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ANTI-MALARIAL TREATMENT: THEN; NOW AND FUTURE ASPECTS

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ABSTRACT

Malaria is a life-threatening disorder affecting various regions of the world. A lot of population is under the danger even though many drugs have been designed and discovered. Drug-resistance is alarming situation from long time ago. This review focuses on many of the drugs that have been discovered so far. Scientists are also looking forward for other newer targets for eradicating malaria. A brief review on developmental research on anti-malarial vaccines has also been covered in this digest.

Keywords: Malaria, Vaccines, Scientists.

INTRODUCTION

Malaria is a life-threatening blood disease caused by a parasite that is transmitted to humans by the **infected *Anopheles*** mosquito. Malaria is a preventable and treatable disease [1]. The parasites include plasmodium vivax and plasmodium falciparum; other species are also known but are endemic to certain regions of the world. The female anopheles mosquito is considered to be the vector for the transmission of parasite.

In the human body, the parasites multiply in the liver, and they then infect red blood cells. Symptoms of malaria include headache, fever and vomiting, and usually appear between 10 and 15 days after the infected mosquito bite. If not treated, malaria may quickly become life-threatening by disrupting the blood supply to vital organs. In many parts of the world, the parasites have developed resistance to a large number of antimalarial medicines [2].

About 3.4 billion people – half of the world's population – are at risk of malaria. In 2013, there were about 207 million malaria cases (with an uncertainty range of 135 million to 287 million) and an estimated 627 000 malaria deaths with an uncertainty range of 473000 to 789000. Increased prevention and control measures have led to a reduction in malaria mortality rates by 42% globally since 2000 and by 49% in the WHO African Region.People living in the poorest countries are the most vulnerable to malaria. In 2013, 85% of all malaria deaths occurred in the WHO African Region, mostly among children under 5 years of age [3].

Key interventions to control malaria include: prompt and effective treatment with artemisinin-based combination therapies; use of insecticidal nets by people at risk; and indoor residual spraying with insecticide to control vector mosquitoes [2].

Pathogenesis

On the bite of an infected mosquito, the parasites enter the blood, resulting in high levels of parasitemia [4]. The parasite is introduced as an infectious form (sporozoite) which travels through the blood to the liver where it multiplies asexually to produce multiple merozoites, which can invade red blood cells [5]. These may continue to multiply asexually, prolonging the infection, but can also form gametocytes that are taken up by feeding mosquitoes and complete the cycle by fusing to form zygotes (ookinetes) that develop into new sporozoites. Clinical malaria occurs during the asexual blood stage when the parasite leaves the liver and begins to invade and multiply within red blood cells. The immune

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response against malaria is not fully understood, although both humoral and cell-mediated immunity are involved and various T-cell subsets are required [6].

Anti-Malarial Treatment

Until the 1930s, quinine was the antimalarial drug of choice. After war broke out in the Pacific region at the end of the year 1941, also the Dutch quinine plantations in East Indies became inaccessible, and synthetic alternative drugs like Chloroquine were used. These drugs were successful for some time, but after some years, Plasmodium parasites developed resistance to chloroquine and other antimalarial drugs, meaning that new treatments were the need of the hour.

Artemisinin also called *qinghaosu*, was used as an antimalarial drug derived from *Artemisia annua also known as the* sweet wormwood plant. Artemisinin is a sesquiterpene lactone which is a compound made up of three isoprene units bound to cyclic organic esters and is distilled from the dried leaves or flower clusters of *A. annua* [10].

The antipyretic (fever-reducing) properties of the plant were first recognized in the 4th century by Chinese physicians. The active agent, called *qinghaosu*, was isolated from the plant in the 1970s; this compound became widely known as artemisinin. Today, there are several derivatives of artemisinin, including artesunate and artemether, which are used in the treatment of malaria [11].

The drug is particularly useful in the treatment of infections involving Chloroquine-resistant parasites and infections involving multidrug-resistant *P. falciparum*, which is the deadliest of the malaria protozoans[13]. Artemisinin targets *Plasmodium* organisms in the schizont stage of development. Schizonts, which mature from sporozoites the form of parasite are transmitted to humans in the salivaof female *Anopheles* mosquitoes,contain insoluble metal iron called hemozoin.

Hemozoin is formed within schizonts when they feed on hemoglobin in the cytoplasm of human red blood cells. Artemisinin contains 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-a kind of "dirty bomb".

In the year 2003, a research team headed by Dr.Krishna at St George's Hospital and Medical School in London discovered that artemisinin inhibited an enzyme called Plasmodium falciparium ATP6 (PfATP6) responsible for a "pump" transporting calcium ions across cell walls in the parasite, this inferred that both iron and the peroxide group are important to its action[12].

Artesunate is unique among the artemisinin-derived agents because it can be administered intravenously. Thus artesunate was used in the treatment of cerebral malaria, which is an acute form of the disease, initiated by the rapid spread of parasites to the brain and by death results within 72 hours if left untreated. Artemisinin appears to have few side effects in humans [11].

Artemisinin is largely obtained from sweet wormwood, which contains less than 1% artemisinin. Making artemisinin from start requires many steps, and is also an expensive process. Two promising routes have been described; one uses "genetically engineered" yeast (Saccharomyces cerevisiae) to produce artemisinic acid, via two chemical constituents' i.e. farnesyl pyrophosphate, and amorpha-4,11-diene. Others have reported a single continuous flow process that makes artemisinin from dihydroartemisinic acid, itself easily made from artemisinic acid [12].

Artemisinin and its derivatives have a short duration of action and target malaria parasites in a specific stage of their life cycle, there is a high rate of disease occurrence associated with the drugs when they are used alone in single-agent therapy [13]. Similarly to the spread of resistance to chloroquine and other antimalarial medicines in the past, there is a possibility that artemisinin resistance will spread or develop independently around the world.As a result, they are usually used in combination with other, longer-acting antimalarial drugs. Examples of first-line artemisinin-based combination therapies (ACT) used in the treatment of malaria include artesunate-mefloquine, artemether-lumefantrine, and artesunate-amodiaquine [15]. Typical partner drugs include lumefantrine (human $t_{1/2}$ = 3–4 days) [24] and piperaquine (human $t_{1/2}$ = 8–16 days) [19]. The most popular combination consists of tablets containing artemether (20 mg) and lumefantrine (120 mg) sold as Coartem™ (Novartis) [20]. Adults take four tablets twice a day for 3 days [21], but compliance to this six-dose regimen is variable [22]. In 2011, the European Medicines Agency (EMA) approved the combination of dihydroartemisinin and piperaquine which is taken once a day for 3 days [23]. The ACTs have supplanted the previously recommended sulfadoxine–pyrimethamine, which in turn replaced chloroquine. Parenteral artesunate is the drug of choice for severe malaria [24].

