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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]

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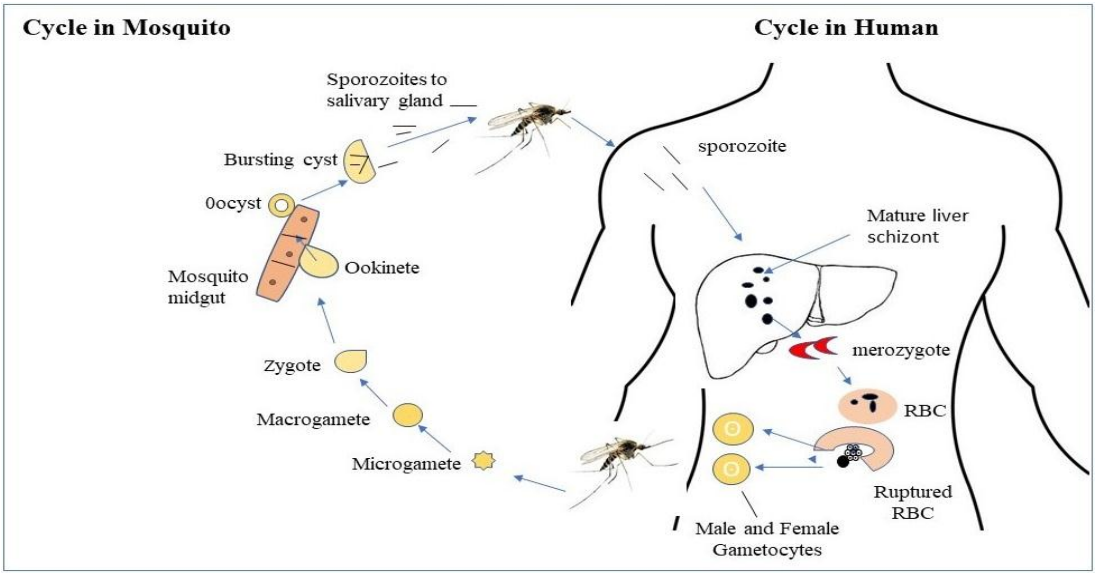

Fig. 1: Life cycle transmission process**.**

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 *in-vivo* and *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

1). 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 Bark	49
Asteraceae	*Acanthospermum austral (*Loelf.) Kuntze	Whole plant	50
	Ageratum conyzoides L.	Aerial parts, leaves	51
	Artemisia gorgonum Webb.	Aerial parts	52
	Struchium sparganophorum (L.) Kuntze	Leaves	51
	Tithonia diversifolia (Hemsl.)A.Gray	Aerial parts	53
	Vernonia amygdalina Delile.	Leaves	54
	Vernonia brasiliana (L.) Druce	Leaves	55
Cochlospermaceae	*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
Fabaceae	*Euphorbia hirta* L.	Whole plant	63
	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	*Ocimum 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 Rottb.)Warb.	Leaves	74
Piperaceae	*Piper umbellatum L.*	Leaves, stem	75
	Pothomorphe peltata (L.)Miq.	Leaves, roots	58
Rhamanaceae	*Ampelozizyphus* amazonicus Ducke.	Roots	76
Rubiaceae	*Crossopteryx febrifuga* (Afzel. Ex G.Don)Benth.	Stem, bark	77
	Morinda lucida Benth.	Barks, leaves	78
	Remijia ferruginea (A.St.Hil.)DC.	Barks	79
	Sarcocephalus latifolius (Sm.) E.A.Bruce	Roots, stem	80
Rutaceae	*Esenbeckia febrifuga* (A.St.Hil)A.Juss.ex Mart.	Stem	81
	Citrus limon (L.) Osbeck	Fruit peel	82
Salicaceae	*Casearia sylvestris* Sw.	Stem bark, root	83
Scrophulariaceae	*Scoparia dulcis* L.	Aerial parts	84
Simaroubaceae	*Picrolemma sprucei* Hook.f.	Roots, stems	85
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. Criab	• miliusacunines A • miliusacunines B	87
	Friesodielsia discolor (Craib.) D.Das	• 30-formyl-20,40-dihydroxy-60- methoxychalcone • Tectochrysin • 8-formyl-7-hydroxy-5-methoxyflavanone	88
	Mitrephora diversifolia (Span)Miq.	• 5-hydroxy-6-methoxyonychine	89
	Greenwayodendron suaveolens (Engl. & Diels.) Verdc.	• *N*-acetylpolyveoline • Polyalthenol	90
Araceae	*Rhaphidophora decursiva* (Roxb.) Schott.	• Polysyphorin • rhaphidecurperoxin • rhaphidecursinol A • rhaphidecursinol B • grandisin • epigrandisin • decursivine • Roridin E	91
Asclepiadaceae	*Gongronema napalense* (Wall.) Decne.	• gongroneside A	92
Asteraceae	*Achillea millefolium* L.	• apigenin 7-O-glucoside • luteolin 7-O-glucoside	93

