalini, S.; Beretta, G.; Iriti, M.; Orsenigo, S.; Basilico, N.; Dall’Acqua, S.; Iorizzi, M.; Fico, G. Phenolic compounds from Achillea millefolium L. and their bioactivity. Acta Biochim. Pol. 2011, 58, 203–209. [PubMed]
35. Chung, I.M.; Seo, S.H.; Kang, E.Y.; Park, W.H.; Park, S.D.; Moon, H.I. Antiplasmodial activity of isolated compounds from Carpesium divaricatum. Phytother. Res. 2010, 24, 451–453. [CrossRef] [PubMed]
36. Köhlera, I.; Jenett-Siemens, K.; Kraft, C.; Siems, K.; Abbiw, D.; Bienzle, U.; Eich, E. Herbal remedies traditionally used against malaria in Ghana: Bioassay-guided fractionation of Microglossa pyrifolia (Asteraceae). Z. Naturforsch. C 2002, 57, 1022–1027. [CrossRef]
37. Ajayiyeoba, E.O.; Ogbole, O.O.; Abiodun, O.O.; Ashidi, J.S.; Houghton, P.J.; Wright, C.W. Cajachalcone: An activity of acetylenic thiophenes from *Echinops hoehnelii* Schweinf. *Molecules* 2017, 22, 1965. [CrossRef] [PubMed]

38. Cai, S.; Risinger, A.L.; Nair, S.; Peng, J.; Anderson, T.J.; Du, L.; Powell, D.R.; Mooberry, S.L.; Chichewicz, R.H. Identification of compounds with efficacy against malaria parasites from common North American plants. *J. Nat. Prod.* 2015, 79, 490–498. [CrossRef] [PubMed]

39. Uchôa, V.T.; de Paula, R.C.; Krettli, L.G.; Santan, A.E.G.; Krettli, A.U. Antimalarial activity of compounds and mixed fractions of *Cecropia pachystachya*. *Drug Dev. Res.* 2010, 71, 82–91. [CrossRef]

40. Zhou, B.; Wu, Y.; Dalal, S.; Merino, E.F.; Liu, Q.F.; Xu, C.H.; Tao, Y.; Ding, J.; Kingston, D.G.I.; Cassera, M.B.; et al. Nanomolar antimalarial agents against chloroquine-resistant *Plasmodium falciparum* from medicinal plants and their structure-activity relationships. *J. Nat. Prod.* 2017, 80, 96–107. [CrossRef] [PubMed]

41. Uys, A.C.; Malan, S.F.; van Dyk, S.; van Zy1, R.L. Antimalarial compounds from *Parinari capensis*. *Bioorg. Med. Chem. Lett.* 2002, 12, 2167–2169. [CrossRef] [PubMed]

42. Auranwiwat, C.; Laphookhieo, S.; Rattanajak, R.; Kamchonwongpaisan, S.; Pyne, S.G.; Ritthiwigrom, T. Antimalarial polyoxygenated and prenylated xanthones from the leaves and branches of *Garcinia mckeaniana*. *Tetrahedron* 2016, 72, 6837–6842. [CrossRef]

43. Graziose, R.; Rojas-Silva, P.; Rathinasabapathy, T.; Dekoc, C.; Grace, M.H.; Poulev, A.; Ann, L.M.; Smith, P.; Raskin, I. Antiparasitic compounds from *Cornus florida* L. with activities against *Plasmodium falciparum* and *Leishmania tarentolae*. *J. Ethnopharmacol.* 2012, 142, 456–461. [CrossRef] [PubMed]

44. Banzouzi, J.T.; Soh, P.N.; Mbatchi, B.; Cavé, A.; Ramos, S.; Retailleau, P.; Rakotonandrasana, O.; Berry, A.; Benoit-Vical, F. *Cogniauxia pololaena*: Bioassay-guided fractionation of defoliated stems, isolation of active compounds, antiplasmodial activity and cytotoxicity. *Planta Med.* 2008, 74, 1453–1456. [CrossRef] [PubMed]

