**Advances of natural product in the control of malarial parasite**

Rupa Saha, Arpita Gope and Anjali Rawani\*

**1** Laboratory of Parasitology, Vector Biology, Nanotechnology, Department of Zoology, The University of Gour Banga, Malda, West Bengal, India, PIN-732103

\***Address of corresponding author**

Dr. Anjali Rawani, Ph.D.

Assistant Professor

Laboratory of Parasitology, Vector Biology, Nanotechnology

Department of Zoology, The University of Gour Banga, Malda,

West Bengal, India, PIN-732103

Email: micanjali@gmail.com

**Abstract**

Malaria is a serious protozoan parasitic disease from tropical regions caused by a species of *Plasmodium* and transmitted by female *Anopheles* mosquitoes. Estimated 3.3 billion of the total world population live in areas with malaria risk and an estimated death of 660,000 per year. Plant-derived natural products have played a fundamental role in the control of malaria. Synthetic drugs are dangerous and have numerous side effects. Medicinal plants have been used in the treatment of various diseases. Plant derived chemical substances have some beneficial effect on the body. Quinine is the first antimalarial drug found in the bark of *Chinchona* tree, which is native to South America. Another antimalarial drug Artemisinin was discovered in China, a pure drug extracted from *Artemisia annua* which is effective against all malarial parasites. In different countries different plant parts extract derived herbal remedies used in control of malaria which are affordable, safer and effective than any chemical compound. In this review I discussed region wise plants used for antiplasmodial activity.

**Keywords:** Malaria, Malarial Parasite, Quinine, Artemisinin, Chloroquine, Antimalarial drugs, Antiplasmodial activity, Medicinal Plants, Plant extract

# Introduction

# The term malaria is obtained from the Italian ‘mal’aria’, which means ‘bad air’, from the early association of the disease with marshy areas (Tuteja, 2007). Malaria is a serious and sometimes fatal disease caused by a protozoan parasite that commonly infects a certain type of mosquito which feeds on humans (https://www.cdc.gov). Malaria is one of the most common mosquito-borne diseases in the tropical and subtropical countries, particularly in sub- Saharan Africa (Karunamoorthi and Ilango, 2010). Each year nearly 290 million people are infected with malaria, and more than 400,000 people die because of this disease (mayoclinic.org). Nearly half of the world's population will be susceptible to malaria by 2022. According to the latest world malaria report, in 2020 there was 241 million cases of malaria, compared to 227 million cases in 2019 ([https://www.who.int](https://www.who.int/)).

# The species is transmitted through female *Anopheles* mosquito. It is a most important single group of insects in terms of public health problem, which transmit a number of diseases, such as malaria, filariasis, dengue, Japanese encephalitis, chikungunya, and yellow fever, cause millions of deaths every year in almost all tropical and subtropical countries and many other parts of the world (Ghosh et al. 2012). The parasite is spread through the bites of infected mosquitoes (mayoclinic.org). People who get malaria are typically very sick with high fevers, shaking chills, and flu-like illness (https://www.cdc.gov). Malaria remains one of the most serious problems and the major cause of mortality and morbidity in the endemic regions. There are currently 109 malarious countries and territories, of which 45 countries are in the list of World Health Organization (WHO).

# Therefore, to control the malaria disease there is a need to check the *Plasmodium* proliferation inside the body of the host. For this purpose, there is an urgent requirement for inexpensive and effective anti-malarial drugs (Rajakumar & Rahuman, 2011). Plant-derived natural products have played a crucial role in the control of malaria. Medicinal plants constitute an effective source of both traditional and modern medicine (Inbaneson et al. 2012). Medicinal plants have been used in the treatment of various diseases because they possess potential pharmacological activities including antineoplastic, antimicrobial, antioxidant, anti- inflammatory, analgesics, anti-diabetic, anti-hypertensive, antidiarrheal and other activities (Shaikh and Patil, 2020). The antimalarial potential of compounds derived from plants is proven by examples such as quinine, which was the first anti-malarial drug of plant origin, isolated from the bark of Cinchona tree (Rubiaceae) by Pierre Joseph Pelletier and Joseph Caventou (Achan et al. 2011), and artemisinin, obtained from *Artemisia annua* discovered by Tu Youyou. The choice of plants for testing for antimalarial activity is made based on the traditional perception of a given plant's effectiveness in the treatment of malaria. Plant derived chemical substances have some beneficial effect on the body (Akinmoladun et al. 2007). The therapeutic value of a medicinal plant is determined by its phytoconstituents, either singularly or in combination. People in the countryside, wholly or partially, use medicinal plants for prevention as well as cure of various disease especially malaria. Because traditional healers are widely recognised by the community and are available, people tend to prefer using herbal medicines. Herbal remedies as being more affordable, safer and fruitful compared to the modern medicine. Resistance to anti- malarial drugs is proving to be a challenge in malaria control in most parts of the world (Nguta et al. 2010a). The finest and most popular medicine for treating malaria, chloroquine, has lost effectiveness against parasites since the early 1960s. Therefore, to effectively manage malaria, new knowledge, products, tools and new drugs are immediately needed (Omulokoli et al. 1997). The most potent and economical treatment for malaria would be an effective vaccination, and its possible long-term effects might even include its eventual eradication. Although substantial progress has been made, areal break through towards a malaria vaccine is still missing (Nguta et al. 2010). Natural products could provide starting points in drug discovery. Traditional herbal remedies have served as a solid foundation for the creation of anti-malarial lead compounds for many years.

