# Review on Anti-Malarial Drugs Development from the Nature and Synthetic origin in Malaria Research

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***Abstract :*** The most deadly human parasitic infection Malaria is responsible for the million of deaths throughout the world. It is generally transmitted by female Anopheles mosquito infected with parasites *Plasmodium vivax*, *Plasmodium falciparum*, *Plasmodium malariae*, *Plasmodium ovale*, *Plasmodium knowlesi* but the *Plasmodium falciparum* is the major one. *Plasmodium falciparum* has developed resistance against currently available anti malarial drugs quinine, chloroquine, mefloquine, and artemisinin in the market. So there is a vital need to discover the novel anti-malarial drugs. In these connection natural products especially from the plant sources has played an important role in the development of anti malarial compounds due to their efficiency, safety, low cost and availability for thousands of years. In this connection, a number of medicinal plants are the potential source of anti-malarial agents. In this review, comparative studies of the synthetic and natural product anti malaria agents are reported.

***Index Terms*:-** Malaria, Synthetic drugs, Alkaloids, Terpenes, Flavanoids, Phenolics, Quinones.

## I. INTRODUCTION

Malaria is a devastating parasitic infectious disease through the world wide[1].Two hosts via human and mosquito are involved in the parasitic disease. It is caused by plasmodium species transmitted from the blood of an infected person and pass to a health human by a female *Anopheles* mosquito[2]. The five identified species of the parasite responsible for infecting human malaria are *Plasmodium falciparum, P. vivax, P. ovale, P. malariae and P. knowlesi.* Of these, *P. falciparum* and *P.vivax* account for more than 95% of deaths infected by malaria[3].The last World Health Organization report (2016) tracks a dramatic decline in the global malaria burden over resent years (2000-2015). 91 countries and territories have ongoing malaria transmission and about 3.2 billion people-almost half of the world's populations are still at risk of malaria. In 2015 alone, there were an estimated 212 million new cases of malaria and 429000 death, (WHO, 2016)[4]. Despite years of continual efforts, it is still one of the major causes of morbidity and mortality, especially in young children under five years of age and pregnant woman[3]. So, the risk of the serious parasitic disease can be reduce by prevention of the contacts between the human and *Anopheles* mosquito through the use of insecticides treated bed nets, insecticides and environmental care in the absence of an effective vaccine or anti-malaria drugs[5]. Malaria ranks fourth among the major infectious diseases in causing deaths after pneumococcal acute respiratory infections, HIV/AIDS and tuberculosis, and accounts for approximately 2.6% of the total disease burden of the world[6]. Presently used anti-malarial synthetic drugs are chloroquine, amodiquine, quinine and quinidine, Mefloquine and primaquine, pyrimethamin/ sulfadoxine and atovaquone/ proguanil, Artesunate, Artemether, Dihydroartemisinin, Tetracycline, Doxycycline, Clindamycin, Azithromycin and so on. But the parasites have been growing their high resistance power against the synthetic drugs. Besides this the drugs are costly also and so many side effects like High fever, Profuse, sweating, Headache, Nausea, Vomiting, Abdominal pain Diarrhea, Anemia, Muscle pain, Convulsions, Coma, Bloody stools[7]. So, recently, the researchers are hunting for the natural source drugs which are more potent and effective than synthetic drugs. Some examples of recent natural antiplasmodial compounds are isolated like phenolic derivatives (Lupinifolin, Citflavanone, 8-Prenyldaidzein, Corylin etc), alkaloids (morphinan, tazopsine etc.) terpenoids (corymbolone, mustakone etc.) steroids etc from the plants. Natural source drugs are cheap and widely available also. Thus natural product structures continue to play a highly significant role in the discovery of drugs destined for the treatment of human disease[8].

## II. Sign and symptoms of malaria

The signs and symptoms of malaria typically begin 8-25 days following infection but may occur latter in those who have taken anti-malaria medications as prevention[9]. The symptoms of malaria are flu-like symptoms. The common symptoms of malaria include shaking chills that can range from moderate to severe, high fever, profuse sweating, headache, nausea, vomiting, abdominal pain, diarrhea, anemia, muscle pain, convulsions, coma, and bloody stools[7].

## III. Life cycle of Parasite

Anopheles mosquitoes and humans are the main spreader of Malaria. The mosquito firstly bites to a human through the spreading of the sporozoites into the bloodstream and then transfer it into the liver. Then sporozoites are multiplied into merozoites by infecting the liver cell through rupturing the liver cells and come back into the blood stream and thereby infecting the RBC by the formation of the ring forms, trophozoites and schizonts that in turn produce further merozoites. Sexual forms, if are produced, which can be taken up by a mosquito, infects the insect and continue the life cycle[9].