Table 2: Continued.

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 • 6E-geranylgeraniol-19-oic acid	95
	Echinops hoehnelii Schweinf.	• 5-(penta-1,3-diynyl)-2-(3,4-dihydroxybut-1-ynyl)-thiophene • 5-(penta-1,3-diynyl)-2-(3-chloro- 4-acetoxy-but-1-yn)-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	
Chrysobalanceae	*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

Table 2: Continued.

Family	Species	Compounds	References
Euphorbiaceae	*Strophioblachia fimbricalyx* Boerl.	• 9-O demethyltrigonostemone • 3,6,9-trimethoxyphenanthropolone	105
Fabaceae	*Cajanus cajan* (L.) Millsp.	• Cajachalcone	106
	Piptadenia pervillei Vatke	• catechin 5-gallate • catechin 3-gallate	107
	Prosopis glandulosa Torr.	• Prosopilosidine	108
Fagaceae	*Quercus laceyi* Small	• kaempferol 3-O-glucosides	97
Hypericaceae	*Vismia orientalis* Engl.	• vismione D	109
	Psorospermum glaberrimum Hochr.	• 3-geranyloxyemodin anthrone • acetylvismione D	110
Lamiaceae	*Phlomis brunneogaleata*Hub.-Mor.	• chrysoeriol 7-O-β-D- glucopyranoside • luteolin 7-O-β-D-glucopyranoside	111
	Salvia radula Benth.	• betulafolientriol oxide • salvigenin	112
Lauraceae	*Cryptocarya nigra* Kosterm.	• 2-hydroxyatherosperminine	113
Loganiaceae	*Strychnos icaja* Baill.	• 15-hydroxyvomicine • N-methyl-sec-iso-pseudostrychnine	114
Lythraceae	*Ammannia multiflora* Roxb., *Ammannia baccifera* L.	• 4-hydroxy-α-tetralone • ammaniol • tetralone-4-O-β-D-glucopyranoside	115
Malvaceae	*Thespesia danis* Oliv.	• Gossypol	116
Menispemaceae	*Stephania venosa* Spreng.	• Stephanine • crebanine • *O*-methylbulbocapnine	73
	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 • 2-(10β-geranyl-50β-hydroxy-20- oxocyclohex-30-enyl) acetic acid	118
Moraceae	*Ficus fistulosa* Reinw. ex Blume	• verrucarin L acetate	119
	Ficus septica Burm. f.	• dehydrotylophorine • dehydroantofine • tylophoridicine	120

Table 2: Continued.

Family	Species	Compounds	References
Myristicaceae	*Knema glauca* (Bl.) Warb.	• malabaricone	120
Papaveraceae	*Meconopsis simplicifolia* (D.Don)Walp.	• benzylisoquioline, • simplicifolianine	121
	Corydal iscalliantha D.G.Long	• Cheilanthifoline	49
	Stephania rotunda Lour.	• Cepharanthine • palmatine • pseudopalmatine	122
Piperaceae	*Piper sarmentosum* Roxb.	• sarmentine • 1-piperettyl pyrrolidine	123
	Piper tricuspe (Miq.)C.DC.	• 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.)	• naucleaorine • epimethoxynaucleaorine • oleanolic acid • 3α,23-dihydroxyurs-12-en-28-oic acid	125
Rutaceae	*Citropsis articulate* (Willd. ex Spreng.)Swingle & M. Kellerm.	• 5-hydroxynoracronycine • 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 • Gallocatecin	130
Tiliaceae	*Grewia bilamellata* Gagnep.	• Nitidanin • 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