# About malarial parasites

# Malaria parasites are eukaryotic single celled micro-organisms belongs to the Phylum Apicomplexa, class Sporozoa, genus *Plasmodium* (Tuteja, 2007; Igweh, 2012). There are more than 100 species of *Plasmodium*, which can infect numerous animal species such as reptiles, birds, and various mammals (Igweh,2012), but only five species of *Plasmodium* can infect humans under natural conditions: *Plasmodium vivax, Plasmodium ovale and Plasmodium malariae* and deadly *Plasmodium falciparum* causing malaria whereas *Plasmodium knowlesi* hardly possess any threat to humans (Tu, 2016)*.* These species differ morphologically, immunologically, in their geographical distribution, in their relapse patterns and in their drug responses (Tuteja, 2007). In addition, there is one species that naturally infect macaques which has recently been identified to be a cause of zoonotic malaria in humans (There are some additional species which can exceptionally or under investigational conditions, infect humans).

# Types of Human Malarial Parasites

# *P. falciparum*, is the agent of severe, potentially fatal malaria, which is found worldwide in tropical and subtropical. *P. falciparum* multiples quickly in the blood, and can thus cause severe blood loss (anemia). The infected parasites can block small blood vessels. When this happen in the brain, cerebral malaria occurs, which can be fatal.

# *P. vivax is a species that is primarily found in Asia, Latin America, and a few parts in Africa.* It is probably the most widespread human malaria parasite. *P. vivax* and *P. ovale*, have dormant liver stages named “hypnozoites” that may remain in this organ for weeks to many years, resulting in relapses of malaria infection.

# *P. ovale* is primarily found in Africa, particularly West Africa.It is biologically and morphologically related to *P. vivax*. however, differently from *P. vivax*. This explains the greater prevalence of *P. ovale* (rather than *P. vivax*) in most of Africa.

# *P. malariae* is the only human malaria parasite species that found worldwide, has a quartan cycle (three-day cycle). If untreated, it causes a long-lasting, chronic infection that in some cases can last lifelong. In some chronically infected patients *P. malaria* can cause severe complications such as the nephritic syndrome.

# *P. knowlesi* is found throughout Southern Asia as a natural pathogen of long-tailed and pigtailed macaques. *P. knowlesi* has a 24 –hour replication cycle and so they can rapidly progress from an uncomplicated to a severe infection.

# *P. berghei* causes malaria of certain rodents especially laboratory mice and rats. The erythrocytic cycle requires 22-24 hours. *P. berghei* infections may also affect the brain and can be cause cerebral complication to the laboratory mice.

# Plant extraction and their use in the control of malarial parasites

# The goal of plant extraction is to extract out the specific components from plants. It is a process for separating solids from liquids in which a solid object (the plant) is brought into contact with a liquid (the solvent). The plant components are then solubilised and contained within the solvent (https://www.berkem.com). Plants extracts are considered to be the most pressing sources of biomolecules, which can be screened from plant parts (https://www.sciencedirect.com).

# Plants have always been considered to be a possible alternative and rich source of new drugs. Several plants are often used in combination in traditional practice. Whole plants or fusions of plants are used rather than isolated compounds. Crude plant extracts have greater in vitro or and in vivo antiplasmodial activity than isolated constituents at an equivalent dose. It is easily available. It has low side effects than chemical compounds. Plant derived products are cost effective.

# Materials and Method

# Information was collected by searching published literature in the Google Scholar, Research Gate, PubMed for research article, reviews, books and other reports and the data was taken 10-15 years ago from current year. Identification of published reports was done using various key word searches such as malaria, malarial parasite, quinine, artemisinin.

**Role of plant extracts in the control of malarial parasites**

Traditional medicinal plants have been the main source of antimalarial drugs, with the two major drugs quinine and artemisinin being used worldwide for the treatment of malaria (Wright and Phillipson 1990; Thomson, 1993). The majority of antimalarial medications currently in use, including quinine and artemisinin, were either derived directly from plants or were created using chemical models of chemicals derived from plants. (Schwikkard et al, 2006). These medicines include quinoline compounds, sulfadoxine/pyrimethamine, mefloquine (Lariam), lumefantrine, doxycycline, artemisinin, and artemisinin-based combination therapies (ACTs) (Tu, 2016).

**Quinine -** Quinine, as a component of the bark of Cinchona (quina-quina) tree, was the first drug used effectively to treat malaria, from as early as the 1600s, when it was referred to as the “Jesuit’s bark,” “Cardinal bark,” or “Sacred bark” (Achan, 2011). Before 1820, the cinchona bark was first dried, ground to a fine powder, and then mixed into a liquid (commonly wine) before being drunk. Pierre Joseph Pelletier and Joseph Caventou collected quinine from the bark, separated it, and gave it a name in 1820. Quinine, an alkaloid, acts by interfering with the growth and reproduction of the malarial parasites, which inhabit the red blood cells (erythrocytes) ([https://www.britannica.com](https://www.britannica.com/)).

Quinine is a cinchona alkaloid that belongs to the aryl amino alcohol group of drugs. Quinine has rapid schizonticidal action against intra-erythrocytic malaria parasites (Achan, 2011). It is also gametocytocidal for *Plasmodium vivax* and *Plasmodium malariae*, but not for *Plasmodium falciparum*.

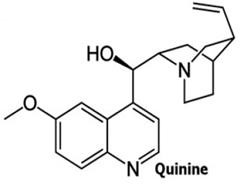


Fig 1: Chemical Structure of Quinine

However, quinine has a high level of toxicity and a short pharmacological half-life, limiting its usage (Camargo et al. 2009; Muregi, 2010). Quinine and other cinchona alkaloids such as quinidine, cinchonine and cinchonidine are all effective against malaria (NCBI). Quinine has analgesic qualities as well, but not antipyretic ones. The anti-malarial mechanism of action of quinine is unknown (Achan, 2011).

Quinine was obtained directly from the Peru tree Cinchona (*Cinchona succiruba*) [Rubiacae] plant.