45. Hadi, V.; Hotard, M.; Ling, T.; Salinas, Y.G.; Palacios, G.; Connelly, M.; Rivas, F. Evaluation of *Jatropha isabelli* natural products and their synthetic analogs as potential antimalarial therapeutic agents. *Eur. J. Med. Chem.* 2013, 65, 376–380. [CrossRef] [PubMed]

46. Seephonkai, P.; Sangdee, A.; Bunchalee, P.; Pyne, S.G. Cytotoxic and antiplasmodial compounds from the roots of *Strophodiola chinensis*. *J. Nat. Prod.* 2009, 72, 1892–1894. [CrossRef] [PubMed]

47. Ajayieoba, E.O.; Ogbole, O.O.; Abiodun, O.O.; Ashidi, J.S.; Houghton, P.J.; Wright, C.W. *Cajalcalone*: An Antimalarial Compound from *Cajanus cajan* Leaf Extract. *J. Parasitol. Res.* 2013, 2013, 703781. [CrossRef] [PubMed]

48. Ramanandraibe, V.; Grellier, P.; Martin, M.T.; Deville, A.; Joyeux, R.; Ramanitrasimbaho, D.; Mouray, E.; Rasoanaivo, P.; Mambu, L. Antiplasmodial phenolic compounds from *Psorospermum glaberrimum*. *J. Ethnopharmacol.* 2008, 72, 417–421. [CrossRef] [PubMed]

49. Samoylenko, V.; Ashfaq, M.K.; Jacob, M.R.; Tekwani, B.L.; Khan, S.I.; Manly, S.P.; Joshi, V.C.; Walker, L.A.; Muhammad, I. Indolizidine, antiinfective and antiparasitic compounds from *Cecropia pachystachya*. *J. Nat. Prod.* 2015, 78, 797–802. [CrossRef] [PubMed]

50. Mbwambo, Z.H.; Apera, S.; Moshi, M.J.; Kapingu, M.C.; Van Miert, S.; Claeyns, M.; Brun, R.; Cos, P.; Pieters, L.; Vlietinck, A. Anthranoid compounds with antiprotozoal activity and cytotoxicity. *J. Nat. Prod.* 2007, 70, 92–98. [CrossRef] [PubMed]

51. Ndjakou Lenta, B.; Devkota, K.P.; Ngouela, S.; Fekam Boyom, F.; Naz, Q.; Choudhary, M.I.; Tsamo, E.; Rosenthal, P.J.; Sewald, N. Anti-plasmodial and cholinesterase inhibiting activities of some constituents of *Psorospermum luberrimum*. *Chem. Pharm. Bull.* 2008, 56, 222–226. [CrossRef] [PubMed]

52. Zhu, S. Small Molecules with Antimalarial Activity. U.S. Patent 2013/0023552 A1, 24 January 2013.

53. Kirnizbekmez, H.; Calis, I.; Perozzo, R.; Brun, R.; Dönmez, A.A.; Linden, A.; Rüedi, P.; Tasdemir, D. Inhibiting activities of the secondary metabolites of *Phlomis brunneogaleata* against parasitic protozoa and plasmodial enoyl-ACP Reductase, a crucial enzyme in fatty acid biosynthesis. *Planta Med.* 2004, 70, 711–717. [CrossRef] [PubMed]

54. Kamatou, G.P.; Van Zyl, R.L.; Davids, H.; Van Heerden, F.R.; Lourens, A.C.U.; Viljoen, A.M. Antimalarial and anticancer activities of selected South African Salviaspecies and isolated compounds from *S. radula*. *S. Afr. J. Bot.* 2008, 74, 238–243. [CrossRef]

55. Tchinda, A.T.; Tamze, V.; Ngono, A.R.N.; Ayimele, G.A.; Cao, M.; Angenot, L.; Frédéric, M. Alkaloids from the stem bark of *Strychnos icaja*. *Phytochem. Lett.* 2012, 5, 108–113. [CrossRef]
56. Upadhyyaya, H.C.; Sisodia, B.S.; Agrawal, J.; Pal, A.; Darokar, M.P.; Srivastava, S.K. Antimalarial potential of extracts and isolated compounds from four species of genus Ammannia. *Med. Chem. Res.* 2014, 23, 870–876. [CrossRef]

