

Current Medicines for Malaria Including Resistance Issues

Dejen Nureye¹, Mohammed Salahaddin^{1,2}, Ameha Zewudie¹

¹Department of Pharmacy, College of Medicine and Health Sciences, Mizan-Tepi University, Aman Campus, Mizan-Aman, Ethiopia, ²Department of Biomolecular Sciences, Pharmacology Division, University of Mississippi, Mississippi, United States of America

Abstract

Malaria is an old disease and continues to be a major health problem in many countries. In spite of decrement in morbidity and mortality due to malaria, the transmission is still active throughout the world. Hence, appropriate treatment is needed to handle malaria in addition to preventive measures. However, unavailability of new drugs and the occurrence of resistant *Plasmodium* strains toward many conventional antimalarial drugs including artemisinins are the major obstacles in combating malaria infection. Thus, experts from all directions of our planet are in search of novel compounds, and many new chemical entities, such as artefenomel, ferroquine, KAE609, KAF156, DSM265, methylene blue, MMV39048, DDD107498, SJ733, and MMV253, have been under drug development process. While many agents are in the pipeline, most of them are not able to kill both gametocytes and hypnozoites.

Keywords: Antimalarial drugs, clinical trials, malaria, novel compounds, resistance, traditional medicines

INTRODUCTION

Malaria is a common and life-threatening disease in many tropical and subtropical areas.^[1] Not only health- and social-related impacts, but there is also a severe economic burden of malaria in several countries, particularly in Africa.^[2,3] A study done at Sub-Saharan countries has revealed that the total annual costs of malaria in children was estimated to be 37.8, 131.9, and 109.0 million US dollars nationwide in Ghana, Tanzania, and Kenya, respectively. There is also a research report from Mozambique, which shows a high economic cost associated with malaria care to households and the health system in the country.^[4] In spite of the absence of large-scale studies, the economic burden of malaria was concluded to be substantial in Ethiopia indicating that reducing malaria burden through universal access and utilization of effective malaria control and treatment services could contribute to the poverty reduction as well.^[2,5]

The infection and death rate by malaria decreased globally. Regardless of the decrement in the prevalence and the incidence of malaria, its transmission is still dynamic around the globe.^[6] Therefore, malaria control requires an integrated approach including prompt treatment with effective antimalarial agents.^[7] Despite decades of intense research, no licensed malaria vaccines are available until now.^[3] A lot, but

we need a better understanding of immunity and the parasite to improve vaccines. In Phase-III testing, a circumsporozoite protein vaccine (RTS, S/AS01) reduced clinical malaria in children – the first proven antiparasite vaccine. However, young infants do not respond well, and implementation studies with mortality endpoints are awaited. Irradiated *Plasmodium falciparum* sporozoites such as PfSPZ, which is closer to pivotal Phase-III trials, can be manufactured and have been shown to prevent infection in some African countries. Most recently, African trials of gamete protein vaccines started and placental malaria vaccines entered human testing. Blood-stage targets of protective antibodies remain unknown, but new proteins implicated in erythrocyte invasion and egress offer promise.^[8] Limitations in efficacy, absence of standard predictive biomarkers of protective efficacy, and the need to constantly update vaccine formulations due to antigenic polymorphism further underscore the current reliance on

Address for correspondence: Dejen Nureye,

Department of Pharmacy, College of Medicine and Health Sciences,
Mizan-Tepi University, Aman Campus, P.O. Box 260, Southwest,
Mizan-Aman, Ethiopia.
E-mail: dejenureye@gmail.com

Access this article online

Quick Response Code:



Website:
www.jpharmacol.com

DOI:
10.4103/jpp.JPP_23_20

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Nureye D, Salahaddin M, Zewudie A. Current medicines for malaria including resistance issues. J Pharmacol Pharmacother 2020;11:90-9.

Received: 28-02-2020

Revised: 22-09-2020

Accepted: 03-10-2020

Web Publication: 23-12-2020

chemotherapy.^[9] However, the occurrence of resistance among commonly used drugs is a major problem. As a result, old and novel chemicals are under per-clinical and clinical studies.

According to the consensus on malaria control and elimination in the Asian-Pacific countries, the resistance to artemisinin (core ingredient in the most effective malaria treatment so-called artemisinin combination therapies [ACTs]) puts at risk the gains we have made to date to combat malaria and may seriously jeopardize further progress in malaria control and elimination.^[10] Thus, the world is in urgent need of novel antimalarial drugs since, once drug-resistant parasites have emerged and selected over sensitive ones, it would be really difficult to prevent the spread of drug resistance.^[11] In discovering new antimalarial compounds, history has taught us how the knowledge of traditional medicines is valuable.^[12] Despite the widespread development of resistance and difficulties in poor areas to afford and access effective antimalarial drugs, currently used and potent drugs, such as artemether, chloroquine and quinine, are obtained from plant sources. Hence, it is imperative to focus on traditionally used medicinal plants for the discovery of possible new innovative antimalarial sources for the future.^[13] In addition to previously identified targets of drug discovery, experts are in search of new targets and lead compounds. This review aims to present the traditional and novel developments in antimalarial compounds, including genomic basis of resistance. Really, this paper is important for undergraduate and postgraduate medical and health science students to access more information during their seminar preparations regarding recent medicines used to manage malaria.

GENETIC BASIS OF ANTIMALARIAL DRUG RESISTANCE

According to their chemical structure and activity, the available antimalarial agents are grouped into five classes as shown in Table 1.^[14,15] The key targets of modern antimalarial drugs are asexual blood stages of the parasite [Figure 1],^[16] responsible for the malaria symptoms. The two protozoan parasites (*P. falciparum* and *Plasmodium vivax*) that cause most of the human malaria cases have developed resistance to nearly all known antimalarials. The ability of these parasites to develop resistance is primarily due to high numbers of parasites in the infected person's bloodstream during the asexual blood stage of infection in conjunction with the mutability of their genomes.^[17]