ACTs comprise semisynthetic artemisinin derivatives paired with distinct chemical classes of longer acting drugs. These artemisinin derivatives are exceptionally potent against the pathogenic asexual blood stages of Plasmodium parasites and also act on the transmissible sexual stages[11]. These combinations increase the rates of clinical and parasitological cures and decrease the selection pressure for the emergence of antimalarial resistance. Although these combination therapies also have proved valuable in the prevention of emergence of artemisinin-resistant parasites, the persistent use of single-agent artemisinin therapy in some parts of the world has led to the development of resistant parasites and ultimately high rates of treatment failure in these areas.In the Greater Mekong sub region, patients with

resistant parasites still recover after treatment, provided that they are treated with an ACT containing an effective partner drug. However, there is a real risk of parasites developing resistance to all available medicines. For example, in western Cambodia, ACT options have become so limited in the past few years that until recently a non-ACT drug, Atovaquone-Proguanil, was recommended as first-line treatment [15]. The national malaria program has now switched back to ACTs but the program will apply *directly observed treatment* for all patients, and monitor resistance through molecular markers. WHO recommends that the country changes its treatment policy by switching to an ACT with a different partner drug, if the treatment failure rate is higher than 10% after treatment with an ACT[13].Drugs like Naphtoquine in combination with Artimisinin can be effective in a single dose of eight tablets [15].

Other drugs too showed some antimalarial effects, these were also drugs for the elimination of hypnozoites (primaquine),preferred combination for prophylaxis (atovaquone–proguanil) [28], and the active metabolite of proguanil (cycloguanil) [29]. Experimental data are reported for primaquine [25], atovaquone [26.27], proguanil, and its active metabolite cycloguanil.
Mefloquine is sold as a racemate (Lariam), and causes a relatively high incidence of depression, psychosis and nightmares.

While both enantiomers are active, the (-)-enantiomer is believed to cause the neurological side effects by binding the adenosine receptors in the brain[31]. In an effort to select the next generation of quinoline methanol derivatives that could serve as are placement for mefloquine, the Walter Reed Army Institute of Research screened for analogs with a lower brain penetration, and identified WR621308[30,32]. WR621308 has a substantially lower permeability across MDCK cell monolayers than mefloquine, suggesting lower brain exposures.

Another artemisinin-type molecule known as artemisone was reported in 2006. It is 8-10 times more potent that artemether in vitro and 4-10 times more potent in mice. It combines high activity against the malarial parasite with other desirable features including low lipophilicity (solubility in fat) and negligible neurotoxicity and cytotoxicity)[11]. Combination with Mefloquine can be used as a single dose therapy. Similarly combination of Artimisinin derivatives with Mefloquine can also be used as a single dose therapy[32].

The main mechanism for the activity of the antimalarial action of artemisinin is thought to involve the cleavage of the peroxide bond by Fe(II) found in heme proteins, thus generating toxic oxygen radicals. Newer molecules have been synthesized, which contain the endoperoxide ring, as an substitute for antimalarial drugs. Many of the molecules are under discovery processes hence they are not named but contain a coding name. 1,2,4- Triozolanes and 1,2,4,5-Tetraozones[37,41] are the basic molecules, these help in the stabilization of the endoperoxide groups. Substituents on the 3rd and 5th position in 1,2,4-trioxolanes differ in the different derivatives. Adamantane ring is the substituent on the 3th position of the oxolanes as well as the oxones, making them a potent antimalarial drug[14]. Some of the important derivatives of these classes of drugs are RKA 182[35], OZ 439[36] and OZ 277. These drugs are being tested for their therapeutic efficacy. They too may prove as a potential therapy in the forthcoming years. The first-generation ozonide OZ277[40], known as arterolane, inhibits the growth of chloroquine-resistant (K1) and chloroquine-sensitive (NF54) parasite strains with an IC 50=1.6–1.8nM. In 2012, Ranbaxy launched the combination of arterolane maleate and piperaquine phosphate as a 3-day treatment in India.The second-generation peroxide OZ439 (EC50 = 3.4-4.0nM) is now in Phase IIa studies. It features an 80- aryl rather than an 80-alkyl group. The Central Drug Research Institute, Lucknow, India, is investigating the trioxane CDRI-97/78 in Phase I studies [36-38]. The key step in the construction of the trioxane core is an ‘ene’ reaction between an allylic alcohol and singlet oxygen, to give peroxide. Additional artemisinin derivatives, ozonides, and 1,2,4-trioxanes have been reported to have potencies comparable to artemether, but were not shown to possess obvious advantages.

The prototypical 4-aminoquinoline chloroquine has been widely used for treating malaria since World War II. Chloroquine exerts its antimalarial action by interfering with the formation of hemozoin within the parasite’s digestive vacuole. Hemozoin is a crystalline derivative of heme that the parasite makes as a way of disposing of toxic heme released upon hemoglobin digestion. Resistance to chloroquine is now found in all areas of the world, and involves multiple mutations in the P. falciparum chloroquine resistance transporter, PfCRT. These mutations result in an in- creased efflux of chloroquine from the acidic digestive vacuole to the cytosol of the parasite.

Ferroquine [42] was found to be active against chloroquine- resistant plasmodium strains, and is currently undergoing Phase II clinical trials. Ferroquine, unlike chloroquine, accumulates in the digestive vacuole of the chloroquine-resistant parasites.