57. Sproge, K.; Staek, D.; Ziegler, H.L.; Jensen, T.H.; Holm-Møller, S.B.; Jaroszewski, J.W. Combining HPLC-PDA-MS-SPE-NMR with circular dichroism for complete natural product characterization in crude extracts: Levorotatory gossypol in *Theospesia danis*. *J. Nat. Prod.* 2008, 71, 516–519. [CrossRef] [PubMed]

58. Buchanan, M.S.; Davis, R.A.; Duffy, S.; Avery, V.M.; Quinn, R.J. Antimalarial benzylisoquinoline alkaloid from the rainforest tree *Doraphora sassafra*. *J. Nat. Prod.* 2009, 72, 1541–1543. [CrossRef] [PubMed]

59. Kubo, M.; Yatsuzuka, W.; Matsushima, S.; Harada, K.; Inoue, Y.; Miyamoto, H.; Matsumoto, M.; Fukuyama, Y. Antimalarial phenanthroindolizine alkaloids from *Piper sarmentosum*. *Chem. Pharm. Bull.* 2016, 64, 957–960. [CrossRef]

60. Rukachaisirikul, T.; Siriwattanakit, P.; Sukcharoenphol, K.; Wongvein, C.; Ruttanaweang, P.; Ngadji, B.T.; Connolly, J.D.; Okunji, C.C.; Iwu, M.M.; Schuster, B.M. Antiplasmodial agents from the leaves of *Glossotrichy bromipes*. *Planta Med.* 2004, 70, 437–440. [PubMed]

61. Ogunkunle, A.T.; Oyelakin, T.M.; Enitan, A.O.; Oyewole, F.E. A quantitative documentation of the composition of two powdered herbal formulations (antimalarial and haematinic) using ethnomedicinal information from ogbomoso, Nigeria. *Evid. Based Complement. Altern. Med.* 2014, 1–8. [CrossRef]

62. Oyekunle, A.T.; Oyelakin, T.M.; Enitan, A.O.; Oyewole, F.E. In vitro cytotoxicity studies of 20 plants used in Nigerian antimalarial ethnomedicine. *Int. J. Mol. Sci.* 2018, 19, 1382. [CrossRef]

63. Ludere, M.T.; van Ree, T.; Vleggaar, R. Isolation and relative stereochemistry of lippialactone, a new antimalarial compound from *Lippia javanica* (Piperaceae). *Phytochemistry* 2008, 1, 1–8. [CrossRef]

64. Kuo, P.C.; Damu, A.G.; Lee, K.H.; Wu, T.S. Cytotoxic and antimalarial constituents from the roots of *Eurycoma longifolia*. *Biosorg. Med. Chem.* 2004, 12, 537–544. [CrossRef] [PubMed]

65. De Andrade-Neto, V.F.; Pohlit, A.M.; Pinto, A.C.; Silva, E.C.; Nogueir, K.L.; Melo, M.R.; Henrique, M.C.; Amorim, R.C.; Silva, L.F.; Costa, M.R.; et al. In vitro inhibition of *Plasmodium berghei* by substances isolated from Amazonian antimalarial plants. *Mem. Inst. Oswaldo Cruz* 2007, 102, 359–365. [CrossRef] [PubMed]

66. Ludere, M.T.; van Ree, T.; Vleggaar, R. Isolation and relative stereochemistry of lippialactone, a new antimalarial compound from *Eurycoma longifolia*. *Eur. J. Med. Chem.* 1991, 26, 345–349. [CrossRef]

67. Adepiti, A.O.; Elujoba, A.A.; Bolaji, O.O. In vivo antimalarial evaluation of MAMA decoction on *Plasmodium berghei* in mice. *Parasitol. Res.* 2014, 113, 505–511. [CrossRef] [PubMed]