Chloroquine resistance for *falciparum* is due to point mutations in the gene encoding *P. falciparum* chloroquine resistance transporter (*pfcr*) and P-glycoprotein transporter proteins (*P. falciparum* multidrug resistance protein [*pfmdr*]), resulting in reduced drug accumulation in the food vacuole (membrane-enclosed cell vacuole with a digestive function).^[18] Chloroquine resistance is more challenging to detect in *vivax* since parasitemia is generally lower relative to *falciparum*. In addition, it is difficult to distinguish *vivax* recrudescence from relapses due to reactivation of dormant liver parasites in endemic settings. There is also no robust *in vitro* culture system for *vivax* as there is with *falciparum*, so confirmation with *in vitro* susceptibility testing is even more challenging than with *falciparum*. Even though *P. vivax* chloroquine resistance transporter-o (*pvcrt-o*) is orthologous to *pfcr*, there is no clear direct association between chloroquine resistance and mutations in *pvcrt-o*. One current study in patients with recurrent *vivax* infections in the Brazilian Amazon found that chloroquine resistance was associated with increased copies of gene encoding *pvcrt-o*.^[17] Amodiaquine and its slowly eliminated active metabolite desethylamodiaquine are structurally related to chloroquine; this explains the cross-resistance observed in the field, where parasites were reported to harbor mutations on *pfcr* and *pfmdr1* after amodiaquine treatment failure.^[19] Therefore, amodiaquine is used in combination therapy with sulfadoxine-pyrimethamine (SP) for prophylaxis and artesunate for treatment. Currently, piperaquine has been combined with

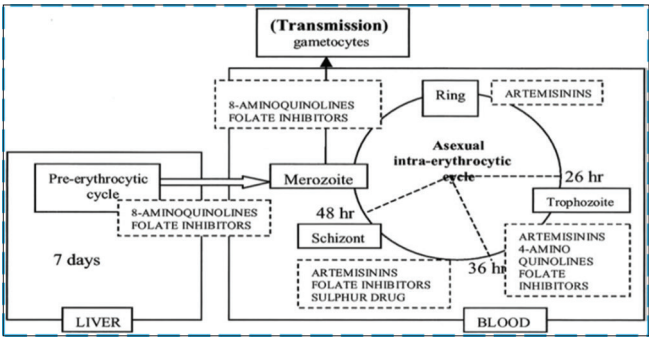


Figure 1: *Plasmodium* life cycle with phases targeted by antimalarial drugs. 4-Aminoquinolines target the parasite at the stage where hemoglobin is degraded by parasite protease enzymes. 4-aminoquinolines such as chloroquine and amodiaquine have no effect on the pre-eythrocytic liver stages of parasite development

Table 1: Classification of antimalarial drugs		
Major classes	Groups	Specific agents
Quinolines	4-aminoquinolines	Chloroquine, amodiaquine, and piperaquine
	8-aminoquinolines	Primaquine and tafenoquine
Arylaminoalcohols	-	Quinine, mefloquine, halofantrine, and lumefantrine
Antifolate compounds	-	Pyrimethamine, proguanil, dapsone, and sulfadoxine
Artemisinin and its derivatives	First generation	Dihydroartemisinin, artesunate, arteether, and artemether
	Second generation	Artemisone
Hydroxynaphthoquinone	-	Atovaquone

dihydroartemisinin (DHA) in co-formulated tablets that have shown excellent efficacy (without apparent drug resistance) and safety for the treatment of *falciparum* malaria. However, now, resistance has been reported (from Western Cambodia) to be associated with a point mutation of *pfprt* and amplification of *plasmepsin 2* and *3* genes in *falciparum* parasites. The *plasmepsin* genes encode aspartic proteases that function as hemoglobinsases in the parasite's digestive vacuole. The mechanism of resistance is not clearly identified; however, one hypothesis mentioned that increased hemoglobin digestion due to the amplification decreases concentrations of the reactive heme species that piperazine binds, thereby overcoming the inhibition of heme detoxification by piperazine.^[17]

Records of resistance to quinine are rare, but isolated cases have been reported from Thailand, North India, East Africa, and South America.^[19] The mechanism of resistance to quinine appears to be more complex. *In vitro* cross-resistance between quinine, the other aryl aminoalcohols, and the 4-aminoquinolines is observed, suggesting that there may be a common genetic mechanism of resistance. Mutations in *pfmdr1* and *pfprt* have been found to confer decreased parasite susceptibility to quinine. Yet, they are not sufficient to cause resistance, implying that there are additional genes involved. Researchers used quantitative trait loci analysis to detect the genes associated with quinine resistance in 71 *falciparum* isolates from diverse locations and identified *pfmdr1*, *pfprt*, and *P. falciparum* Na⁺/H⁺ exchanger-1 (*pfmhe-1*), which encodes *falciparum* Na⁺/H⁺ exchanger-1 and is on chromosome 13. Resistance to mefloquine by both *falciparum* and *vivax* was found to be primarily mediated by increased *mdr1* copy number (amplification), rather than through-point mutations similar to chloroquine and antifolate drugs. Primaquine resistance in *vivax* is difficult to determine as it is confounded by reinfections in malaria-endemic regions. A study that performed whole-genome sequencing of *vivax* from known relapses occurred despite primaquine treatment has found polymorphisms in several putative resistance genes. However, there are currently no known genetic markers of primaquine and tafenoquine resistance.^[17]

In contrast with chloroquine resistance, which took many years to develop, resistance to antifolates developed much faster. The genetic mechanism of antifolate resistance is more straightforward in comparison to chloroquine resistance, with single-point mutations in the genes encoding either dihydrofolate reductase (DHFR) – *pfldhfr* in *falciparum* and *pvdhfr* in *vivax* malaria or dihydropteroate synthase (DHPS) – *pfhdps* in *falciparum* and *pvdhps* in *vivax* malaria. Mutations in *dhfr* decrease the overall enzyme efficacy and result in a fitness cost for the parasite. After changes in the first-line malaria treatment from sulfa drugs to ACTs, a decline in triple and quadruple *dhfr* mutants has been seen in certain areas. However, in countries where SP is part of the ACT or is used as intermittent preventive therapy, these mutants remain prevalent. In addition, the persistence of the parasites carrying *dhfr* mutations may be attributed to

the use of trimethoprim-sulfamethoxazole for prophylaxis or treatment for opportunistic infections in HIV-positive persons. Interestingly, *falciparum* parasites in Southeast Asia are able to develop a compensatory mutation for the fitness cost incurred by the mutant *dhfr*. A genome scanning study of *falciparum* strains first identified an amplification surrounding GTP-cyclohydrolase 1 (*gch1*), which encodes an enzyme in the folate biosynthesis pathway that is upstream from DHFR and DHPS. The amplification reduces the cost of acquiring the drug resistance mutations that further downstream in the folate synthesis pathway.^[17] Atovaquone, available as 750 mg tablets, acquires resistance related to a single mutation of cytochrome b gene of the parasite.^[20]

