PROSPECT OF NATURAL COMPOUNDS AGAINST MALARIA: A REVIEW

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Malaria is one of the leading life-threatening vectors borne diseases prevalent in tropical and subtropical regions of the world. The traditional system of medicine uses drugs of plant origin. Quinine and artemisinin, two naturally occurring plant chemicals, are traditionally used to treat malaria. The present reviews have emphasized the anti-malarial activity of plants that are effective against emerging resistance. The aim of the present study was to analyze the concept and objectives of isolated natural compounds, their mechanism of action, and plant parts used for malaria treatment in the traditional system of medicine. 113 isolated compounds, plant parts used from 49 species, and molecular mechanism of 70 anti-malarial natural compounds from various plant species were explored. These plants were traditionally used for malaria treatment worldwide. They are therapeutically more effective, safer, and traditionally reported for having high cure rates. There is an urgent need for the development of novel drugs to treat malaria. These isolated compounds may be explored for the development of antimalarial drugs against plasmodium-resistant strains.

Keywords: Anti-malarial, Natural compounds, Chemical nature, Medicinal plants.

INTRODUCTION

Malaria is assuredly one of the most destructive and deadly among all parasitic-contaminated diseases in the developing world.¹ In tropical and subtropical areas, malaria is a very common and life alarming disease. In accordance with the latest report from WHO in December 2021, estimated cases of malaria worldwide were 241 million, resulting in 627000 deaths that represented 14 million more cases and nearly 69000 more deaths as compared to the preceding year. Malaria is a life-threatening vector-borne disease caused by the protozoal parasite plasmodium. Female Anopheles mosquitoes which bite during dusk and dawn time is the main carrier of the malarparasites (Fig 1). It is an acute febrile disease having an incubation period of approximately 7 days or a little more. P. falciparum, P. malariae, P. ovale and P. vivax are mainly these four species of plasmodium that is causative of malaria in human beings. P. falciparum, the most prevalent malaria parasite, has about 99.7% of cases reported in the African Region.² P. falciparum is responsible for the majority of serious complications viz fever, headache, cough, muscular inflammation, weakness, vomiting, abdominal pain, and diarrhea.³ Other related symptoms are pulmonary edema, digestive convulsions, the collapse of circulatory vessels, and organ failures like kidneys, sometimes followed by coma and death.

Along with their transmission rate resistance of parasite species is also increasing side by side. Multidrug-resistant malaria has been a global scourge for the last 50 years. Resistance was primarily seen in P. falciparum, the most virulent human malaria parasite.⁴ Since 1960, P. falciparum strains show drug resistance, particularly to chloroquine. Due to the resistance behavior, various problems arise in malaria treatment virtually in all malaria-endemic zone of the world.⁵
Unfortunately, in Africa, artemisinin (natural compound) resistance has also been reported but there is no evidence that resistance is present today.\(^6\) So, there is a constant need for searching for new anti-malarial compounds to face the ever-present and future resistance of parasites to currently available drugs.\(^7\) Reduced effects and increasing resistance of drugs have forced the selection of natural compounds. The traditional use of plants is widely documented all over the world for malaria and fever treatment. Natural products are still considered a crucial source in the discovery and development of therapeutic agents. Pan et al.,\(^8\) reported 2000 plant extracts that are used to treat \(P. falciparum\) malarial strains. During the last 17 years time period, 175 anti-malarial natural plant compounds were discovered. Although compound extraction from plants is a tedious and time-consuming process they are one with a high cure rate. The results of plant products for malaria treatment currently influence the researcher to find out new compounds.

Plant-based products exhibit a diverse range of medicinal properties such as anthelmintic, anti-diabetic, anti-fungal, anti-bacterial, anti-viral, anticancerous contraceptive, and sedative.\(^9\) Plant products were used in veterinary, Ayurvedic, and Unani herbal treatment methods during the prehistoric period and presently have wide applications in the pharmaceutical industry for a variety of pharmacological properties. The plant-based products are considered safe due to their property of rapid breakdown of the essential active element and for the development of multidrug resistance potential agents. The nutraceutical benefits of plants as an antioxidant in comparison to synthetic ones have drawn the attention of the food business.\(^10\)

### Approaches to find out anti-malarial compounds

The choice of plants for malaria treatment can be based on both biodiversity exploration and their use for fever treatment. After that, the plant has an active compound which is having higher remedy rate in both \textit{in-vivo} and \textit{in-vitro} conditions should be selected. The following mentioned strategies are used to review and identify natural compound selection from plant species.

- Ethno-botanical-based selection and extraction.
- Efficacy and Clinical trial basis (both in vivo and vitro condition).
- Compound isolation and their bioactivity.
- On the basis of anti-plasmodial activity.
- On the basis of their parasitic action and their target site.

### Medicinal plants used for the treatment of malaria

Natural compounds, mainly plant-based, have been traditionally used as anti-malarial medicines for the last decades. Various plant parts were used as a source of medicine from ancient times and continue to serve as a base for the number of drugs designed today (Table
Medicinal plants are commonly used for the prevention and treatment of various diseases and ailments. Along with growing evidence of *Plasmodium* resistance, most anti-malarial drugs are not affordable. Safety and high cure rate necessitate the use of medicinal drugs which are prepared from plants and commercially available at affordable prices. According to recent surveys, isolated compounds from the extract of various plant species show anti-plasmodial activity (Table 2).

**Table 1:** Plants and their parts used in malaria treatment.

| Family          | Species                                      | Part used          | Reference |
|-----------------|----------------------------------------------|--------------------|-----------|
| Annonaceae      | *Hexalobus crispiflorus* A. Rich.            | Stem bark          | 45        |
|                 | *Pachypodantium confine* Engler and Diels.   | Stem bark          |           |
| Apocynaceae     | *Aspidosperma vargasii* A. DC.               | Bark               | 46        |
|                 | *Aspidosperma desmanthum* Benth. ex Müll.Arg. | Bark               |           |
|                 | *Cryptolepis sanguinolenta* Lindl.           | Leaves, roots      | 47        |
|                 | *Geissospermum sericeum* Miers.              | Bark               | 48        |
|                 | *Peschiera fuchsiaefolia* A. DC.             | Stem bark, root    | 49        |
| Asteraceae      | *Acanthospermum austral* (Loefl.) Kuntze     | Whole plant        | 50        |
|                 | *Ageratum conyzoides* L.                     | Aerial parts, leaves| 51       |
|                 | *Artemisia gorgonum* Webb.                  | Aerial parts       | 52        |
|                 | *Struchium sparganophorum* (L.) Kuntze       | Leaves             | 51        |
|                 | *Titonia diversifolia* (Hemsl.)A.Gray       | Aerial parts       | 53        |
|                 | *Vernonia amygdalina* Delile.                | Leaves             | 54        |
|                 | *Vernonia brasiliana* (L.) Druce             | Leaves             | 55        |
| Cochlospermaeae | *Cochlospermum tinctorium* Perrier ex A. Rich.| Tubercles          | 56        |
| Combretaceae    | *Guiera senegalensis* J.F.Gmel.              | Roots              | 57        |
| Cucurbitaceae   | *Cucurbita maxima* Duchesne                 | Seeds              | 58        |
|                 | *Momordica balsamina* L.                    | Aerial parts       | 59        |
| Cyperaceae      | *Cyperus rotundus* L.                        | Root               | 60        |
| Euphorbiaceae   | *Bridelia cathartica* Bertol.                | Roots, stem        | 61        |
|                 | *Bridelia ferruginea* Benth.                 | Barks              | 62        |
|                 | *Euphorbia hirta* L.                        | Whole plant        | 63        |
| Fabaceae        | *Andira inermis* (Wright) DC.                | Stem barks, leaves | 64        |
|                 | *Senna abbreviata* Oliv                      | Leaves             | 65        |
|                 | *Senna occidentalis* (L.) Link               | Leaves             | 66        |
|                 | *Cassia siamea* Lam.                         | Leaves             | 67        |
| Hypencaceae     | *Harungana madagascariensis* Lam. Ex Poir.   | Roots              | 57        |
| Lamiaceae       | *Occimum gratissimum* L.                     | Leaves             | 68        |
|                 | *Meriandra dianthera* (Roth ex Roem. & Schult.)Briq. | Leaves       | 69        |
| Lauraceae       | *Dehaasia longipedicellata* (Ridl.) Kosterm. | Barks              | 70        |
| Meliaceae       | *Cedrela odorata* L.                         | Wood, leaves       | 71        |
| Menispermaceae  | *Abuta grandifolia* (Mart.) Sandwith         | Leaves, barks      | 72        |
|                 | *Stephania venosa* (Bl.)Spreng              | Tubers             | 73        |
Table 1: Continued.

| Family            | Species                                      | Part used  | Reference |
|-------------------|----------------------------------------------|------------|-----------|
| Myristicaceae     | *Pycnanthus angolensis* (Welw.) Warb.        | Bark       | 51        |
|                   | *Virola surinamensis* (Rol.ex Roth.) Warb.    | Leaves     | 74        |
| Piperaceae        | *Piper umbellatum* L.                        | Leaves, stem| 75        |
|                   | *Pothomorphe peltata* (L.) Miq.              | Leaves, roots| 58        |
| Rhamanaceae       | *Ampelozizyphus amazonicus* Duck.            | Roots      | 76        |
| Rubiaceae         | *Crossopteryx febrifuga* (Afzel. Ex G.Don)Benth. | Stem, bark | 77        |
|                   | *Morinda lucida* Benth.                      | Barks, leaves| 78        |
|                   | *Remifia ferruginea* (A.St.Hil.) DC          | Barks      | 79        |
| Rutaceae          | *Sarcocephalus latifolius* (Sm.) E.A.Bruce   | Roots, stem| 80        |
| Solanaceae        | *Cestrum laevigatum* Schltdl.               | Leaves     | 51        |
| Urticaceae        | *Cecropia pachystachya* Trecul.             | Leaves, stem| bark, roots| 86        |

Table 2: Natural anti-malarial compound isolated from plant.

