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A Brief Review on Malaria and Current Antimalarial Drugs.

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Abstract
Malaria remains one of the most devastating infectious diseases in the world, both from the point of view of mortality and morbidity and its worldwide occurrence in tropical and subtropical regions. It is one of the most severe public health problems in many developing countries including India, where young children and pregnant women are the most affected. The emergence, spread and severity of the disease had led to the development of currently available antimalarial drugs as an approach of modern malaria chemotherapy. However, because of rapid development of resistance has severely limited their use alone, but in combination with the drugs of same category or with other drugs could be used successfully in the treatment and prevention of acute and sever cases of chloroquine or multidrug-resistant *P. falciparum* and other forms of malaria infection. Moreover, in this challenging situation, based on novel rational drug design and traditional random screening method of drug discovery programs multiple general approaches can be pursued towards development of new antimalarial drugs with novel modes of action, which would be effective against multi-drug resistant malaria.

Key Words
Malaria, Antimalarial Drugs.

Introduction
Malaria is one of the most devastating infectious diseases faced by the humanity in this century. According to the World Health Organization, it is estimated that approximately 40% of the world population lives in malaria endemic areas, with 300-500 million clinical cases and 1.5-2.7 million deaths per year globally, and up to 1 million of those deaths are among children younger than 5 years old. Malaria is a leading cause of morbidity and mortality, particularly in the tropical and sub-tropical regions of the world, and it remains one of the most widespread diseases in the world[1-3]. It is one of the most severe public health problems in many developing countries, where young children and pregnant women are the most affected[4, 5]. In the South East Asian Region of WHO, out of about 1.4 billion people living in 11 countries, 1.2 billion (85.7%) are exposed to the risk of malaria and most of who live in India[6]. Of the 2.5 million reported cases in the South East Asia, India alone contributes about 70% of the total cases. Currently, 80.5% of the 109 billion population of India lives in malaria risk areas. Of this, 4.2%, 32.5% and 43.8% live in areas of high, moderate and low risk to malaria respectively[7].

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Disease: Causative agent and transmission
Human malaria is caused by protozoan parasites of the genus *Plasmodium*, *P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale* are four well known species of human malaria parasite[8,9] and more recently another species, *P. knowlesi* has been documented[10]. Each species presents slightly different clinical symptoms. *Plasmodium falciparum* is the most widespread, and causing most severe and potentially fatal malaria[11]. Parasites are transmitted from one person to another by an insect vector, the female *Anopheline* mosquito. This is the principal mode of transmission of malaria disease. There are six recognised primary vectors of malaria in India viz., *Anopheles culicifacies, An. stephensi, An. dirus, An. fl uviatilis, An. minimus* and *An. Sundaicus*. During night time hours (between 5 PM and 7 AM, with maximum intensity at midnight); these female mosquito bite the man for a blood meal which it needs to nourish its eggs, it inoculates the sporozoites into human blood stream, thus spreading the infection. Male mosquitoes do not transmit the disease. The other possible modes of transmission are blood transfusion (Transfusion malaria) which is fairly common in endemic areas; mother to the growing fetus (Congenital malaria) in which intrauterine transmission of infection from mother to child occurs (during pregnancy) and also placenta

becomes heavily infested with the parasites; accidental transmission through needle stick injury can occur among drug addicts who share syringes and needles. Infected organ transplantation is also a favorable mode of transmission of the disease[4, 12, 13].

Clinical manifestations

Humans infected with malaria parasites can develop a wide range of symptoms. These vary from asymptomatic infections (no apparent illness), to the classic symptoms of malaria (fever, chills, sweating, headache, muscle pains), to severe complications (cerebral malaria, anemia, kidney failure) that can result in death. The severity of the symptoms depends on several factors, such as the species (type) of infecting parasite and the human's acquired immunity and genetic background[12]. Depending on the type of attack and subsequent occurrence of signs and symptoms, the disease can be categorized as follows:

