

Drug Resistant Malarial Parasite Versus Natural Plant Alkaloids

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ABSTRACT

Malaria is a significant public health concern in developed countries. Every year, the epidemic destroys a vast amount of citizens and has an economic impact on many nations. Resistance of the causative factor, the plasmodium parasite, to current treatments such as mefloquine, artemisinin-based combination therapy (ACT), and chloroquine is a major problem in control and prevention of malaria across the world. This necessitates a hasty search for new compounds, especially those derived from natural resources like medicinal plants. Plants, especially used in Ayurveda, may offer bioactive compounds and lead structures that can be used to produce modified variants with improved activity and/or lower toxicity. Alkaloids have been identified as essential phytoconstituents with intriguing biological properties over time. Quinine, an alkaloid isolated from the Cinchona flower, was the first effective antimalarial compound. The impact of different plant-derived alkaloids on the malarial parasite, which has established resistance to existing synthetic drugs due to concurrent usage, is the subject of this review.

Keywords: Alkaloids, Antimalarial, Malaria, Malarial parasite, Quinine, Plasmodium, Phytoconstituents.

INTRODUCTION

Malaria is the most common insect-borne illness, afflicting roughly half of human humanity and being widespread in over a hundred countries [1]. Malaria is an infectious vector-borne bacterial disease triggered by a protozoan parasite that causes substantial morbidity and mortality in developed countries. Malaria is the most prevalent primary health issue in tropical and emerging countries in Southeast Asia and Sub-Saharan Africa, claiming the lives of one to two million people per year and infecting an estimated 300-500 million people. Malaria is caused mainly through female Anopheles mosquito bites. *Plasmodium falciparum* causes the most extreme type of malaria i.e., cerebral malaria. This disorder has extraordinarily high fatality rates, and it is believed that about 50 percent of human civilization is at danger [2]. Due to lack of an appropriate vaccine, drug therapy has been the major focus of malaria prevention. Due to the proliferation of drug-resistant parasites, the effectiveness of common antimalarial drugs including chloroquine is slowly dwindling [3]. Although a variety of chemotherapeutic efforts to help with malaria eradication, none have been successful, owing to the advent of drug resistant types that have rendered quinine, chloroquine, mefloquine, and primaquine useless in the overwhelming majority of malaria-endemic areas [4].

The usage of conventional herbal medicines is one hopeful avenue for modern inexpensive malaria drugs. Medicinal plants have remained a significant source of new medicines, despite pharmaceutical industries' recent successes in logical drug design and synthetic chemistry techniques. The indigenous community are using a variety of herbals to cure a variety of diseases, including malaria. Ethno-medicinal and ethnobotanical research also opened up a world of possibilities for drug discovery and synthesis [5]. Since earlier civilizations, various cultural practices have linked use of plant species as therapeutic herbs to treat particular ailments. This medical knowledge is handed on over the centuries all across the globe. Orthodox healers around the world use a variety of herbal plants to cure malaria. Antimalarial plants have been described in a wide variety of plant types. Several plant varieties have been described as antimalarial medicinal plants by ethnopharmacological and ethnobotanical research. This analysis aims to provide a concise overview of a variety of alkaloids derived from medicinal plants that can be used to cure malaria when synthetic medicines are no longer effective.

Malarial vectors and parasite

Female anopheles mosquito is also known as malaria vectors. The causative agent of malaria is a protozoal *Plasmodium* parasite. The tropical climate offers an ideal breeding environment for a wide variety of mosquito species. In India, there are 61 species of anopheles in the subgenera *Anopheles* and *Celia*, with the prospect of further being discovered when new species are discovered under various classes or complexes [6]. *Plasmodium malariae*, *Plasmodium falciparum*, *Plasmodium ovale*, and *Plasmodium vivax*, are the four parasite organisms that induce malaria in humans; amongst them, *Plasmodium vivax* and *Plasmodium falciparum* are the most prevalent scientifically, but *P. falciparum* is the deadliest, causing severe complications such as cerebral malaria. In India, nine anopheline vectors spread three Plasmodial species: *Plasmodium falciparum*, *Plasmodium vivax*, and *Plasmodium malariae*.