| Family          | Species                                      | Compounds                                      | References |
|-----------------|----------------------------------------------|------------------------------------------------|------------|
| Annonaceae      | *Miliusa cuneata* W.G. Craib                   | miliusacunines A                               | 87         |
|                 | *Friesodielsia discolor* (Craib.) D.Das       | miliusacunines B                               |            |
|                 | *Mitrephora diversifolia* (Span) Miq.        | 30-formyl-20,40-dihydroxy-60-methoxychalcone   | 88         |
|                 |                                               | Tectochrysin                                   |            |
|                 |                                               | 8-formyl-7-hydroxy-5-methoxyflavanone          |            |
|                 | *Greenwayodendron suaveolens* (Engl. & Diels.) Verdc. | 5-hydroxy-6-methoxyonychene                  | 89         |
|                 |                                               | N-acetylpolyveoline                            |            |
|                 |                                               | Polyalthenol                                   |            |
| Araceae         | *Rhaphidophora decursiva* (Roxb.) Schott.    | Polysyphorin                                  | 91         |
|                 |                                               | rhaphidecurperoxin                             |            |
|                 |                                               | rhaphidecursinol A                             |            |
|                 |                                               | rhaphidecursinol B                             |            |
|                 |                                               | grandisin                                     |            |
|                 |                                               | epigrandisin                                  |            |
|                 |                                               | decursivine                                   |            |
|                 |                                               | Roridin E                                     |            |
| Asclepiadaceae  | *Gongronema napalense* (Wall.) Decne.         | gongroneside A                                 | 92         |
| Asteraceae      | *Achillea millefolium* L.                    | apigenin 7-O-glucoside                         | 93         |
|                 |                                               | luteolin 7-O-glucoside                         |            |
| Family | Species | Compounds | References |
|--------|---------|-----------|------------|
| Carpesium | *divaricatum* Siebold. & Zucc. | 2-isopropenyl-6-acetyl-8-methoxy-1,3-benzodioxin-4-one | 94 |
| Microglossa | *pyrifolia* (Lam.) Kuntze | E-phytol | 95 |
| Echinops | *hoehnelii* Schweinf. | 5-(penta-1,3-diyln)-2(3,4-dihydroxybut-1-ynyl)-thiophene | 96 |
| Buxaceae | *Buxus sempervirens* L. | 23-O-(trans)-feruloyl-23-hydroxybetulin | 97 |
| Cecropiaceae | *Cecropia pachystachya* Trecul. | β-sitosterol, tormentic acid | 86 |
| Chloranthaceae | *Chloranthus. Fortunei* (A. Gray.) Solms | fortunilide, sarglabolide, shizukaol, chlorahololide | 98 |
| Chloranthus | *multisachys* C.Pei | chloramultilide B |  |
| Chloranthus | *serratus* (Thunb.) Roem. & Schult. and *Chloranthus spicatus* (Thunb.) Makino | spicachlorantin |  |
| Sarcandra | *glabra* (Thunb.) Nakai | sarcandrolide |  |
| Chrysobalaneae | *Parinari capensis* Harv. | 10-hydroxy-13-methoxy-9-methyl-15-oxo-20-norkaur-16-en-18-oic acid γ-lactone, 10,13-dihydroxy-9-methyl-15-oxo-20-norkaur-16-en-18-oic acid γ-lactone | 99 |
| Clusiaceae | *Garcinia mckeaniana* Craib | Mckeanianones, Bannaxanthones | 100 |
| Connaraceae | *Rourea minor* (Gaertn.) Alston | rourinoside, rouremin, 1-(26-hydroxyhexacosanoyl)-glycerol | 101 |
| Cornaceae | *Cornus florida* L. | 3-epideoxyflindissol, ergosta-4,6,8,22-tetraene-3-one, 3β-O-trans-coumaroyl betulinic acid, 3β-O-cis-coumaroyl betulinic acid | 102 |
| Cucurbitaceae | *Cogniauxia podolaena* Baill. | Cucurbitacin, 20-epibryonolic acid | 103 |
| Ebenaceae | *Diospyros quaesita* Thwaites | betulinic acid 3-caffeate | 104 |
| Family          | Species                              | Compounds                                                      | References |
|-----------------|--------------------------------------|                                                               |------------|
| Euphorbiaceae   | *Strophioblachia fimbricalyx* Boerl. | • 9-O demethyltrigonostemone                                  | 105        |
|                 |                                      | • 3,6,9-trimethoxyphenanthropalone                             |            |
| Fabaceae        | *Cajanus cajan* (L.) Millsp.          | • Cajachalcone                                                | 106        |
|                 | *Piptadenia pervillei* Vatke          | • catechin 5-gallate                                          | 107        |
|                 | *Prosopis glandulosa* Torr.           | • catechin 3-gallate                                          |            |
|                 |                                      | • Prosopilosidine                                             | 108        |
| Fagaceae        | *Quercus laceyi* Small                | • kaempferol 3-O-glucosides                                   | 97         |
| Hypericaceae    | *Vismia orientalis* Engl.             | • vismione D                                                  | 109        |
|                 | *Psorospermum glaberrimum* Hochr.    | • 3-geranylxyemodin anthrone                                  | 110        |
|                 |                                      | • acetylvismione D                                            |            |
| Lamiaceae       | *Philomis brunnneogaleata*Hu b.-Mor. | • chrysoeriol 7-O-β-D-glucopyranoside                         | 111        |
|                 |                                      | • luteolin 7-O-β-D-glucopyranoside                            |            |
|                 | *Salvia radula* Benth.               | • betulafolientriol oxide                                     | 112        |
|                 |                                      | • salvigenin                                                  |            |
| Lauraceae       | *Cryptocarya nigra* Kosterm.          | • 2-hydroxyatherosperminine                                   | 113        |
| Loganiaceae     | *Strychnos icaja* Baill.             | • 15-hydroxyvomicine                                          | 114        |
|                 |                                      | • N-methyl-sec-isopseudostrychnine                            |            |
| Lythraceae      | *Ammannia multiflora* Roxb.           | • 4-hydroxy-a-tetralone                                       | 115        |
|                 | *Ammannia baccifera* L.               | • ammanniol                                                   |            |
|                 |                                      | • tetralone-4-O-β-D-glucopyranoside                           |            |
| Malvaceae       | *Thespesia danis* Oliv.               | • Gossypol                                                    | 116        |
| Menispemaceae   | *Stephania venosa* Spreng.            | • Stephanine                                                  | 73         |
|                 |                                      | • crebanine                                                   |            |
|                 |                                      | • O-methylbulbocapnine                                        |            |
|                 | *Stephania zippeliana* Miq.           | • Xylopine                                                    | 67         |
| Monimiaceae     | *Doryphora sassafras* Endl.           | • 1-(4-hydroxybenzyl)-6,7-methylenedioxy-2-methylisoquinolinium Trifluoroacetate | 117        |
|                 | *Glossocalyx brevipes* Benth.         | • methyl 2-(10β-geranyl-50β-hydroxy-20-oxocyclohex-30-enyl) acetate | 118        |
|                 |                                      | • 2-(10β-geranyl-50β-hydroxy-20-oxocyclohex-30-enyl) acetic acid |            |
| Moraceae        | *Ficus fistulosa* Reinw. ex Blame     | • verrucarin L acetate                                        | 119        |
|                 | *Ficus septica* Burm. f.              | • dehydrotylophorine                                          | 120        |
|                 |                                      | • dehydroantofine                                             |            |
|                 |                                      | • tylorphoricine                                              |            |
### Table 2: Continued.

| Family              | Species                                           | Compounds                                      | References |
|---------------------|---------------------------------------------------|-----------------------------------------------|------------|
| Myristicaceae       | *Knema glauca* (Bl.) Warb.                        | • malabaricone                                 | 120        |
| Papaveraceae        | *Meconopsis simplicifolia* (D.Don)Walp.           | • benzylisosquilline, • simplicifolanine       | 121        |
|                     | *Corydal iscalliantha* D.G.Long                   | • Cheilanthifoline                             | 49         |
|                     | *Stephania rotunda* Lour.                         | • Cepharanthine, • palmatine, • pseudopalmatine | 122        |
| Piperaceae          | *Piper sarmentosum* Roxb.                         | • sarmentine, • 1-piperetyl pyrrolidine        | 123        |
|                     | *Piper tricuspe* (Miq.)C.D.C.                     | • Dictyochromenol, • 20E,60E 2-farnesyl hydroquinone, • 3-farnesyl-p-hydroxy benzoic acid | 124        |
| Platanaceae         | *Platanus occidentalis* L.                        | • kaempferol 3-O-rhamnosides                   | 97         |
| Rubiaceae           | *Nauclea orientalis* L. (L.)                      | • naucleorine, • epimethoxynaucleorine, • oleanolic acid, • 3α,23-dihydroxyurs-12-en-28-oic acid | 125        |
| Rutaceae            | *Citropsis articulate* (Willd. ex Spreng.)Swingle & M. Kellerm. | • 5-hydroxynoracroncine, • 1,5-dihydroxy-2,3-dimethoxy-10-methyl-9-acridone | 126        |
|                     | *Zanthoxylum chiloperone* var. angustifolium Engl. | • trans-avicennol, • canthin-6-one, • 5-methoxycanthin-6-one | 127        |
|                     | *Zanthoxylum chalybeum* Engl.                     | • Nitidine                                     | 128        |
|                     | *Zanthoxylum rhoifolium* Lam.                     |                                               |            |
| Simaroubaceae       | *Eurycoma longifolia* Jack                        | • Pasakbumin, • Eurycomanone                   | 129        |
| Theaceae            | *Picrolemma spruce* Hook.f.                       | • Neosergeolide                                | 46         |
|                     | *Camellia sinensis* (L.) Kuntze                   | • Mefloquine, • Galloclatecin                  | 130        |
| Tiliaceae           | *Grewia bilamellata* Gagnep.                      | • Nitidain, • 2α,3β-dihydroxyolean-12-en-28-oic acid, • Grewin, • 2,6-dimethoxy-1-acetonylquinol, • 3α,20-lupandiol | 131        |
| Verbenaceae         | *Lippia javanica* (Burm.f.)Spreng                | • Lippialactone                                | 132        |
Established natural anti-malarial compounds/products.

Quinine
Quinine was the first and most widely used compound throughout the 1600s to 1800s to control infectious malaria. Quinine was documented as an effective anti-malarial compound during the seventeenth century. Quinine contains an aryl amino alcohol group and is basic in nature therefore, always presented as a salt. In 1820, Pelletier and Caventou isolate the quinine from Cinchona bark which belongs to the Rubiaceae family. Cinchona genus is evergreen trees and shrubs of the tropical and sub-tropical region. Quinine is not produced by all the species of Cinchona, but C. officinalis, C. calisaya and C. pubescens species of Cinchona can produce quinine. From Cinchona total of 36 alkaloids are extracted, out of these only quinines, cinchonine, quinidine, and cinchonidone are effective natural compounds with a cure rate of ~98%. Quinine plays a crucial role in malaria management during 1st trimester of pregnancy. The half-life of quinine approximately ranges between 11-18 hours. Quinine has rapid action against malaria parasites during the intra-erythrocytic stage. They strongly bind to blood proteins and inhibit heme polymerase which converts toxic heme into nontoxic hemozoin that is nontoxic to the malarial parasite (Fig. 2). For P. vivax and P. malariae, it acts as gametocytocidal but not for P. falciparum. People started taking quinine in the 17th century and resistance to quinine was first reported in 1910.