Uncomplicated malaria

It is a symptomatic infection without signs of severity and/or evidence of vital organ dysfunction[14]. The clinical manifestations of this type include typical and atypical features. The typical/classical (but rarely observed) malaria attack lasts 6-10 hours. It consists of: **a cold stage** (shaking chills, shivering; lasts for 15 min to 1 hr, usually at mid- day between 11 a.m. to 12 noon)**; a hot stage** (high grade even reaching above above106^{o}F, headaches, vomiting; lasts for 2 to 6 h); and finally **a sweating stage** (profuse sweating, fever return to normal temperature, tiredness; persist for 2-4 h). The febrile paroxysms are usually accompanied by atypical symptoms. These include atypical fever, headache, muscle ache, back pain, joint pains, chest pain, malaise, nausea, sometimes vomiting, cough, delirium, breathlessness, acute abdomen, jaundice, weakness anxiety and restlessness, altered behavior, acute psychosis, puffiness of lids etc.[1, 4, 12].

Complicated or severe malaria

It is characterized by signs of severity and/or evidence of vital organ dysfunction[14]. This occurs when *P. falciparum* infections are complicated by serious organ failures or abnormalities in the patient's blood or metabolism. P*lasmodium falciparum* malaria is the cause of all the mortality and most of the morbidity in malaria, although, rarely, *P. vivax* or *P. ovale* also produce serious complications, debilitating relapses, and even death. The manifestations of severe malaria includes: cerebral malaria with abnormal behavior, impairment of consciousness, seizures, coma, or other neurologic abnormalities; severe anaemia due to haemolysis; hemoglobinuria due to haemolysis; pulmonary edema or acute respiratory distress syndrome (ARDS); abnormalities in blood coagulation and thrombocytopenia; cardiovascular collapse and shock; altered sensorium; convulsions, jaundice, hypotension, prostration, hyperpyrexia, renal failure etc [4]. Malaria produces significant immune suppression and this can result in secondary infections. Common among them are pneumonia, aspiration bronchopneumonia (in the elderly), urinary tract infection, colitis etc. Meningitis and enteric fever have also been reported. In *P. falciparum* malaria, severe infection can lead to septicaemic shock (algid malaria). Persistence of fever, neutrophilic leucocytosis and hepatosplenomegaly are also focal signs of 2^{o} infection[12].

Malaria diagnosis

Malaria is diagnosed by the clinical symptoms and by microscopic examination of the blood. Although reliable diagnosis cannot be made on the basis of signs and symptoms alone because of the non-specific nature of clinical malaria, In areas where malaria is prevalent, clinical diagnosis usually results in all patients with fever and no apparent other cause being treated for malaria[5].

Light microscopy

Simple light microscopic examination of intracellular parasites on Giemsa-stained blood films is the most widely practiced and useful method for definitive malaria diagnosis. Stained thick and thin blood smears are used to diagnose malaria, to differentiate between the species of parasite, to quantify the level of parasitemia (parasite density), and also to distinguish clinically important asexual parasite stages from gametocytes which may persist without causing symptoms[5,12]. A second method is a modification of light microscopy called the quantitative buffy coat method. It involves staining of the centrifuged and compressed red cell layer with fluorescent acridine orange (in microhaematocrit tubes) and its examination under UV light. It is quicker to perform and more sensitive than normal light microscopy[5].

Antigen detection tests (also known as rapid or "dipstick" tests)

A third diagnostic approach involves the rapid detection of parasite antigens using rapid immunochromatographic techniques (ICT Malaria P. f. test). This technique is based on the "dipstick" format, (also called: Malaria Rapid Diagnostic Tests, Antigen-Capture Assay or "Dipsticks") have become available for the diagnosis of malaria. Compared with light microscopy and QBC, this test yielded rapid and highly sensitive diagnosis of *P. falciparum* infection but requires high per-test cost and an inability to quantify the density of infection[5,12].

Molecular tests

Detection of parasite genetic material through polymerase-chain reaction (PCR) techniques is becoming a more frequently used tool in the diagnosis of malaria. Specific primers have been developed for each of the four species of human malaria, which is helpful for detecting mixed infections. It is possible to detect <10 parasites per 10μL of blood[5].

Serology

Specific serological markers have been identified for each of the four species of human malaria parasites for detecting anti-malaria antibodies in serum specimens. Antimalarial antibodies can be detected by immunofluorescence or enzyme immuno assay[5].