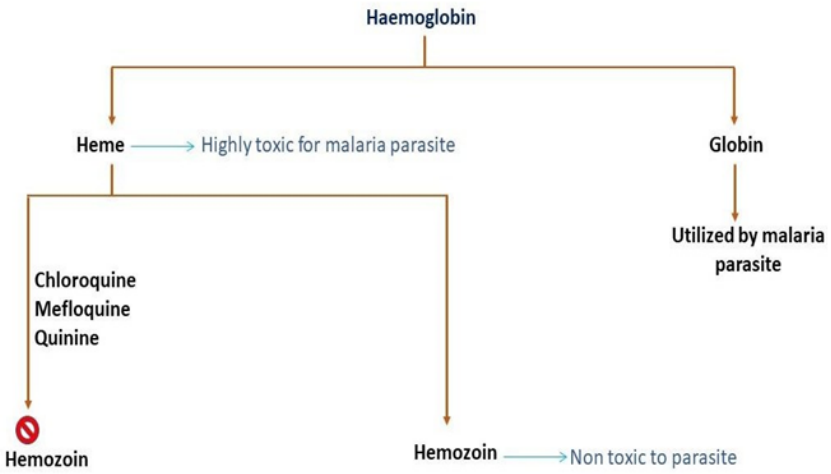

Fig. 2: Mechanism of action of quinine.

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 cinchonidine are effective natural compounds with a cure rate of ~98% .[11] Quinine plays a crucial role in malaria management during 1st trimester of pregnancy. The half-life of quinine approximately ranges between 11-18 hours.[12] 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).[13] 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.[14] In very rare cases, chloroquine use can also lead to neuropsychiatric problems, photosensitization and ringing in the ears.[15] Sometimes hair, skin and nail alterations may also arise.[14]

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[16] 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.[17] ACT technique is commonly used against chloroquine resistance species of *plasmodium*

viz. *P. falciparum*. Arteether, artemether, and sodium artesunate are semisynthetic derivatives of artemisinin.[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*[19] as shown in Table 3.

Lapinone

The synthetic compound lapinone is a naphthoquinone that showed effective potential against *P. vivax* [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*.[21]