In the 20th century, synthetic alternatives to quinine were evolved (Karunamoorthi et al. 2013). In 1940, quinine was used as a template for the synthesis of chloroquine, another antimalarial drug. The first widely used antimalarial drug was quinine, a natural product extracted from the bark of the tree *Cinchona calisaya,* which is native to South America. In the late 19th century, Synthetic derivatives of quinine, such as 8- aminoquinoline primaquine and 4-aminoquinoline choloroquine, can be traced back to the pioneering work of Ehrlich on Methylene Blue. These drugs can cause parasitic death by blocking the polymerization of the toxic by-product of haemoglobin degradation, heme, into insoluble and nontoxic pigment granules, resulting in cell lysis and parasite cell autodigestion (Olliaro and Yuthavong, 1999). As a second line treatment for uncomplicated malaria, the World Health Organization (WHO, 2010) guidelines suggest a combination of quinine plus doxycycline, tetracycline, or clindamycin (advised when the first- line medicine fails or is not available) and quinine plus clindamycin for treatment of malaria in the first trimester of pregnancy. In India resistance has emerged against quinine in north eastern states and Kolar district in Karnataka (Farooq and Mahajan, 2004). Quinine has a low therapeutic index, and adverse effects with its use are substantial (WHO). The side effects typically encountered at therapeutic dosages are referred to as cinchonism, with mild forms including tinnitus, modest impairment of hearing, headache, and nausea. Impairment of hearing is usually concentration dependent and reversible (Karlsson et al. 1990). More severe manifestations include vertigo, vomiting, abdominal pain, diarrhoea, marked auditory loss, and visual symptoms, including loss of vision (White, 1996).

**Artemisinin**

There are at least six species in the Artemisia family according to the plant taxonomy, which includes *Artemisia annua* L*.*, *Artemisia apiacea* Hance, *Artemisia scoparia* Waldst. et kit., *Artemisia capillaries* Thunb., *Artemisia japonica* Thunb., and *Artemisia eriopoda* Bunge. But only *Artemisia annua* L. contains a meaningful quantity of artemisinin (Tu et al. 2009). In the 1970s, artemisinin was detected as a pure drug extracted from the plant *Artemisia annua.* Artemisinin, also known as qinghaosu, an antimalarial drug derived from the sweet wormwood plant. Artemisinin is a sesquiterpene lactone (a compound made up of three isoprene units bound to cyclic organic esters) and is purified from the dried leaves or flower clusters of *Artemisia annua* (https://www.britannica.com). In 1972, the active ingredient was filtered and first named qinghaosu (essence of qinghao), and then later renamed artemisinin (Meshnick, 2002).

Artemisinin is showed efficacy against all the genus *Plasmodium* that causes malaria. The drug is extremely useful in the treatment of infections involving chloroquine-resistant parasites and multidrug-resistant *P. falciparum*, which is the deadliest of the malaria protozoans (https://www.britannica.com). Artemisinin-based combination therapies are now approved by the World Health Organization (WHO) as first-line treatment of uncomplicated falciparum malaria in all areas in which malaria is endemic (WHO, 2006).

Artemisinin derivatives were used in China by the 1980s. Western interest in these agents began to grow as multidrug resistant *Plasmodium falciparum* strains began to spread, especially in Southeast Asia. By the early 1990s, artemisinin derivatives were being widely used in Thailand, Burma and Vietnam (McIntosh and Olliaro, 1998). Replacing ineffective, failing treatments (chloroquine and sulfadoxine– pyrimethamine) with artemisinin-based combination therapies has reduced the morbidity and mortality associated with malaria. Artemisinin resistance would be disastrous for global malaria control (Ramani, 2016).

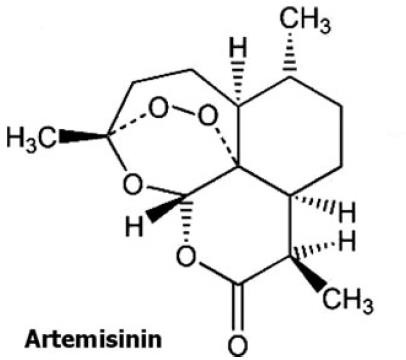


Fig 2: Chemical Structure of Artemisinin

Artemisinin and its derivatives display a very important new class of antimalarials; they are becoming more and more commonly used throughout the world. Artesunate, artemether, arteether, and dihydroartemisinin are the most significant artemisinin derivatives. The artemisinin derivatives act quickly and are eradicated quickly. Their rapid onset makes them especially effective against malaria (Meshnick, 2002). Artemisinin and its derivatives were used as monotherapies, but it became gradually accepted that antimalarials, like antituberculosis and antiretroviral drugs, should be used in combination. Artelinate, a semi-synthetic artemisinin derivative, was created, but it was never used for anything more than animal research. Another artemisone is now being created. Artiflene, a structurally dissimilar peroxide and proved an effective antimalarial in clinical trials, but it was eventually abandoned because of high production costs and lack of evident advantages over the artemisinin derivatives (White, 2008).

Artemisinin targets *Plasmodium* organisms in the schizont stage of development. Schizonts, which develop from sporozoites—the form of parasite transmitted to humans in the saliva of *Anopheles* [mosquitoes](https://www.britannica.com/animal/mosquito-insect) contain insoluble [iron](https://www.britannica.com/science/iron-chemical-element) called hemozoin. Hemozoin is formed within schizonts as they feed on haemoglobin in the cytoplasm of human red blood cells. Artemisinin involves a peroxide group that reacts with hemozoin, and this reaction is suspected to result in the production of radicals that attack parasite proteins, thereby killing the organisms (<https://www.britannica.com>).

Artemisinin probably administered orally, intramuscularly, or as a suppository. The drug reaches pea[k plasma](https://www.britannica.com/science/plasma-biology) levels within hours after administration and acts quickly, significantly reducing malaria parasite burden in the first few days of treatment. Artesunate is unique among the artemisinin-derived agents. It enables the drug to take immediate effect. Artesunate is used in the treatment of [cerebral](https://www.merriam-webster.com/dictionary/cerebral) malaria, which is characterized by the rapid spread of parasites to the [brain](https://www.britannica.com/science/brain) and by death within 72 hours if left untreated. Artemisinin appears to have few side effects in humans (<https://www.britannica.com>).