Modern approach of treatment: Malaria chemotherapy

Although traditional medicines often form the foundation for modern drugs, a sound knowledge of the life cycle of the malaria parasite helps to select appropriate modern approach of malaria chemotherapy. The knowledge and understanding of the biochemistry of malaria-parasites had led to identification of many potential targets for newer drugs and to the identification of possible mode(s) of action of the drugs already in use to manage the disease. Chemotherapy has traditionally played an important role in the treatment and control of malaria. In *Plasmodium* life cycle, the asexual blood stages (rings, trophozoites, schizonts) are responsible for the severe and life-threatening clinical symptoms of malaria and thus are the main target of most of the drugs of modern malaria chemotherapy either for treatment or for chemoprophylactic use. The sexual blood stages (gametocytes) do not cause any known pathology and thus are not a primary target of malaria treatment.

Classification of antimalarial drugs

There are generally three classes of drugs for treating malaria and each is classified according to its therapeutic action against the different life cycle stages of the parasites in human hosts:

(a) Schizonticides (interfere with the growth and multiplication of merozoites),

- Exoerythrocytic schizonticides: active against the merozoites in the hepatic or primary tissue schizont, e.g. 8-aminoquinolines are fall into this class;
- Erythrocytic schizonticides: useful against the merozoites in the erythrocytic phase of the life cycle, e.g. quinine and 4-aminoquinolines, 9-aminoacridines are included in this category;

(b) Sporozoitocides (active against sporozoites of parasites), e.g. primaquine, Proguanil etc. They also act against liver schizonts.

(c) Gametocytocides (destroy gametocytes in red blood cells), e.g. chloroquine, artemisinin etc.[4,15,16].

Chemical classification of currently available antimalarial drugs is depicted in Table 1.

Currently available antimalarial drugs

The current antimalarial drugs for treatment and prophylactic use are discussed below:

a) Quinoline based antimalarials

Quinoline based antimalarial agents (Fig. 1) are structural derivatives of quinine, used widely in the treatment and chemoprophylaxis of un-complicated or acute *falciparum* as well as *vivax* malaria. However, because of rapid development of resistance has severely limited their use alone, but in combination with the drugs of same category or with other drugs can be used successfully in the treatment of acute and sever cases of chloroquine or multidrug-resistant *P. falciparum* infection[17.18.19]. Table 2 describes briefly quinoline based antimalarial drugs of clinical use.

b) Folate antagonists

These compounds inhibit the synthesis of parasitic pyrimidines, and thus parasitic DNA. There are two groups of antifolates: (i) the dihydrofolate reductase (DHFR) inhibitors that are diaminopyrimidines and biguanides like pyrimethamine, trimethoprim and proguanil, chlorproguanil, respectively and (ii) the dihydropteroate synthase (DHPS) inhibitors that are sulphonamides and sulfones like sulfadoxine, sulfalene and dapsone, respectively[5] (Fig. 2).

