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Review Article

Therapeutic Potential of Plant Based Natural Compounds for Malaria - Recent Advances and Future Perspective

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Abstract

This review illustrates recent advances in the investigations of natural antimalarial drugs and, their efficacy and modes of action with special reference to quinine and artemisinin. Owing to the high prevalence and severity, malaria is a major health challenge for the world. The ancient literature indicates the application of medicinal plants for the treatment of malaria, but the validation of these formulations is still not well known. The discovery of quinine and chloroquine and their applications has helped control malaria to an extent, but the development of drug resistance has posed challenges to treatment. The discovery of artemisinin opens up a new vista for the treatment of malaria. Artemisinin based combination therapy is presently considered a novel approach for the treatment of malaria. Besides quinines and artemisinins, several other groups of phyto-compounds have shown promise as potential antimalarial drugs. Currently, plant based drug development has emerged as a frontier area of research in the development of a new antimalarial agent. Further, the *in-silico* optimization of plant-based principles as relatively better anti-malarial regimen may add new dimensions in the health care domain. Potentially, future antimalarial regimens will consist of drugs to be a combination of antimalarial compounds, immune modulator(s) and folic acid. Such combinations will kill the parasite and overcome their side effects. However, extensive systematic studies are required to understand the mode of action, efficacy, stability, toxicity and safety of natural antimalarial therapeutics.

Keywords: *Antimalarial Agent; Quinine; Artemisinin; Medicinal Plant; Natural Compounds; In-Silico Approach*

Background and Historical Perspective

Malaria is a common cause of fever around the globe. It is a serious parasitic disease, may be acute or chronic and is a major cause of morbidity and mortality in tropical regions of the world. Among countries of the Africa continent, about 50% of the population of Zimbabwe suffer from malarial infection every year [1]. According to a report released by the World Health Organisation (WHO), about 207 million people have suffered from malaria and most of the cases (80%) and the deaths (90%) were from Africa [2]. Malaria is mainly caused by five species of *Plasmodium: P. falciparum, P. knowlesi*, *P. malariae, P. ovale, P. vivax* and is transmitted by *Anopheles* mosquitoes. Among these, *P. falciparum* and *P. vivax* are the most deadly forms predominating in the African region. Malaria is primarily diagnosed by the recurrence of high fever at a regular interval (depending upon type of species infection), shivering, sweating, headache and body pain occurring as body temperature rises. Serological examination shows the presence of parasites (different stages) in the blood.

Effective treatment of malaria was initiated with the discovery of the first antimalarial drug quinine. Quinine was isolated in 1820 from the bark of a plant from *Cinchona* species (Rubiaceae). Quinine is the oldest and most important antimalarial drug frequently prescribed

for the treatment of malaria [3]. Most commonly used antimalarial agents belong to the following classes of compounds: the quinolines such as quinine, chloroquine, mefloquine, amodiaquine, primaquine; the antifolates such as sulfadoxine, pyrimethamine and proguanil; the hydroxylnaphthaquinones such as atovaquone and the artemisinin derivatives such as artemisinin, artesunate, artemether, arteether [4].

Chloroquine (CQ) was first synthesized in 1940 and used for the cure of malaria [5]. Due to the extensive and prolonged use of CQ, the malarial parasites especially *P. falciparum* developed drug resistance against chloroquine [6]. Earlier, CQ was used frequently as an antimalarial drug. In recent years, however, applications of chloroquine (CQ) and antifolates (sulfadoxine-pyrimethamine, S/P) have been reported to be relatively ineffective for the treatment of malaria in most endemic areas [7]. The emergence and rapid spread of multi-drug-resistant (MDR) strains of *P. falciparum* is a major limiting factor for the prophylaxis and treatment of malaria. Since the choice of antimalarial drugs is limited, the affected nations with poor clinical settings have failed to control of this disease [7]. The World Health Organization (WHO) has recommended combinations that include artemisinin and its derivatives for the treatment of malaria. Presently, combination therapy (CT) is the most effective treatment of resistant strains of malaria [7,8]. However, there is incomplete knowledge regarding the mechanism of action and metabolism of most of the antimalarial agents. Various research groups have shown interest in the development of new active compounds as an alternative to currently used antimalarial drugs [9]. In this quest, the plant-based agents may offer promise as efficacious cost effective, safe therapies with fewer side effects and used for the treatment of various diseases including cancer [10,11].