**IV. Currently available synthetic drugs**

Recently available anti malarial drugs work only on the erythrocytic stage of the infection without concerning pre-erythrocytic (hepatic) stage. For this reason a demand of novel class of anti malarial compounds to manage the malarial infection by all stages of all five species of human malaria. Currently available anti malarial drugs are classified into four major categories. Only single drug is unable to eliminate the all the strains of malaria. Repeatedly one or more combination of drugs have to be administered to the malaria patients. The geographic location of infection, the severity of disease presentation and more likely Plasmodium species are the factors of anti-malarial dosing therapy[3].

**IV.1.Quinoline derivatives:**

This type of drugs are mainly classified into three categories 4-amino quinoline, 4-methanol quinoline and 8-amino quinoline. Drugs belongs to this class are chloroquine, amodiquine quinine and quinidine, Mefloquine and primaquine. These drugs are acting by the inhibition of heme polymerase activity by the consumption of parasite food vacuole and prevents the of the crystallization in the Plasmodium food vacuole by the formation of the complex with heme[11]. Amodiaquine is more potent than chloroquine, in the connection of faster clinical recovery[12].

**IV.2. Antifolates:**

It is mainly categorised into three categories namely Folate antagonist, sulfa combination Napthoquinone, Folate antagonist combination. Drugs of this category are pyrimethamin/ sulfadoxine and atovaquone/ proguanil. Folate antagonist target the dihydrofolate reductase (DHFR) activity of the parasite's bifunctional DHFR-thymidylate synthetase (TS) protein, whereas the sulfa drugs affect the dihydropteroate synthetase (DHPS) activity of the bifunctional hydroxymethylpterin pyrophosphokinase (HPPK)-DHPS protein, all of these drugs acting as competitive inhibitors of the natural substrates[3]. Atovaquone-proguanil is highly efficacious against P. falciparum, including strains that are resistant to chloroquine and mefloquine, with cure rates of 98%[13].and shows synergistic effect[14].

**IV.3. Artemisinin derivatives :**

Categories of this derivative is Sesquiterpene lactone endoperoxides and the drugs are Artesunate Artemether Dihydroartemisinin[3]. The Endoperoxide Bridge in its molecule given to interact with heme iron in the parasite and produces oxygen radicals. The given free radical selectively binds to membrane proteins, causes lipid peroxidation, damages endoplasmic reticulum, inhibits protein synthesis and ultimately results in lysis of the parasite[15].This drugs are more used in the market for fast reduction of the parasite growth, rapid clearance of clinical symptoms[13], low toxicity[16], greater hydrolytic stability and better half life[17].

**IV.4. Antimicrobial :**

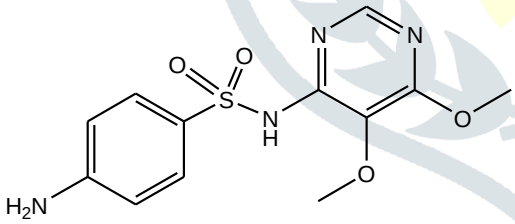
The drugs of this class are Tetracycline, Doxycycline, Clindamycin, Azithromycin[3]. Antiplasmodial activity of these agents produced by acting against 70S ribosomes in the parasite mitochondrion[18]. Clindamycin is a well tolerated drug with mild and fleeting side effects[3].

**V. Side effects of the synthetic drugs:-**

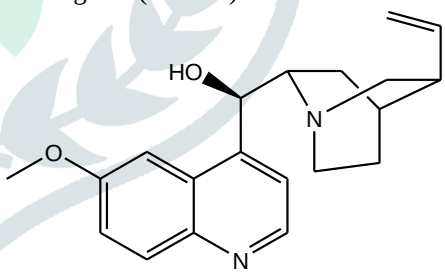
The major side effects of these drugs include nausea, vomiting, vaginal itching or discharge, heartburn, stomach and joint pain [19].