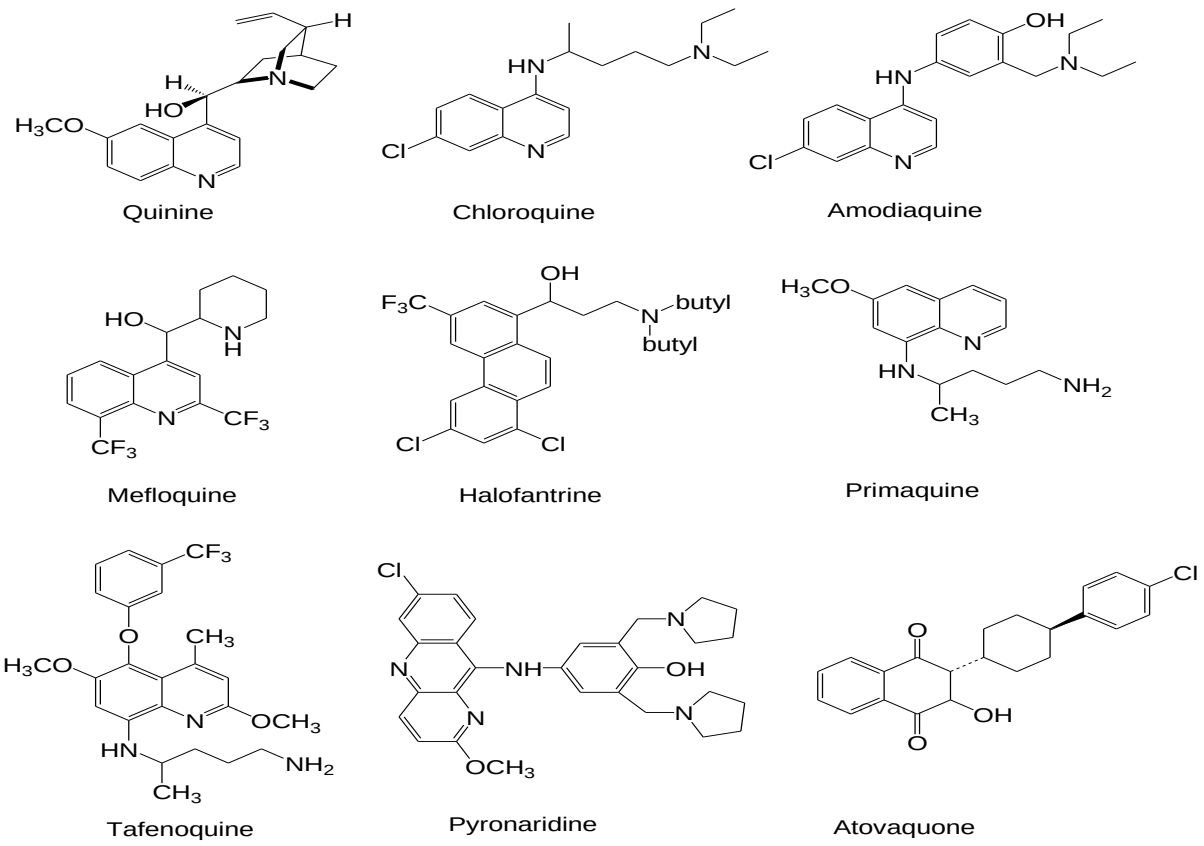

Fig. 1: Structures of quinoline based antimalarial drugs[1, 17]

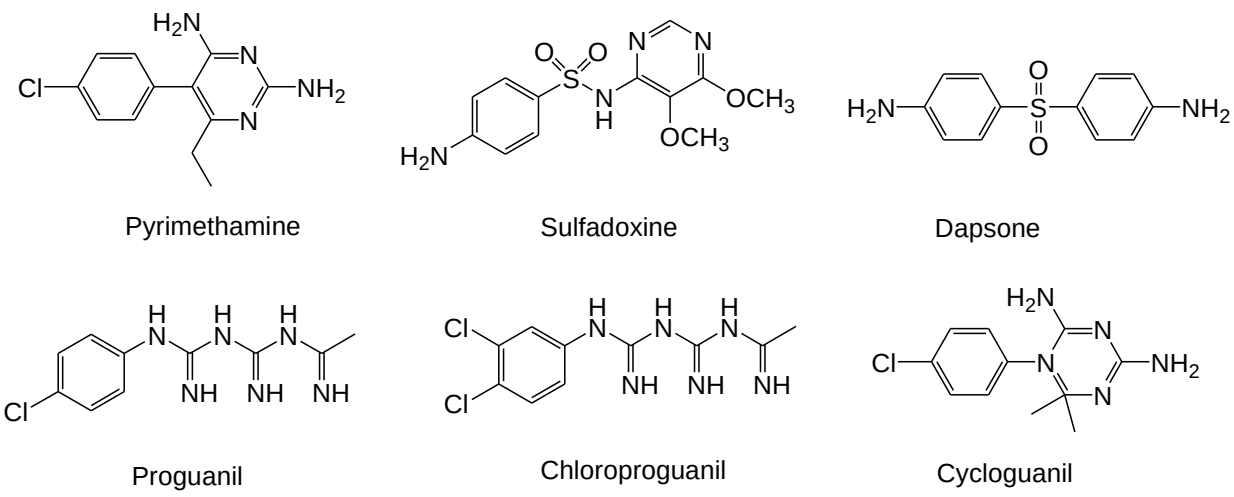

Fig. 2: Structures of folate antagonists[1,17]