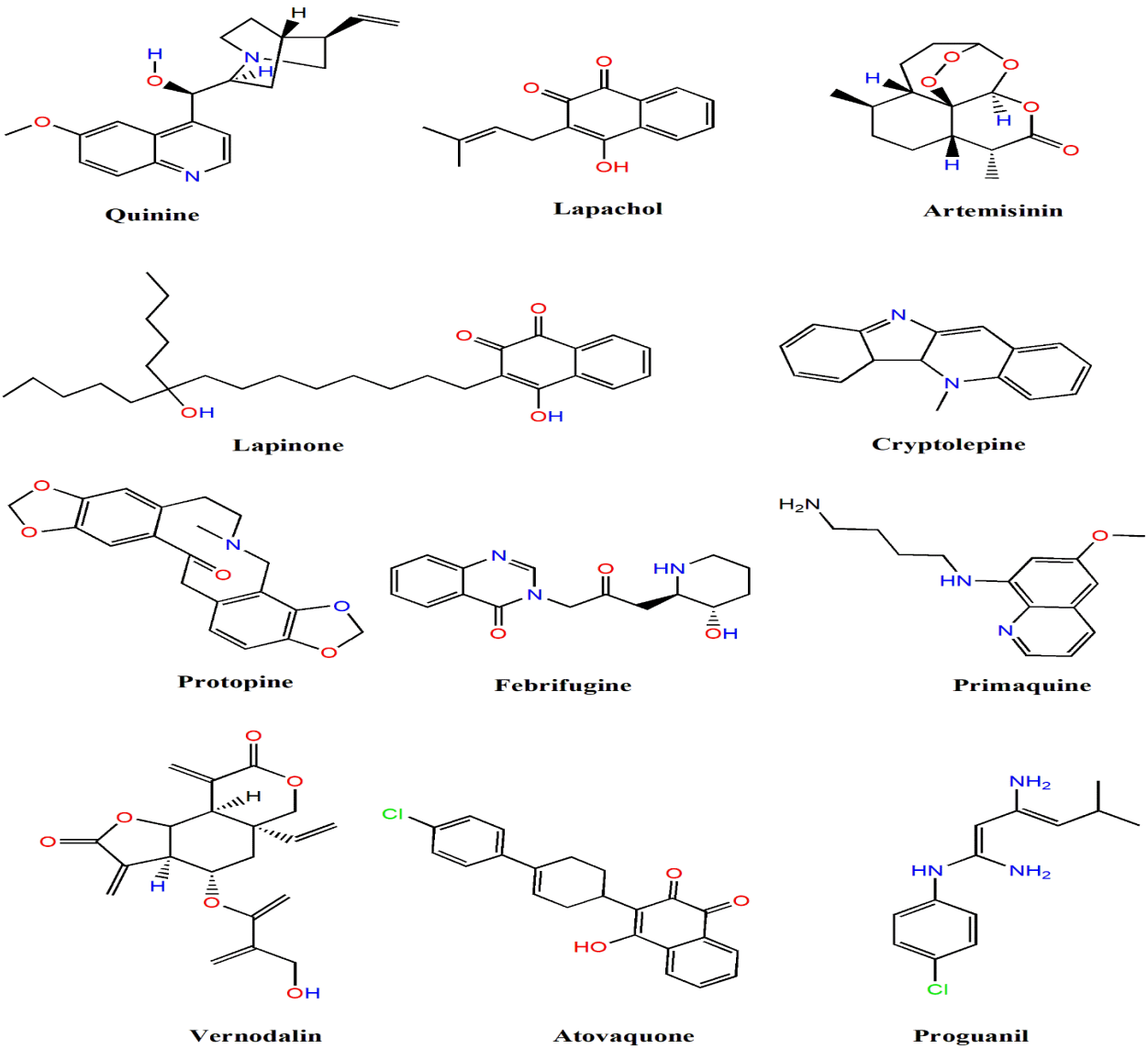

Fig. 3A: Established natural anti-malarial compounds**.**

Protopine

This alkaloid is isolated from the Bhutanese medicinal plant *Corydalis calliantha* (Fumariaceae).[22] It showed *in vitro* anti-plasmodial activity against multidrug-resistant (K1) and wild-type (TM4) strains of *P. falciparum*.[23]

Febrifugine

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

Primaquine

Primaquine is an 8-aminoquinoline (synthetic compound), has unique antimalarial activity and prevents relapse in *P. ovale* and *P. vivax* malarial plasmodium strains and potent gametocytocidal activity in *P. falciparum* infections.[25]

Vernodalin

Vernodalin is isolated from *V. colorata* plant[26] and its anti-plasmodial activity has been reported[27] against *P. falciparum*.[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 *P. falciparum* [29] and is also used to prevent malaria in travelers.[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.[29]

Chloroquine

It is a 4-aminoquinolone (Fig.3B) antimalarial agent used to prevent and treat acute forms of malaria caused by *P. vivax, P. malariae, P. ovale,* in addition to sensitive forms of *P. falciparum*.[30]