68. De Andrade-Neto, V.F.; Pohlit, A.M.; Pinto, A.C.; Silva, E.C.; Nogueir, K.L.; Melo, M.R.; Henrique, M.C.; Amorim, R.C.; Silva, L.F.; Costa, M.R.; et al. In vitro inhibition of *Plasmodium falciparum* by substances isolated from Amazonian antimalarial plants. *Mem. Inst. Oswaldo Cruz* 2007, 102, 359–365. [CrossRef] [PubMed]

69. Karunamoorthi, K.; Tsehaye, E. Ethnomedicinal knowledge, belief and self-reported practice of local inhabitants on traditional antimalarial plants and phytotherapy. *J. Ethnopharmacol.* 2012, 141, 143–150. [CrossRef] [PubMed]

70. Adepiti, A.O.; Elujoba, A.A.; Bolaji, O.O. In vivo antimalarial evaluation of MAMA decoction on *Plasmodium berghei* in mice. *Parasitol. Res.* 2014, 113, 505–511. [CrossRef] [PubMed]

71. Karunamoorthi, K.; Tsehaye, E. Ethnomedicinal knowledge, belief and self-reported practice of local inhabitants on traditional antimalarial plants and phytotherapy. *J. Ethnopharmacol.* 2012, 141, 143–150. [CrossRef] [PubMed]

72. Ludere, M.T.; van Ree, T.; Vleggaar, R. Isolation and relative stereochemistry of lippialactone, a new antimalarial compound from *Eurycoma javanica*. *Fitoterapia* 2013, 86, 188–192. [CrossRef] [PubMed]

73. Ajayeoba, E.O.; Abiodun, O.O.; Falade, M.O.; Ogbole, N.O.; Ashidi, J.S.; Happi, C.T.; Akinboye, D.O. In vitro cytotoxicity studies of 20 plants used in Nigerian antimalarial ethnomedicine. *Phytomedicine* 2006, 13, 295–298. [CrossRef] [PubMed]

74. Adepiti, A.O.; Elujoba, A.A.; Bolaji, O.O. In vivo antimalarial evaluation of MAMA decoction on *Plasmodium berghei* in mice. *Parasitol. Res.* 2014, 113, 505–511. [CrossRef] [PubMed]

75. Ougunkunle, A.T.; Oyelakin, T.M.; Enitan, A.O.; Oyewole, F.E. A quantitative documentation of the composition of two powdered herbal formulations (antimalarial and haematinic) using ethnomedicinal information from ogbomoso, Nigeria. *Evid. Based Complement. Altern. Med.* 2014, 1–8. [CrossRef] [PubMed]

76. Ougunkunle, A.T.; Oyelakin, T.M.; Enitan, A.O.; Oyewole, F.E. A quantitative documentation of the composition of two powdered herbal formulations (antimalarial and haematinic) using ethnomedicinal information from ogbomoso, Nigeria. *Evid. Based Complement. Altern. Med.* 2014, 1–8. [CrossRef] [PubMed]

77. Rasoanaivo, P.; Petitjean, A.; Ratsimamanga-Urverg, S.; Rakoto-Ratsimamanga, A. Medicinal plants used to treat malaria in Madagascar. *J. Ethnopharmacol.* 1992, 37, 117–127. [CrossRef]
86. Sadiq, M.B.; Tharaphan, P.; Chotivanich, K.; Tarning, J.; Anal, A.K. In vitro antioxidant and antimalarial activities of three plants used in Thai ethnomedicine and their interactions with chloroquine (CQ) against a CQ-tolerant rodent parasite, in mice. *J. Ethnopharmacol.* 2007, 111, 190–195. [CrossRef] [PubMed]

87. Zhu, S.; Zhang, Q.; Gudise, C.; Wei, L.; Smith, E.; Zeng, Y. Synthesis and biological evaluation of febrifugine analogues as potential antimalarial agents. *Bioorg. Med. Chem.* 2009, 17, 4496–4502. [CrossRef] [PubMed]

88. Satish, P.V.V.; Sunita, K. Antimalarial efficacy of *Pongamia pinnata* (L) Pierre against *Plasmodium falciparum* (3D7 strain) and *Plasmodium berghei* (ANKA). *BMC Complement. Altern. Med.* 2017, 17, 438. [CrossRef] [PubMed]