Worldwide drug resistance is the worst public health concern and the most notable problem faced by malaria control programs. Chloroquine induces serious complications on an accumulative dose of 1000 mg or more. Pigmentary retinitis with an irreversible loss of visual field is one of the most serious reaction results of a heavy dose of chloroquine. In very rare cases, chloroquine use can also lead to neuropsychiatric problems, photosensitization and ringing in the ears. Sometimes hair, skin and nail alterations may also arise.

Artemisinin
In spite of frequent research, it’s necessary to take into account the specific concern to find out resistance-free compounds to overcome the problem of the continuous increase of malarial resistance. Artemisinin has the most significant contribution to anti-malarial research in the history of medicinal plants. Artemisinin obtained from the leaves of Artemisia annua in 1972 belongs to the Asteraceae family. Although artemisinin is an effective natural compound against chloroquine resistance species of plasmodium as shown in Fig. 3A. In the case of resistant malaria, ACT (artemisinin-based combination therapy) offers a better option than quinine. Artemisinin alone therapy is unwise because of the potential risk of resistance development in malarial parasites. It can be used either alone or in conjunction with another antimalarial drug. Artemisinin has a smaller half-life so it is now widely used in artemisinin-based combination therapies (ACT) with drugs that have a longer half-life. ACT technique is commonly used against chloroquine resistance species of plasmodium.
viz. *P. falciparum*. Arteether, artemether, and sodium artesunate are semisynthetic derivatives of artemisinin.\(^\text{18}\)

**Lapachol**

It is a natural phenolic compound obtained from the bark of the lapacho tree *Tabebuia avellanedae* and other species of the same genus (Fig. 3A). South America is the native place where these species are found. It is a naphthoquinone used as an antimalarial agent having activity against *P. falciparum*\(^\text{19}\) as shown in Table 3.

**Lapinone**

The synthetic compound lapinone is a naphthoquinone that showed effective potential against *P. vivax*\(^\text{20}\) and destroys malarial parasites by suppressing the respiratory enzyme of parasitized cells.

**Cryptolepine**

It is an indolequinone alkaloid isolated from the roots of *Cryptolepis sanguinolenta*, a family Periplocaceae used in the treatment of malaria in West Africa. It has gametocytocidal properties against the late stage (IV/V) gametocytes of *P. falciparum* NF54 and also has shown potent in vitro antimalarial activities against both chloroquine-resistant *P. falciparum* and chloroquine-sensitive *P. falciparum*.\(^\text{21}\)

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Fig. 3A: Established natural anti-malarial compounds.
Protopine
This alkaloid is isolated from the Bhutanese medicinal plant Corydalis calliantha (Fumariaceae).\textsuperscript{22} It showed in vitro anti-plasmodial activity against multidrug-resistant (K1) and wild-type (TM4) strains of \textit{P. falciparum}.\textsuperscript{23}

Fefribugine
It is an alkaloid of quinazoline obtained from the roots of \textit{Dichroa febrifuga}, belongs to the Saxifragaceae family shows considerable antimalarial activity against \textit{P. falciparum}. It shows powerful in-vitro antimalarial activity against both chloroquine-sensitive \textit{P. falciparum} FCR-3 and chloroquine-resistant \textit{P. falciparum} K1.\textsuperscript{24}

Primaquine
Primaquine is an 8-aminoquinoline (synthetic compound), has unique antimalarial activity and prevents relapse in \textit{P. ovale} and \textit{P. vivax} malarial plasmodium strains and potent gametocytocidal activity in \textit{P. falciparum} infections.\textsuperscript{25}

Vernodalin
Vernodalin is isolated from \textit{V. colorata} plant\textsuperscript{26} and its anti-plasmodial activity has been reported\textsuperscript{27} against \textit{P. falciparum}.\textsuperscript{28}

Atovaquone
Atovaquone (synthetic organic compound) belongs to the naphthoquinone class of drugs, used as a fixed-dose combined with proguanil to treat children and adults with complicated malaria cases caused by \textit{P. falciparum}\textsuperscript{29} and is also used to prevent malaria in travelers.\textsuperscript{146}

Proguanil
It is one of the antimalarial product drugs most commonly used for prophylactic purposes, usually combined with chloroquine or atovaquone in malaria prophylaxis and with atovaquone in the treatment of malaria.\textsuperscript{29}

Chloroquine
It is a 4-aminoquinolone (Fig.3B) antimalarial agent used to prevent and treat acute forms of malaria caused by \textit{P. vivax}, \textit{P. malariae}, \textit{P. ovale}, in addition to sensitive forms of \textit{P. falciparum}.\textsuperscript{30}

\textbf{Fig. 3B:} Established natural anti-malarial compounds.
**Artesunate and artemether**
Both are semi-synthetic artemisinin compounds used to prevent or treat malaria caused by *P. falciparum*. Artesunate is water-soluble and it is usually administered orally but in severe cases, usually being administered by the intravenous route. Artemether is oil soluble and is usually administered intramuscularly.\(^{31}\)

**Strictosamide**
It is a glycoalkaloid isolated from the stem bark of *Nauclea pobeuinii*, a family of Rubiaceae, used in traditional medicine against malaria. It has shown *in-vitro* and *in-vivo* anti-plasmodium activity against *P. falciparum* (chloroquine-sensitive Ghana-strain).\(^{32}\)

**Berberine**
It is a protoberberine alkaloid and obtained from many plants *viz.* *Berberis aristata*, *Berberis vulgaris*, *Hydrastis canadensis*, *Coptis chinensi*. It has been extensively studied as a promising antimalarial drug.\(^{33}\) Sripalaijareon et al.,\(^{34}\) extracted berberine from *Arcangelisia flava* having activity against *P. falciparum* by inhibiting telomerase activity in a dose-dependent manner.

**Gedunin**
It is isolated from *Trichilia pallida*, the Meliaceae family, mainly obtained from seeds having antimalarial activity against *P. falciparum*. It shows *in-vitro* tests against chloroquine-sensitive W2 and chloroquine-resistant D6.\(^{35}\)

**Symplostatin 4**
Sym 4 was isolated from the species *Symploca\(^{36}\)* and has been recognized as a potent nonmoral antimalarial agent against *P. falciparum*.\(^{37}\)

**Hinokitiol**
It is a naturally occurring mono-terpenoid found in the wooden part of trees in the Cupressaceae family. Hinokitiol (β-thujaplicin) is considered a zinc ionophore that helps in the transport of zinc into the cell. It has been widely used in various therapeutic ailments such as anti-viral, anti-fungal, anti-cancer, and oral pathogen control.\(^{38}\)

**Nitidine**
Nitidine, an alkaloid obtained from *T. asiatica* (Rutaceae) has an antimalarial activity reported by Gakunju et al.,\(^{39}\) (Fig. 3C) and this compound was tested against different strains of falciparum.\(^{40}\) It performs its action in a similar fashion to chloroquine by inhibiting the formation of β-haematin.

![Fig. 3C: Established natural anti-malarial compounds.](image-url)
Fraxetin
It is isolated from the leaves of *Lawsonia inermis* and has reported anti-plasmodial activity in-vivo against *P. berghei* strain. It performs this action by suppressing the oxidative damage by augmenting the antioxidant endogenous system.  

Oroidin
It is an alkaloid isolated from *Agelas oroides*, and has antimalarial activity against *P. falciparum*.  

Anthecularin
It is a sesquiterpene lactone, isolated from aerial parts of Greek *Anthemis auriculata* (Asteraceae). Anthecularin showed anti-plasmodial activity against *P. falciparum*.  

Possible mechanism of action
Organic natural compounds of small size enter the cell by crossing the membrane surface barrier. Transmembrane biological proteins play a crucial function as solute receptors and transfer them across. Anti-malarial products/compounds lock the life cycle of malarial-causing parasites. In this section, we enlist the mechanism of action and target site of potential active natural (Fig. 4) and their derivative organic compounds used in malaria treatment (Table 3).

*Fig. 4: Comparative mechanism of action of natural compounds.*

Table 3: Mechanism action of natural compounds.

| Action/ target site | Natural products | References |
|---------------------|------------------|------------|
| DNA intercalation   | • Cryptolepine   | 21         |
|                     | • Artemisinin    | 133        |
| Fe (II) catalyses free radical alkylation of proteins and heme group | • Yingzhaosu | 134 |
| Inhibition of heme polymerase | • Quinine | 135 |
| Inhibit food vacuole falcipains by targeting Falcipain 2 | • 2,3,6-Trihydroxy benzoic acid, • 2,3,6-Trihydroxy methyl Benzoate | 136 |
Table 3: Continued.