This review provides a critical account of plant-based principles as crude extracts, essential oil and active constituents with diverse chemical structures that may be useful proved as antimalarial drugs. This review also summarizes the structures, mode of action and limitations of almost all major antimalarial compounds with special focus on combination therapy and explores their development.

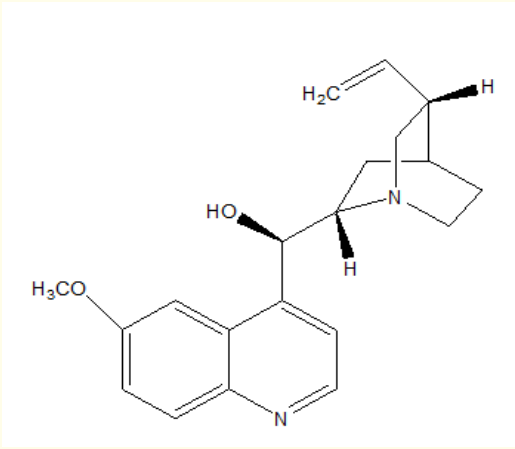
Methodology

A comprehensive bibliographic search was conducted made to obtain an in-depth insight into plants with antimalarial properties, including plant-based compounds such as quinines, artemisinins and other related phytochemicals. Several research papers on the subject were identified using scientific search engines and databases such as Science Direct (http://www.sciencedirect.com), PubMed (http://www.ncbi. nlm.nih.gov/pubmed), Google Scholar (http://scholar. google.com), Scopus (http://www.scopus.com), SciFinder (http://www.libnet.ulg.ac.be/en/eresources/scifinder-scholar), and Researchgate. Information regarding sources, structure of phytochemicals with antimalarial properties, their mode(s) of action(s) and future approaches for the development of new drugs was collected. A total of 85 research papers / reports including original articles, review articles, book chapters, books and several websites and WHO health reports on malaria dated from 1958 until May 2017 were identified. Chemical structures of the compounds were researched using Google. com and then redrawn using the freeware version of the software ACD/ChemSketch (version 15.01). IUPAC name was searched and recorded for the compounds.

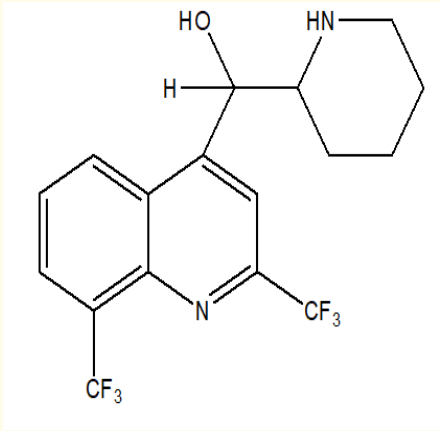
Prevention and treatment of malaria

Antimalarial medications are designed to either prevent or treat malaria. These drugs may be used for all or some of the following: (a) Treatment of malaria in infected individuals, (b) Prevention of infection in immune compromised people (malaria prophylaxis) in endemic regions, (c) Routine intermittent treatment of groups of people in endemic regions [12,13].