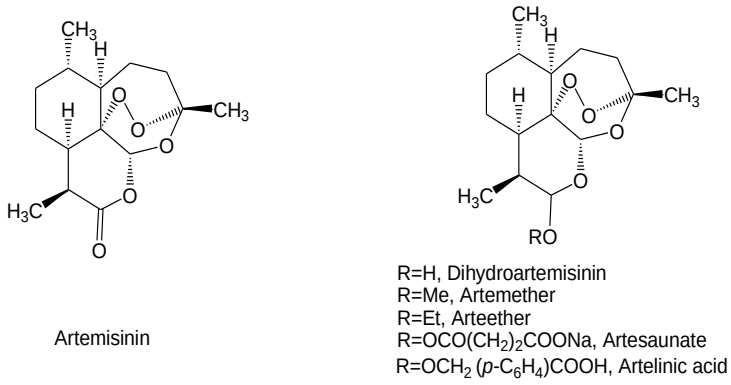

Fig. 3: Structures of artemisinin and its derivatives[1,17]

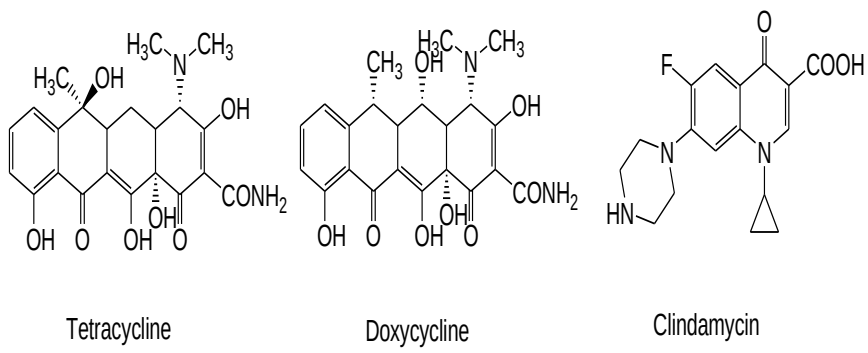

Fig. 4: Structures of antibiotics.

c) Artemisinin and its derivatives

Artemisinin, an active constituent of *Artemisia annua* (sweet wormwood), is fast acting against multidrug-resistant *P. falciparum* strain. The artemisinin drugs (including its derivatives) are now considered as the most important new antimalarials (Fig. 3), used for the treatment of severe malaria[9]. The various artemisinin derivatives include dihydroartemisinin (DHA), artemether, arteether, (oil soluble ethers), artesunate (water-soluble hemisuccinate), artelinic acid. These are all cyclic endoperoxudes or sesquiterpene lactone compounds. Artemisinin and related peroxidic antimalarial agents exert their parasiticidal activity subsequent to reductive activation by haem, which is released as result of haemoglobin digestion by *Plasmodium* parasite. This irreversible redoxreaction produces carbon-centered free radicals, which lead to alkylation of haem and proteins (enzymes) [17].

d) Antibiotics

Antibiotics also play a major role in the treatment and prophylaxis of malaria. Tetracycline and chloramphenicol are well tolerated and effective as antimalarial drugs. Tetracycline and its analogues doxycycline, azithromycin, clindamycin (Fig. 4) are used as prophylactic agents against *P. falciparum*; that are known to block translation by binding reversibly to the 30S subunit and distorting it in such a way that the anticodons of the charged tRNAs cannot align properly with the codons of the tRNA[5, 9,17]. Table 3 describes briefly folate antagonists, artemisinin including its derivatives, and antibiotics of clinical use.

Conclusion

Resistance to antimalarial drugs is proving to be a challenging problem in malaria prevention and control in most parts of the world. Since early 1960s the sensitivity of the parasites to chloroquine has been on the decline. Newer antimalarials were discovered in an effort to tackle this problem, but all these drugs are either expensive or have undesirable side effects. Moreover, after a variable length of time, the parasites, especially the *P. falciparum* species, have emerged resistance to newer currently available drugs which has severely limited the choice of these drugs[20]. However, Based on novel rational drug design and traditional random screening method of drug discovery programs, multiple general approaches can be pursued towards development of new antimalarial drugs with novel modes of action, which would be effective against multi-drug resistant malaria.