| Action/ target site                                                                 | Natural products                                                                 | References |
|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|------------|
| Inhibit type II fatty acid synthase (FAS II) enzymes by targeting *Plasmodium falciparum* enoyl-ACP reductase (PfFabI) and *Plasmodium falciparum* β- ketoacyl ACP reductase (PfFabG) | • 4-Acetoxyanthecotulide  
• 4-Hydroxyanthecotulide,  
• Anthecularin,  
• 4-Acetoxyanthecotulide  
• 4-Hydroxyanthecotulide,  
• Anthecularin,  
• Axisonitrile-3,  
• Diisocynoacianide,  
• 1,3,6-Trihydroxy-2-(3-methyl butadienyl)-7-methoxy-8-(3-methyl but-2-enyl) xanthen-9 one,  
• 2-(6-O-Benzoyl-β-dglucopyranosyloxy)-7-(1a, 2a, 6a-trihydroxy-3-oxocyclohex-4-enoyl)-5-hydroxybenzyl alcohol,  
• Bergenin  
• Bromophycolide A,  
• Dimethylisoborreverine,  
• Fraxetin  
• Nitidine,  
• 1,3,6-Trihydroxy-2-(3-methyl butadienyl)-7-methoxy-8-(3-methyl but-2-enyl) xanthen-9 one,  
• 2-(6-O-Benzoyl-β-dglucopyranosyloxy)-7-(1a, 2a, 6a-trihydroxy-3-oxocyclohex-4-enoyl)-5-hydroxybenzyl alcohol,  
• Bergenin  
• Bromophycolide A,  
• Dimethylisoborreverine,  
• Fraxetin  
• Nitidine,  
• 1,3,6-Trihydroxy-2-(3-methyl butadienyl)-7-methoxy-8-(3-methyl but-2-enyl) xanthen-9 one,  
• 2-(6-O-Benzoyl-β-dglucopyranosyloxy)-7-(1a, 2a, 6a-trihydroxy-3-oxocyclohex-4-enoyl)-5-hydroxybenzyl alcohol,  
• Bergenin  
• Bromophycolide A,  
• Dimethylisoborreverine,  
• Fraxetin  
• Nitidine,  
• 1,3,6-Trihydroxy-2-(3-methyl butadienyl)-7-methoxy-8-(3-methyl but-2-enyl) xanthen-9 one,  
• 2-(6-O-Benzoyl-β-dglucopyranosyloxy)-7-(1a, 2a, 6a-trihydroxy-3-oxocyclohex-4-enoyl)-5-hydroxybenzyl alcohol,  
• Bergenin  
• Bromophycolide A,  
• Dimethylisoborreverine,  
• Fraxetin  
• Nitidine,  
• 1,3,6-Trihydroxy-2-(3-methyl butadienyl)-7-methoxy-8-(3-methyl but-2-enyl) xanthen-9 one,  
• 2-(6-O-Benzoyl-β-dglucopyranosyloxy)-7-(1a, 2a, 6a-trihydroxy-3-oxocyclohex-4-enoyl)-5-hydroxybenzyl alcohol,  
• Bergenin  
• Bromophycolide A,  
• Dimethylisoborreverine,  
• Fraxetin  
• Nitidine,  
• Evernic acid,  
• Psoromic acid,  
• JB42C,  
• Tral-1,  
• JB42C,  
• Tral-1,  
• JB42C,  
• Tral-1,  
• JB42C,  | 137  
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Table 3: Continued.

| Action/ target site                                                                 | Natural products                                                                                         | References |
|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|------------|
| Inhibit *Plasmodium falciparum* Hsp70-1 (PfHsp70-1) chaperone function               | • Lapachol,                                                                                               | 147        |
|                                                                                     | • Malonganenone A,                                                                                         |            |
|                                                                                     | • Malonganenone B,                                                                                         |            |
|                                                                                     | • Malonganenone C,                                                                                         |            |
| Inhibit type II fatty acid synthase (FAS II) enzymes by targeting *Plasmodium falciparum* enoyl-ACP reductase (PfFabI) | • 3- O-Methylquercetin,                                                                                   | 148        |
|                                                                                     | • Isowighteone,                                                                                             | 149        |
|                                                                                     | • Luteolin 7- O-β-d-Glucopyranoside,                                                                         | 150        |
|                                                                                     | • Methylenebissantin,                                                                                       | 151        |
|                                                                                     | • Mucusisofavone C,                                                                                         | 151        |
|                                                                                     | • Oroidin,                                                                                                 |            |
| Inhibit food vacuole falcipains by targeting Falcipain 2/2'3                         | • Symplostatin 4,                                                                                          | 152        |
| Inhibit *Plasmodium falciparum* glyoxalase I (PfGLOI)                                | • Hinokitiol,                                                                                               | 153        |
|                                                                                     | • Puberulic acid,                                                                                            |            |
|                                                                                     | • Tropolone,                                                                                                |            |
| Inhibition of type II fatty acid synthase (FAS II) enzymes by targeting *Plasmodium falciparum* β-hydroxyacyl-ACP dehydratase (PfFabZ) | • Bromopyrrolohomarginin                                                                                   | 154        |
|                                                                                     | • Catechin gallate,                                                                                         |            |
|                                                                                     | • Vulpic acid,                                                                                              |            |
| Production of ROS and lipid peroxidation Product by targeting Trafficking, transmembrane and vesicular transport parasite proteins | • Plakortin                                                                                               | 155        |
| Protein degradation by inhibition of Pf20S by targeting proteasome β5 subunit        | • Carmaphycin B,                                                                                           | 156        |
| Protein synthesis blocking by inhibition of HSP90                                  | • Gedunin,                                                                                                 | 157        |
| Targeting cytoplasmic prolyl-tRNA synthetase (PfcPRS)                               | • Febrifugine,                                                                                             | 156        |
| Unknown                                                                             | • Curcumin,                                                                                                | 21         |
| Unknown                                                                             | • Strictosamide,                                                                                            | 133        |
| Unknown                                                                             | • Vernodalin,                                                                                                | 157        |
| Unknown                                                                             | • Allocryptopine,                                                                                           | 158        |
|                                                                                     | • Berberine,                                                                                                |            |
|                                                                                     | • Protopine,                                                                                                |            |

Promise potential of natural drugs

Since the emergence of malaria and its increasing resistance, the diverse nature of plant species have been explored in traditional and ethnomedicinal fields. In the current therapeutic era, anti-malarial constituents mainly consist of natural products and their derivatives (quinine, ART, mefloquine, artesunate, etc.). Natural product derivatives act as molecular templates due to their historical high cure rate and diverse chemical composition. In current designed literature, many natural compounds having anti-malarial activity have been considered. In the absence of standard synthetic infeasibility, analogs of these compounds may be created to investigate the anti-malarial or anti-plasmodial extent. Structural variations may be further used to improve potential activity and elimination of toxicity.

Conclusion

Recent work emphasized on utilization of plant extracts for environmental remediation
as a substitute for the concern of toxicity and incendiary related to the chemical synthesis of pharmaceutical drugs. Also results adequately embellished the environmentally friendly approach which can handle biodegradable stuff effectively and has astounding relevance for an in-situ strategy for concurrent eradication. In this review, plant-based natural compounds have been enlisted that exhibit anti-malarial/ anti-plasmodial activity. According to a recent review of the last decade, various anti-malarial compounds have been isolated from plants, and these compounds exhibit significant activity against various anti-malarial strains both in-vitro and in-vivo conditions along with no or lesser side effects as cited for chemically synthesized drugs with less resistant development.

In spite of the number of anti-malarial compound discoveries, resistance against Plasmodium species is increasing in a parallel fashion. Natural anti-malarial compounds present in the plant have a complex mixture with other secondary metabolites so their extraction itself a major challenge to identify compounds for the specific activity. Considering resource limitations in this regard it is generally admired that new natural compounds should be discovered which are effective and curative remedies in malarial treatment. Particularly research on traditional medicine from plants leads to the development of new anti-malarial agents. Regardless of the approach, it is necessary to take into account specific concerns, including the cost of the compound. It seems that new approaches for the development of anti-malarial drugs should be considered, or old ones revisited.

Conflict of interest

Authors declare that there is no conflict of interest.

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REFERENCES

1. S.M. Alasil and K.A. Abdullah, "An Epidemiological Review on Emerging and Re-Emerging Parasitic Infectious Diseases in Malaysia", Open Microbiol J, 13(1), 112-20 (2019).
2. World Malaria Report, (2021). https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2021.
3. A. Bartolini and L. Zammarchi, "Clinical aspects of uncomplicated and severe malaria", Mediterr J Hematol Infect Dis, 4(1), e2012026 (2012).
4. K.K. Dayanand, R.N. Achur and D. C. Gowda, "Epidemiology, drug resistance, and pathophysiology of Plasmodium vivax malaria", J Vector Borne Dis, 55(1),1-8 (2018).
5. M. Bushman, R. Antia, V. Udhayakumar and J.C. de Roode, "Within-host competition can delay evolution of drug resistance in malaria", PLoS Biol, 16(8), e2005712 (2018).
6. F. Lu, R. Culleton, M. Zhang, A. Ramaprasad, L. Von Seidlein, H. Zhou, G. Zhu, J. Tang, Y. Liu, W. Wang and Y. Cao, "Emergence of indigenous artemisinin-resistant Plasmodium falciparum in Africa", N Engl J Med, 376(10), 991-993 (2017).
7. R.G. Ridley, "Medical need, scientific opportunity and the drive for antimalarial drugs", Nature, 415(6872),686-693 (2002)
8. W. H. Pan, X. Y. Xu, Shi N, S. W. Tsang and H. J. Zhang, "Antimalarial activity of plant metabolites", Int J Mol Sci, 19(5), 1382 (2018).
9. M. Pattanayak and P.L. Nayak, "Green synthesis and characterization of zero-valent Iron nanoparticles from the leaf extract of Azadirachta indica (Neem)", World J Nano Sci Tech, 2(1), 06-09 (2013).
10. G. Nahak and R.K. Sahu, "Evaluation of antioxidant activity of flower and seed oil of Azadirachta indica A. juss", J Appl Nat Sci, 3 (1), 78-81 (2011).
11. M. Kluska, A. Marciniuk-Kluska, D. Pruksa and W. Pruksa, "Analytics of Quinine and its Derivatives", Crit Rev Anal Chem, 46(2), 139-145 (2016).
12. A. Jamaludin, M. Mohamed, V. Navaratnam, N. Mohamed, E. Yeoh and W. Wernsdorfer, "Single-dose comparative kinetics and bioavailability study of quinine hydrochloride, quinidine
sulfate and quinidine bisulfate sustained-release in healthy male volunteers”, *Acta Leiden*, 57(1), 39-46 (1988).
13. J. Achan, A.O. Talisuna, A. Erhart, A. Yeka, J.K. Tibenderana, F.N. Baliraine, P.J. Rosenthal, and U. Alessandro, “Quinine, an old anti-malarial drug in a modern world: role in the treatment of malaria”, *Malar J*, 10, 144 (2011).
14. T. J. Stokkermans, A. Goyal, P. Bansal and G. Trichonas, “Chloroquine and Hydroxychloroquine Toxicity”, In: StatPearls. Publishing, Treasure Island (FL), 2020.
15. A.N. Styka and D.A Savitz, “Chloroquine, In Assessment of Long-Term Health Effects of Antimalarial Drugs When Used for Prophylaxis, National Academies of Sciences, Engineering, and Medicine”, *National Academies Press (US)*, 2020.
16. C.X. Liu, “Discovery and development of artemisinin and related compounds”, *Chin Herb Med*, 9(2), 101-104 (2017).
17. L. Tilley, J. Strainer, N.F. Gnädig, S.A Ralph and D.A. Fidock, “Artemisinin action and resistance in *Plasmodium falciparum*”, *Trends Parasitol*, 32(9), 682-686 (2016).
18. G.T. Edwin, M. Korsik and M.H. Todd, “The past, present and future of anti-malarial medicines”, *Malar J*, 18(1), 93 (2019).
19. R. Verpoorter, "Comprehensive Natural Products Chemistry II: Development and Modification of Bioactivity/Vol. Ed.: Rob Verpoorter, Hung-Wen (Ben) Liu, 3. Elsevier, 2010.
20. G. Fawaz and F.S. Haddad, "The effect of lapinone (M-2350) on *P. vivax* Infection in Man1", *Am J Trop Med Hyg*, 31, 569-571 (1951).
21. A.D. Forkuo, C. Ansah, K.M. Boadu, J. N. Boampong, E.O. Ameyaw, B. A. Gyan, A.T. Arku, and M.F. Ofori, "Synergistic anti-malarial action of cryptolepine and artemisinins", *Malar J*, 15, 89 (2016).
22. S. Tenzin, "Traditional Medicine Formulary of Bhutan (2nd edn)", Institute of Traditional Medicine Services: Ministry of Health, Thimphu, Bhutan, 2007.
23. P. Wangchuk, J.B. Bremner, R. Rattanajak and S. Kamchonwongpaisan, "Antiplasmodial agents from the Bhutaneese medicinal plant *Corydalis calliantha*, *Phytother Res*, 24(4), 481-485, (2010).
24. V.K. Mishra, M. Mishra, S. Mishra, P. Sahu and S.K. Kashaw, "Febrifugine analogues: Promising antimalarial agents", *Asian J Pharm Pharmacol*, 1(1), 10-15 (2015).
25. G. Camarda, P. Jirawatcharadech, R.S. Priestley, A. Saif, S. March, M.H. Wong, S. Leung, A.B. Miller, D.A. Baker, P. Alano, and M.J. Paine, "Antimalarial activity of primaquine operates via a two-step biochemical relay", *Nat Commun*, 10(1),3226 (2019).
26. T. Rabe, D. Mullholland and J. Van Staden, "Isolation and identification of antibacterial compounds from Vernonia colorata leaves", *J Ethnopharmacol*, 80(1), 91-94 (2002).
27. A.M. Kaou, V. Mahiou-Leddet, S. Hutter, S. Ainouddine, S. Hassani, I. Yahaya, and E. Ollivier, "Antimalarial activity of crude extracts from nine African medicinal plants", *J Ethnopharmacol*, 116(1), 74-83 (2008).
28. J.C. Chukwujekwu, C.A. Lategan, P.J. Smith, F.R. Van Heerden and J. Van Staden, "Antiplasmodial and cytotoxic activity of isolated sesquiterpene lactones from the acetone leaf extract of *Vernonia colorata*, *S Afr J Bot*, 75(1), 176-179 (2009).
29. K. McKeage and L.J. Scott, "tovaquone/proguanil: a review of its use for the prophylaxis of Plasmodium falciparum malaria", *Drugs*, 63(2003), 597–603 (2003).
30. D.G. Lalloo and D.R. Hill, "Preventing malaria in travelers", *B M J*, 336(7657), 1362-1366. (2008).
31. J.O. Adebayo, H. Tijjani, A.P. Adegunloye, A.A. Ishola, E.A. Balogun and S.O. Malomo, "Enhancing the antimalarial activity of artemesunate", *Parasitol Res*, 119(9), 2749–2764 (2020).
32. J.Y. Xu, K. Foubert, L. Dhooghe, F. Lemiere, K. Cimanga and K. Mesia, "Chromatographic profiling and identification of two new iridoid-indole alkaloids by UPLC-MS and HPLC-SPE-
NMR analysis of an antimalarial extract from *Nauclea pobeguini*", *Planta Med*, 5(2), 316-319 (2012).