**Chloroquine**

*Plasmodium falciparum* malaria is a vital health problem, particularly in sub-Saharan Africa. Chloroquine was the preferred antimalarial medication in the second half of the 20th century because it was secure, affordable, and extremely effective against susceptible malaria parasites. Since Southeast Asia and South America experienced the emergence of chloroquine resistance more than 40 years ago, these regions have generally stopped using chloroquine as a falciparum malaria treatment (Djimdé et al. 2001). Chloroquine was close to the ideal antimalarial drug and was used for decades due to its high efficacy against all species of malaria parasites and its high tolerance (Krettli et al. 2001). Increasing rates of chloroquine resistance contribute to the rising morbidity and mortality from malaria in Africa. Given the lack of affordable alternatives, chloroquine remains the first-line antimalarial agent in most African countries.

The most important of these drugs was chloroquine, which was extensively used, especially beginning in the 1940s (Yakoub et al. 1995). With heavy use, chloroquine resistance developed slowly. Resistance of Plasmodium falciparum to chloroquine was seen in parts of Southeast Asia and South America by the late 1950s, and was widespread in almost all areas with falciparum malaria by the 1980s (Achan, 2011).

The wide distribution and ready availability of chloroquine nevertheless made considerable inroads against the morbidity and mortality from the disease, especially in villages of sub-Saharan Africa, where malaria parasites each year infect nearly every child. The two parasite species that cause the majority of human malaria infections, *Plasmodium falciparum* and *Plasmodium vivax*, have developed chloroquine resistance as a result of chloroquine's enormous success and extensive use over the years (Wellems and Plowe, 2001). Chloroquine’s efficacy is thought to lie in its ability to break hematin detoxification in malaria parasites as they grow within their host’s red blood cells (Chou,1980; Dorn, 1998). Hematin is discharged in large amounts as the parasite consumes and digests hemoglobin in its digestive food vacuole. Hematin is detoxified by polymerization into innocuous crystals of hemozoin pigment and perhaps also by a glutathione-mediated process of destruction (Zhang et al. 1999). Chloroquine binds with hematin in its µ-oxodimer form and also adsorbs to the growing faces of the hemozoin crystals (Dorn et al. 1998; Sullivan et al. 1996; Pagola et al. 2000), disrupting detoxification and poisoning the parasite. Chloroquine-resistant *P. falciparum* survives by decreasing accumulation of the drug in the digestive vacuole (Verdier et al. 1985); however, the mechanism by which this occurs has not been determined.

# Table 1: Information on anti-malarial plants, their families, used plant parts, IC50 Value, target organism from different countries with references