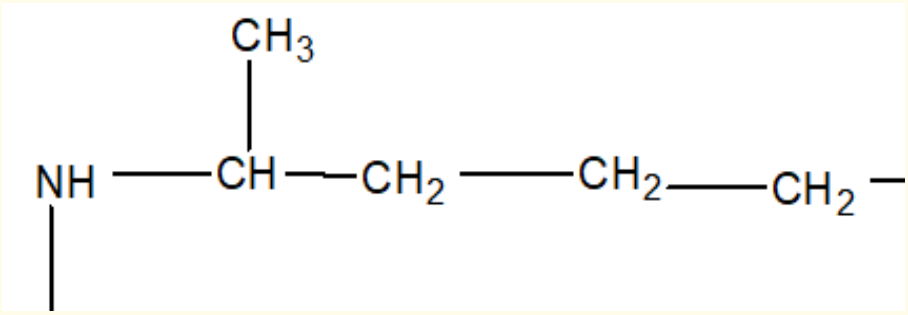
Antimalarial drugs have been placed into two major classes since the 1940s, i.e. antifolates and sulpha drugs. The cinchona alkaloids are the most frequently used antimalarial drugs. Earlier tetracyclines and the derivatives of artemisinin were less commonly used for the treatment of malaria. Now artemisinin has been shown to be the most prominent and effective drug against both the wild type and resistant species of malarial parasite [13]. Use of a reverse pharmacology approach has also been suggested for the development of some new potent drugs by taking the example of *A. mexicana* [14].



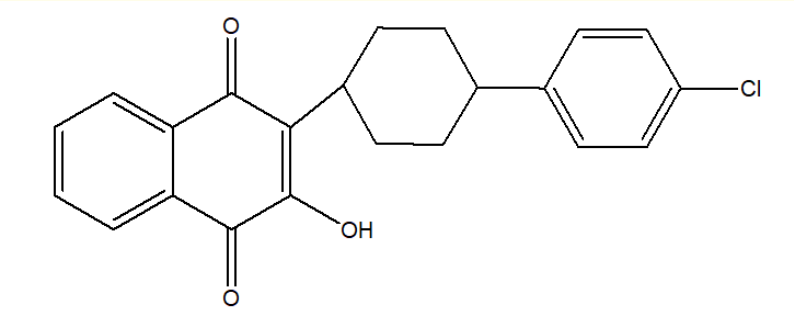
A- Quinine (2-ethenyl-4-azabicyclo [2.2.2]oct-5-yl)- (6-methoxyquinolin-4-yl)-methanol).



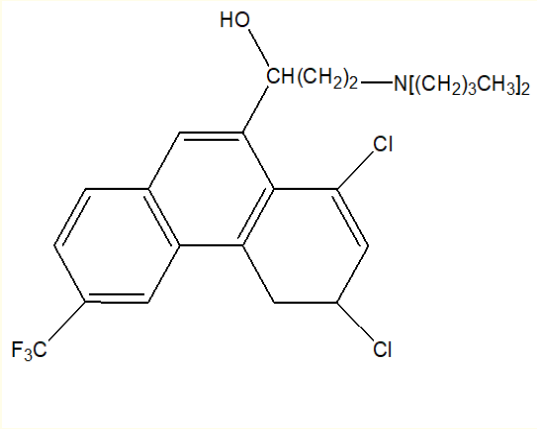
B- Mefloquine ([2,8-bis(trifluoromethyl)quinolin-4-yl]-piperidin-2-ylmethanol).



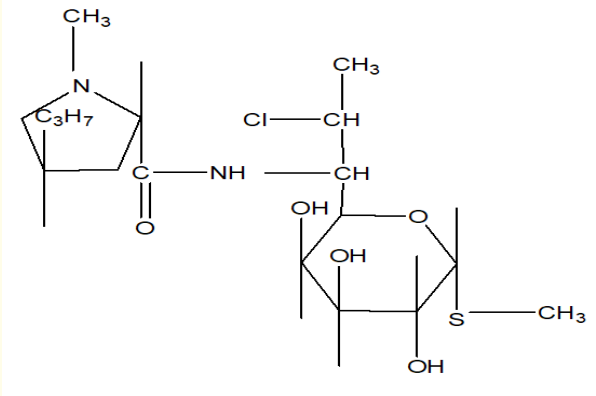
C- Chloroquine (N'-(7-chloroquinolin-4-yl)-N,N-diethyl-pentane-1,4-diamine).