It was also shown that replacing the expensive ferrocene moiety of ferroquine with asimple and inexpensive benzene ring as structures shown in figure 13, retains activity against chloroquine-resistant strains (K1, W2)[43]. Because of its basicity,it is expected to accumulate like other 4-aminoquinolines in the acidic (pH=5) environment of the food vacuole. The fused ‘dimeric quinoline’ is active in vitro against drug-resistant strains, and in mouse when administered orally at 80 mg/kg[44]. Amodiaquine is also active against most chloroquine-resistant strains; however in hepatitis,

myelotoxicity and agranulocytosis restrict its use intreating acute malaria.

Amodiaquine is rapidly absorbed after oral administration in humans, and rapidly metabolized drug, mostly, via N-deethylation. In addition, two reactive metabolites are formed, namely imine and aldehyde, and are the likely cause of the hepatotoxicity and agranulocytosis respectively.

N-tert-Butyl isoquine (GSK36979) was designed to avoid the formation of quinone imines, and it has entered Phase I studies. In spite of the excellent exposures and quantitative oral bioavailabilities in animal model testing, its development was discontinued due to exposures insufficient to demonstrate drug safety superior to chloroquine[45-47].

Some of the most important malaria drugs, cycloguanil and pyrimethamine are inhibitors of Dihydrofolate Reductase (DHFR). DHFR converts 7,8-dihydrofolate into tetrahydrofolate, which is acofactor involved in one-carbon transfer reactions and an important molecule in the biosynthesis of nucleic acids. Inhibition of DHFR arrests DNA replication, but resistance continues to be widespread due to mutations in the enzyme. About 125 million pregnancies are at risk of malaria every year, and 10,000 women and 200,000 babies die as a result of malarial infections[48].

The Intermittent Preventative Treatment (IPT) is recommended for pregnant women and lactating mothers, but drug-resistance to the currently adopted IPT (sulfadoxine–pyrimethamine) substantiates new and effective regimens. Both azithromycin and chloroquine have demonstrated its safety and effectiveness in children and pregnant women over a number of years. Also, the azithromycin–chloroquine combination is synergistic against chloroquine-resistant strains of P. falciparum[49].As well as, azithromycin is a slow-acting antimalarial, with a maximum antiparasitic effect occurring only after two cycles of intra erythrocytic development. Finding azithromycin analogs with improved activity in mouse models of malaria has been challenging[50–52]. In the medicinal chemistry route, the two enantiomers were separated by chiral chromatography[53]. NITD-609 has an excellent potency.NITD-609 is also a potent inhibitor of gametocytogenesis and its mechanism of action is by blocking the transmission to mosquitoes[54].

Albitiazolium is a drug that is in Phase II clinical trials[55]. The understanding of its mechanism has recently been redefined[56].Albitiazolium acts primarily by inhibiting the transport of choline into the parasite[57]. The parasite requires choline to generate phosphatidylcholine, the important lipid of its cell membranes, as it replicates and forms new membranes.

An important property of albitiazolium is that it irreversibly accumulates in the Plasmodium up to 1000-fold. Itworks by inhibiting parasite growth and cures mice with an ED50 = 0.2 mg/kg/day. Also efficacious when given orally, but with a much lower ED 50 = 13 mg/kg/day, suggesting an oral bioavailability of the order of 2% (mouse)[58].

A research project undertaken by the University of Texas Southwestern, the University of Washington, Monash University, and GlaxoSmithKline reported the preclinical candidate DSM265, has entered Phase I studies in 2013[59]. DSM265 inhibits PfDHODH selectively over its human counterpart (IC50 = 33 nM and 2500 nM, respectively). Genzyme reported DHODH inhibitor 62 as a potential drug development candidate[60]. Benzimidazole inhibits PfDHODH and parasite growth.

The Broad Institute and the Harvard Medical School discovered a molecule against chloroquine resistant strain Dd2 Genzyme's Genz-668764 single enantiomeric nuclei, of which the absolute configurationnot yet published. Genz-668764 inhibits P. falciparum in vitro and is active in mouse at doses of the order of 100 mg/kg/day [61]. Broad Institute's diversity-oriented synthesis (DOS) library led to the discovery of the new extremely potent molecule:ML238 [62].

The screening network funded by the WHO Special Program for Research and Training in Tropical Diseases (TDR)reported the results of a 10,000 compound screen against seven whole organism pathogens responsible for tropical diseases in humans, including the intra-erythrocytic forms of P. falciparum. The most potent screening hit was TDR84420 with an EC 50 = 326 nM [63].

GSK reported a series of highly potent 2-pyrimidinecarbonitriles as inhibitors of falciparin-2 and falciparin-3. Falciparins are cysteine proteases that function to hydrolyze the host hemoglobin to provide amino acids for parasite protein synthesis [64].

Febrifugine is the active component of the Chinese herb Chang Shan, and is an antimalarial because of its rapid effect, efficacy and availability. However, acute liver toxicity has obstructed its use as aclinical drug [65].

Several additional active compounds were identified by various approaches, including the potent marine natural product salinosporamide A [66], SSJ-183 [67-69], prodiginin [69] tsitsikammamine C,[70]and the iridoidextracted from traditional African herbal remedies [71-76].

Currently, most approved malaria drugs target only the blood stages of the disease. The two exceptions are the combination of atovaquone and proguanil which is also effective in clearing parasites from the liver, and primaquine[77]. The latter clears not only liver schizonts but also hypnozoites, the dormant liver-stage parasites in P. vivax and P. ovale infections, thus providing what is known as a radical cure[78]. Hypnozoites are long-lasting reservoirs responsible for recurring malaria episodes in the absence of mosquito bites, and are a major health concern,

especially in the case of P. vivax. The search for liver stage drugs has been severely hampered by the lack of culture techniques and by cumbersome primate animal models. It has been suggested that for prophylactic treatment, compounds without blood stage activity might be preferred in order to minimize the risk of the emergence of drug-resistant parasites. Primaquine is adrug that acts slowly[79], and is therefore given together with other drugs, for example, chloroquine. Its mechanism of action is unclear, but it is believed to be mediated by reactive metabolites which destroy the mitochondrial structure of the parasite. Primaquine, however, causes hemolytic anemia in people with glucose-6 -phosphate dehydrogen ase (G6PD) deficiencies, which occur in 10% of the population[80], and are particularly prevalent in malaria endemic countries[81]. In fact, the spatial extent of P. vivax malaria overlaps widely with that of G6PD deficiency[81]. Additionally, compliance with the primaquine 14-day treatment regimen is difficult. The primaquine analog tafenoquineis currently in Phase IIb/III clinical trials and has proven activity against hypnozoites . Tafenoquine has the same G6PD deficiencyliability as primaquine, but has the advantage of being administered as a single dose treatment. Recent drug discovery efforts have focused specifically on targeting the asymptomatic liver stage sporozoites and hypnozoites in order to provide an ideal and novel, non-8-aminoquinoline drugs without the G6PD liability [82-84].