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Country** | **Family** | **Plant name** | **Used plant**  **parts** | **IC50**  **value** | **Target organism** | **References** |
| Angola | Annonaceae | *Hexalobus crispiflous* | Stem bark | 2.0  µg/mL | in vitro activity against *P. falciparm* | Boyom et al. 2003 |
| *Pachypodantium confine* | Stem bark | 16.6  µg/mL |
| Euphorbiaceae | *Euphorbia hirata* | Whole plant | 6  µg/mL | In vitro activity against *P. falciparm* | Tona et al., 2016 |
| *Bridelia ferruginea* | Bark | 400  mg/kg | In vivo in mice *P. berghei* | Kolawole and Adesoye, 2010 |
| Benin | Asteraceae | *Acanthospermum hispidum* | Aerial parts | 7.5  µg/mL | Dichlorometh ane extracts In vitro activity against *P. falciparum* | Bero et al., 2009 |
| Rubiaceae | *Keetia leucantha* | Leaves | 13.8  µg/mL |
| Twigs | 11.3  µg/mL |
| Polygalace ae | *Carpolobia lutea* | Aerial Parts | 19.4  µg/mL |
| Loganiace ae | *Strychnos spinosa* | Leaves | 15.6  µg/mL |
| Burkina Faso | Asteraceae | *Dicoma tomentosa* | Whole plant | 7.90  µg/mL | Dichlorometh ane extracts In vitro activity against *P. falciparum* | Jansen et al.  2010 |
| Clusiaceae | *Psorospermum senegalense* | Leaves | 10.03  µg/mL |
| Rubiaceae | *Gardenia sokotensis* | Leaves | 14.01  µg/mL |
| Euphorbia ceae | *Achromanes difformis* | Leaves | 7.0  µg/mL | In vitro activity against *P. falciparum* | Bidla et al. 2004 |
| Cleomaceae | *Cleome rutidosperma* | Leaves | 9.2  µg/mL |
| Cameroon | Annonaceae | *Annona muricata* | Leaves | 20  µg/mL | In vitro activity against *P. falciparum* | Titanji et al., 2008 |
| *Hexalobus crispiflorus* | Essential oil | 2  µg/mL | In vitro activity against *P.*  *falciparum* |
| Apocynac eae | *Picralia nitida* | Roots | 0.2  µg/mL | Dichlorometh ane extracts In vitro activity against *P.*  *falciparum* |
|  |  | Stem bark | 0.5  µg/mL |
|  |  | Fruit rind | 1.5  µg/mL | Aqueous extracts. In vitro activity against *P.*  *falciparum* |
| Euphorbia ceae | *Alchornea cordifolia* | Leaves | 0.2- 0.5  µg/mL | In vivo in mice *P*. *berghei* |
| Lamiaceae | *Holshundia opposite* | Root bark | 5.6  µg/mL | Hexane extracts. In vitro activity against *P.*  *falciparum* |
| Poaceae | *Cymbopogon citratus* | Leaves | 6- 9.5  µg/mL | In vivo in mice *P. berghei* |
| Ghana | Poaceae | *Bambusa vulgaris* | Leaves | 0.49µg/ mL | Ethyl acetate extracts In vitro activity against *P.*  *falciparum* | Komlaga et al. 2016 |
| Phyllantha ceae | *Phyllanthus fraternus* | Whole plant | 0.44  µg/mL | Methanol extracts In vitro activity against *P. falciparum* |
| Legumino sae | *Senna siamea* | Root | 22.89  µg/mL |
| Lamiaceae | *Tectona grandis* | Leaves | 0.92  µg/mL |
| Combretac  eae | *Terminalia*  *ivorensis* | Leaves | 5.70  µg/mL |
| India | Lamiaceae | *Ocimum sanctum* | Leave | 35.58  µg/mL | Ethanol extracts In vitro activity against *P. falciparum* | Inbaneson et al. 2012 |
| *Ocimum canum* | 53.50  µg/mL |
| *Ocimum basilicum* | 43.81  µg/mL |
| Apocynaceae | *Catharanthus*  *roseus* | Leaves | 49.63  µg/mL | Ethanol extracts In vitro activity against *P. falciparum* | Ravikumar et al. 2012 |
| *Thevetia*  *peruviana* | Seeds | 58.83  µg/mL |
| Cucurbitac eae | *Coccinea grandis* | Leaves | 69.00  µg/mL |
| Fabaceae | *Prosopis juliflora* | Leaves,  bark and flower | >100  µg/mL |
| *Acacia nilotica* | Bark | 59.80  µg/mL |
| Meliaceae | *Azadirachta indica* | Bark | 29.77  µg/mL |
| Rubiaceae | *Morinda pubescns* | Leaves | 62.70  µg/mL |
| Asteraceae | *Parthenium hysterophous* | Whole plant | 6 µg/mL | Ethanol extracts In vitro activity against *P.falciparm* | Singh et al.  2014 |
| Apocynaceae | *Holarrhena pubescens* | Leaves | 7 µg/mL |
| Myrtaceae | *Corymbia citriodora* | Leaves | 5 µg/mL |
| Annonaceae | *Annona squamosa* | Leaves | 2.1µg/mL |
| Apocynaceae | *Wrightia arborea* | Leaves | 25  µg/mL | In vitro activity against *P. falciparum* | Simonsen et al. 2001 |
| Boraginaceae | *Heliotropium europaeum* | Root | 43  µg/mL |
| Stem | 35  µg/mL |
| Flacourtiaceae | *Casearia elliptica* | Leaves | 9  µg/mL |
| Lythraceae | *Ammannia multiflora* | Root | 18  µg/mL |
| Mimosaceae | *Prosopis juliflora* | Fruit and Flower | 24  µg/mL |
| Moraceae | *Ficus benghalesis* | Stem | 26  µg/mL |
| Kenya | Euphorbiaceae | *Phyllanthus reticulats* | Leaves | 10.0  µg/mL | In vitro activity against *P. falciparum* | Omulokoli et al. 1997 |
| *Suregada zanzibariesis* | 1.5  µg/mL |
| Rubiaceae | *Pentas longiflora* | Roots | 20.0  µg/mL | Methanol extracts In vitro activity against *P. falciparum* | Wanyoie et al. 2004 |
| Amaranthaceae | *Cyathula polycephla* | Roots | 47.2  µg/mL |
| *Cyathula cylindrial* | Leaves | 49.0  µg/mL |
| Mozambique | Euphorbiaceae | *Bridelia cathartca* | Roots, stem | 0.05  µg/mL | Ethanol and aqueous extract In vitro activity against *P.*  *falciparum* | Silva et al.  2011 |
| Cucurbitaceae | *Momordica balsamina* | Aerial parts | 4.6 µM | In vitro activity against *P.*  *falciparum* |
| Fabaceae | *Senna occidentais* | Leaves | 19.3  µg/mL | Hexane extract In vitro activity against *P.*  *falciparum* |
| *Senna abbreviata* | Leaves | 111.0  mg/kg/ wt | In vivo in mice *P. berghei* |
| Rubiaceae | *Crossopteryx febrifuga* | Stem bark | >10  µg/mL | Methanol extract In vitro activity against *P.*  *falciparum* |  |
| Peru | Menispermacae | *Abuta rufescens* | Bark | 2.3  µg/mL | Dichlorometh ane extract In vitro activity against *P. falciparum* | Roumy et al. 2007 |
| Leaves | 7.9  µg/mL |
| Solanaceae | *Cyphomandra hartwegii* | Leaves | 10.0  µg/mL |
| Lacistemaceae | *Lacistema aggregatm* | Bark | 7.4  µg/mL |
| Sierra Leone | Menispermaceae | *Triclisia patens* | Woodand bark | 8  µg/mL | Ethanol extracts In vitro activity against *P. falciparum* | Marshall et al. 1990 |
| Apocynaceae | *Landolphia dulcis* | Wood | 31  µg/mL |
| Annonaceae | *Xylopia aethiopca* | Wood | 31  µg/mL |
| Amaranthaceae | *Cyathula prostrata* | Leaves | 50  µg/mL |
| São Tomé and Príncipe | Asteraceae | *Ageratum conyzoides* | Aerial parts and leaves | 55  µg/mL | Dichlorometh ane fraction In vitro activity against *P.*  *falciparum* | Silva et al.  2011 |
| *Struchium sparganophorm* | Leaves | < 10  µg/mL | Petroleum ether fraction In vitro activity against *P.*  *falciparum* |
| *Tithonia diversifolia* | Aerial parts | 15  µg/mL | Ethanol extract In vitro activity  against *P.*  *falciparum* |
| Meliaceae | *Cedrela odorata* | Wood, leavs, stem barks | 1.37  µg/mL | Ethanol extract In vitro activity  against *P. falciparm* |
| Solanaceae | *Cestrum laevigatum* | Leaves | 50  µg/mL | Dichlorometh ane fraction In vitro activity against *P. falciparum* |
| Uganda | Asteraceae | *Microglossa pyrifolia* | Leaves | 1.24  µg/mL | Ethyl acetate extract against *P.*  *falciparum* | Adia et al.  2015 |
| Lamiaceae | *Clerodendrm rotundifolium* | Leaves | 1.98  µg/mL | Aqueous extract against *P.*  *falciparum* |
| Yamen | Euphorbiaceae | *Acalypha*  *fruticosa* | Leaves | 1.6  µg/mL | Aqueous extract against *P. falciparum* | Alshawsh et al. 2009 |
| Meliaceae | *Azadirachta*  *indica* | Leaves | 2.0  µg/mL |
| Cucurbitaceae | *Dendrosicyos*  *socotrana* | Leaves | 2.3  µg/mL |
| Burseraceae | *Boswellia elongate* | Bark | 26.7  µg/mL | Methanol extract against *P.*  *falciparum* |