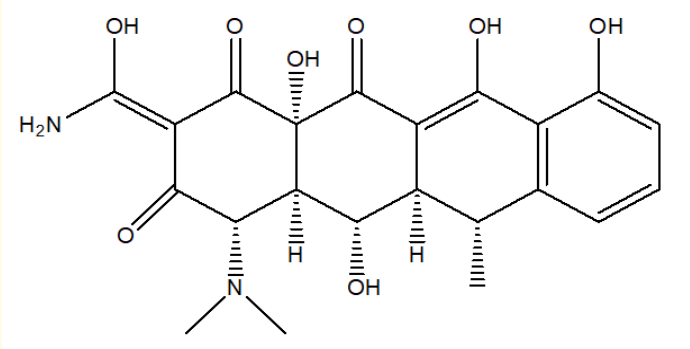
D- Atovaquone (trans-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthalenedione).



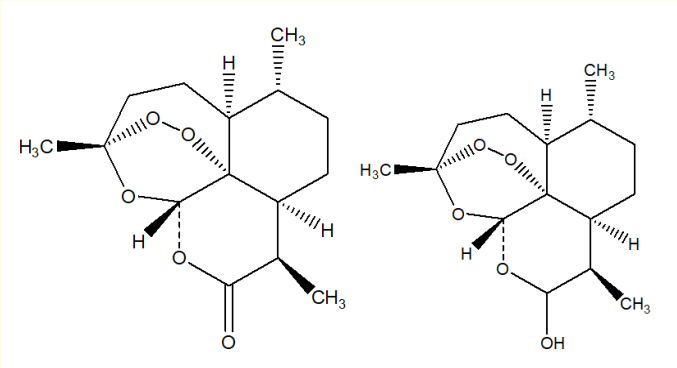
E- Halofantrine (3-(dibutylamino)-1-[1,3-dichloro-6-(trifluoromethyl)phenanthren-9-yl]propan-1-ol;hydrochloride).



F- Clindamycin (methyl 7-chloro-6,7,8-trideoxy-6-{[(4R)-1-methyl-4-propyl -L-prolyl]amino}-1-thio-L-threo-α-D-galacto-octopyranoside).



G- Doxycycline (4S,4aR,5S,5aR,6R,12aR)-4-(dimethylamino)-1,5,10,11,12a-pentahydroxy-6-methyl-3, 12-dioxo-4a,5,5a,6-tetrahydro-4H-tetracene-2-carboxamide.



H- Artemisinin I- Dihydroartemisinin.

Figure 1: *Chemical Structure commonly used antimalarial drugs: A- Quinine, B- Mefloquine, C- Chloroquine, D- Atovaquone, E- Halofantrine, F- Artemisinin, G- Dihydroartemisinin.*

Plants used for malaria treatment

A large number of plants have been reported to have antimalarial activity. Plant extracts have been prepared from different parts of plants and have been used for isolation of different antimalarial agents with significant activity against species of *Plasmodium*. Different groups of phytochemicals such as alkaloids, phenolic compounds, flavonoids, terpenes, lignans etc. isolated from various families of plants have also been shown to possess antimalarial activity. Some of the more important plants exhibiting antimalarial property are listed in table 1. In addition, a long list of plants with anti-plasmodial activity has already been summarised in another review paper [15]. Various researchers have also documented a large number of plant based natural antimalarial compounds [16]. Other researchers are actively involved in exploring anti-malarial activity of plants from the Africa continent [17] and Brazilian Amazon region [16]. It has been demonstrated that the use of plant-based principles may be promising for the development of novel antimalarial drugs with improved efficacy, safety and cost effectiveness. Quinines and artemisinins appear to be are the two most promising groups of plant based antimalarial compounds.