Atovaquone works by targetting the electron transport chain (ECT) of the mitochondrion, and specificallythe cytochrome bc1 complex [86]. Additional quinones have been reported, without obvious advantage[88,89], and progress was seen with pyridones. GSK reported a back up to pyridone GW844520, amolecule targeting cytochrome bc1; hydroxymethyl derivative remarkably improved the mouse oral bioavailability (approximately 50%) as compared to GW844520 (20%) [90].

O'Neill group, University of Liverpool, researched for molecular compounds that would inhibit another enzyme involved in the ECT, namely NADH:ubiquinone reductase (PfNDH2). Asuccession of in silico screens, HTS, and medicinal chemistry research led to CK-2-25, specificfor PfNDH2, and has been potent in mouse [91].

The first screening examples have been reported, such as the imidazolopiperazines described above [85]. Additionally, a set of 5300 biologically active compounds , which included 640 FDA-approved drugs, was screened and structurally diverse compounds with varied known biological functions were identified to also inhibit the malarial liver stages.

In addition, there is agrowing interest in signal peptide peptidases such as NITD-731 which inhibits P. yoelii liver stages with EC 50 = 7.8 nM. Cladosporin and NITD-731 inhibit liver stages with novel mechanisms of action. EC 50 values are reported for the drug-sensitive strains 3D7 and D10 [92].

Tafenoquine [93], NITD609 and GNF156 [94] were shown to have transmission- blocking activities in vitro. Tafenoquine was also found to delay sporozoite formation in P. vivax . Interestingly, a recently developed gametocyte drug screening assay identified methylene blue, as a potent inhibitor of gametocyte development across all stages.

Anti-Malarial Vaccines

Due to the over increasing problems in the treatment for malaria, a need for vaccine was necessary to make the population immune to malaria. Vaccine development was the need of the hour especially for the endemic sub-Saharan regions of Africa andmid-East Asia.

Stages of Vaccine Action [98-100]

The initial stage in the life cycle, following inoculation, is a relatively short "pre-erythrocytic" or "hepatic" phase. A vaccine at this stage must have the ability to protect against sporozoites invading and possibly inhibiting the development of parasites in the hepatocytes (through inducing cytotoxic T-lymphocytes that can destroy the infected liver cells).

The second phase of the life cycle is the "erythrocytic" or blood phase. A vaccine here could prevent merozoite multiplication or the invasion of red blood cells. The antibodies could potentially be directed. Another approach would be to attempt to block the process of erythrocyte adherence to blood vessel walls. It is thought that this process is accountable for much of the clinical syndrome associated with malarial infection; therefore a vaccine given during this stage would be therapeutic and hence administered during clinical episodes to prevent further deterioration.

The last phase of the life cycle that has the potential to be targeted by a vaccine is the "sexual stage". This would not give any protective benefits to the individual inoculated but would prevent further transmission of the parasite by preventing the gametocytes from producing multiple sporozoites in the gut wall of the mosquito. A policy directed at eliminating the parasite from areas of low prevalence or to prevent the development and spread of vaccine-resistant parasites. This type of transmission-blocking vaccine is potentially very important. The evolution of resistance in the malaria parasite occurs very quickly, potentially making any vaccine redundant within a few generations. This approach to the prevention of spread is therefore essential.

Another approach is to target the protein kinases, which are present during the entire lifecyle of the malaria parasite. A collection of structural data, inhibitory profiles and target validation has set the foundation and support for targeting the malarial kinome. Pursuing protein kinases as

cancer drug targets has generated a wealth of information on the inhibitory strategies that can be useful for antimalarial drug discovery [95].

The full-length *P. falciparum* reticulocyte-binding protein homologue (PfRH5) is highly susceptible to cross-strain neutralizing vaccine-induced antibodies, out-performing all other antigens delivered by the same vaccine platform. Despite being susceptible to antibody, PfRH5 is unlikely to be under substantial immune selection pressure; there is minimal acquisition of anti-PfRH5 IgG antibodies in malaria-exposed individuals. The data challenge the widespread beliefs that any merozoite antigen that is highly susceptible to immune attack would be subject to significant levels of antigenic polymorphism, and that erythrocyte invasion by *P. falciparum* is a degenerate process involving a series of parallel redundant pathways[96].

A study was carried out by researchers from the National Institute of Allergy and Infectious Disease in the US. The vaccine tested in this study is composed of live but weakened Plasmodium falciparum sporozoites, taken from the salivary gland of mosquitoes and weakened with radiation. Previous studies where this vaccine (called PfSPZ) was injected into the muscle showed very limited protection against malaria[97].

Completely effective vaccine is not yet available for malaria, although several vaccines are under development. SPf66 was tested extensively in endemic areas in the 1990s, but clinical trials showed it to be insufficiently effective. The SPf66 vaccine was one of the first malaria vaccines to be tested extensively in endemic areas. SPf66 is a synthetic peptide vaccine containing antigens from the blood stages of malaria linked together with an antigen from the sporozoite stage. SPf66 has had 10 trials in Africa, Asia, and South America. Results were initially promising, but further trials showed only a small effect in some trials, and no effect in Africa. There is no evidence that SPf66 is effective enough to be introduced on a routine basis for prevention of malaria [98].

Randomized controlled trials comparing blood-stage vaccines (other than SPf66) against *P. falciparum*, *P. vivax*, *P. malariae*, or *P. ovale* with placebo, control vaccine, or routine antimalarial control measures in people of any age receiving a challenge malaria infection. Five trials of MSP/RESA vaccine with 217 participants were included; all five reported on safety, and two on efficacy. No severe or systemic adverse effects were reported at doses of 13 to 15 µg of each antigen (39 to 45 µg total). One small efficacy trial with 17 non-immune participants with blood-stage parasites showed no reduction or delay in parasite growth rates after artificial challenge [99].