Table 1 – Distribution of different malarial vectors in India [7]

No.	Vectors	Distribution
1.	<i>Anopheles culicifacies</i>	Rural areas
2.	<i>Anopheles fluviatilis</i>	Hilly areas and foothill areas
3.	<i>Anopheles stephensi</i>	Urban area
4.	<i>Anopheles minimus</i>	Northeastern states
5.	<i>Anopheles nivipes</i>	Northeastern states
6.	<i>Anopheles dirus</i>	Northeastern states
7.	<i>Anopheles sundanicus</i>	Andaman and nicobar island
8.	<i>Anopheles annularis</i>	Jharkhand, orissa, west bengal
9.	<i>Anopheles varuna</i>	Wide distribution

Life cycle of malarial parasite

Sporozoites, the infective level ingested into subcutaneous capillaries with saliva, join hepatocytes in mosquito-borne transmission. Each sporozoite starts an asexual replication process within the hepatocytes, leading to the development of a schizont comprising thousands of merozoites. Merozoites are released into the bloodstream as mature schizonts are ruptured. In *P. falciparum*, the hepatic schizogony lasts around 5.5 days. *P. vivax* infections may cause some of the parasite to stay dormant in the form of hypnozoites in liver cells for months or even years. Since only a small amount of liver cells are compromised, hepatic schizogony is asymptomatic. Merozoites quickly enter red cells and invade them, triggering an asexual multiplication mechanism (erythrocytic schizogony) [8].

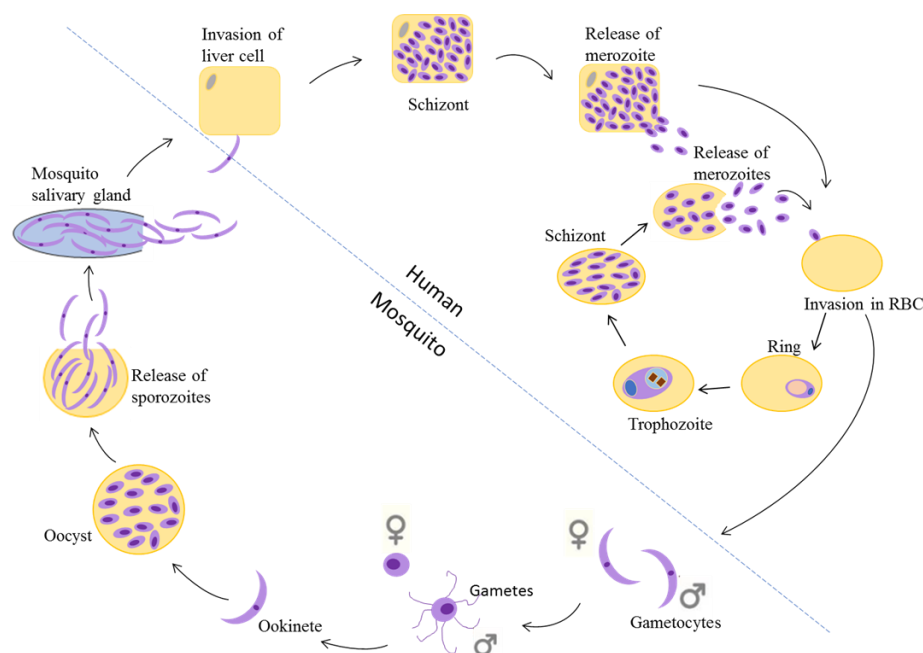


Fig. 1 – Depicting life cycle of malarial parasite

Symptoms of malaria

Severe malaria is described by WHO as unrousable coma or impaired consciousness, prostration (i.e., severe weakness in which the patient becomes unable to move or walk and needs support), several convulsions (>2 episodes in 24 hr.), failure to feed, respiratory distress (acidotic breathing), deep breathing, shock or circulatory collapse, with systolic B.P < 70 mm Hg in adults, hemoglobinuria, vital organ dysfunction, clinical jaundice, pulmonary oedema (radiological) and abnormal spontaneous bleeding. Hematological investigation demonstrated hypoglycemia (blood glucose < 40 mg/dl), metabolic acidosis (plasma bicarbonate < 15 mmol/l), hemoglobinuria, severe normocytic anemia (packed cell volume < 15%, Hb < 5 g/dl), hyperparasitaemia (> 5% or 250,000/μl in areas of high stable malaria transmission intensity or > 2% or 100,000/μl in low intensity transmission areas), jaundice (serum bilirubin > 3mg/dl), renal impairment (serum creatinine > 3mg/dl) and hyperlactatemia (lactate > 5 mmol/l) [9].