S. No.	Name of plant	Family	Parts used	Activity/target	References
1	*Aloe pulcherrima*	Asphodelaceae	R	Anti-plasmodial activity	[41]
2	*Amaranthus spinosus*	Amaranthaceae	SB	Anti-plasmodial activity	[42]
3	*Andrographis paniculata*	Acanthaceae	R	*in vitro* for schizontocidal activity	[12]
4	*Annona squamosa*	*Annonaceae*	SB	*Cytotoxicity test against chloroquine resistant P. falciparum*	[43]
5	*Azadirachta indica*	Meliaceae	SC	*in vitro* culture of *P. falciparum*	[12]
6	*Caesalpinia bonducella*	Caesalpiniaceae	R	Anti-plasmodial activity	[44]
7	*Carica papaya*	Caricaceae	L & AP	*In vitro* anti-plasmodial activities	[45]
8	*Cassia obtusifolia*	Caesalpiniaceae	L	*Larvicidal and oviposition activity*	[46]
9	*Cassia occidentalis*	Caesalpiniaceae	Leaf	Anti-plasmodial activity	[47]
10	*Copaifera reticulata*	Fabaceae	ND	Anti-malarial activity	[48]
11	*Croton cajucara*	Euphorbiaceae	B & LI	*In vitro* and *in vivo* anti-malarial activity	[49]
12	*Datura innoxia*	Solanaceae	L & AP	*In vitro* antiplasmodial activities	[45]
13	*Datura stramonium*	Solanaceae	L	Larvicidal and mosquito repellent activities	[50]
14	*Dissotis melleri*	Melastomataceae	AP	Antiplasmodial activity	[51]
15	*Erythrina abyssina*	Leguminoceae	SB	Anti-malarial properties against *P. falciparum*	[52,53]

Table 1: *List of plants having anti-malarial activity.*

Note: *L: Leaf; S: Stem; R: Root; SC: Seed Cake; St: Shoot; LI: Leaf Infusion; WP: Whole Plant; LD: Leaf Decoction; Rz: Rhizome; S: Seed; AP: Aerial Parts; SB: Stem Bark; RB: Root Bark; ND: Not Defined.*

Quinine and its related compounds

The first report of the use of Cinchona bark tree for treatment of fever was documented in the early 1600s. Quinine was isolated from the bark of Cinchona tree. The discovery of quinine is considered one of the most important achievements in medical history of the 17th century. The use of quinine as a drug was reported as the first success in the treatment of malaria [18]. Quinine is an alkaloid and belongs to the aryl amino alcohol group. It is a basic compound and always remains present in the form of a salt. In comparison to the other salts of quinine (for example hydrochloride, sulphate, bisulphate, and gluconate salts) dihydrochloride is most frequently used against malarial parasites [18]. However, there are certain limitations associated with the use of this drug. These limitations include 1) development of resistance in *P. falciparum* by the use of dichloroquine, 2) lack of antipyretic property, 3) side effects known as chinchonism (nausea, headache, mild hearing impairments etc.) with long term use, and 4) the ability to cross the placental barrier. These limitations have resulted in restricted applications of quinine drugs. Quinines derivatives include chloroquine, amodiaquine, pyrimethamine, proguanil, sulphonamides, mefloquine, atovaquone and primaquine. These compounds may be used either alone or in combination with other compounds. Some of these drugs have similar mode of action with quinine, while others differ. Chemically being an alkaloid, quinine accumulates in the food vacuoles of *Plasmodium* species. Quinine inhibits the hemozoin biocrystallization,- thus facilitating an aggregation of cytotoxic heme molecules. Derivatives of quinine such as chloroquine are more effective than quinine as a blood schizonticidal agent. Quinimax, a mixture of quinine, quinidine and cinchonine is also used for the treatment of severe malaria [19].