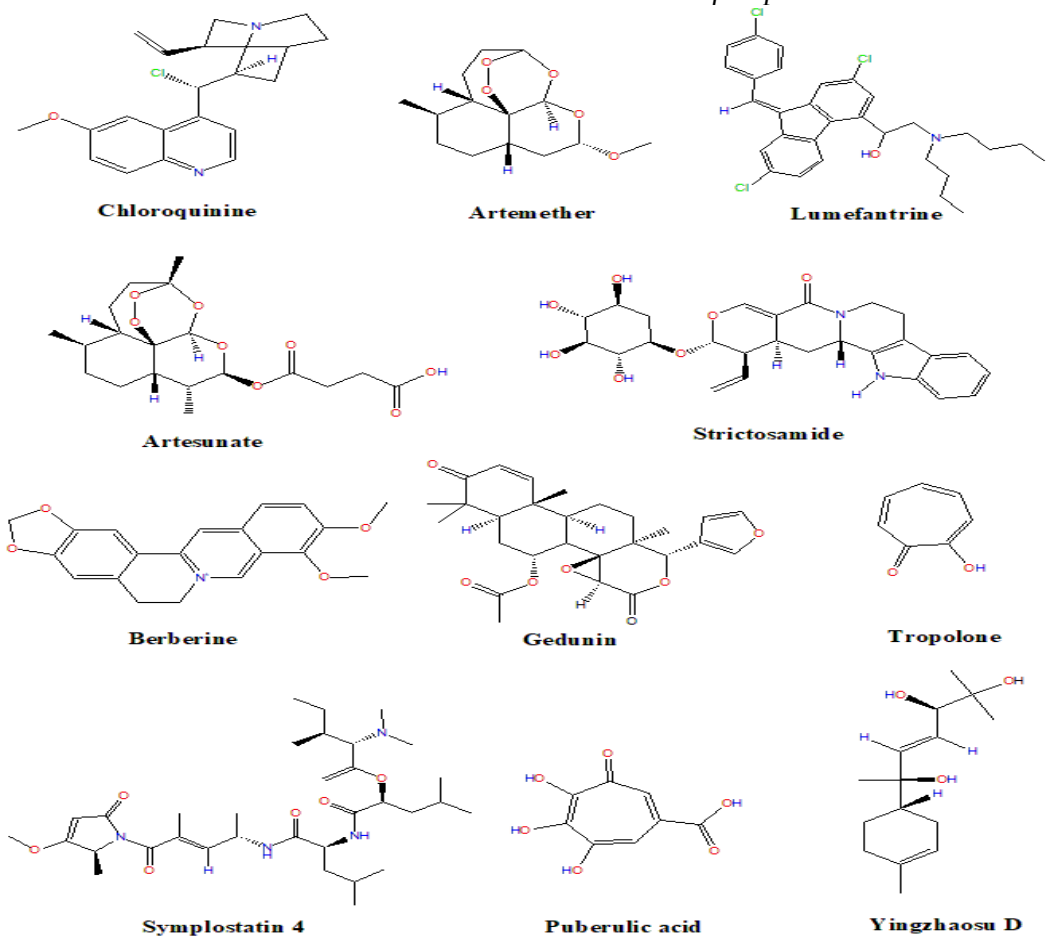

Fig. 3B: Established natural anti-malarial compounds.

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 Rubiaceace, 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] Sriwilaijareon 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 Meliaceace 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 ailment cures 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.