Prevalence of malaria in India

Every year, 1.5–2 million malaria cases are recorded in India, with *P. vivax* (Pv) and *P. falciparum* (Pf) dividing the cases equally [10]. According to the Government of India's annual report, *P. falciparum* was responsible for 38.6% of all cases throughout the world [11]. India is very often assumed to be a *P. vivax*-dominated nation in the global malaria study world. There could be over 1 million reports of *P. falciparum* in India, compared to over 700,000 cases of *P. vivax*. In various parts of India, and even inside states, the relative ratio of *P. vivax* to *P. falciparum* differs greatly. The majority of *P. falciparum* infections are found in the northern hilly districts, Indo-Gangetic plains, southern Tamil Nadu, and northwestern India with the remainder being *P. vivax*. Ancient ethnic tribes live mostly in woodland habitats (30–90 percent *P. falciparum*) in states of hyperendemic malaria and the largest ratio of *P. falciparum*. Nearby fringe areas may be meso to super endemic, but *P. falciparum* still predominates (90 percent or even more) [12]. In other parts of the state, *P. falciparum* prevalence may be as poor as 10 to 30 percent. In India, the proportion of *P. falciparum* to *P. vivax* has risen steadily over the last 30 years, reaching about 60 percent.

Mechanism of resistance of certain antimalarial drugs

Quinine, a quinoline-based drug, and later chloroquine, a chloroquine-based drug, were both successful treatments for malaria before quinoline tolerance emerged and spread across the world. Artemisinin proved to be a wise, fast-acting, and potent drug towards chloroquine-resistant malaria in the face of this scenario. However, artemisinin tolerance in the context of delayed parasite clearance is now on the horizon, raising fears that humanity will be left without an appropriate malaria treatment [13]. Drug tolerance, which is widespread in most antimalarials, is caused by random mutations that reduce the drug's vulnerability. A single point mutation causes drug resistance in certain antimalarials, while drug resistance in other groups of antimalarials can include several mutations [14]. Other causes that lead to antimalarial drug resistance include inadequate patient enforcement, drug imbalance, drug-drug reactions, malaria presumptive therapy, and insufficient drug consistency.

1. Mechanism of Resistance in Artemisinin's

Young ring types, which enter a quiescence condition after exposure to artemisinin and then restart development after the artemisinin is removed, are thought to be responsible for plasmodium parasite tolerance to artemisinin [15]. Pfk13, a gene, plays a role in this mechanism [16]. Its low bioavailability encourages the plasmodium parasite to establish drug resistance.

2. Mechanism of Resistance in Quinolines

Resistance mechanisms in quinolines like chloroquine are not well known. The medication chloroquine is linked to a higher degree of drug efflux. Drug resistance has been documented in chloroquine tolerant parasites, which deliver the drug at a faster pace than chloroquine responsive parasites [17]. Chloroquine's preference for heme, which results in decreased chloroquine absorption, also contributes to chloroquine tolerance [18]. The *Plasmodium falciparum* chloroquine resistance transporter (PfCRT) is also involved in the parasite's chloroquine resistance [19].

3. Mechanism of Resistance to Hydroxynaphthoquinones and Diaminopyrimidines

In plasmodium parasites, resistance to hydroxynaphthoquinones like atovaquone is said to be rapid, and it is triggered by a single-point mutation in the cytochrome-b gene [20]. Mutations in the dihydrofolate reductase gene cause plasmodium parasites to be resistant to diaminopyrimidine-based antimalarials including pyrimethamine. By excluding steric and hydrogen bond associations, these alterations decrease the binding association among dihydrofolate and pyrimethamine reductase [21].