Resistance to artemisinin by *falciparum* has now been detected in five countries of Greater Mekong Subregion: Cambodia, Lao People's Democratic Republic, Myanmar, Thailand, and Vietnam. These resistant strains have the capacity to spread to different parts of the world including Ethiopia and to subsequently become a global threat for malaria control and treatment.^[7,21] Although different studies associate artemisinin resistance with mutation in *P. falciparum* encoded sarcoendoplasmic reticulum Ca²⁺-ATPase6 (*pfatp6*), *pfmdr1*, *P. falciparum* ferredoxin, *P. falciparum* apicoplast ribosomal protein s10, *pfmdr2*, or *pfprt* genes of *falciparum*, these mutations are thought to represent a background upon which the *kelch13* mutations are especially likely to occur. The genetic mediator (s) of *vivax* resistance against artemisinin compounds is/are not reported till now. Resistance to lumefantrine in field isolates has not yet been convincingly demonstrated. However, amplification of the *pfmdr1* gene in *falciparum* and *P. vivax* multidrug resistance protein 1 in *vivax* has been associated with increased risk for treatment failure with coartem®. Antibacterial drugs such as tetracycline, doxycycline, clindamycin, and azithromycin also have antiparasmodial activity although in general their action is slow for malaria treatment. They are recommended only in combination with other antimalarial drugs. Apicoplast ribosomal RNA (23 SrRNA) mutation-mediated *falciparum* resistance to clindamycin has been found in field isolates. There are no clear markers of doxycycline resistance that have been identified thus far.^[17,19]

NOVEL COMPOUNDS IN THE PIPELINE

As mentioned above, the occurrence of resistant strains and the absence of new drugs are the limiting aspects in the battle against malaria. These factors prompt the continuing need of research for new classes of antimalarial drugs and a re-examination of the existing ones. Hence, ozonides (synthetic peroxides) are proved to be useful substitutes for artemisinin. The first-generation ozonide OZ277 (discovered in 2004) subsequently called arterolane was developed through a partnership between Medicines for Malaria Venture (MMV) and Ranbaxy. After a limited Phase-III trials on combination effects of arterolane maleate and piperazine phosphate, the combined drug has got approval under the trade name Synriam

in India in 2013, followed by the approval in seven African Nations in 2014.^[22]

Multiple novel combination therapies including azithromycin-chloroquine,^[23] pediatric pyronaridine-artesunate, pediatric dihydroartemisinin piperaquine,^[24] and trimethoprim-sulfamethoxazole^[22] are in Phase-III trials. Lots of new compounds are in Phase-II clinical developments [Table 2]. The new organometallic drug ferroquine (SR97193) is currently undergoing Phase-II clinical trials as a combination therapy with artesunate.^[25] Ferroquine retains activity against chloroquine- and piperaquine-resistant parasites *in vitro* and has a long elimination half-life of 16 days. It is only moderately efficacious as monotherapy; however, when combined with artesunate (daily dose of 4 or 6 mg/kg ferroquine plus artesunate 4 mg/kg for 3 days), the polymerase chain reaction-corrected efficacy at 28 days for the treatment of uncomplicated *falciparum* malaria was 99%.^[26] OZ439, a synthetic trioxolane, possesses curative and transmission-blocking ability and is active against artemisinin-resistant parasites. Much like the current peroxide-containing antimalarial drugs, the exact mechanism of action for OZ439 has yet to be discovered, but it is believed that oxidative stress plays a major role as displayed in Figure 2.^[27] OZ439 (discovered in 2011 by a partnership between Monash University, the University of Nebraska, and the Swiss Tropical and Public Health Institute [STPHI]) possesses significantly lower solubility and slightly lower potency than OZ277.^[27] Unlike all other synthetic peroxides and artemisinin derivatives, OZ439 (artefenomel) completely cured *Plasmodium berghei*-infected mice at a single oral dose of 20 mg kg⁻¹ and showed superior prophylactic activity compared to most antimalarials. In 2015, following reports on its safety and pharmacokinetic profiles, a combination with ferroquine was progressed into a Phase-II trial, to evaluate the efficacy of a single oral dose regimen in adults and children aimed at replacing the current three doses prescribed

for artemisinin derivatives.^[9] Artefenomel-ferroquine is a combination of ferroquine and a fast- and long-acting synthetic ozonide, artefenomel, which has an elimination half-life of 46–62 h. An advantage of this product is that neither of the constituent drugs has been deployed as monotherapy previously.^[26]

Novartis currently has two new antimalarials (KAE609 [cipargamin] and KAF156) in Phase-II clinical testing [Table 2].^[28] The establishment of artemisinin resistance raises the concern of cross-resistance with artemether and artefenomel due to chemical similarities between the two groups of compounds. By contrast, cipargamin and KAF156 are structurally unrelated to the artemisinin derivatives. KAE609 has an inhibitory effect on *falciparum* cation channel/P-type ATPase-4 transporter, resulting in a buildup of Na⁺ inside the parasite, leading to cell death. Cipargamin was discovered by a partnership between Novartis, the STPHI, and the Wellcome Trust. It is equipotent against drug-resistant strains and was found to be as effective as artesunate against *falciparum* and *vivax* malaria. KAE609 shows a good safety profile, with low cytotoxicity, cardiotoxicity, and mutagenic activity and is able to clear parasitemia rapidly in adults with uncomplicated *falciparum* or *vivax* malaria at a dose of 30 mg/day for 3 days. It also displays low clearance from the body, long half-life, and excellent bioavailability.^[27]

KAF156 (identified in 2008 by Novartis and The Scripps Research Institute) is with potential to treat and prevent malaria and has an elimination half-life of around 48 h. KAF156 is shown to have potent *in vitro* activity against both asexual and sexual blood stages and the pre-erythrocytic liver stages of the malarial parasite. In the causal prophylactic rodent malaria model, a single oral dose of 10 mg/kg was shown to be fully protective. KAF156 has also shown transmission blocking ability in the *berghei* model. A recent Phase-II study

Table 2: Promising new antimalarial agents in Phase-II clinical development

Class	Name	Activity (target)	Development partner	Remark	References number
Second-generation peroxide	OZ439 (artefenomel)	Active against blood stage of <i>falciparum</i> and <i>vivax</i> malaria	MMV and Sanofi	Being tested in Phase-IIb combination trial with piperaquine, and with ferroquine	[22,25]
4-aminoquinoline (organometallic)	SR97193 (ferroquine)	Active against chloroquine-resistant strains	MMV	Currently in combination trial with artesunate	[25]
Synthetic spiroindolone analog	KAE609 (cipargamin)	Blood schizonticide for <i>vivax</i> and <i>falciparum</i>	MMV and Novartis	Currently in Phase-IIb trials (NCT03334747)	[27,28]
Second-generation imidazolopiperazine	KAF156	It acts at multiple stages of the parasite life cycle	»	Now in Phase-IIb trial in combination with lumefantrine (NCT03167242)	[29,30]
	DSM265	Long-acting agent with blood and liver stage activity and also active against drug resistant parasites	Takeda, MMV, and UT Southwestern	Completed human study in combination with OZ439 (NCT02389348).	[27,29]
Phenothiazine derivative	Methylene blue	Has blood stage activity and also active against mature male and female <i>falciparum</i> gametocytes	University of Heidelberg	Completed Phase-II trial as a combination with primaquine (NCT02851108) in 2017	[26]
3,5-diaryl-2-aminopyridine	MMV048	Has prophylactic and transmission-blocking activity	MMV	Currently in Phase-IIa clinical trials in Ethiopia	[27]