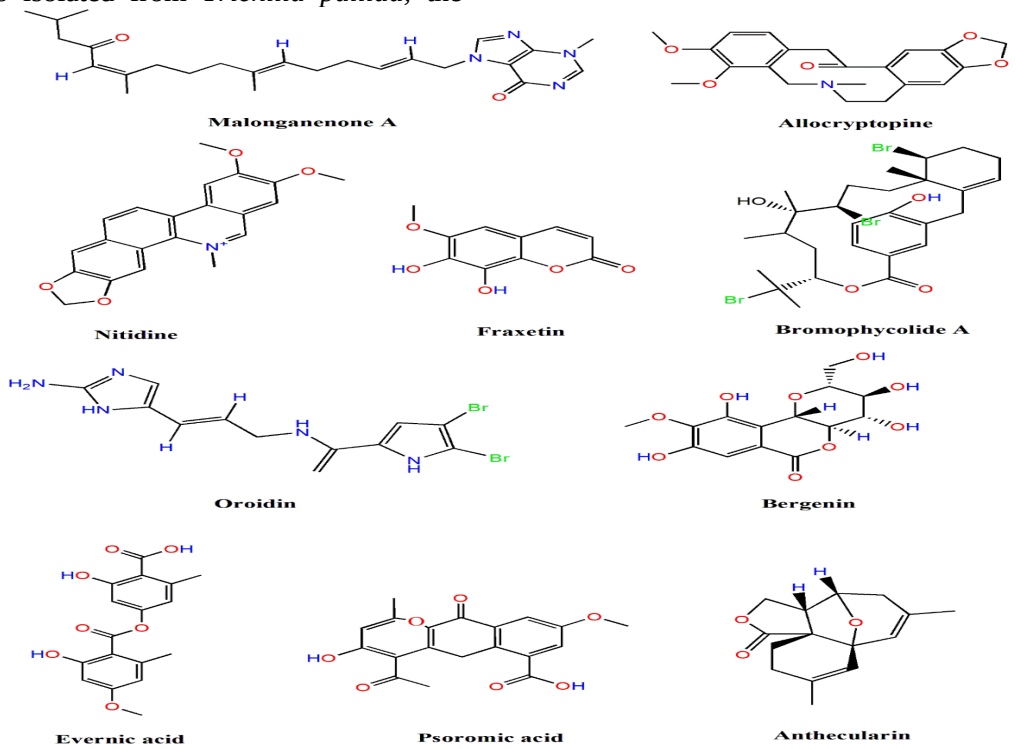

Fig. 3C: Established natural anti-malarial compounds.

Fraxetin

It is isolated from the leaves of *Lawsonia inermis* and has reported anti-plasmodial activity *in-vivo* against *P. berghei* stain. It performs this action by suppressing the oxidative damage by augmenting the antioxidant endogenous system.[41]

Oroidin

It is an alkaloid isolated from *Agelas oroides*, and has antimalarial activity against *P. falciparum*.[42]

Anthecularin

It is a sesquiterpene lactone, isolated from aerial parts of Greek *Anthemis auriculata* (Asteraceae). Anthecularin showed anti-plasmodial activity against *P. falciparum*.[43]

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.[44] 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).

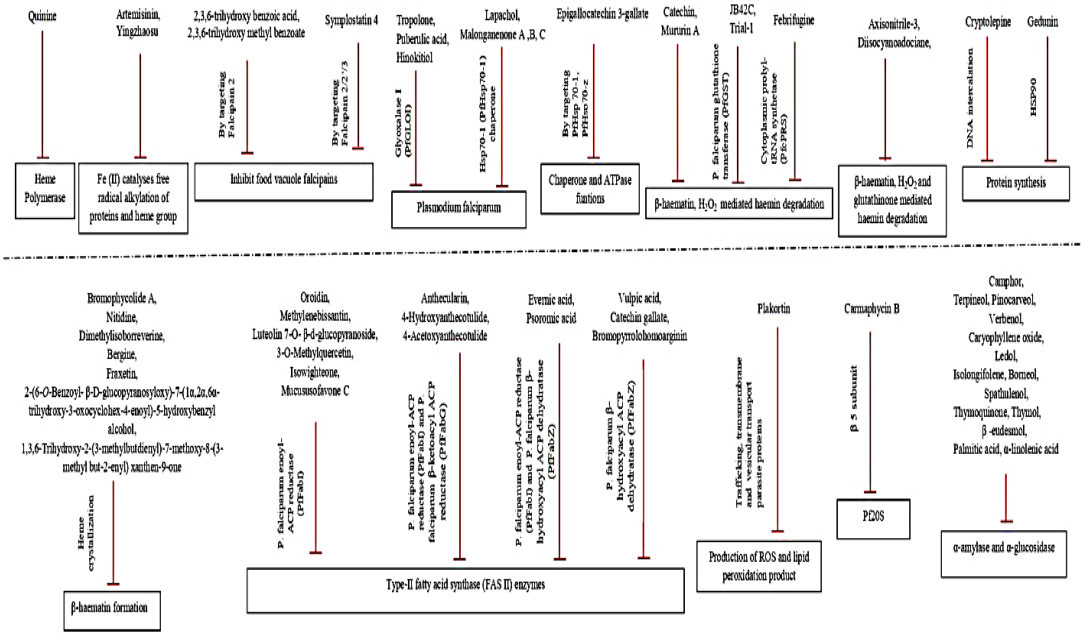

Fig. 4: Comparative mechanism of action of natural compounds.