**Conclusion**

Malaria is a vital global public health problem, and the alarming spread of drug resistance and limited number of effective drugs now available. The utilisation of conventional herbal remedies is one potential source for such economical therapies. Since ancient time traditional herbal medicinal plants have been a part of human life. The therapeutic success of two important plant-derived compounds, quinine and artemisinin, against malaria has encouraged researchers to search new antimalarial drugs from plants. Worldwide over 1000 plant species have been used as a source of traditional antimalarial phytotherapy for many centuries. Researchers have been searching for new plants in different countries which is effective for malarial parasite. Different plants parts such as leaves, roots, stem, bark, flower, fruits aerial parts are being used. Sometimes combination of two or more plants from different families have been used. In different countries different plant parts extract derived herbal remedies used in control of malaria which are affordable, safer and effective than any chemical compound. From the perspective of side effects associated with synthetic drugs, herbal drugs represent a better cure of human diseases. Further exploration of the medicinal plants discussed in this review may provide leads to development of new drugs and better approaches for treatment of malarial disease.

**References**

Achan J, Talisuna AO, Erhart A, Yeka A, Tibenderana JK, Baliraine FN, Rosenthal P J, D' Alessandro U. (2011). Quinine, an old anti-malarial drug in a modern world: role in the treatment of malaria. Malaria journal, 10 (1): 1-12.10.1186/1475-2875-10-144.

Adia MM, Emami SN, Byamukamaa R, Faye I, Karlson AKB. (2015). Antiplasmodial activity and phytochemical analysis of extracts from selected Ugandan medicinal plants. Journal of Ethonopharmacology, 186: 14-19.

Akinmoladun AC, Ibukun EO, Afor E, Obuotor EM, & Farombi EO. (2007). Phytochemical constituent and antioxidant activity of extract from the leaves of *Ocimum gratissimum*. Scientific Research and Essays, 2 (5):163-166.https://doi. org/10.5897/SRE. 9000731.

Alshawsh MA, Mothana RA, Al-Shamahy HA, Alsllami, SF, & Lindequist U. (2009). Assessment of antimalarial activity against *Plasmodium falciparum* and phytochemical screening of some Yemeni medicinal plants. Evidence-based Complementary and alternative Medicine, 6 (4) : 453-[456.https://doi.org/10.1093/ecam/nem148](https://doi.org/10.1093/ecam/nem148).

Bero J, Ganfon H, Jonville MC, Frédérich M, Gbaguidi F, DeMol P, Moudachirou M, Leclercq JQ. (2009). In vitro antiplasmodial activity of plants used in Benin in traditional medicine to treat malaria. Journal of Ethnopharmacology, 122 (3) : 439-444. 10.1016/j.jep.2009.02.004.

Bidla G, Titanji VPK, Joko B, El-Ghazali G, Bolad A, Berzins K. (2004). Antiplasmodial activity of seven plants used in African folk medicine. Indian J Pharmacol, 36 : 244-250.

Boyom FF, Ngouana V, Zollo PHA, Menut C, Bessiere JM, Gut J, & Rosenthal PJ. (2003). Composition and anti-plasmodial activities of essential oils from some Cameroonian medicinal plants. Phytochemistry, 64 (7) : 1269 - [1275. https://doi.org/10.1016/j.phytochem.2003.08.004](https://d.docs.live.net/92e3f3bb1a7eeacb/Documents/Desktop/1275.%20https:/doi.org/10.1016/j.phytochem.2003.08.004).

Carmargo LM, de Oliveira S, Basano S, & Garcia CR. (2009). Antimalarials and the fight against malaria in Brazil. Therapeutics and Clinical Risk Management, 5: 311 - 317. [doi.org/10.2147/tcrm.s4571.](https://dx.doi.org/10.2147%2Ftcrm.s4571)

Chou AC, Chevli R, Fitch CD. (1980). Ferriprotoporphyrin IX fulfills the criteria for identification as the chloroquine receptor of malaria parasites. Biochemistry, 19 (8) :1543 – 1549. doi:10.1021/bi00549a600.

Djimdé A, Doumbo OK, Cortese JF, Kayentao K, Doumbo S, Diourté Y, Dicko A, Su X-Z, Nomura T, Fidock DA, Wellems TE, Plowe, CV. (2001). A molecular marker for chloroquine-resistant *falciparum* malaria. New England journal of medicine, 344 (4): 257-263. 10.1056/NEJM200101253440403.

Dorn A, Vippagunta SR, Matile H, Jaquet C, Vennerstrom JL, Ridley RG. (1998). An assessment of drug-haematin binding as a mechanism for inhibition of haematin polymerisation by quinoline antimalarials. Biochemical pharmacology, 55 (6): 727-736. [doi.org/10.1016/S0006-2952(97)00510-8.](https://doi.org/10.1016/S0006-2952(97)00510-8)

Farooq U & Mahajan RC. (2004). Drug resistance in malaria. Journal of vector borne diseases, 41(3 - 4): 45-53.