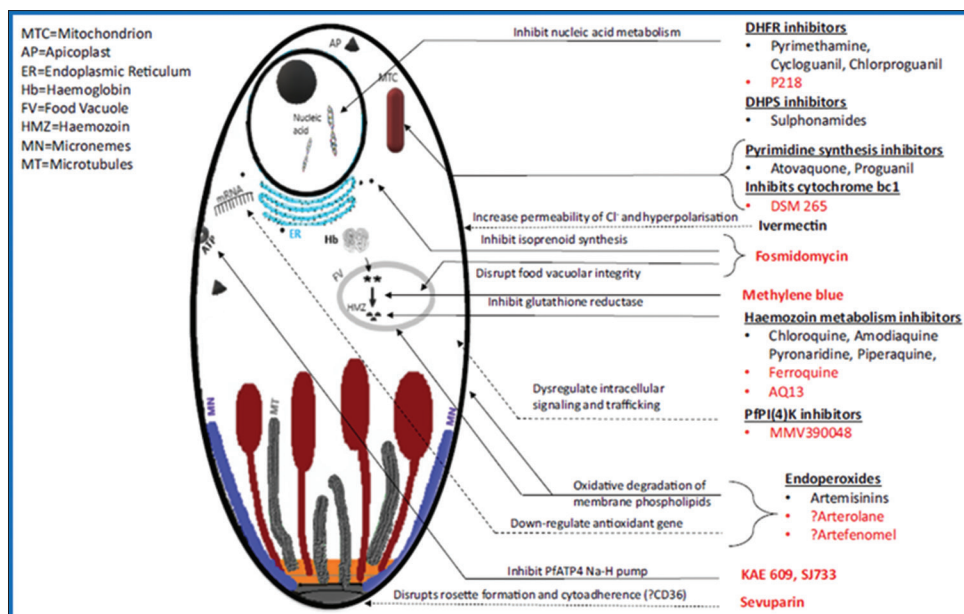


Figure 2: Schematic representation of intra-erythrocytic trophozoite showing sites of action of newer antimalarials. Agents in red are still in development

among adults with acute *vivax* or *falciparum* malaria at five centers in Thailand and Vietnam has shown that KAF156 cleared parasites more rapidly than SP or Malarone® though this rate was slightly slower than artemisinin and DSM265. In addition, therapeutic responses to the treatment with KAF156 suggested effectiveness against *falciparum* and *vivax* infections resistant to all currently available antimalarial drugs without evident safety concerns. The mechanism of action of KAF156 is still unclear. Through the culturing of resistant strains, mutations have been identified in three genes: *P. falciparum* cyclic amine resistance locus, UDP-galactose, and acetyl-CoA transporters.^[9,27]

DSM265 is another compound that complete Phase-IIa trials [Table 2] and inhibit dihydroorotate dehydrogenase enzyme both in *falciparum* and *vivax* species.^[31] DSM265 was discovered through collaboration between the University of Texas, (UT) Southwestern, the University of Washington, and Monash University. It has an excellent safety profile and has a very low clearance rate and a long half-life in humans.^[29] *In vitro* studies suggest a relatively low barrier to resistance selection, so measures to protect this drug such as matching with a partner with similar elimination kinetics and only deploying as part of a fixed-dose combination will be important.^[26] Artemisone (second-generation semi-synthetic artemisinin derivative developed at the Hong Kong University of Science and Technology), a drug in Phase-II study, provides a single-dose cure in Aotus monkeys infected with *falciparum* malaria at 10 mg/kg when combined with mefloquine 5 mg/kg.^[31] Artemisone has shown to be efficacious as artesunate and possess improved pharmacokinetic properties such as longer half-life and lower toxicity (neurotoxicity and cytotoxicity) than the first-generation artemisinins.^[32] It was withdrawn from Phase-II/III trials (NCT00936767) in 2010.^[27] Fosmidomycin,

a natural antibacterial agent that inhibits an enzyme involved in the synthesis of isoprenoids (1-deoxy-D-xylulose 5-phosphate reductoisomerase),^[24] is under combination therapy trial (NCT02198807) with piperazine in Phase-II^[24] to kill blood schizonts of uncomplicated *falciparum* malaria.^[33] AQ-13, a modified chloroquine (only differing to chloroquine in the amine side chain), last completed Phase-II trial at the end of 2017 (NCT01614964),^[27] retains activity against chloroquine-resistant parasites.^[34] The data showed no serious adverse events, and asexual parasites were cleared by day 7 in both groups.^[9]

Methylene blue, a drug used to treat methemoglobinemia, acts by inhibiting *falciparum* glutathione reductase and as a result prevents hem polymerization. It is being developed in combination (Phase-II) with artesunate-amodiaquine as a strategy to protect against the emergence of artemisinin resistance secondary to its *falciparum* schizonticidal effect and to reduce transmission owing to gametocytocidal activity.^[35] Rosiglitazone, an antidiabetic drug, is currently in clinical trials as an adjunctive therapy for severe malaria (NCT02694874). Imatinib, a cancer therapy, is now in Phase-II trials (NCT03697668) as a triple combination with DHA-piperazine.^[27] Polysaccharide heparin analog sevuparin (DF02), which is taken as an adjunctive therapy, retains the antiadhesive effects of heparin without the antithrombin properties and has been shown to block merozoite invasion, cytoadherence, and rosetting.^[36] Sevuparin, a drug treating sickle cell disease, was completed its Phase-I/II trials (NCT01442168) in 2014 as a combination with atovaquone-proguanil.^[27] MMV390048 is an aminopyridine currently in Phase-IIa trials (NCT02880241), and its target was identified to be lipid *P. falciparum* phosphatidylinositol 4-kinase (*PfPI4K*). This