There is also a cumulative risk of toxicity when antiretroviral and antimalarial drugs are given to the same patients. Synergistic approaches involving the control of malaria as a strategy to fight HIV/AIDS and vice versa are therefore needed in co-endemic areas. Plant biotechnology has emerged as a promising approach to tackle poverty-related diseases because plant-derived drugs and vaccines can be produced inexpensively in developing countries [101].

Drugs that target the liver and transmission stages have the potential to be transformed, but research efforts have been hampered by the absence of high-throughput screens. New imaging techniques are solving this problem, with an innovative clinical compound having liver stage activity. Drug discovery efforts directed towards the liver and transmission stages are in their infancy but are receiving increasing attention as targeting these stages could be instrumental in eradicating malaria.

Fig 1. The complete lifecycle of a malarial parasite in human and mosquito [7]

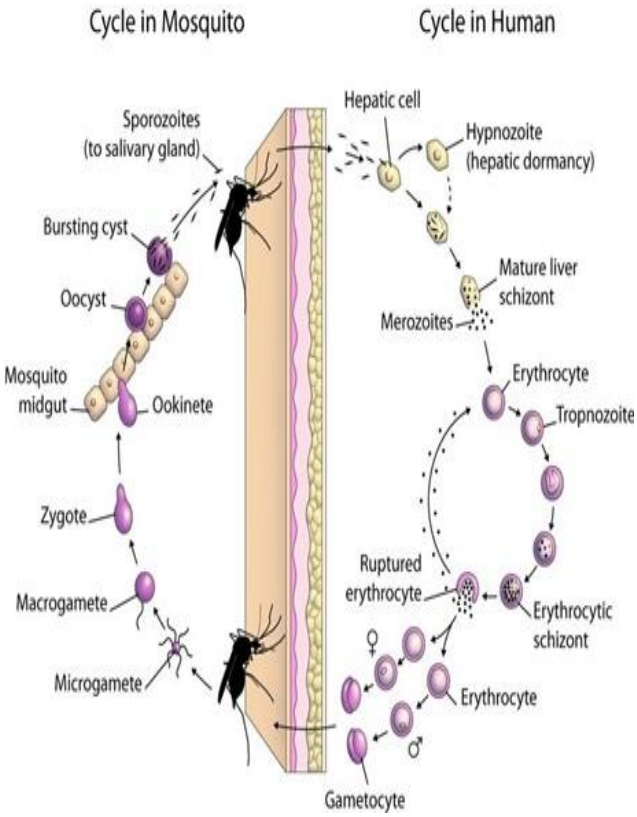


Fig 2. Quinine: First drug to be used for the treatment of malaria [8]

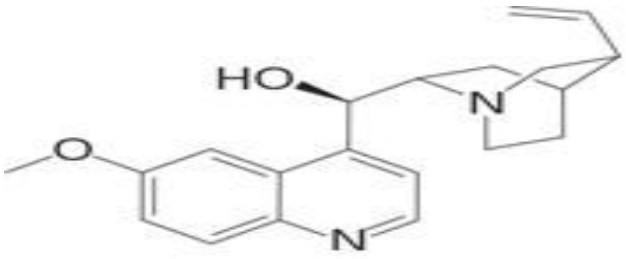
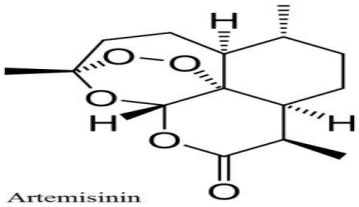


Fig 3. Chloroquine: Alternative remedy for malaria after Quinine [9].

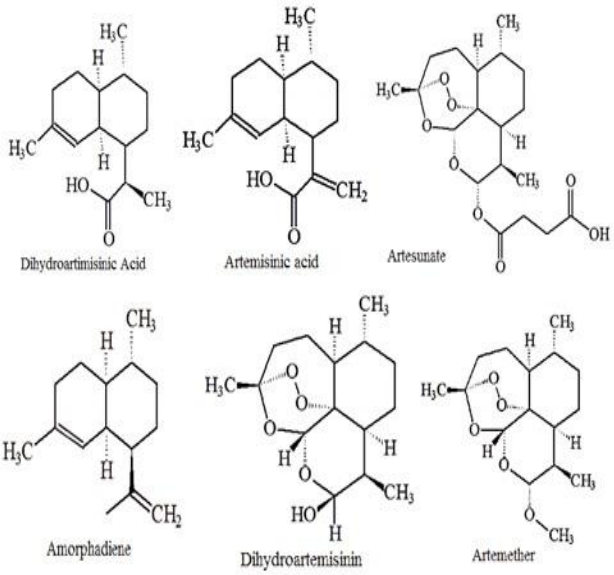
Chloroquine

Fig 4. Artemisinin is a sesquiterpene lactone, a compound made up of three isoprene units bound to cyclic organic esters[10].



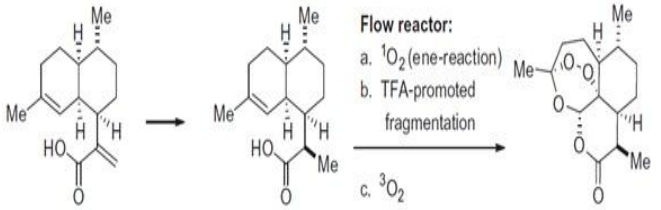
Artemisinin

Fig 5. Derivatives of Artimisinin



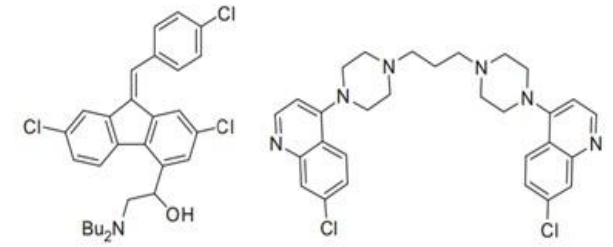
Dihydroartimisinic Acid | Artemisinic acid | Artesunate | Amorphadiene | Dihydroartemisinin | Artemether

Fig 6. Flow reaction for the production of Artimisinin from its precursor Artemesinic Acid[12].