Artemisinin and its derivatives

Artemisinins is a group of natural compounds isolated from the *Artemisia annua* (family, Asteraceae). Artemisinin is a new class of anti-malarial agents belongings to the sesquiterpene trioxane group and having an endoperoxide bond where the endoperoxide moiety plays an important role. The 1, 2, 4trioxane ring of artemisinin is unique in nature and plays an important role in anti-malarial activity

[20]. Aside from the anti-malarial activity of artemisinin, several other pharmacological actions have been reported; including treatment of various cancers, inflammatory diseases, viral, protozoal, helminthic, and fungal infections [21], autoimmune arthritis [22] and histamine related problems [23]. Artemisinins have several derivatives (artemether, artesunate, dihydroartemisinin) that have similar or greater efficacy in prevention of malarial infection. Dihydroartemisinin is over 200 times more effective than artemisinin in reducing 3H-hypoxanthine uptake. Current artemisinin production requires its extraction from the cultivated herb, *Artemisia annua* L., which is a "generally regarded as safe" (GRAS) herb suitable for human consumption. In present scenario, Artemisinin-based Combination Therapy (ACT) may be the best option for treatment of resistant malaria parasites that evolved due to use of other antimalarial drugs [24]. Previous studies have shown that the quantity of artemisinin was 40 times greater in the blood stream of mice when crude drug (dried whole plant material extract) was fed as compared the use of the pure drug [25]. Artemisinins act more rapidly against malarial parasites as compared to other antimalarial drugs. They work by inhibiting major metabolic processes such as protein synthesis, nucleic acid synthesis and glycolysis [26].

Other antimalarial agents

Doxycycline, halofantrine and clindamycin have also been used for prevention and treatment of malaria. Doxycycline is chemically similar to tetracycline and derived from oxytetracycline. Doxycycline acts as a bacteriostatic agent. It binds with the 30S ribosomal subunit and inhibits bacterial protein synthesis. It is highly effective against the malarial parasite and it has been used for chemoprophylaxis of chloroquine-resistant malaria. However, doxycycline is known to effects on the bone growth and may result in permanent enamel hypoplasia of the teeth. It is therefore not prescribed for pregnant and lactating women as well as for the children aged less than 8 years.

Halofantrine is a phenanthrene methanol, chemically similar to quinine. It has potential schizontocidal activity against all *Plasmodium* sps. Concerns with long-term use of halofantrine include its high cost and cardiotoxicity. Clindamycin is derived from lincomycin and it has low blood schizonticidal activity. It is used for treatment of drug resistant *P. falciparum* species in combination with quinine. In comparison to the other antibiotics, clindamycin is more toxic and is used only in cases where the tetracyclines are not effective.

Miscellaneous phytochemical compounds

Traditional knowledge, ethnomedical data and the use of plant-based medicines have generated insights towards prevention and treatment of malaria by identifying and developing new antimalarial drugs. Several plant based compounds with different chemical structures and antimalarial activities have been reviewed [20]. The active constituents isolated from various parts of different plants include leaf (*Azadirachta indica*), tubers (*Cyperus rotundus, Stephania erecta*), bark (*Brunsvigiara dulosa*), stem (*Quassia indica*), fruit (*Brucea javanica*), root (*Alstonia angustifolia*), and root (*Zanthoxyl umgilletii, Margarita riadiscoidea*) etc [27-30]. *H. madagascariensis* has been shown to be a rich source of the quinines bazouanthrone, harunganin, harunganol A, harunganol B and the terpenes feruginin A, friedelan-3-one and betulinic acid. These phytochemicals have been shown to exhibit *in vitro* antimalarial activity against *P. falciparum* [31]. Different fractions of plant extracts from *A. indica* have shown anti-plasmodial activity against sexual and asexual stages of *Plasmodium* [32].