blood schizonticidal drug has destructive activity on multiple stage of the parasite with possible efforts for chemoprevention as it inhibits gametocytogenesis and oocyst formation.^[30,37] Albitiazolium (SAR97276) or bisthiazolium salt, discovered and developed by Sanofi in 2005, has also reached Phase-II clinical study (NCT01445938); however, further investigation was terminated in 2012.^[27] It acts mainly by deterring the transport of choline in to the parasite.^[38] Discovered in 2012 by a team at the Cape Town University, South Africa, MMV048 has shown 99.3% reduction in parasitemia in the *berghei* mouse model at a single dose of 30 mg/kg with no signs of parasites after 30 days. This highlights the potential of this compound to act as a single-dose treatment. Its target is *Pf*PI4K which was recently revealed as a new mode of action for antimalarial drugs. PI4K is a eukaryotic enzyme that phosphorylates lipids, allowing them to regulate intracellular signaling and trafficking. Inhibition of the ATP-binding pocket of PI4K leads to disruption of the intracellular distribution of PI4-phosphate, which in turn results in decreased late-stage parasite development. MMV048 is now in Phase-II clinical trials.^[27]

Quinoline-4-carboxamide DDD107498, previously known as M5717, is an additional treatment panorama that was developed in 2015 by the Drug Discovery Unit in Dundee. It is an inhibitor of *P. falciparum* translational elongation factor 2 (*Pf*eEF2) with activity against the pre-erythrocytic and blood stages as well as mature male and female gametocytes. Hence, it can act as curative and transmission-blocking drug. *Pf*eEF2 is responsible for catalyzing the translocation of mRNA and tRNA. The overall efficacy of drugs that target this elongation factor may be increased due to the expression of *Pf*eEF2 in multiple stages of the parasite life cycle.^[3,39] DDD107498 showed excellent activity against several drug-resistant strains and exhibited greater potency than artesunate in *ex vivo* assays against *falciparum* and *vivax* clinical isolates from Indonesia. The compound also displayed excellent pharmacokinetic properties in preclinical species, including good oral bioavailability and long plasma half-life (critical for chemoprophylaxis and single-dose treatment). Owing to its *Pf*eEF2 inhibition and its ability to clear blood-stage parasites completely, DDD107498 satisfies the requirements to be a long duration partner and could be used as part of a combination therapy with a fast-acting compound. In the late 2017, DDD107498 was cleared for progression from the development to Phase-I clinical trials for volunteers in Australia (NCT03261401).^[9,27]

A dihydroisoquinolone compound (+)-SJ733, which inhibits gametocytogenesis and blood schizonts in *falciparum* and *vivax*, is now in human trial. The preclinical trials showed that SJ733 (an inhibitor of *Pf*ATP4) worked against malaria parasites that are resistant to the current frontline drugs. It binds to a malaria parasite protein that serves as a sodium pump to interfere with the protein or to disrupt the malaria parasite's ability to remove excess sodium from red blood cells.^[40,41] As sodium builds up, infected cells become less flexible and then

removed by the immune system or get caught in the small blood vessels. A total of 38 healthy volunteers were recruited as part of the Phase-Ia study in Memphis and Phase-Ib study in Brisbane, Australia. The 23 healthy volunteers in Memphis received increasing doses of SJ733 to understand dosing, safety profile, and metabolism, including absorption. Based on those results, the 15 Australian volunteers received SJ733 after being infected with malaria to understand the antimalarial effectiveness of this new compound. No significant SJ733 treatment-related side effects were identified in any of the volunteers.^[42]

In addition, CDRI97/78 (fast-acting trioxane first synthesized in 2001 by a team at the Council of Scientific and Industrial Research in India), ACT-451840 (phenylalanine-based compound developed in 2016 through collaboration between Actelion Pharmaceuticals and the STPHI, P218 (2,4-diaminopyridine analog and *Pf*DHFR inhibitor discovered by BIOTEC Thailand in 2012), and GSK369796 (N-tert-butyl isoquine developed at the Liverpool School of Tropical Medicine in 2009) are also among drugs under/completed Phase-I studies.^[22,30] CDRI97/78 (blood schizonticidal compound) was well-tolerated in healthy adult volunteers with a half-life of around 12 h. It has shown few and not severe adverse effects. ACT-451840 has the potential to be a fast-acting drug with a long half-life. This agent has shown efficacy against multiple life cycle (asexual and sexual) stages of both *falciparum* and *vivax* parasites and also harbors additional gametocytocidal activity and thereby transmission-blocking properties. The novel two-step mechanism of action for binding to *Pf*DHFR allows P218 to overcome the resistance that has emerged from the use of pyrimethamine. P218 has also shown high selectivity to the binding of malarial over human DHFR, which translates into reduced toxicity. *In vivo* studies have shown P218 to be highly efficacious against *falciparum* and *chabaudi* in mice with ED₉₀ values of 1 and 0.75 mg/kg, respectively. Along with its high potency and good safety profile, P218 has the potential to be a replacement for pyrimethamine combination with cycloguanil in areas where *Pf*DHFR resistance has emerged. P218 has currently completed Phase-I trials (NCT02885506). GSK369796 was designed as an alternative to amodiaquine. It completed preclinical studies and Phase-I trial was ended in 2008 (NCT00675064).^[27]

DM1157, a part of a class of compounds known as "reversed chloroquines," was designed to overcome chloroquine-resistant (the parasites expel the drug before it can affect them) strains of *falciparum* malaria. Like chloroquine, DM1157 (discovered in 2010 by a research team in Portland State University and further developed by DesignMedix) interferes with the parasite's metabolism, but it also inhibits the parasite's ability to expel the drug. It is currently in Phase-I trials (NCT03490162) to evaluate its safety and pharmacokinetics in humans, which is sponsored by the National Institute of Allergy and Infectious Diseases. Results of earlier tests in animals suggest that DM1157 could have the same safety and efficacy as chloroquine.^[27,43]

Human trials of new antimalarial drugs are in the pipeline after Kenyan scientists successfully used a derivative from bacteria to kill a parasite that causes malaria. The Kenya Medical Research Institute and global health partners say that the breakthrough could potentially lead to the development of a new way of tackling malaria. The same bacteria known to kill dangerous pathogens including scabies and river blindness can also be applied in malaria. The promise of a new treatment comes after trials in Burkina Faso found that ivermectin, a conventional drug used for nonmalaria parasitic diseases, reduced transmission rates. Through repeated treatment, the medication worked by making the blood of the people lethal to the mosquitoes. The study also found that ivermectin can kill *P. falciparum*, a malaria parasite in mosquitos that had fed on humans who had been administered the drug. The research is more focused on pregnant women and children as they are more vulnerable, and the researchers are getting very motivating leads. In a few years, new malaria drugs could be in the market if the current research findings are to go by.^[44]