33. W. D. Sheng, M.S. Jiddawi, X. Q. Hong and S.M. Abdulla, "Treatment of chloroquine-resistant malaria using pyrimethamine in combination with berberine, tetracycline or cotrimoxazole", *East Afr Med J*, 74, 283-294 (1997).

34. N. Sriwilaijareon, S. Petmitr, A. Mutirangura, M. Ponglikitmongkol and P. Wilairat, "Stage specificity of *Plasmodium falciparum* telomerase and its inhibition by berberine", *Parasitol Int*, 51(1), 99-103 (2002).

35. T.M. Braga, L. Rocha, T.Y. Chung, R.F. Oliveira, C. Pinho, A.I. Oliveira, J. Morgado, and A. Cruz, "Biological Activities of Gedunin—a Limonoid from the Meliaceae Family", *Molecules*, 25(3), 493 (2020).

36. K. Taori, Y. Liu, V.J. Paul and H. Luesch, "Combinatorial strategies by marine cyanobacteria: symplostatin 4, an antimitotic natural dolastatin 10/15 hybrid that synergizes with the coproduced HDAC inhibitor largazole", *Chem Bio Chem*, 10(10), 1634-1639 (2009).

37. T. Conroy, J.T. Guo, N.H. Hunt and R.J. Payne, "Total synthesis and antimalarial activity of symplostatin 4", *Org Lett*, 12(23), 5576-5579 (2010).

38. B.X. Hoang and B. Han, "A possible application of hinokitiol as a natural zinc ionophore and anti-infective agent for the prevention and treatment of COVID-19 and viral infections", *Med Hypotheses*, 145, 110333 (2020).

39. D. M. N. Gakunju, E.K. Mberu, S.F. Dossaji, A.I. Gray, R.D. Waigh, P.G. Waterman, and W. M. Watkins, "Potent anti-malarial activity of the alkaloid nitidine, isolated from a Kenyan herbal remedy", *Antimicrob. Agents Chemother*, 39(12), 2606-2609 (1995).

40. C. Praveena and C. Veeresham, "Quantitative Determination of Nitidine from Roots and Plant Tissue Culture Extracts of *Toddaalia asiatica* (Linn.) Using HPTLC", *Am J Anal Chem*, 5(2),42144 (2014).

41. D.K. Singh, H.S. Cheema, A. Saxena, S. Singh, M.P. Darokar, D.U. Bawankule, K. Shanker and S. Luqman, "Fraxetin and ethyl acetate extract from *Lawsonia inermis* L. ameliorate oxidative stress in *P. berghei* infected mice by augmenting antioxidant defence system", *Phytomed*, 36, 262-272 (2017).

42. J.V. Kurhekar, "Antimicrobial lead compounds from marine plants", *In Phytochemicals as Lead Compounds for New Drug Discovery*, 2020, 257-274 (2020).

43. A. Karioti, H. Skaltsa, A. Linden, R. Perozzo, R. Brun and D. Tasdemir, "Anthecularin, a sesquiterpene lactone with a novel ring system from Anthemis auriculata exert dual inhibitory activity against plasmodial FabG and FabF enzymes", *Planta Med*, 73(09), 194 (2007).

44. K. Basore, Y. Cheng, A.K. Kushwaha, S.T. Nguyen and S.A. Desai, "How do antimalarial drugs reach their intracellular targets?", *Frontiers Pharmacol*, 6, 91 (2015).

45. F.F. Boyom, V. Ngouana, P. H. A. Zollo, C. Menut, J.M. Bessiere, J. Gut and P.J. Rosenthal, "Composition and anti-plasmodial activities of essential oils from some Cameroonian medicinal plants", *Phytochemistry*, 64(7), 1269-1275 (2003).

46. V. F. De Andrade-Neto, A.M. Pohlit, A.C.S. Pinto, E.C.C. Silva, K.L. Nogueira, M.R. Melo, M.C. Henrique, R.C. Amorim, L.F.R. Silva, M. R.Costa and R. Nunomura, "In vitro inhibition of *Plasmodium falciparium* by substances isolated from Amazonian antimalarial plants", *Mem Inst Oswaldo Cruz*, 102(3), 359-366 (2007).

47. G.L. Boye and O. Ampofo, "Proceedings of the first International symposium on Cryptolepine, Kumasi, Ghana, University of Science and Technology, 1983.

48. J.C. Steele, N.C. Veitch, G.C. Kite, M.S. Simmonds and D.C. Warhurst, "Indole and β-Carboline Alkaloids from *Geissospermum sericeum*", *J Nat Prod*, 65(1), 85-88 (2002).

49. E. Federici, G. Palazzino, M. Nicoletti and C. Galeffi, "Antiplasmodial activity of the
alkaloids of *Pechiera fuchshiaeefolia*, *Planta Med*, 66(1), 93-95 (2000).

50. L.H. Carvalho and A.U. Krettli, "Antimalarial chemotherapy with natural products and chemically defined molecules", *Mem Inst Oswaldo Cruz*, 86(2), 181-84 (1991).

51. M.C. Madureira, A.P. Martins, L. Salgueiro, J. Paiva and A. Proença da Cunha, "Medicinal Plants and Traditional Medicine in the Gulf of Guinea–S. Tome and Príncipe Islands", *Recent Progress in Medicinal Plants*, 7,361-381 (2002).

52. R. Ortet, O.P. Thomas, E.L. Regalado, J.A.Pino, J.J. Filippi and M.D. Fernandez, "Composition and biological properties of the volatile oil of *Artemisia gorgonum* Webb", *Chem Biodivers*, 7(5), 1325-1332 (2010).

53. E. Goffin, P. Ziemons, P. De Mol, M.D. De Madureira, A.P. Martins, A.P. Da Cunha, G. Philippe, M. Tits, L. Angenot and M. Frederich, "Vitro antiplasmodial activity of *Tithonia diversifolia* and identification of its main active constituent: Tagitin C", *Planta Med*, 68(6), 543-545 (2002).

54. S.C. Masaba, "The antimalarial activity of *Vernonia amygdalina Del* (Compositae)", *Trans R Soc Trop Med Hyg*, 94(6), 694-695 (2000).

55. T.M. Almeida Alves, T.J. Nagem, L.H. Carvalho, A.U. Krettli and C.L. Zani, "Antiplasmodial triterpene from *Vernonia brasiliana*", *Planta Med*, 63(6), 554-555 (1997).

56. F. Benoit, A. Valentin, Y. Pelissier, C. Marion, Z. Dakuyo, M. Mallie and J.M. Bastide, "Antimalarial activity in vitro of *Cochlospermum tinctorium* tubercle extracts", *Trans R Soc Trop Med Hyg*, 89(2), 217-218 (1995).

57. C. Ancolio, N. Azas, V. Mahiou, E. Ollivier, C. Di Giorgio, A. Keita, P. Timon-David, and G. Balansard, "Antimalarial activity of extracts and alkaloids isolated from six plants used in traditional medicine in Mali and Sao Tome", *Phytother Res*, 16(7), 646-649 (2002).