Ghosh A, Chowdhury N, Chandra G. (2012). Plant extracts as potential mosquito larvicides. The Indian journal of medical research, 135 (5) : 581-598.

https:/[/www.botanic.jp/pl](http://www.botanic.jp/plants-aa/akakin_2.jpg)a[nts-aa/akakin\_2.jpg](http://www.botanic.jp/plants-aa/akakin_2.jpg)

<https://www.britannica.com/science/artemisinin>

<https://www.britannica.com/science/quinine> <https://www.cdc.gov/malaria/about/index.html>

<https://www.mayoclinic.org/diseases-conditions/malaria/symptoms-causes/syc-20351184> https:/[/www.ncbi.nlm.nih.gov/pm](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3121651/#%3A~%3Atext%3DQuinine%20and%20other)c

[https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/plant-extract) [science/plant-extract](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/plant-extract)

<https://www.who.int/news-room/fact-sheets/detail/malaria>.

Igweh JC. (2012). Biology of Malaria Parasites. In: Malarial Parasite, Ed; Okwa O. Intech Publisher: 11-36.doi: 10.5772/34260.

Inbaneson SJ, Sundaram R, Suganthi P. (2012). In vitro antiplasmodial effect of ethanolic extracts of traditional medicinal plant Ocimum species against Plasmodium falciparum. Asian Pacific Journal of tropical medicine, 5 (2):103- 106. doi.org/10.1016/S1995-7645(12) 60004-2.

Jansen O, Angenot L, Tits M, Nicolas JP, De Mol P, Nikiéma JB, Frederich M. (2010). Evaluation of 13 selected medicinal plants from Burkina Faso for their antiplasmodial properties. Journal of Ethnopharmacology, 130 (1) : 143- 150.doi.org/10.1016/j.jep.2010.04.032.

Karlsson KK, Hellgren U, Alván G, & Rombo L. (1990). Audiometry as a possible indicator of quinine plasma concentration during treatment of malaria. Transactions of the Royal Society of Tropical Medicine and Hygiene, 84 (6) : 765- 767.https://doi.org/10.1016/0035-9203(90)90069-Q.

Karunamoorthi K, & Ilango K. (2010). Larvicidal activity of Cymbopogon citratus. European review for medical and pharmacological sciences, 14 (1) : 57-62.

Karunamoorthi, K. and Sabesan, S. (2013) Insecticide Resistance in Insect Vectors of Disease with Special Reference to Mosquitoes: A Potential Threat to Global Public Health. Health Scope, 2 : 4-18. <http://dx.doi.org/10.5812/jhs.9840>.

Kolawole OM, & Adesoye AA. (2010). Evaluation of the antimalarial activity of Bridelia ferruginea benth bark. Can J Pure Appl Sci, 4:1039-1044.

Komlaga G, Cojean S, Dickson RA, Beniddir MA, Albouz SS, Mensah MLA, Agyare C, Champy P, Loiseau PM. (2016). Antiplasmodial activity of selected medicinal plants used to treat malaria in Ghana. Parasitology Research, 115 (8) : 3185-3195. 10.1007/s00436-016-5080-8.

Koudouvo K, Karou DS, Kokou K, Essien K, Aklikokou K, Glitho IA, Simpore J, Sanogo R, De Souza C, Gbeassor M. (2011). An ethnobotanical study of antimalarial plants in Togo Maritime Region. Journal of ethnopharmacology, 134 (1) :183-190. doi.org/10.1016/j.jep.2010.12.011.

Krettli AU, Andrade-Neto V F, Brandão MD. GL, Ferrari W. (2001). The search for new antimalarial drugs from plants used to treat fever and malaria or plants ramdomly selected: a review. Memórias do Instituto Oswaldo Cruz, 96 (8):1033-1042.

Marshall SJ, Russell PF, Phillipson JD, Kirby GC, Warhurst DC, Wright CW. (1990). Antiplasmodial and antiamoebic activities of medicinal plants from Sierra Leone. Phytotherapy Research, 14 (5) : 356-358.doi.org/10.1002/1099- 1573.

McIntosh H, Olliaro P. (1998). Artemisinin derivatives for treating severe malaria. Cochrane Database of Systematic Reviews, 3. doi: 10.1002/14651858.CD000527.

Meshnick SR. (2002). Artemisinin: mechanisms of action, resistance and toxicity. International journal for parasitology, 32 (13):1655-1660. doi.org/10.1016/S0020- 7519(02)00194-7.

Muregi FW & Ishih A. (2010). Next-generation antimalarial drugs: hybrid molecules as a new strategy in drug design, Drug Dev Res ; 71(1) : 20–32. doi: 10.1002/ddr.20345.

Nguta JM, Mbaria JM, Gakuya DW, Gathumbi PK, Kiama SG. (2010). Antimalarial herbal remedies of Msambweni, Kenya. Journal of Ethnopharmacology, 128 (2) : 424- 432. doi.org/10.1016/j.jep.2010.01.033.

Olliaro PL & Yuthavong Y. (1999). An overview of chemotherapeutic targets for antimalarial drugdiscovery. Pharmacology & therapeutics, 81 (2) : 91-110. doi.org/10.1016/S0163-7258(98)00036-9.

Omulokoli E, Khan B, Chhabra SC. (1997). Antiplasmodial activity of four Kenyan medicinal plants. Journal of ethnopharmacology, 56 (2) : 133- 137. doi.org/10.1016/S0378-8741(97)01521-3.

Pagola S, Stephens PW, Bohle DS, Kosar AD, Madsen SK. (2000). The structure of malaria pigment β-haematin. Nature, 404 (6775) : 307-310. doi.org/10.1038/35005132.

Paniker CJ. (2018). Paniker's Textbook of Medical Parasitology. JP Medical Ltd : 66-67.ISBN: 978-93-5270-186-5.