After identification of a lead compound, optimization of the structure can begin. This largely involves investigation of the structural activity relationship of the drug, optimizing for properties such as potency (both *in vitro* and *in vivo*), solubility, and metabolic stability. The candidate must also be assessed for any possible toxicity (e.g., dosing, cytotoxicity/genotoxicity levels) in preclinical trials. NPC1161B (the chiral 8-aminoquinoline derivative), developed at the University of Mississippi, was in the late preclinical studies for relapse prevention. This compound has a multi-stage activity, and there is a development plan to see whether this single enantiomer drug has a more favorable hematological toxicity profile than tafenoquine in Phase-I. AN13762 (blood schizonticidal), a novel class of benzoxaborole antimalarial compounds, is emerged in 2017 as the lead compound, showing excellent activity in *in vitro* and *in vivo* (preclinical) studies. It has multi-strain efficacy and the ability to act rapidly. It has been shown to be equally potent across a wide range of drug-resistant strains. AN13762 has exhibited similar *in vivo* clearance rate when compared to artesunate. The precise mechanism of action for AN13762 remains unknown, although initial studies on hit compound AN3661 identified a potential target as the *P. falciparum* cleavage and polyadenylation specificity factor 3.^[26,27,45]

Triaminopyrimidine MMV253 (identified by AstraZeneca in 2015) and an aminomethylphenol JPC-3210 (active against multidrug-resistant *falciparum in vitro*) are long-acting blood schizonticidal agents present in early preclinical experiments.^[46,47] MMV253 (previously AZ13721412) has shown good *in vitro* potency and *in vivo* efficacy. When screened against numerous mutant-resistant strains with various mechanisms of resistance, MMV253 showed no spontaneous reduction in potency which can be attributed to its novel mode of action (*Pf*ATP4 inhibition). Good *in vitro*–*in vivo* correlation was shown with a predicted human half-life of ~ 36 h (which is long compared to another

fast-killing drug, artemisinin, which has a human half-life of 1 h). As of late 2016, the pharmaceutical company Cadila Healthcare owns the license for the compound series and is now doing further lead development to progress the drug through preclinical trials. At the same time that the parasite is regulating its Na⁺ concentration through *Pf*ATP4, it also imports H⁺ through the same pathway. To regulate this increasing H⁺ concentration and maintain an intracellular pH of ~ 7.3, the parasite uses a complementary V-type ATPase transporter to efflux H⁺. MMV253 has been shown to inhibit the V-type H⁺ ATPase as its mechanism of action. UCT943 (identified in 2016 by a team at the University of Cape Town, South Africa, in the same campaign as MMV048) is a key compound in a novel class of 2-aminopyrazine antimalarials that has shown single-dose curing ability *in vivo* and potential as a clinical candidate. UCT943 is potent across multiple parasite life stages of both *falciparum* and *vivax*. The target of UCT943 is *Pf*PI4K. UCT943 was in originally in place as a backup to MMV048; however, due to preclinical toxicity, this candidate has been withdrawn.^[27] A Mannich base compound, MK-4815 (2-aminomethyl-3,5-di-tert-butylphenol), showed potent *in vitro* activity against *falciparum* clinical isolates, and 100% survival was observed in mice orally treated with 25, 12.5, or 6.25 mg kg⁻¹ of the drug once on the day of infection and then twice daily for an additional 4 days. Though comparable volume of distribution of the drug at steady state was observed in mice and rhesus monkey, the compound exhibited lower clearance and extended half-life in the monkeys, indicating superior pharmacokinetic parameters in the higher species. Even though its mechanism of action still remains unclear, it appears to involve the mitochondrial electron transport chain of the parasite. Due to its structural simplicity, efficacy against multidrug-resistant *falciparum* strains, good pharmacokinetic profile, and ability to cure acute *berghei* infection at a single 50 mg/kg⁻¹ dose, MK-4815 has potential as an antimalarial drug and in fact is presently under further evaluation as a preclinical candidate by MMV.^[9]

In an attempt to identify the antimalarial drugs with novel mode of action, Kato *et al.* found a lead compound coded as BRD7929. It was shown to target the cytosolic *falciparum* phenylalanyl-tRNA synthetase. This enzyme serves to enable transfer-RNAs to deliver the amino acid phenylalanine to nascent proteins during RNA translation and protein synthesis. This bicyclic azetidine exhibited *in vivo* efficacy in *falciparum* and *berghei*-infected mice at single, low doses. The compound was also highly potent against the liver and asexual stages of *falciparum* and showed transmission-blocking ability at concentrations that achieved single-dose cures of asexual blood-stage infections. Although BRD7929 displayed good oral bioavailability (80%), improved aqueous solubility, and a long half-life in mice (~32 h), moderate cytotoxicity was observed thus presenting possible setbacks, which would have to be addressed during further optimization. Nonetheless, the ability of this lead chemical to eliminate blood-stage (asexual and sexual) and liver-stage parasites suggests that this compound

has the potential to cure the disease, provide prophylaxis, and block transmission. Currently, a tetraoxane-based antimalarial drug candidate, E209 that can overcome *PfK13* Cys-580-Tyr-dependent artemisinin resistance was identified. Further evaluation revealed retention of *in vitro* potency against sensitive and multidrug-resistant *falciparum* parasite isolates, with no observable cross-resistance with artemisinin. Compound E209 also exhibited equipotent *ex vivo* activity against *vivax* and *falciparum* Indonesian clinical isolates, while screening for gametocytocidal activity showed a transmission reducing profile consistent with the endoperoxides. Equally important, *in vivo* experiments in *P. berghei*-infected mice demonstrated complete parasite clearance with an estimated oral ED₅₀ of 4 mg/kg⁻¹ after three doses and a 66% cure rate after a single oral dose of 30 mg/kg⁻¹. This compound therefore has the potential for deployment in a superior combination treatment with a partner drug devoid of existing *in vivo* resistance liabilities, hence offers a significant improvement on current ACTs, and provides an urgently required alternative drug for malaria treatment and elimination. Moreover, its effectiveness against *vivax* and gametocytocidal activity indicates the potential of E209 to prevent relapse and block transmission, respectively.^[9]