58. C.Z. Amorim, C.A. Flores, B.E. Gomes, A.D. Marques, R.S.B. Cordeiro, Screening for antimalarial activity in the genus Potomorphe, *J. Ethnopharmacol.*, 24(1), 101-106 (1988).

59. C. Ramalhete, D. Lopes, S. Mulhovo, J. Molnar, V.E. Rosario and M.J.U. Ferreira, "New antimalarials with a triterpenic scaffold from *Momordica balsamina*", *Bioorg Med Chem*, 18(14), 5254-5260 (2010).

60. A. Kamala, S.K. Middha and C.S. Karigar, "Plants in traditional medicine with special reference to *Cyperus rotundus* L. A review", *3 Biotech*, 8(7), 309 (2018).

61. Jurg, T. Tomas and J. Pividal, "Antimalarial activity of some plant remedies in use in Marracuene, southern Mozambique", *J Ethnopharmacol*, 33(1-2), 79-83 (1991).

62. O.M. Kolawole and A.A. Adesoye, "Evaluation of the antimalarial activity of *Bridelia ferruginea* benth bark", *Can J Pure Appl Sci*, 4(1), 1039-1044 (2010).

63. L. Tona, N.P. Ngimbi, M. Tsakala, K. Mesia, K. Cimanga and S. Apers, T. De Bruyne, L. Pieters, J. Totte and A.J. Vlietinck, "Antimalarial activity of 20 crude extracts from nine African medicinal plants used in Kinshasa, Congo", *J Ethnopharmacol*, 68(1-3), 193-203 (1999).

64. Kraft, K. Jenett-Siems, K. Siems, M.P. Gupta, U. Bienzle and E. Eich, "Antiplasmodial activity of isoflavones from *Andira inermis*", *J Ethnopharmacol*, 73(1-2), 131-135 (2000).

65. E. Innocent, M. Moshi, P. Masimba, Z. Mbwambo, M. Kapingu and A. Kamuhabwa, "Screening of traditionally used plants for in vivo antimalarial activity in mice", *Afr J Tradit Complement Altern Med*, 6(2), 163-167 (2009).

66. L. Tona, R.K. Cimanga, K. Mesia, C.T. Musuamba, T. De Bruyne, S. Apers, N. Hernans, S. Van Miert, L. Pieters, J. Totte and A.J. Vlietinck, "In *vitro* antiplasmodial activity of extracts and fractions from seven medicinal plants used in the Democratic Republic of Congo", *J Ethnopharmacol*, 93(1), 27-32 (2004).

67. N. Tajuddeen and F.R. Van Heerden, "Antiplasmodial natural products: an
update", *Malar J*, 18(1), 404 (2019).
68. K. Kaur, M. Jain, T. Kaur and R. Jain, "Antimalarials from nature", *Bioorg Med Chem*, 17(9), 3229-3256 (2009).
69. K. Hagazy, G.G. Sibhat, A. Karim, G.H. Tekulu, G. Periasamy and M.G. Hibon, "Antimalarial activity of *Meriandra dianthera* leaf extracts in *Plasmodium berghei* infected mice", *Evid Based Complement Altern Med*, 2020, 8980212 (2020).
70. K. H. Leong, "Antiplasmodial and antioxidant isoquinoline alkaloids from *Dehaasia longipedicellata*, *Planta Med*, 80(07), 599-603 (2014).
71. D.H. Bray, D.C. Warhurst, J. D. Connolly, M.J. Oneill and J.D. Phillipson, "Plants as sources of antimalarial drugs. Part 7. Activity of some species of Meliaceae plants and their constituent limonoids", *Phytother Res*, 4(1), 29-35 (1990).
72. J.C. Steele, M.S. Simmonds, N.C. Veitch and D.C. Warhurst, "Evaluation of the anti-plasmodial activity of bisbenzylisoquinoline alkaloids from *Abuta grandifolia*, *Planta Med*, 65(5), 413-416 (1999).
73. P.M. Le, V. Srivastava, T.T. Nguyen, B. Pradines, M. Madamet, J. Mosnier, T.T. Trinh and H. Lee, "Stephanine from *Stephania venosa* (Blume) Spreng showed effective antiplasmodial and anticancer activities, the latter by inducing apoptosis through the reverse of mitotic exit", *Phytother Res*, 31(9), 1357-1368 (2017).
74. N.P. Lopes, M.J. Kato, H.D.A. Eloisa, J.G. Maia, M. Yoshida, A.R. Planchart and A.M. Katzin, "Antimalarial use of volatile oil from leaves of *Virola surinamensis* (Rol.) Warb. by Waiapi Amazon Indians", *J Ethnopharmacol*, 67(3), 313-319 (1999).
75. C.M. Roersch, *Piper umbellatum L.*, a comparative cross-cultural analysis of its medicinal uses and an ethnopharmacological evaluation, *J. Ethnopharmacol.*, 131, 522-37 (2010).
76. A.U. Krettli, V.F. Andrade-Neto, M. D. G.L.Brandao and W. Ferrari, "The search for new antimalarial drugs from plants used to treat fever and malaria or plants randomly selected: a review", *Mem Inst Oswaldo Cruz*, 96(8), 1033-1042 (2001).
77. T.O. Elufioye and J.M. Agbedahunsi, "Antimalarial activities of *Tithonia diversifolia* (Asteraceae) and *Crossopteryx febrifuga* (Rubiaceae) on mice in vivo", *J Ethnopharmacol*, 93(2-3), 167-171 (2004).
78. K. Koumaglo, M. Gbeassor, O. Nikabu, C. De Souza and W. Werner, "Effects of three compounds extracted from *Morinda lucida* on *Plasmodium falciparum*, *Planta Med*, 58(6), 533-534 (1992).
79. V.F. Andrade-Neto, M.G. Brandão, J.R. Stehmann, L.A. Oliveira and A.U. Krettli, "Antimalarial activity of Cinchona-like plants used to treat fever and malaria in Brazil", *J Ethnopharmacol*, 87(2-3), 253-256 (2003).
80. P. Abreu and A. Pereira, "New indole alkaloids from *Sarcocophalus latifolius*, *Nat Prod Lett*, 15(1), 43-48 (2001).
81. M.F. Dolabela, S.G. Oliveira, J.M. Nascimento, J.M. Peres, H. Wagner and M.M. Povoa, "*In vitro* antiplasmodial activity of extract and constituents from *Esenbeckia febrifuga*, a plant traditionally used to treat malaria in the Brazilian Amazon", *Phytomed*, 15(5), 367-372 (2008).
82. K.M. Shija, R.S. Nondo, D. Mloka, R.Z. Sangeda and G.M. Bwire, "Effects of lemon decoction on malaria parasite clearance and selected hematological parameters in *Plasmodium berghei* ANKA infected mice", *BMC Complement Med Ther*, 20(1), 24 (2020).
83. M. L. De Mesquita, P. Grellier, L. Mambu, J.E. De Paula and L.S. Espindola, "*In vitro* antiplasmodial activity of Brazilian Cerrado plants used as traditional remedies", *J Ethnopharmacol*, 110(1), 165-170 (2007).
84. M.A. Riel, D.E. Kyle and W.K. Milhous, "Efficacy of scopadulcic acid against *Plasmodium falciparum* in vitro", *J Nat Prod*, 65(4), 614-615 (2002).
85. S. Bertania, G. Bourdy, I. Landau, J. C. Robinson, P. H. Esterred and E. Deharo, "Evaluation of French Guiana traditional antimalarial remedies", *J Ethnopharmacol*, 98(1-2), 45-54 (2005).
86. V.T. Uchoa, R.C. de Paula, L.G. Krettli, A.E.G. Santana and A.U. Krettli, "Antimalarial activity of compounds and mixed fractions of Cecropia pachystachya", Drug Dev Res, 71(1), 82-91 (2010).

87. T. Promchai, A. Jaidee, S. Cheenpracha, K. Trisuwan, R. Rattanajak, S. Kamchonwongpaisan, S. Laphookhieo, S.G. Pyne and T. Rithiwigrom, "Antimalarial oxoprotoberberine alkaloids from the leaves of Miliusa cuneate", J Nat Prod, 79(4), 978-983 (2016).

88. U. Prawat, D. Phupornprasert, A. Butsuri, A.W. Salae, S. Boonsri and P. Tuntiwachwuttikul, "Flavonoids from Friesodielsia discolor", Phytochem Lett, 5(4), 809-813 (2012).

89. Mueller, R.A. Davis, S. Duffy, V.M. Avery, D. Camp and R.J. Quinn, "Antimalarial activity of azafluorenone alkaloids from the Australian tree Mitrephora diversifolia", J Nat Prod, 72(8), 1538-1540 (2009).

90. D. M. Muganza, B. Fruth, J.L. Nzunzu, E. Tuenter, K. Foubert, P. Cos, L. Maes, R.C. Kanyanga, V. Exarchou, S. Apers and L. Pieters, "In vitro antiprotozoal activity and cytotoxicity of extracts and isolated constituents from Greenwayodendron suaveolens", J Ethnopharmacol, 193, 510-516 (2016).

91. H. Zhang, S. Qiu, P. Tamez, G.T. Tan, Z. Aydogmus, N.V. Hung, N.M. Cuong, C. Angerhofer, D. Doel Soejarto, J. M. Pezzuto and H.H. Fong, "Antimalarial agents from plants II. Decursivine, a new antimalarial indole alkaloid from Rhaphidophora decursiva", Pharma Biol, 40(3), 221-224 (2002).

92. A. Libman, H. Zhang, C. Ma, B. Southavong, K. Sydara, S. Bouamanivong, G.T. Tan, H.H. Fong and D.D. Soejarto, "A first new antimalarial pregnane glycoside from Gongronema napalense", Asian J Trad Med, 3(6), 203-210 (2008).

93. S. Vitalini, G. Beretta, M. Iriti, S. Orsenigo, N. Basilico, S. Dall Acqua, M. Iorizzi and G. Fico, "Phenolic compounds from Achillea millefolium L. and their bioactivity", Acta Biochim Pol, 58(2), 203-209 (2011).

94. I.M. Chung, S.H. Seo, E.Y. Kang, W.H. Park, S.D. Park and H.I. Moon, "Antiplasmodial activity of isolated compounds from Carpesium divaricatum", Phytother Res, 24(3), 451-453 (2010).

95. I. Kohler, K. Jenett-Siemens, C. Kraft, K. Siems, D. Abbwi, U. Bienzle and E. Eich, "Herbal remedies traditionally used against malaria in Ghana: bioassay-guided fractionation of Microglossa pyrifolia (Asteraceae)", Z Naturforsch C, 57,1022-1027 (2002).