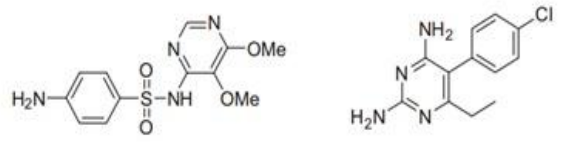
Artemisinic Acid | Dihydroartemisinic Acid | Artemisinin

Fig 7. Drugs used along with artemisinin as first-line artemisinin-based combination therapies (ACT) in the treatment of malaria[24].



Lumefantrine
EC_{50} = 0.45 nM (W2)
ED_{99} = 18 mg/kg

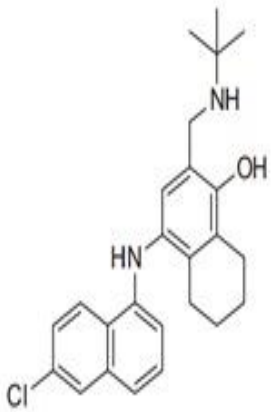
Piperaquine
EC_{50} = 12.5 nM (W2)
ED_{50} = 4.5-6.4 mg/kg



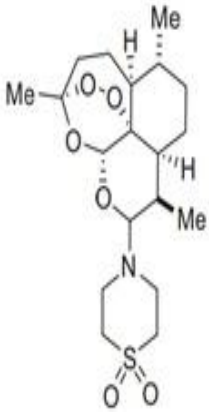
Sulfadoxine
EC_{50} = 30 nM (3D7)

Pyrimethamine
EC_{50} = 20-23 nM (3D7)

Fig 8. ACT combination with Naphthoquine can be effective as a single dose due to slow clearance of the drug [15]



Naphthoquine



Artemisone
EC_{50} = 0.88 nM (3D7)
ED_{50} = 2 mg/kg/day

Fig 9. Alternative Drugs used in the treatment of Malaria [25-29]

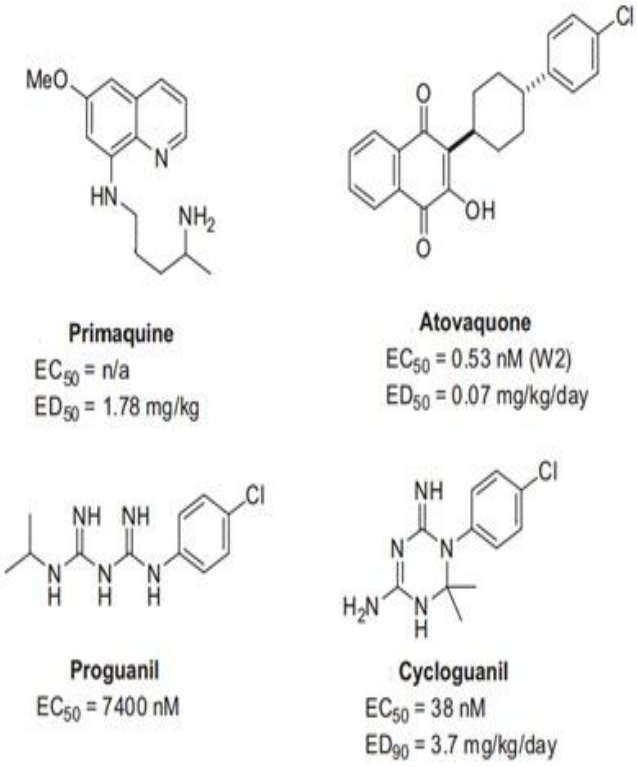


Fig 10. Mefloquine and its enantiomers, mefloquine is a racemate, and the reported stereochemistry for mefloquine is relative, not absolute. EC 50 values are reported for the multi-drug resistant strain W2 [30]

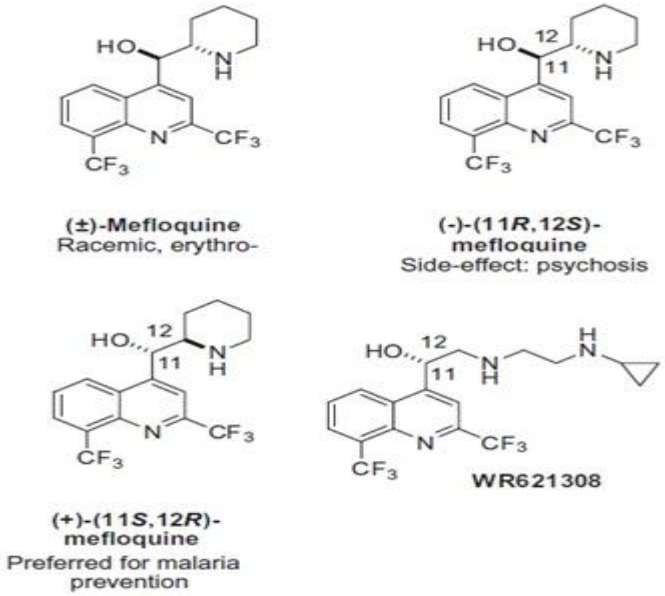


Fig 12. The ozonides [35-41]

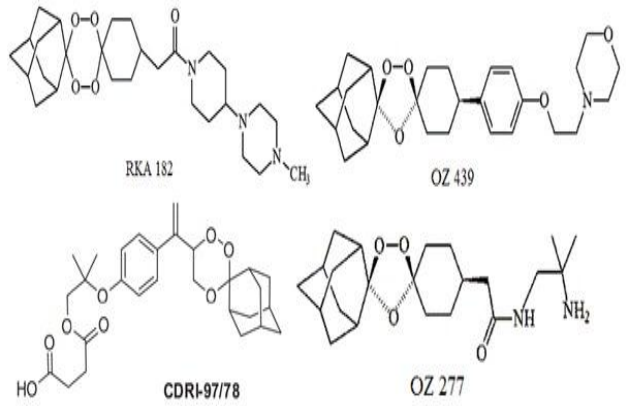


Fig 13. 4-Aminoquinoline. EC 50 values are reported for the drug-sensitive strain 3D7 and the multi-drug resistant strains W2 and K1