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Table 1: Chemical classification of the current antimalarial drugs[1, 15, 17]

Chemical class	**Examples**
4-aminoquinolines	Chloroquine (CQ), hydroxychloroquine, amodiaquine etc.
8-aminoquinolines	Pamaquine, primaquine, pentaquine, tafenoquine etc.
Arylamino alcohols (Quinoline methanol)	Quinine & quinidine
i. 4-quinolinemethanol	Mefloquine
ii. 9-phenanthrene methanol	Halofantrine, Lumefantrine
9-aminoacridines	Quinacrine, acriquine, aminoacrichin etc.
Biguanides	Proguanil, chloroproguanil, bromoguanil, cycloguanil etc.
Diaminopyrimidines	Pyrimethamine, trimethoprim
Hydroxynaphthoquinone	Atovaquone
Benzonaphthyridine dvt.	Pyronaridine
Sulfonamides	Sulfadoxine, Sulfamethoxazole
Sulfones	Dapsone
Sesquiterpene lactone enoperoxides	Atemisinin, artemether, arteether, artesaunate, artelinic acid etc.
Antibiotics	Tetracycline, doxycycline, clindamycin, azithromycin etc.

Table 2: Quinoline-based antimalarials of clinical use [1, 16, 20]

Drug	**Target of action**	**Mode of action**	**Adverse effects**	**Clinical uses**
Chloroquine	Blood-stage schizonticide	Direct heme binding, Inhibit heme Fe(II)FPIX Polymerase,	GI upset, itching, dizziness, psoriasis etc.	Treatment and chemoprophylaxix of sensitive parasites
Quinine	Erythrocytic schizonticide	Same as CQ	Tinnitus, vertigo, syncope, headache etc.	Treatment of CQ-resistant *P. falciparum*
Mefloquine	Blood-stage schizonticide	Formation of toxic substance, Swelling of food vacuole	Vomiting, headache, insomnia etc.	Chemoprophylaxix and treatment of *P. falciparum*
Primaquine	Tissue-stage schizonticide & gametocytocide	Generation of toxic metabolites, Oxygen radicals in Plasmodial mitochondria	GI upset, anorexia, elevated methemoglobinaemia	Radical cure and terminal prophylaxix of *P. vivax* & *P. ovale*
Halofantrine/ Pyronaridine	Erythrocytic schizonticide	Inhibit heme polymerase, Inhibit vacuolar degradation	GI upset, cardiac arrest	Treatment of CQ-resistant *P. falciparum*
Atovaquone	Blood-stage schizonticide	Inhibit mitochondrial electron transport	GI upset, stomatitis	Treatment and chemoprophylaxix of *P. falciparum*, in combination with proguanil

Table 3: Folate antagonists, artemisinin including its derivatives, and antibiotics of clinical use[1, 16, 20]

Drug	Target of action	Mode of action	Adverse effects	Clinical uses
Pyrimethamine/ Sulfadoxine	Blood-stage schizonticide	Inhibitor of dhfr-ts /dhps, thereby, inhibit parasitic DNA	Headache. SJS, Skin rash	Treatment of CQ-resistant *P. falciparum* (in combination as SP)
Proguanil	Erythrocytic schizonticide	Inhibit dhfr and stops pyrimidine biosynthesis	GI upset, nausea, Vomitting	Chemoprophylaxis (with CQ)
Artemisinin and its derivatives	Erythrocytic schizonticide & gametocytocide	Formation of iron catalysed free radical, Alkylation of heme, Membrane damage by free radical	Neurotoxicity, anorexia, dizziness	Treatment of multidrug- resistant *P. falciparum*
Tetracycline/Doxycycline	Blood-stage schizonticide	Inhibit mitochondrial protein synthesis, block nucleic acid synthesis	Nausea, vomiting, diarrhoea	Treatment and chemoprophylaxis of *P. falciparum*

dhfr-ts: Dihydrofolate reductase-thymidylate synthase, dhps: Dihydrofolate pteroate synthase,
SJS: Steven's Johnson Syndrome.

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