4. Mechanism of Resistance to 4-Quinolinemethanols

4-quinolinemethanols resistance like mefloquine is due to an overexpression of Pgh-1, which increases mefloquine efflux from the parasite's food vacuole [22]. In the absence of pfmdr1 amplification, however, mefloquine tolerance is probable [23].

5. Mechanism of Resistance to Sulphonamides

The mutant DHPS enzyme has a lower affinity for sulfadoxine, which leads to plasmodium parasite tolerance [24].

Alkaloids showing antimalarial activity

Plants' antimalarial behavior is attributed to a variety of phytoconstituents, comprising terpenes, alkaloids, flavonoids, and hormones. Alkaloids are a class of compounds with a wide range of biological functions, including antimalarial action. They are a structurally diverse group of compounds that contain a heterocyclic ring with N atom and are originated from amino acids [25]. Alkaloids were extracted from a variety of natural sources and have been shown to have active antimalarial efficacy [26].

Table 2 – Medicinal plants and isolated alkaloids

No.	Medicinal plant	Common name	Family	Alkaloid extracted
1.	<i>Alstonia macrophylla</i> [27]	Hard milkwood	Apocynaceae	Alstoniaphyllines A, Alstoniaphyllines B
2.	<i>Caesalpinia minax</i> [28]	-	Fabaceae	Caesalminines A and B
3.	<i>Actinodaphne macrophylla</i> [29]	Medang	Lauraceae	10-demethylxylopinine
4.	<i>Ficus septica</i> [30]	Figs	Moraceae	seco-Phenanthroindolizine
5.	<i>Meconopsis simplicifolia</i> [31]	Blue poppy	Papaveraceae	Simplicifolianine
6.	<i>Hymenocardia acida</i> [33]	-	Phyllanthaceae	Hymenocardine-H
7.	<i>Zanthoxylum simullans</i> [34]	Chinese pepper	Rutaceae	Acridone alkaloids

Various alkaloids isolated from medicinal plants and their antimalarial activity are –

1. Indole Alkaloids

Several indole alkaloids have lately been extracted and demonstrated to have potent antiplasmodial action. *Alstonia macrophylla* bark was studied chemically, and a new indole alkaloid, alstoniaphylline C, 2 new nitrogenous derivatives, alstoniaphyllines A and B, as well as 8 recognised alkaloids, namely alstonisine, were discovered. With an IC₅₀ of 7.6 μ M, compound alstonisine has antiplasmodial action against *P. falciparum* [27].

2. Terpenoidal and Steroidal Alkaloids

Various alkaloids with different terpenoidal backbones, such as indoloterpene, bisindolomonoterpenic alkaloids, and cassanetype diterpenes, have recently extracted from medicinal plants (*Polyalthia oliveri*, *Strychnos nuxvomica*, and *Caesalpinia minax*) and shown to have strong antimalarial efficacy. From the seeds of *Caesalpinia minax*, Ma et al. [28] extracted 2 new diterpene alkaloids, with a tetracyclic cassane-type

diterpenoid skeleton and c-lactam loop (Fabaceae). Caesalminines A and B have IC₅₀ values of 0.42 and 0.79 μ M, respectively, indicating antiplasmodial behavior.

3. Isoquinoline, Benzyloisoquinoline, and Hasubanane Alkaloids

From the bark of *Actinodaphne macrophylla*, Fadaeinasab et al. [29] extracted 7 isoquinoline alkaloids. Cycleanine, 10-demethylxylopinine, reticuline, laurotetanine, bicuculine, -hydrastine, and anolobine have in vitro antiplasmodial action against *P. falciparum* 3D7, with IC₅₀ values varying from 0.05 to 3.11 μ M for cycleanine, 10-demethylxylopinine, reticuline, laurotetanine, bicuculine, -hydrastine. The most active compound was discovered to be 10-demethylxylopinine.