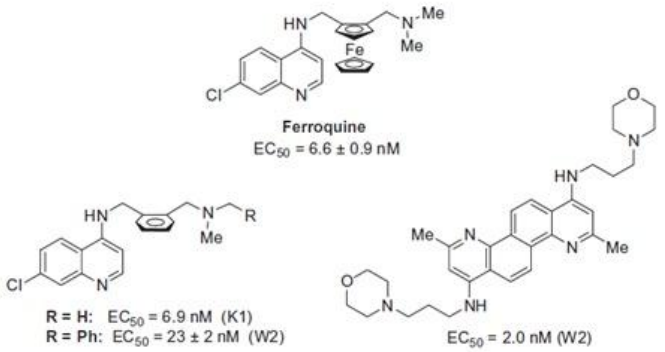


Fig 14. Amodiaquine and derivatives

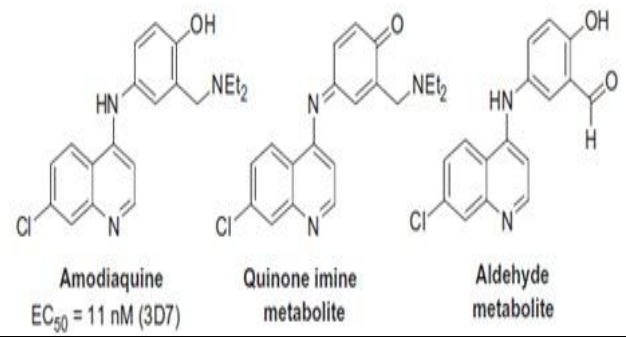


Fig 15. N-tert-Butyl isoquine (GSK36979)

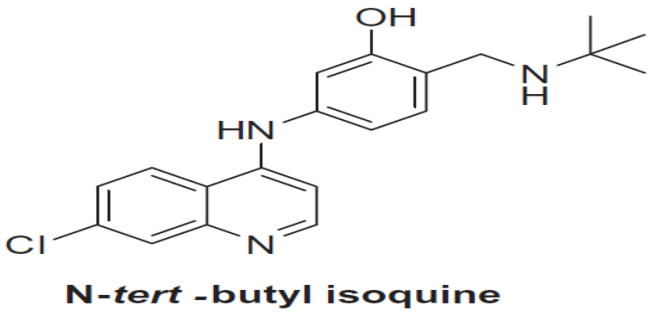


Fig 16. DHFR Inhibitors

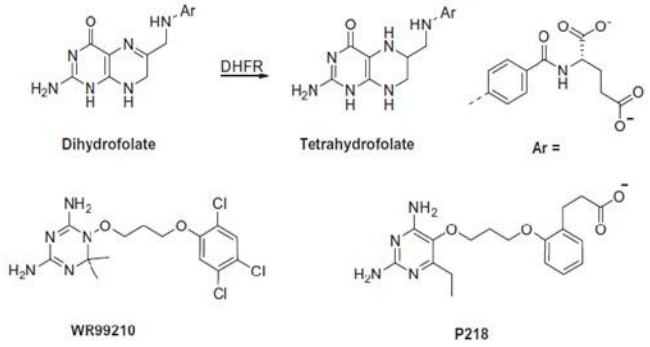


Fig 17. Albitazolium- Choline transport inhibitor

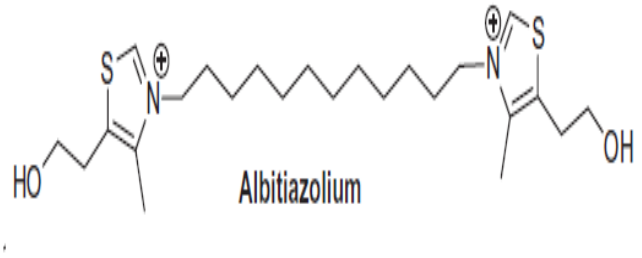


Fig 18. A) Pathway for synthesis of Uridine monophosphate. B) DHODH inhibitors.