Rajakumar G, & Rahuman AA. (2011). Larvicidal activity of synthesized silver nanoparticles using Eclipta prostrata leaf extract against filariasis and malaria vectors. Acta tropica, 118 (3):196-203.

Ramani S, Parija SC, Mandal J, Hamide A, Bhat V. (2016). Detection of chloroquine and artemisinin resistance molecular markers in Plasmodium falciparum: A hospital-based study. Tropical Parasitology, 6: 69-77. 10.4103/2229-5070.175110.

Ravikumar S, Inbaneson SJ, Suganthi P. (2012). In vitro antiplasmodial activity of ethanolic extracts of South Indian medicinal plants against Plasmodium falciparum. Asian Pacific Journal of Tropical Disease, 2 (3):180-183. doi.org/10.1016/S2222- 1808(12)60043-7.

Roumy V, Garcia-Pizango G, Gutierrez-Choquevilca AL, Ruiz L, Jullian V, Winterton P, Fabre N, Moulis C, Valentin A. (2007). Amazonian plants from Peru used by Quechua and Mestizo to treat malaria with evaluation of their activity. Journal of ethnopharmacology, 112 (3) : 482-489. doi.org/10.1016/j.jep.2007.04.009.

Schwikkard S & Van HFR. (2006). Antimalarial activity of plant metabolites. Nat Prod Rep, 19 : 675 – 692.

Shaikh JR, & Patil MK. (2020). Qualitative tests for preliminary phytochemical screening: An overview. International Journal of Chemical Studies, 8 (2) : 603- 608. doi.org/10.22271/chemi.2020.v8.i2i.8834.

Silva JRDA, Ramos ADS, Machado M, de Moura DF, Neto Z, Canto-Cavalheiro MM, Figueiredo P, do Rosário VE, Amaral ACF, Lopes D. (2011). A review of antimalarial plants used in traditional medicine in communities in Portuguese-speaking countries: Brazil, Mozambique, Cape Verde, Guinea-Bissau, São Tomé and Príncipe and Angola. Memorias do Instituto Oswaldo Cruz, 106:142-158. doi: 10.1590/s0074-02762011000900019.

Simonsen HT, Nordskjold JB, Smitt UW, Nyman U, Palpu P, Joshi P, Varughese G. (2001). In vitro screening of Indian medicinal plants for antiplasmodial activity. Journal of ethnopharmacology, 74: 195-204. doi.org/10.1016/S0378-8741(00)00369-X.

Singh N, Kaushik NK, Mohanakrishnan D, Tiwari SK, Sahal D. (2014). Antiplasmodial activity of medicinal plants from Chhotanagpur plateau, Jharkhand, India. Journal of ethnopharmacology, 165:152-162. doi.org/10.1016/j.jep.2015.02.038.

Sullivan DJ, Gluzman IY, Russell DG, Goldberg DE. (1996). On the molecular mechanism of chloroquine's antimalarial action. Proceedings of the National Academy of Sciences, 93 (21): 11865-11870. doi.org/10.1073/pnas.93.21.11865.

Thomson, J. G. 1933. Immunity in malaria. Trans R. Soc. Trop Med. Hyg. 26: 483-514.

Titanji VP, Zofou D, Ngemenya MN. (2008). The antimalarial potential of medicinal plants used for the treatment of malaria in Cameroonian folk medicine. African journal of traditional, complementary, and alternative medicines, 5 (3): 302.

Tona L, Ngimbi NP, Tsakala M, Mesia K, Cimanga K, Apers S,De Bruyne T, Pieters L, Totte J, &

Tu Y. (2016). Artemisinin—a gift from traditional Chinese medicine to the world (Nobel lecture). Angewandte Chemie International Edition, 55(35):10210-10226. doi.org/10.1002/anie.201601967.

Tuteja R. (2007). Malaria− an overview. The FEBS journal, 274 (18): 4670-4679.

Tu X, Manohar S, Jagota A, Zheng M. (2009). DNA sequence motifs for structure-specific recognition and separation of carbon nanotubes, 460; doi:10.1038/nature08116.

Verdier F, Le Bras J, Clavier F, Hatin I., Blayo, M. C. (1985). Chloroquine uptake by Plasmodium falciparum infected human erythrocytes during in vitro culture and its relationship to chloroquine resistance. Antimicrobial Agents and Chemotherapy, 27(4) : 561-564. doi.org/10.1128/AAC.27.4.561.

Wanyoike GN, Chhabra SC, Lang’at-Thoruwa CC, Omar SA. (2004). Brine shrimp toxicity and antiplasmodial activity of five Kenyan medicinal plants. Journal of ethnopharmacology. 90 :129-133. 10.1016/j.jep.2003.09.047.

Wellems TE, & Plowe CV. (2001). Chloroquine-resistant malaria. The Journal of infectious diseases, 184 (6) : 770-776. doi.org/10.1086/322858.

White NJ (1996). The treatment of malaria. N Engl J Med, 335 (11) : 800-806.

White NJ. (2008). Qinghaosu (artemisinin): the price of success. Science. doi.org/10.1126/science.1155165.

WHO guidelines for the treatment of malaria. Geneva: World Health Organization, 2006.

WHO: Malaria treatment guidelines. 2010.

Wright CW, & Phillipson JD. (1990). Natural products and the development of selective antiprotozoal drugs. Phytotherapy Research, 4(4):127-139. doi.org/10.1002/ptr.2650040402.

Yakoub AdenAbdi OE GL, Orjan E, & Hellgren U. (1995). Handbook of Drugs for Tropical Parasitic Infections.

Zhang J, Krugliak M, Ginsburg H. (1999). The fate of ferriprotorphyrin IX in malaria infected erythrocytes in conjunction with the mode of action of antimalarial drugs. Molecular and biochemical parasitology, 99 (1): 129-141.doi.org/10.1016/S0166-6851(99)0000.