89. Moghadamtousi, S.Z.; Goh, B.H.; Chan, C.K.; Shabab, T.; Kadir, H.A. Biological activities and phytochemicals of *Swietenia macrophylla* King. *Molecules* 2013, 18, 10465–10483. [CrossRef] [PubMed]

90. Falade, M.O.; Akinyeoba, D.O.; Gbotosho, G.O.; Ajayiyeoba, E.O.; Happi, T.C.; Abiodun, O.O.; Oduola, A.M. In vitro and In Vivo Antimalarial Activity of *Ficus thonningii* and *Swietenia macrophylla* of Eastern Rajasthan. *Indian J. Ethnopharmacol.* 2010, 3121050. [CrossRef] [PubMed]

91. Teinkela, J.E.M.; Noundou, X.S.; Nguemfo, E.L.; Meyer, F.; Wintjens, R.; Isaacs, M.; Mpondo Mpondo, A.E.; Hoppe, H.C.; Krause, R.W.M.; Azebaze, A.G.B. Biological activities of plant extracts from *Ficus elastica* and *Selaginella vogelli*: An antimalarial, antitrypanosomal and cytotoxicity evaluation. *Saudi J. Biol. Sci.* 2018, 25, 117–122. [CrossRef] [PubMed]

92. Ansah, C.; Gooderham, N.J. The popular herbal antimalarial, extract of *Cryptolepis sanguinolenta*, is potently cytotoxic. *Toxicol. Sci.* 2002, 70, 245–251. [CrossRef] [PubMed]

93. Kazuki, T.; Yasunori, Y.; Masao, K. Constituents of the leaves and roots of *Ligularia stenocephala* Matsum. *J. Nat. Med.* 2006, 60, 329–330.
94. Lane, A.L.; Stout, E.P.; Lin, A.S.; Prudhomme, J.; le Roch, K.; Fairchild, C.R.; Franzblau, S.G.; Hay, M.E.; Aalbersberg, W.; Kubanek, J. Antimalarial bromophycolides J-Q from the Fijian red alga Callophyccus serratus. *J. Org. Chem.* **2009**, *74*, 2736–2742. [CrossRef] [PubMed]

95. Teasdale, M.E.; Prudhomme, J.; Torres, M.; Braley, M.; Cervantes, S.; Bhatia, S.C.; la Clair, J.J.; le Roch, K.; Kubanek, J. Pharmacokinetics, metabolism, and in vivo efficacy of the antimalarial natural product bromophycolide A. *ACS Med. Chem. Lett.* **2013**, *4*, 989–993. [CrossRef] [PubMed]

96. Yang, F.; Wang, R.P.; Xu, B.; Yu, H.B.; Ma, G.Y.; Wang, G.F.; Dai, S.W.; Zhang, W.; Jiao, W.H.; Song, S.J.; et al. New antimalarial norterpene cyclic peroxides from Xisha Islands sponge Diacarnus megaspinorhabdosa. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 2084–2087. [CrossRef] [PubMed]

97. World Health Organization. *World Health Report 2002*; WHO Press: Geneva, Switzerland, 2002.

98. De Ridder, S.; van der Kooy, F.; Robert Verpoorte, R. *Artemisia annua* as a self-reliant treatment for malaria in developing countries. *J. Ethnopharmacol.* **2008**, *120*, 302–314. [CrossRef] [PubMed]

99. Dharani, N.; Rukungu, G.; Abiy Yenesew, A.; Mbora, A.; Mwaura, L.; Dawson, I.; Jamnadass, R. Common Antimalarial Trees and Shrubs of East Africa; World Agroforestry Centre and the Kenya Medical Research Institute: Nairobi, Kenya, 2010.

100. Loua, J.; Traore, M.S.; Camara, A.; Balde, M.A.; Maes, L.; Pieters, L.; Balde, A.M. Biological and phytochemical investigations on Caesalpinia benthamiana, a plant traditionally used as antimalarial in Guinea. *Evid. Based Complement. Altern. Med.* **2017**, *2017*, 9438607. [CrossRef] [PubMed]

© 2018 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).