SC83288, an amicarbalide derivative developed in 2017 by a team at Heidelberg University, is the only agent in preclinical investigation that is going to treat severe malaria.^[48] This compound was shown to be fast-acting and cured *falciparum* infection in a humanized mouse model, with preclinical pharmacokinetic and toxicological studies revealing no apparent shortcomings. While the precise mode of action is unknown, *PfATP6* was identified as a putative determinant of resistance to SC83288. However, it has been shown that SC83288 does not directly inhibit this target, suggesting that *PfATP6* may have a less direct role in its mechanism of action. SC83288 has been evaluated against artemisinins, showing no cross-resistance. *Pfmdr2* has been identified as another possible mechanism of resistance, facilitating the clearance of the drug from the parasite. Its distinct chemotype, ability to rapidly kill parasites, potentially new mechanism of activity, and good safety indices than artesunate and quinine support the clinical development of SC83288 as an intravenous application for the treatment of severe malaria when combined with a slow-acting partner drug. At present, Heidelberg University Hospital and the German Centre for Infection Research are collaboratively in the process of conducting the regulatory preclinical procedures with the hope of initiating clinical trials in due course.^[9,27]

A 4 (1*H*)-quinolone derivative ELQ-300, structurally engineered from pyridone analog by Oregon Health and Science University, was potently inhibited blood stages of *falciparum* and *vivax* malaria in clinical field isolates, as well as liver stages and transmissible stages of the parasite. ELQ-300 is proved to be highly selective against plasmodial cytochrome *bc₁* complexes similar to atovaquone, suggesting diminished potential for side effects due to inhibition of the host enzyme. It was also established as a slow-acting drug with a delayed

parasite reduction ratio similar to atovaquone and exhibited strong synergy with proguanil. Mutant selection experiments failed to achieve variants, suggesting a significantly low propensity for resistance. The compound was highly potent in *berghei*-infected mice with an ED₅₀ of 0.016 mg/kg⁻¹ per day and cures produced with doses as low as 0.1 mg/kg⁻¹ per day, thus offering the potential as a combination partner aimed at a single-dose cure. Additional safety evaluation indicated no significant off-target pharmacological activities. A major obstacle to the clinical development of ELQ-300 relates to its relatively poor aqueous solubility, which limits absorption to the extent that only low blood concentrations can be achieved with oral doses. Although these low blood concentrations are sufficient for therapy, the levels remain too low to establish an acceptable safety margin required for clinical development. An approach aimed at designing bioreversible alkoxycarbonate ester prodrugs has recently been successfully explored to overcome the physicochemical hurdles of ELQ-300 and to attain bloodstream concentrations sufficing for safety and toxicology studies, as well as achieving single-dose cures.^[9] It is also possible to list Genz-668764, ML238, ACT-213615, SAR121, and TDR84420 within the new chemical entity group.^[3,26]

Besides, a pyrazole amide 21A092, which targets sodium channel (ATPase4) similar to KAE609 and SJ733, is in preclinical discovery phase.^[49] Dantrolene was identified as a novel inhibitor of plasmodial surface anion channel, and it may be a lead compound for antimalarial drug development.^[50] Acridinones such as WR249685 and T3.5, new class of selective malaria parasite mitochondrial *bc1* inhibitors, had a great potential to become novel antimalarial drugs.^[51,52] Some antibiotics that have shown potential effects on malaria parasite have been recently studied *in vitro* or *in vivo* intensively. Macrolide antibiotics were identified for the first time that they inhibit *in vitro* RBC invasion by merozoite of *Plasmodium* species. This result directs the development of safe and effective macrolide antibiotics with dual modalities to combat malaria and reduce the parasite's options for resistance. Other antibiotics, such as quinolones, tigecycline, co-trimoxazole, or fusidic acid, could be used to prevent malaria in the future. Antiadhesion adjunctive therapies, including levamisole, are under research in the laboratory.^[53-55] *In vivo* and *in vitro* studies showed that an acriflavine (antibacterial and anticancer drug) impairs DNA replication foci formation in *berghei* and affects the enzymatic activities of apicoplast-specific gyrase protein. This interesting work tells us the potential of this old drug to become future antimalarial drug.^[56] The receptor protein *PfATP6* has been identified as the common target of artemisinin and curcumin. The work was initiated to assess the antimalarial activity of six curcumin derivatives based on their binding affinities and to correlate the *in silico* docking outcome with *in vitro* antimalarial screening results. The *in vitro* results superimpose the results obtained from the *in silico* study, thereby encouraging development of promising curcumin leads in the battle against malaria.^[57] One approach to discover new

biologically active compounds is to combine a steroid skeleton with structural elements endowed with appropriate biological activities. There is a recent report that said low molecular weight aryl methyl amino steroids with varying constitutions of the basic gonane core exhibit excellent antimalarial activity.^[9] Moreover, a team of researchers has discovered thioredoxin enzymes, which are different from the human one but critical for the survival of *Plasmodium* by balancing redox state inside the parasite. Hence, the team is working with industry partners to create new drugs, which will effectively target this enzyme and kill the parasite without affecting the human host.^[58]