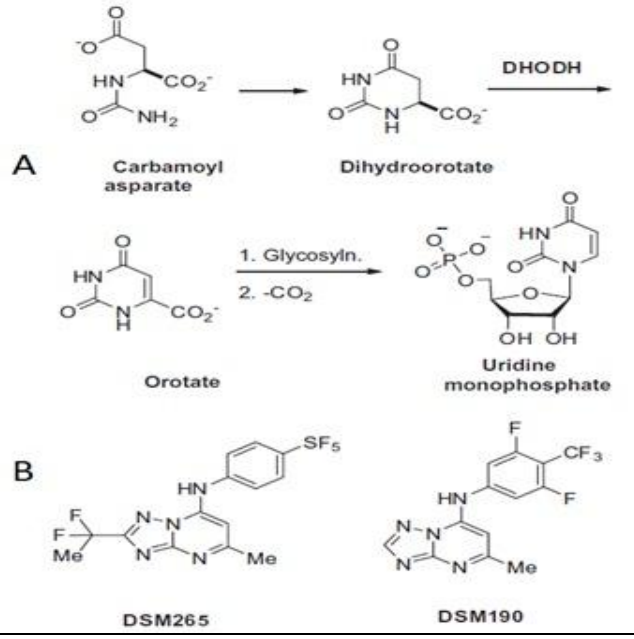


Fig 19. New moieties from phenotypic screenings

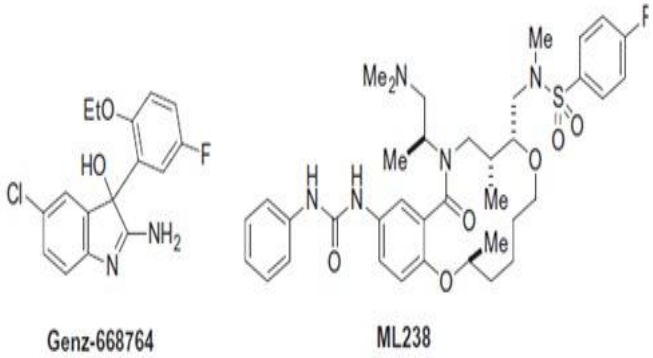


Fig 20. Other moieties from phenotypic screenings

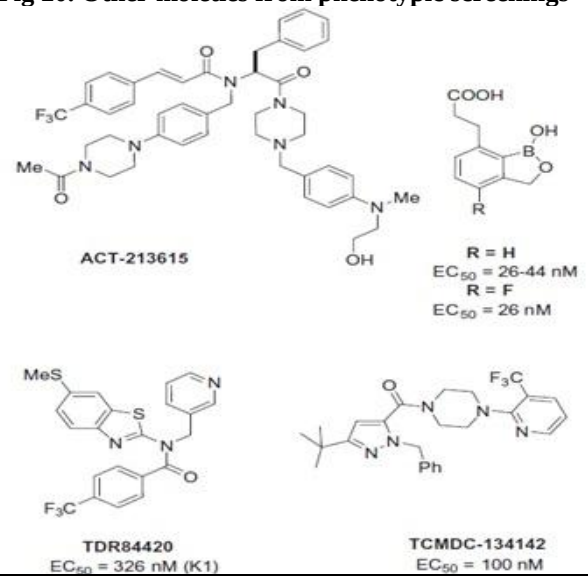


Fig 21.New scaffolds from targeted approaches

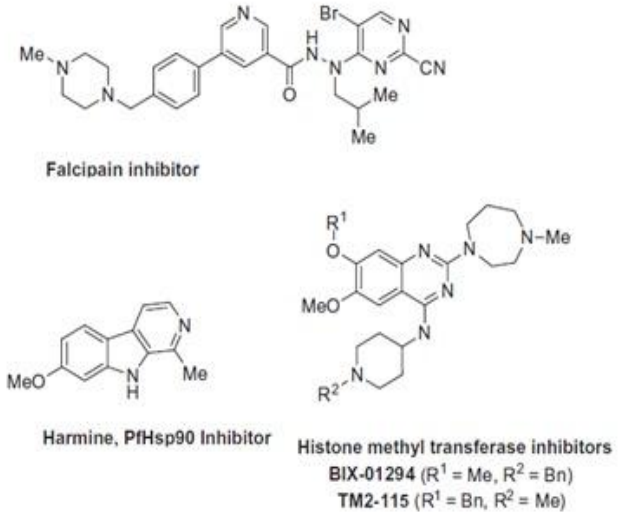


Fig 22. Febrifugine and its improved analog

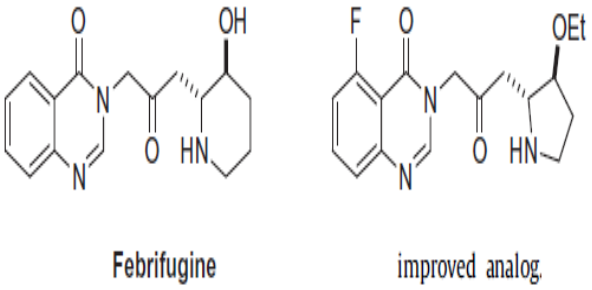


Fig 23. New molecules from various approaches, A) Salinosporamide and SSJ-183, B)Tsitsikammamine C and its deruivatives. EC 50 values are reported for drug-sensitive (3D7, NF54)and multi-drug resistant (Dd2,K1)strains

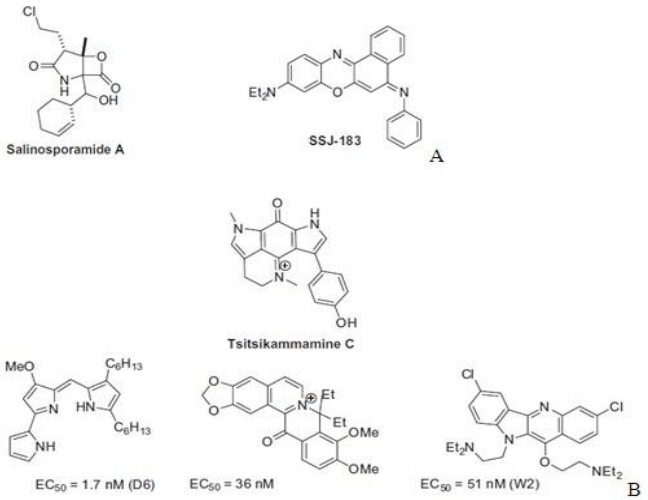


Fig 24. Primaquine and tafenoquine

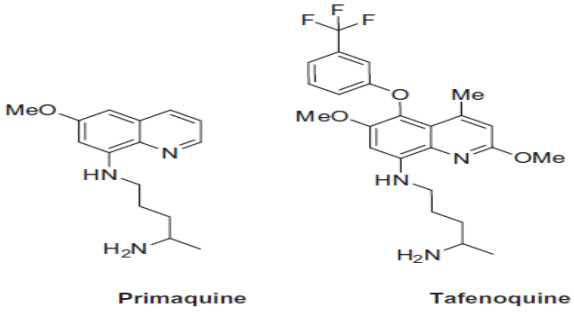
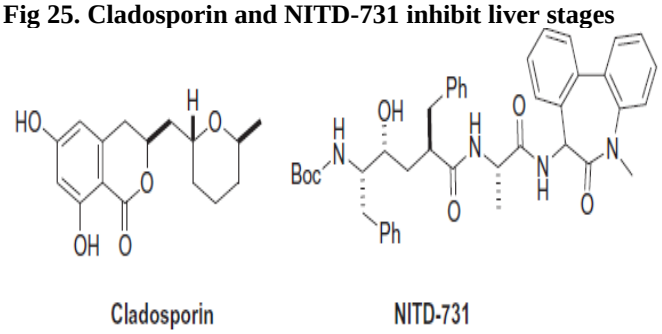


Fig 25. Cladosporin and NITD-731 inhibit liver stages



TEST RESULTS

Dose	Infected Patients/Total patients	Dosage Frequency (IV)
Highest	3/9	4
Highest	0/6	5
Higher	3/15	4
Low	16/17	4
Control	11/12	4

CONCLUSION

As declared by WHO, we should be able to completely eradicate malaria by 2050. Discovery of an ideal antimalarial drug is still the need of the hour. An ideal, cheap and effective vaccine is also the necessary to help eradicate malaria. Research scientists have stated to have this idealistic propagated till 2035. Let's strive for a malaria free world!

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