Mode of action of antimalarial drugs

Most antimalarial drugs inhibit RNA and DNA synthesis by different mechanisms [4,13]. Some antimalarial drugs also inhibit protein synthesis and act as schizontocides [33]. In brief, chloroquine induces the rapid degradation of ribosomes and dissimilation of ribosomal RNA and finally inhibits biosynthesis of RNA and DNA. Sometimes, protein synthesis inhibition was also observed as a secondary effect of chloroquine [4]. Chloroquine accumulates in the food vacuoles of parasites [34]. It binds to heme (or FP) and forms a complex known as FP-chloroquine complex. This complex is highly toxic for the parasite's cells and disrupts membrane function. Finally, cell lysis and autodigestion of the parasitic cell take place [4]. The mode of action of quinine is somewhat similar to that of chloroquine. However, the exact mechanism of action of artemisinin and its derivatives is not well understood. It is presumed that the biological activity of artemisinin depends on the endoperoxide bond. The artemisinin's without this bond have no antimalarial activity. The endoperoxide bond, artemisinin may interact with heme or iron and finally disintegrates into free radicals [35]. Several researchers have reviewed in detail the modes of

actions of antimalarial drugs as well as the mechanisms of development of drug resistance in parasite [4,13,33,36]. The mode of action of different antimalarial drugs are varied to each other. Exact mechanism is unknown but quinine accumulated in the food vacuoles and inhibits heme polymerisation and heme catalase activity. While chloroquine Inhibits DNA and RNA biosynthesis and induces the degradation of ribosomes and the dissimilation of ribosomal DNA and inhibition of protein synthesis [4]. On the other hand, antifolates inhibits dihydrofolate reductase and/or dihydropteroate synthase. Inhibition of the biosynthesis of pyrimidines, purine and some amino acids were also reported [4].

Combination therapy

The development of resistance in malarial parasites has been found to pose a serious threat in treatment and prevention of malaria. Use of a single drug causes development of drug resistance issues. In order to overcome this problem, combination therapy (CT) is needed and has been found to be an effective alternative approach for prevention of malaria. CT is the simultaneous use of two or more antimalarial drugs having different biochemical targets and modes of actions. Several researchers have studied the use of CT and evidence supports its use. However, CT is ten times more expensive than classical mono-drug therapy. CT can be divided into two broad categories: artemisinin-based combinations (ACs) and non-artemisinin-based combinations (NACs). Determination of most-appropriate dose and formulation of CT for malaria is needed.

Artemisinin-based combination therapies (ACTs)

Artemisinin is more useful for the treatment of complicated malaria caused by drug resistant *P. falciparum* species. In order to avoid the development of resistance against this drug, artemisinin is only recommended in combination with another non-artemisinin based drug. ACTs may cause a reduction in gametocytes transmission and, thus may reduce the risk of chances of spreading of resistant alleles [37]. Therefore, the ACTs should be preferred over NACTs (e.g. amodiaquine plus sulfadoxine-pyrimethamine) for the treatment of uncomplicated *P. falciparum* malaria [11]. ACTs result in fewer side effects; and development of resistant strains has not yet been reported. This is not to say however, that resistant strains may no emerge in future [37]. Most commonly used ACTs include artesunate with amodiaquine (Coarsucam or ASAQ), artesunate with mefloquine (Artequin or ASMQ), artemether with lumefantrine (Coartem or AL), artesunate and sulfadoxine/pyrimethamine (Ariplus or Amalar plus), dihydroartemisinin with piperaquine (Duo-Cotecxin, or Artekin), pyronaridine and artesunate (Pyramax). These combinations play an important role in malaria eradication and treatment as they are more efficient and result in low levels of toxicity. Other anti-malarial combinations such as chlorproguanil-dapsone with artesunate have been reported to exhibit relatively higher efficacy but with serious side effects [38]. In CT, ASMQ was found to be highly efficient for clearance of fever and parasitemia when compared to artemether-benflumetol (CGP 56 697; Novartis) [39].