96. H. Bitew, W. Mammo, A. Hymete and M. Yeshak, "Antimalarial activity of acetylenic thiophenes from Echinops hoehnelii", Molecules, 22(11), 1965 (2017).

97. S. Cai, A.L. Risinger, S. Nair, J. Peng, T.J. Anderson and L. Du, "Identification of compounds with efficacy against malaria parasites from common north American plants". J Nat Prod, 79(3), 490-498 (2015).

98. B. Zhou, Y. Wu, S. Dalal, E.F. Merino, Q.F. Liu, C.H. Xu, T. Yuan, J. Ding, D.G. Kingston, M.B. Cassera and J.M. Yue, "Nanomolar antimalarial agents against chloroquine-resistant Plasmodium falciparum from medicinal plants and their structure–activity relationships", J Nat Prod, 80(1), 96-107 (2017).

99. A.C. Uys, S.F. Malan, S. Van Dyk and R.L. Van Zyl, "Antimalarial compounds from Parinari capensis", Bioorg Med Chem Lett, 12(16), 2167-2169 (2002).

100. Auranwiwat, S. Laphookhieo, R. Rattanajak, S.G. Pyne, T. Rithiwigrom, Antimalarial polyoxygenated and prenylated xanthones from the leaves and branches of Garcinia mckeaniana, Tetrahedron., 72, 6837-2 (2016).

101. Z.D. He, C.Y. Ma, G.T. Tan, Z. Aydogmus, N.V. Hung, N.M. Cuong, C. Angerhofer, D. Doel Soejarto, J. M. Pezzuto and H.H. Fong, "Rourinoside and rouremin, antimalarial constituents from Rourea minor", Phytochem, 67(13), 1378-1384 (2006).
103. J.T. Banzouzi, P.N. Soh, B. Mbatchi, A. Cave, S. Ramos and P. Retailleau, "Cogniauxia podolaena: bioassay-guided fractionation of defoliated stems, isolation of active compounds", antiplasmodial activity and cytotoxicity", *Planta Med*, 74(12), 1453-1456 (2008).

104. C.Y. Ma, S.F. Musoke, G.T. Tan, K. Sydara, S. Bouamanivong, B. Southavong, D.D. Soejarto, H.H. Fong HH and H.J. Zhang, "Study of antimalarial activity of chemical constituents from *Diospyros quaesita*", *Chem Biodiv*, 5(11), 2442-2448 (2008).

105. P. Seephonkai, A. Sangdee, P. Bunchalee and S.G. Pyne, "Cytotoxic and antiplasmodial compounds from the roots of *Strophioblachia fimbriicalyx*", *J Nat Prod*, 72(10), 1892-1894 (2009).

106. E. O. Ajaiyeoba, O.O. Ogbole, O.O. Abiodun, J.S. Ashidi, P.J. Houghton, C.W. Wright, "Cajalchalcone: An antimalarial compound from *Cajanus cajan* leaf extract", *J Parasitol Res.*, 2013, 303781 (2013).

107. V. Ramanandraibe, P. Grellier, M.T. Martin, A. Deville, R. Joyeau, Ramanitrahambolola D.E. Mouray, P. Rasoanaivo and L. Mambu, "Antiplasmodial phenolic compounds from *Piptadenia pervillei*", *Planta Med*, 74(4), 417-421 (2008).

108. V. Samoylenko, M.K. Ashfaq, M.R. Jacob, B.L. Tekwani, S.I. Khan, S.P. Manly, V.C. Joshi, L.A. Walker, and I. Muhammad, "Indolizidine, antinfective and antiparasitic compounds from *Prosopis glandulosa* var. glandulosa", *J Nat Prod*, 72(1), 92-98 (2009).

109. Z.H. Mbwambo, S. Apers, M.J. Moshi, M.C. Kapingu, S. Van Miert, M. Claeyx, R. Brun, P. Cos, L. Pieters, and A. Vliejinck, "Anthranoid compounds with antiprotozoal activity from *Vismia orientalis*", *Planta Med*, 70(8), 706-710 (2004).

110. B.N. Lenta, K.P. Devkota, S. Ngouela, F.F. Boyom, Q. Naz, M.I. Choudhary, E. Tsamo, P.J. Rosenthal and N. Sewald, "Anti-plasmodial and cholinesterase inhibiting activities of some constituents of *Psorospermum glaberrimum*", *Chem Pharm Bull*, 56(2), 222-226 (2008).

111. H. Kirmizibekmez, I. Calis, R. Perozzo, R. Brun, A.A. Donmez, A. Linden, P. Rüedi and D. Tasdemir, "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*, 70(8), 711-717 (2004).

112. G.P.P. Kamatou, R.L. Van Zyl, H. Davids, F.R. Van Heerden, A.C.U. Lourens and A.M. Viljoen, "Antimalarial and anticancer activities of selected South African Salvia species and isolated compounds from *S. radula*, *S Afr J Bot*, 74(2), 238-243 (2008).

113. A.A. Nasrullah, A. Zahari, J. Mohamad and K. Awang, "Antiplasmodial alkaloids from the bark of *Cryptocarya nigra* (Lauraceae)*", *Molecules*, 18(7), 8009-8017 (2013).

114. A.T. Tchinda, V. Tamze, A.R. Ngono, G.A. Ayimele, M. Cao, L. Angenot and M. Frédérick, "Alkaloids from the stem bark of *Strychnos icaja*, Phytochem", *Lett*, 5(1), 108-113 (2012).

115. H.C. Upadhay, B.S. Sisodia, J. Agrawal, A. Pal, M.P. Darokar and S.K. Srivastava, "Antimalarial potential of extracts and isolated compounds from four species of genus Ammannia", *Med Chem Res*, 23, 870-876 (2014).

116. K. Sprogoe, D. Steerk, H.L. Ziegler, T.H. Jensen, S.B. Holm-Moller and J.W. Jaroszewski, "Combining HPLC-PDA-MS-SPE-NMR with circular dichroism for complete natural product characterization in crude extracts: Levorotatory gossypol in *Thespisia danis*", *J Nat Prod*, 71(4), 516-519 (2008).

117. M.S. Buchanan, R.A. Davis, S. Duffy, V.M. Avery and R.J. Quinn, "Antimalarial benzylisoquinoline alkaloid from the rainforest tree *Doryphora sassafras*", *J Nat Prod*, 72(8), 1541-1543 (2009).

118. J.A. Mbah, P. Tane, B.T. Ngadjui, J. D.
119. H.J. Zhang, P.A. Tamez, Z. Aydogmus, G.T. Tan, Y. Saikawa, K. Hashimoto, M. Nakata, N. Van Hung, N.M. Cuong, D.D. Soejarto and J.M. Pezzuto, "Antimalarial agents from plants. III. Trichotheccenes from Ficus fistulosa and Rhipidophora decursiva", Planta Med, 68(12), 1088-1091 (2002).

120. M. Kubo, W. Yatsuzuka, S. Matsushima, K. Harada, Y. Inoue, H. Miyamoto, M. Matsumoto and Y. Fukuyama, "Antimalarial phenanthroindolizine alkaloids from Ficus septicum", Chem Pharma Bull, 64(7), 957-960 (2016).

121. P. Wangchuk, P.A. Keller, S.G. Pyne, M. Taweechotipatr, A. Tonsonomboon and R. Rattanajak, "Evaluation of an ethnopharmacologically selected Bhutanese medicinal plants for their major classes of phytochemicals and biological activities", J Ethnopharmacol, 137(1), 730-742 (2011).

122. C. Desgrouas, C. Chapus, J. Desplans, C. Travaille, A. Pascual, B. Baghdikian, B. Baghdikian, E. Ollivier, D. Parzy and N. Taudon, "In vitro antimalarial activity of cepharamthine", Malar J, 13, 327 (2014).

123. N. Rangkaew, R. Suttisri, M. Moriyasu and K. Kawanishi, "A new acyclic diterpene acid and bioactive compounds from Knema glauca", Arch Pharma Res, 32(5), 685-692 (2009).

124. A. Saez Vega, B. Rojanoa, S. Blair, C. Segura, B. Figadere, B. Seone and J. Saeza, "Antimalarial and antioxidants compounds from Piper tricuspe (Piperaceae)", Pharmacologyonline, 1, 1-8 (2008).

125. Z. D. He, C. Y. Ma, H. J. Zhang, G. T. Tan, P. Tamez, K. Sydara and H.H. Fong, "Antimalarial constituents from Nauclea orientalis (L.)", Chem Biodivers, 2(10), 1378-1386 (2005).

126. D. Lacroix, S. Prado, D. Kamoga, J. Kasenene and B. Bodo, "Structure and in vitro antiparasitic activity of constituents of Citropsis articulata root bark", J Nat Prod, 74(10), 2286-2289 (2011).

127. G. Cebrian-Torrejon, K. Spelman, K. Leblanc, K. Munoz-Durango, S.T. Gutierrez, M.E. Ferreira, A.R. Arias, B. Figadere, A. Fournet, A. Maciu and P. Grellier, "The antiplasmodium effects of a traditional South American remedy: Zanthoxylum chiloperone var. angustifolium against chloroquine resistant and chloroquine sensitive strains of Plasmodium falciparum", Rev Bras Farmacogn, 21(4), 652-661 (2011).

128. J. Bouquet, M. Rivaud, S. Chevalley, E. Deharo, V. Jullian and A. Valentín, "Biological activities of nitidine, a potential anti-malarial lead compound", Malar J, 11, 67 (2012).

129. P. C. Kuo, A.G. Damu, K.H. Lee and T.S. Wu, "Cytotoxic and antimalarial constituents from the roots of Eurycoma longifolia", Bioorg Med Chem, 12(1), 537-544 (2004).

130. M. Tegar and H. Purnomo, "Tea leaves extracted as anti-malaria based on molecular docking plants", Procedia Environ Sci, 17, 188-194 (2013).

131. C. Ma, H.J. Zhang, G.T. Tan, N.V. Hung, N.M. Cuong, D.D. Soejarto and H.H. Fong, "Antimalarial compounds from Grewia bilamellata", J Nat Prod, 69(3), 346-350 (2006).

132. M.T. Ludere, T. Van Ree and R. Vleggaa, "Isolation and relative stereochemistry of lipiialactone, a new antimalarial compound from Lippia javanica", Fitoterapia, 86, 188-192 (2013).

133. N. Klonis, D.J. Creek and L. Tilley, "Iron and heme metabolism in Plasmodium falciparum and the mechanism of action of artemisinins", Curr Opin Microbiol, 16(6), 722-727 (2013).