4. Phenanthroindolizine Alkaloids

From the twigs of *Ficus septica*, Kubo et al. [30] extracted a new seco-phenanthroindolizine alkaloid, 4a,b-seco-dehydroantofine, as well as three recognized phenanthroindolizine alkaloids, dehydroantofine, tylophoridicine D and dehydrotylophorine. Although compound 4a,b-seco-dehydroantofine has a mild antimalarial activity (IC₅₀ = 4.0 μ M) against the 3D7 strain of *P. falciparum*, the other identified alkaloids have high activity (IC₅₀ = 0.42, 0.028, and 0.058 μ M, respectively).

5. Protoberberine Alkaloids

This genus of compounds is often included in the Papaveraceae family of plants. The alkaloids have a tetracyclic ring system that, depending on the viewing "angle," "mask" a substituted phenethylamine or vanillylamine. Wangchuk et al. [31] conducted phytochemical experiments on *Meconopsis simplicifolia* (Papaveraceae) aerial sections, culminating in the isolation of simplicifolianine, a recent protoberberine-type alkaloid, and 5 other alkaloids. With IC₅₀ levels of 0.78 μ g/mL and 1.29 μ g/mL, compound simplicifolianine had the most active antiplasmodial efficacy against the *P. falciparum* strains K1CB1 (multidrug-resistant strain) and TM4/8.2 (chloroquine-antifolate-sensitive strain).

6. Cyclopeptide Alkaloids

Cyclopeptide alkaloids are macrocyclic polyamide compounds with 13-, 14-, or 15-membered rings. The ring system comprises of a hydroxystyrylamine moiety, an amino acid, and a -hydroxy amino acid; a side chain, made up of one or two more amino acid moieties, is added to the ring [32]. The root bark of *Hymenocardia acida* yielded four cyclopeptide alkaloids. Hymenocardine-H, hymenocardine N-oxide, and Hymenocardinol, a recent cyclopeptide alkaloid with a rare histidine moiety, are among them. With IC₅₀ values ranging from 12.2 to 27.9 μ M, both of the compounds have mild antiplasmodial efficacy, with hymenocardine N-oxide, being the most active having an IC₅₀ value of 12.2 $\pm$ 6.6 μ M [33].

7. Acridone Alkaloids

5 identified acridone alkaloids, as well as other chemicals, were discovered in the root bark of *Zanthoxylum simullans* Hance. Its antimalarial efficacy was evaluated towards 2 strains of *Plasmodium falciparum*, Dd2 and 3D7, respectively. With an IC₅₀ of 18.9 μ g/mL, normelicopidine is the most effective against Dd2 [34].

FUTURE SCOPE

These phytoconstituents need to be studied in greater depth using an ethnopharmacological method. There is a need to continue working on plants in order to find appropriate molecules to use as models for creating new derivatives with better properties. Antimalarials derived from plants must proceed to be researched in order to combat the disease. Malaria removal ought to be given further attention. While it is a ruthless yet attainable aim, it would necessitate the highest degree of commitment and a sense of urgency, since the target year for extinction is not far away.

CONCLUSION

Malaria is the most lethal parasite, and the disorder is worsening owing to *Plasmodium falciparum*'s growing susceptibility to most antimalarial medicines. To combat these synthetic drug-resistant parasites, we have turned to natural chemical constituents derived from plants. Due to repeated therapies with synthetic medications, rapid resistance is developing in different malarial parasites. This is presenting a serious challenge to human society on a global scale. Orthodox healers' use of therapeutic plant-derived alkaloids was found to be genuine. The bisindole alkaloid strychnobailonine, and diterpene alkaloids caesalminines A and B, are among the most intriguing of the newly extracted metabolites. Other identified compounds with low IC₅₀ values, such as 10-demethylxylopinine, cycleanine, and isoquinolines have also been confirmed to have good antimalarial properties. Some of the molecules, on the other hand, have a comparatively strong cytotoxicity profile, although others have not been studied for toxicity. The promising compounds should be subjected to more structural modifications and an analysis of the structure-activity relationship. The antimalarial alkaloids found to have positive action and could be used as therapeutic active agent in drug development to produce formulations with increased potency and reduced toxicity.

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