Non-artemisinin-based combination therapies (NACTs)

Predominant NACTs include sulfadoxine with pyrimethamine (Fansidar/SP), SP with chloroquine, SP with amodiaquine and SP with mefloquine (Fansimef) etc. Have been found to be the predominantly used in non-artemisinin based combination therapies (NACTs) [12]. Sometimes quinine is prescribed with antibiotics such as tetracycline or doxycycline and this combination has a high cure rate. The discovery of artemisinin and ACTs have however made the application of quinine and quinine-based therapy less popular.

Hypothesis for development of future anti-malarial drugs

Future antimalarial drugs regimens should consist of a combination that include: 1) an antimalarial compounds, 2) an immune-booster, and 3) compounds that increase red blood cells or heme content in the body (Figure 2). Several plants and plant based natural compound have been reported as immunoboosters. Immunobooster will increase the immunity results in fast recovery of patients will be done. The Folic acid or other natural or semi synthetic compounds may be used to increase haemoglobin. Maintenance of haemoglobin will decrease the mortality rate and may enhance fast recovery. The combination of these three components may be more useful for the treatment of malaria. However, extensive research is needed to ensure the proper combination and appropriate ratio of the constituents

to achieve optimum results. Metals have been reported for their medicinal properties and have also been used for treatment of various diseases [40]. In this context, metal-based drugs may also be the part of future malarial fever treatment.

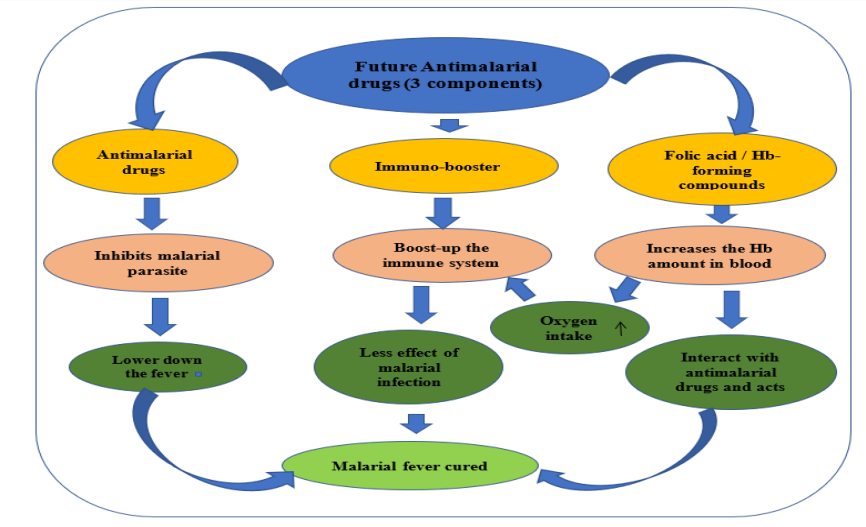


Figure 2: *Diagrammatic presentation of a hypothesis of future anti-malarial drug development.*

Conclusion and Future Prospects

Advances in phytomedicines have contributed significantly supported to traditional ethnopharmacological knowledge and ancient medical literature. India and China have rich traditional medicine systems that are maximally based on plants. In India other medical practices such as water based therapy, yoga (a type of exercise), and touch therapy also do exist. In the 21st century, the researchers have again started looking back to the traditional medicine system for the new drug development. Scientific efforts for searching existing historical literature to find suitable phytochemicals and applying new technologies for production are still in progress. Besides quinine and artemisinins, more plant-based drugs are needed be developed as new anti-malarials to halt the progression of drug resistant species of malaria. Since, malarial parasites also affect the immune system, some efficient immuno-modulatory drugs may be developed which could then be used in combination with antimalarials to boost immunity and reduce adverse effects of drugs, if any. The application of the bioinformatics and biotechnological tools may be prove useful in the development of antimalarial drug as well as in the large scale production of plant-based compounds in the eradication of malaria, respectively.

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Conflict of Interest

Declared none.

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