Table 3: Mechanism action of natural compounds.

Action/ target site	Natural products	References
DNA intercalation	• Cryptolepine	21
Fe (II) catalyses free radical alkylation of proteins and heme group	• Artemisinin	133
Fe (II) catalyzes 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,	137
Inhibit β-haematin, H_2O_2, and glutathione-mediated hemin Degradation	• Axisonitrile-3, • Diisocyanoadociane	138
Inhibit β-haematin formation by haem crystallization	• 1,3,6-Trihydroxy-2-(3-methyl butdienyl)-7-methoxy-8-(3- methyl but-2-enyl) xanthen-9 one, • 2-(6- O-Benzoyl-β-dglucopyranosyloxy)-7- (1α, 2α, 6α-trihydroxy- 3-oxocyclohex-4- enoyl)-5-hydroxybenzyl alcohol, • Bergenin • Bromophycolide A, • Dimethylisoborreverine, • Fraxetin • Nitidine,	139 106 106 140 106 141 140
Inhibition of β-haematin, H_2O_2 mediated haemin degradation	• Catechin-[5,6-e]-4β- (3,4-dihydroxyphenyl) dihydro-2(3H) pyranone, • Mururin A	142
Inhibit chaperone and ATPase functions by targeting PfHsp70-1, PfHsp70-z	• Epigallocatechin 3-gallate	143
Inhibit *α*-amylase and *α*-glucosidase	• Essential oils (camphor, terpineol, pinocarveol, verbenol, caryophyllene oxide, ledol, isolongifolene, borneol, spathulenol, thymoquinone, *β*-eudesmol, and thymol) • Fatty acids methyl esters (palmitic acid methyl ester, *α*-linolenic methyl esters)	144
Inhibit type II fatty acid synthase (FAS II) enzymes by Plasmodium falciparum enoyl-ACP reductase (PfFabI) and Plasmodium falciparum β-hydroxyacylACP dehydratase (Pf FabZ)	• Evernic acid, • Psoromic acid	145
Inhibit β-haematin, H_2O_2 Mediated haemin degradation by targeting *Plasmodium falciparum* glutathione transferase (PfGST)	• JB42C, • Tral-1	146

Table 3: Continued.

Action/ target site	Natural products	References
Inhibit *Plasmodium falciparum* Hsp70-1 (PfHsp70-1) chaperone function	• Lapachol, • Malonganenone A, • Malonganenone B, • Malonganenone C,	147
Inhibit type II fatty acid synthase (FAS II) enzymes by targeting *Plasmodium falciparum* enoyl-ACP reductase (PfFabI)	• 3- O-Methylquercetin, • Isowighteone, • Luteolin 7- O-β-d-Glucopyranoside, • Methylenebissantin, • Mucusisofavone C • Oroidin,	148 149 150 151 151
Inhibit food vacuole falcipains by targeting Falcipain 2/2'/3	• Symplostatin 4	152
Inhibit *Plasmodium falciparum* glyoxalase I (PfGLOI)	• Hinokitiol, • Puberulic acid, • Tropolone,	153
Inhibition of type II fatty acid synthase (FAS II) enzymes by targeting *Plasmodium falciparum* β-hydroxyacyl- ACP dehydratase (*Pf* FabZ)	• Bromopyrrolohomoarginin • Catechin gallate, • Vulpic acid,	154
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 • Berberine • Protopine	158

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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مركبات طبيعية محتملة ضد الملاريا: بحث مرجعي

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الملاريا هي أحد أهم الأمراض التي تهدد الحياة والتي تنقلها 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 ، وآلية عملها ، وأجزاء النبات المستخدمة في علاج الملاريا في النظام التقليدي للطب. تم استكشاف ١١٣ مركبًا مفصولا ، وأجزاء نباتية مستخدمة من ٤٩ نوعًا ، والآلية الجزيئية لـ ٧٠ مركبًا طبيعيًا مضادًا للملاريا من أنواع نباتات مختلفة. كانت هذه النباتات تستخدم تقليديا 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.