**VI. Vaccine:-**

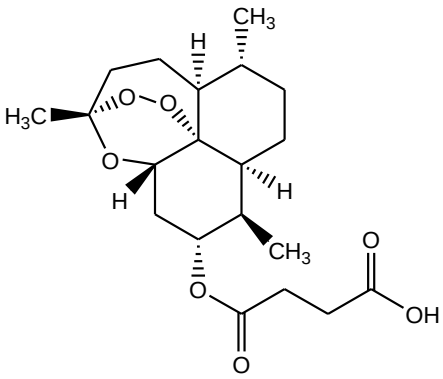
The vaccine has shown 30–50% protection in clinical trials. Currently, various blood-stage antigens are in clinical development as vaccines: apical membrane antigen (AMA1), erythrocyte-binding antigen-175 (EBA-175)], glutamate-rich long protein (GLURP), merozoite surface protein (MSP 1) , MSP 2 and MSP 3 and serine repeat antigen 5 (SERA5)[3].



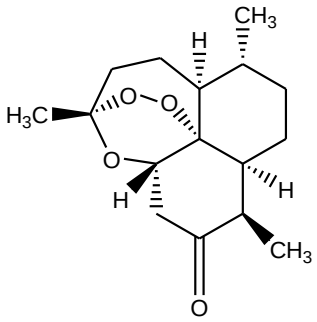

Sulphadoxine




Quinine




Artesunate




Artimisinin

**Figure 1.0 Some synthetic Anti-malarial drugs**

**VII. Natural Source Drugs:-**

Traditional medicines are commonly sold in markets and public places or administered by healers in traditional clinics. Plants have constituted the basis of traditional medicine systems and recently, natural products have been a good source of lead compounds for drug development for thousand years[20]. A large number of antimalarial compounds with a wide variety of structures have been isolated from plants and can play a role in the development of new antimalarial drugs. Some examples of recent natural antiplasmodial compounds are isolated like phenolic derivatives, alkaloids, flavonoids, terpenoids, steroids etc from the plants[21].

**VII.1. Phenolic Derivatives:-**

**VII.1.1. Flavonoids derivatives:-**

Ethyl acetate extract from the stem bark of *Erythrina fusca* Lour[22] and *Erythrina sacleuxii* Hua[23] showed antimalarial activity in vitro against various strains of P. Falciparum. The isolated compound from the plants are Lupinifolin, Citflavanone, 8-Prenyldaidzein, Corylin, Erysubin F, Prostratol C, 2,3-Dihydro-7-demethylrobustigenin etc. [21].

**VII.1.2.Xanthones :**

The methanol extract of the stem bark of *Chrysochlamys tenuis* Hammel resulted in the isolation of 1,5-Dihydroxy-3-methoxy-4-isoprenylxanthone, 1,3,7-Trihydroxy-2,4-diisoprenylaxnthone, Toxyloxanthone-A acts as antiplasmodial activity for their cytotoxicity . Toxyloxanthone A was the most interesting with antimalarial activity due to relatively low cytotoxicity[24].

**VII.1.3.Lignans :**

From the hexane extract of *Holostylis reniformis* Duch. Five lignans were isolated and 4,5-dimethoxy-3′,4′-methylenodioxy-2,7′-cyclolignan-7-one,(7′R,8S,8′S)-30,4′0-dimethoxy-4,5-methylenodioxy-2,7′-cyclolignan-7-one compounds possessed high antiplasmodial activity due to their low toxicity on hepatic cell. So, these compounds are potential candidates for the development of antimalarial drugs[25].

**VII.1.4.Quinones**:

Primin, a natural benzoquinone occurring in *Primula obconica* Hance. was investigated for its antiprotozoal potential and this compound showed moderate activity against K1[26]. A new non-cannabinoid constituent was isolated from *Cannabis sativa* L. namely 5-acetoxy-6-geranyl-3-npentyl- 1,4-benzoquinone which displayed notable antimalarial activity against D6 and W2 clones[27].

**VII.2.Terpenoid compounds and other derivatives:**

**VII.2.1. Sesquiterpenes:**

Two sesquiterpenes, corymbolone and mustakone, isolated from the chloroform extract of the rhizomes of *Cyperus articulatus L*. (Cyperaceae), exhibited antiplasmodial properties against NF54[28]. Fractionation of the dichloromethane extract of the leaves of *Vernonia staehelinoides* Mart. ex Baker (Asteraceae) allowed the isolation of two structurally related hirsutinolides. These compounds displayed strong antiplasmodial activity against D10 and were less effective against K1[29].

**VII.2.2.Diterpenes:**

Geranylgeraniol was isolated from the stems and leaves of *Croton lobatus* L. (Euphorbiaceae), a medicinal plant used in western Africa in traditional folk medicine to cure malaria, pregnancy troubles and dysentery. The compound showed reasonable antiplasmodial activity against K1and good selectivity[30].