134. W. Hofheinz, H. Burgin, E. Gocke, C. Jaquet, R. Masciadri, G. Schmid, H. Stohler and H. Urwyler, "Ro 42-1611 (arteflene), a new effective antimalarial: chemical structure and biological activity", Trop Med Parasitol, 45(3), 261-265 (1994).

135. J.M. Combrinck, T.E. Mabotha, K.K. Ncokazi, M.A. Ambele, D. Taylor, P.J.
Smith, H.C. Hoppe and T.J. Egan, "Insights into the role of heme in the mechanism of action of antimalarials", ACS Chem Bio, 8(1), 133-137 (2013).

136. R.G. Kamkumo, A.M. Ngoutane, L.R. Tchokouaha, P.V. Fokou, E.A. Madiesse, J. Legac, J. J. Kezetas, B.N. Lenta, F.F. Boyom, T. Dimo and W.F. Mbacham, "Compounds from Sorindeia juglandifolia (Anacardiaceae) exhibit potent antiplasmodial activities in vitro and in vivo", Malar J, 11, 382 (2012).

137. A. Karioti, H. Skaltsa, A. Linden, R. Perozzo, R. Brun and D. Tasdemir, "Anthecularin: a novel sesquiterpene lactone from Anthemis auriculata with antiprotozoal activity", J Org Chem, 72(21), 8103-8106 (2007).

138. A. D. Wright, H. Wang, M. Gurrath, G.M. König, G. Kocak, G. Neumann, P. Loria, M. Foley and L. Tilley, "Inhibition of heme detoxification processes underlies the antimalarial activity of terpene isonitrile compounds from marine sponges", J Med Chem, 44(6), 873-885 (2001).

139. D. K. Singh, H.S. Cheema, A. Saxena, S. Singh, M.P. Darokar, D.U. Bawankule, K. Shanker and S. Luqman, "Fraxetin and ethyl acetate extract from Lawsonia inermis L. ameliorate oxidative stress in P. berghei infected mice by augmenting antioxidant defence system", Phytomedicine, 36, 262-272 (2017).

140. E.P. Stout, S. Cervantes, J. Prudhomme, S. France, J.J. La Clair, K. Le Roch and J. Kubanek, "Bromophycolide A targets heme crystallization in the human malaria parasite Plasmodium falciparum", Chem Med Chem, 6(9), 1572-1577(2011).

141. M. Budiarti, A. Maruzy, R. Mujahid, A.N. Sari, W. Jokopriyambodo, T. Widayat and S. Wahyono, "The use of antimalarial plants as traditional treatment in Papua Island", Indonesiana Heliyon, 6(12), e05562 (2020).

142. K.V. Sashidhara, S.P. Singh, S.V. Singh, R.K. Srivastava, K. Srivastava, J.K. Saxena and S.K. Puri, "Isolation and identification of β-hematin inhibitors from Flacourtia indica as promising antiplasmodial agents", Eur J Med Chem, 60, 497-502 (2013).

143. T. Zininga, L. Ramatsui, P.B. Makhado, S. Makumire, I. Achilinou, H. Hoppe, H. Dirr and A. Shonhai, "Epigallocatechin-3-gallate inhibits the chaperone activity of Plasmodium falciparum Hsp70 chaperones and abrogates their association with functional partners", Molecules, 22(12), 2139 (2017).

144. M.S. Demoz, K.P. Gachoki, K.J. Mungai and B.G. Negusse, "Evaluation of the antidiabetic potential of the methanol extracts of Aloe camperi, Meriandra dianthera and a polyherb", J Diabetes Mellit, 208, 112757 (2020).

145. P. Rana, S.M. Ghouse, R. Akunuri, Y.V. Madhavi, S. Chopra and S. Nanduri, "FabI (enoyl acyl carrier protein reductase)-A potential broad spectrum therapeutic target and its inhibitors", Eur J Med Chem, 208, 267 (2015).

146. R. Mangoyi, R. Hayeshi, B. Ngadju, F. Ngandeu, M. Bezabih, B. Abegaz, S. Razafimahefa, P. Rasanoivo and S. Mukanganyama, "Glutathione transferase from Plasmodium falciparum–Interaction with malagashanine and selected plant natural products", J Enzyme Inhib Med Chem, 25(6), 854-862 (2010).

147. I.L. Cockburn, E.R. Pesce, J.M. Pryzbsorki, M.T. Davies-Coleman, P.G. Clark, R.A. Keyzers, L.L. Stephens and G.L. Blatch, "Screening for small molecule modulators of Hsp70 chaperone activity using protein aggregation suppression assays: inhibition of the plasmodial chaperone PfHsp70-1", Biol Chem, 392(5), 431-438 (2011).

148. J.J. Bankeu, R. Khayala, B.N. Lenta, D.T. Younougoué, S.A. Ngouela, S.A. Mustafa, K. Asaad, M.I. Choudhary, S.T. Prigge, R. Hasanov and A.E. Nkengfack, "Isoflavone dimers and other bioactive constituents from the figs of Ficus mucuso", J Nat Prod, 74(6), 1370-1378 (2011).

149. A. Muhammad, I. Anis, Z. Ali, S. Awadelkarim, A. Khan, A. Khalid, M.R. Shah, M. Galal, I.A. Khan and M.I. Choudhary, "Methylenobissantin: A rare methylene-bridged bisflavonoid from
Dodonaea viscosa which inhibits Plasmodium falciparum enoyl-ACP reductase"., Bioorg Med Chem Lett, 22(1), 610-612 (2012).

150. I. L. Lauinger, L. Vivas, R. Perozzo, C. Stairiker, A. Tarun, M. Zloh, X. Zhang, H. Xu P. J. Tonge, S.G. Franzblau and D.H. Pham, "Potential of lichen secondary metabolites against Plasmodium liver stage parasites with FAS-II as the potential target". J Nat Prod, 76(6), 1064-1070 (2013).

151. D. Tasdemir, B. Topaloglu, R. Perozzo, R. Brun, R. O. Neill, N.M. Carballeira, X. Zhang, P.J. Tonge, A. Linden and P. Rüedi, "Marine natural products from the Turkish sponge Agelas oroides that inhibit the enoyl reductases from Plasmodium falciparum, Mycobacterium tuberculosis and Escherichia coli", Bioorg Med Chem, 15(21), 6834-6845 (2007).

152. H. Ohigashi, M. A. Huffman, D. Iizutsu, K. Koshimizu, M. Kawanaka, H. Sugiyama, G.C. Kirby, D.C. Warhurst, D. Allen, C.W. Wright and J. David Phillipson, "Toward the chemical ecology of medicinal plant use in chimpanzees: The case of Vernonia amygdalina, a plant used by wild chimpanzees possibly for parasite-related diseases". J Chem Ecol, 20(3), 541-553 (1994).

153. S.C. Stolze, E. Deu, F. Kaschani, N. Li, B.I. Florea, K.H. Richau, T. Colby, R.A. van der Hoorn, H.S. Overkleeft, M. Bogyo and M. Kaiser, "The antimalarial natural product symplostatin 4 is a nanomolar inhibitor of the food vacuole falcipains", Chem Bio, 19(12), 1546-1555 (2012).

154. A. Ishiyama, M. Iwatsuki, T. Yamamoto, H. Miura, S. Omura and K. Otoguro, "Antimalarial tropones and their Plasmodium falciparum glyoxalase I (pfGLOI) inhibitory activity". J Antibiot, 67(7), 545-547 (2014).

155. O.A. Skorokhod, D. Davalos-Schafler, V. Gallo, E. Valente, D. Ulliers, A. Notarpietro, G. Mandili, F. Novelli, M. Persico, O. Tagliatela-Scaletti and P. Arese, "Oxidative stress-mediated antimalarial activity of plakortin, a natural endoperoxide from the tropical sponge Plakortis simplex", Free Radical Biol Med, 89,624-637 (2015).

156. J.D. Herman, L.R. Pepper, J.F. Cortese, G. Estiu, K. Galinsky, V. Zuzarte-Luis, E.R. Derbyshire, U. Ribacke, A.K. Lukens, S.A. Santos and V. Patel, "the cytoplasmic prolyl-tRNA synthetase of the malaria parasite is a dual-stage target of febrifugine and its analogs", Sci Transl Med, 7(288), 1-21 (2015).

157. G.E. Brandt, M.D. Schmidt, T.E. Prisinzano, B.S. Blagg, "Gedunin, a novel Hsp90 inhibitor: semisynthesis of derivatives and preliminary structure activity relationships", J Med Chem, 51(20), 6495-6502 (2008).

158. G.M. LaMonte, J. Almaliti, B. Bibo-Verdugo, L. Keller, B.Y. Zou, J. Yang, Y. Antonova-Koch, P. Orjuela-Sanchez, C.A. Boyle, E. Vigil and L. Wang, "Development of a potent inhibitor of the Plasmodium proteasome with reduced mammalian toxicity", J Med Chem, 60(15), 6721-6732 (2017).
مركبات طبيعية محتملة ضد الملاريا: بحث مرجعي

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الملاريا هي أحد أهم الأمراض التي تهدد الحياة والتي تنتقلها الأمراض المنتشرة في المناطق الاستوائية وشبه الاستوائية من العالم. يستخدم النظام التقليدي للطب عقاقير من أصل نباتي. تستخدم مادة الكينين والأرتيميسينين، وهما مادتان كيميائيتان نباتيتان طبيعيتان لعلاج الملاريا. أكدت المراجعات الحالية على النشاط المضاد للملاريا للنباتات الفعالة ضد المقاومة الناشئة. كان الهدف من هذه الدراسة هو تحليل مفهوم وأهداف المركبات الطبيعية المفصولة، والآلة عملها، وأجزاء النبات المستخدمة في علاج الملاريا في النظام التقليدي للطب. تم استكشاف 113 مركبًا مفصولاً وأجزاء نباتية مستخدمة من 99 نوعًا، والآلية الجزيئية لـ 70 مركبًا طبيعيًا مضادًا للملاريا من أنواع نباتات مختلفة. كانت هذه النباتات تستخدم تقليديًا لعلاج الملاريا في أنحاء العالم. فهي علاجية أكثر فعالية وأمانًا، ولها معدلات الشفاء مرتفعة. هناك حاجة ملحة لتطوير عقاقير جديدة لعلاج الملاريا. يمكن استكشاف هذه المركبات المفصولة لتطوير الأدوية المضادة للملاريا ضد السلالات المقاومة للبلازموديوم.