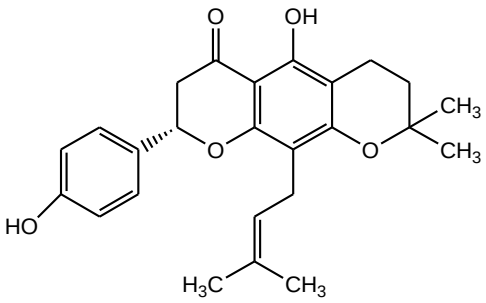
**VII.2.3.Triterpenes:-**

The isolation of betulinic acid 3-caffeate from a sample of the dried leaves, twigs, and branches of *Diospyros quaesita* Thwaites (Ebenaceae). This compound showed strong antimalarial activity against D6 and W2. Evaluation of betulinic acid 3-caffeate in the human oral epidermoid (KB) cancer cell line revealed cytotoxicity[31].

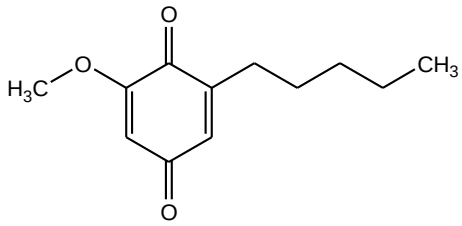
**VII.3.Alkaloids and other derivatives:-**

The methanolic extract of *Albizia gummifera* C.A.Sm. (Leguminosae) was fractionated to isolate five known spermine alkaloids from the alkaloidal fraction, budmunchiamine K, 6-hydroxybudmunchiamine, K,5-normethylbudmunchiamine K,6-hydroxy-5-normethylbudmunchiamine K and 9-normethylbudmunchiamineK. These alkaloids showed good activity on ENT30. Four of these alkaloids were evaluated for activity against *P. berghei* in vivo. The alkaloids showed chemo suppression percentages of parasitaemia in mice ranging from 43 to 72% at 20 mg/kg per day[28]. Decoction of *Strychnopsis thouarsii* Baill. (Menispermaceae) is used in Malagasy traditional medicine to fight malaria[32]. It has been shown that this traditional remedy prevents malaria infection by targeting Plasmodium at its early liver stage[33].

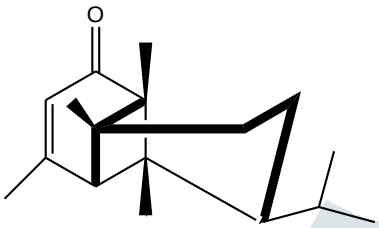
The fractionation of *S. thouarsii* stem barks extracts, led to the isolation the new morphinan alkaloid tazopsine together with sinococuline ,exhibited selective inhibitory activity against *P. yoelii* liver stage in vitro. Tazopsine showed the most potent inhibitory activity with and Sinococuline was both slightly less active and less toxic[32].



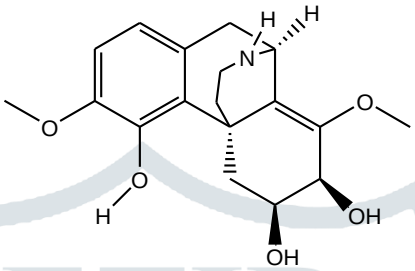
Lupinifolin



Primin



Mustakone



Sinococuline

**Figure 2.0 Some natural Products as Anti-malarial drugs**

**VIII. Conclusion**

Malaria is becoming a major global problem due to massive worldwide health burden by the emergence of drug resistance. The confrontation of malaria parasites to accessible synthetic drugs carries on growing, progressively limiting our power to manage this serious disease. In this connection the investigation of many novel strategies for antimalarial drug invention is now under assessment. Now the researchers are finding novel antimalarial compounds from the nature which is the richest reservoir of the many pharmaceutical compounds that can be used safely in the treatment of the many diseases. Approximately 480 antimalarial compounds are evaluated and they show activity against the P. falciparum. Plant derived antimalarial compounds are mainly phenolic compounds, terpenoids, quinines and alkaloid derivatives. Some of them possess high activity in vitro. As the plant derived compounds are safe, less toxic and more effective they can provide scientific basis on the use of traditional medicines. From the comparative study of the synthetic and natural product anti-malarial compounds, the later is more potent than the former one because of the cheap, wide availability, more potency.

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