CONCLUSION

Malaria is one of the ancient human diseases and remains an important cause of illness and death among adults as well as children in the world. However, an increasing resistance toward currently available antimalarial drugs is a big obstacle in the fight against malaria. The past instances indicate that resistance to the conventional antimalarial medicines will spread to Africa including Ethiopia. As a result, we are in an urgent need of novel, safe, and effective drugs. Some of the newer compounds possess multi-stage activity and are highly potent in inhibiting the parasite multiplication. Those novel agents that have different structure and new mechanism of action than older drugs could be the game changer in combating malaria. The current breakthroughs will still require long-term financial investments, political will, and scientific endeavor to ensure sustainability and translate to more reduction in global burden of malaria.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- WHO. Malaria Control in humanitarian emergencies. An Inter-Agency Field Handbook. 2nd ed.. WHO, Geneva, Switzerland; 2013.
- Hailu A, Lindtjorn B, Deressa W, Gari T, Loha E, Robberstad B. Economic burden of malaria and predictors of cost variability to rural households in South-Central Ethiopia. *PLoS One* 2017;12:e0185315.
- Nureye D, Assefa S. Old and recent advances in life cycle, pathogenesis, diagnosis, prevention, and treatment of malaria including perspectives in Ethiopia. *ScientificWorldJournal* 2020;2020:1-17.
- Alonso S, Chaccour CJ, Elobolobo E, Nacima A, Candrinho B, Saifodine A, *et al.* The economic burden of malaria on households and the health system in a high transmission district of Mozambique. *Malar J* 2019;18:360.
- Tefera DR, Sinkie SO, Daka DW. Economic burden of malaria and associated factors among rural households in Chewaka District, Western Ethiopia. *Clinicoecon Outcomes Res* 2020;12:141-52.
- World Health Organization. World Malaria Report. Geneva, Switzerland: World Health Organization; 2019.
- World Health Organization. WHO Global Malaria Program. Guidelines for the Treatment of Malaria. 3rd ed.. Geneva, Switzerland: World Health Organization; 2015.
- Eradicating malaria: Discoveries, challenges, and questions. *Cell* 2016;167:595-7.
- Okombo J, Chibale K. Recent updates in the discovery and development of novel antimalarial drug candidates. *Medchemcomm* 2018;9:437-53.
- Australian AID. Consensus on Malaria Control and Elimination in the Asia-Pacific. November, 2012. Available from: <https://reliefweb.int/sites/reliefweb.int/files/resources/malaria-consensus-document.pdf>. [Last accessed on 2020 Sep 05].
- World Health Organization. Global Report on Antimalarial Drug Efficacy and Drug Resistance: 2000-2010. Geneva, Switzerland: World Health Organization; 2012.
- Adams M, Alther W, Kessler M, Kluge M, Hamburger M. Malaria in the renaissance: Remedies from European herbals from the 16th and 17th century. *J Ethnopharmacol* 2011;133:278-88.
- Pan WH, Xu XY, Shi N, Tsang SW, Zhang HJ. Antimalarial activity of plant metabolites. *Int J Mol Sci* 2018;19:1382.
- Nicoletta B, Roberta S, Sarah D. Malaria Diagnosis, Therapy, Vaccines, and Vector Control. In: Prato M, editor. Human and Mosquito Lysozymes. Springer, Cham. 2015.
- Na-Bangchang K, Karbwang J. Current status of malaria chemotherapy and the role of pharmacology in antimalarial drug research and development. *Fundam Clin Pharmacol* 2009;23:387-409.
- O'Neill PM, Ward SA, Berry NG, Jeyadevan JP, Biagini GA, Asadollaly E, *et al.* A medicinal chemistry perspective on 4-aminoquinoline antimalarial drugs. *Curr Top Med Chem* 2006;6:479-507.
- Cowell AN, Winzeler EA. The genomic architecture of antimalarial drug resistance. *Brief Funct Genomics* 2019;18:314-28.
- Bray PG, Martin RE, Tilley L, Ward SA, Kirk K, Fidock DA. Defining the role of PfCRT in *Plasmodium falciparum* chloroquine resistance. *Mol Microbiol* 2005;56:323-33.
- Aminake MN, Pradel G. Antimalarial drugs resistance in *Plasmodium falciparum* and the current strategies to overcome them. In: Méndez-Vilas A, editor. Microbial Pathogens and Strategies for Combating Them: Science, Technology and Education. FORMATEX, Badajoz, Spain: 2013. p. 269-82.
- White NJ, Pukrittayakamee S, Hien TT, Faiz MA, Mokuolu OA, Dondorp AM. Malaria. *Lancet* 2014;383:723-35.
- Dondorp AM, Yeung S, White L, Nguon C, Day NP, Socheat D, *et al.* Artemisinin resistance: Current status and scenarios for containment. *Nat Rev Microbiol* 2010;8:272-80.
- Hemingway J, Shretta R, Wells TN, Bell D, Djimdé AA, Achee N, *et al.* Tools and strategies for malaria control and elimination: What do we need to achieve a grand convergence in malaria? *PLoS Biol* 2016;14:e1002380.
- Chandra RS, Orazem J, Ubben D, Duparc S, Robbins J, Vandenbroucke P. Creative solutions to extraordinary challenges in clinical trials: Methodology of a phase III trial of azithromycin and chloroquine fixed-dose combination in pregnant women in Africa. *Malar J* 2013;12:122.
- BIO Ventures for Global Health. Malaria Pipelines. Seattle, Washington: BIO Ventures for Global Health; 2015.
- Biamonte MA, Wanner J, Le Roch KG. Recent advances in malaria drug discovery. *Bioorg Med Chem Lett* 2013;23:2829-43.
- Ashley EA, Phyto AP. Drugs in development for malaria. *Drugs* 2018;78:861-79.
- Tse EG, Korsik M, Todd MH. The past, present and future of anti-malarial medicines. *Malar J* 2019;18:93.
- Spillman NJ, Kirk K. The malaria parasite cation ATPase PfATP4 and its role in the mechanism of action of a new arsenal of antimalarial drugs. *Int J Parasitol Drugs Drug Resist* 2015;5:149-62.
- Novartis. Backgrounder: Malaria Initiative Pipeline; 2014.
- White NJ, Duong TT, Uthaisin C, Nosten F, Phyto AP, Hanboonkunupakarn B, *et al.* Antimalarial activity of KAF156 in *falciparum* and *vivax* malaria. *N Engl J Med* 2016;375:1152-60.
- Phillips MA, Lotharius J, Marsh K, White J, Dayan A, White KL, *et al.* A long-duration dihydroorotate dehydrogenase inhibitor (DSM265) for prevention and treatment of malaria. *Sci Transl Med* 2015;7:296ra111.
- Haynes RK. From artemisinin to new artemisinin antimalarials: Biosynthesis, extraction, old and new derivatives, stereochemistry and medicinal chemistry requirements. *Curr Top Med Chem* 2006;6:509-37.
- Coleman RE, Clavin AM, Milhous WK. Gametocytocidal and sporontocidal activity of antimalarials against *Plasmodium berghei*

- ANKA in ICR mice and *Anopheles stephensi* mosquitoes. *Am J Trop Med Hyg* 1992;46:169-82.
34. Schlitzer M. Antimalarial drugs-What is in use and what is in the pipeline. *Arch Pharm (Weinheim)* 2008;341:149-63.
35. Sulyok M, Rückle T, Roth A, Mürbeth RE, Chalon S, Kerr N, *et al.* DSM265 for *Plasmodium falciparum* chemoprophylaxis: A randomised, double blinded, phase 1 trial with controlled human malaria infection. *Lancet Infect Dis* 2017;17:636-44.
36. Leitgeb AM, Charunwatthana P, Rueangveerayut R, Uthaisin C, Silamut K, Chotivanich K, *et al.* Inhibition of merozoite invasion and transient de-sequestration by sevuvarin in humans with *Plasmodium falciparum* malaria. *PLoS One* 2017;12:e0188754.
37. Chibale K. How Africa Is Helping Expand the Global Antimalarial Drug Pipeline. *The Conversation*; August, 2016. Available from: <https://theconversation.com/how-africa-is-helping-expand-the-global-antimalarial-drug-pipeline-63527>. [Last accessed on 2020 Sep 05].
38. Caldarelli SA, Hamel M, Duckert JF, Ouattara M, Calas M, Maynadier M, *et al.* Disulfide prodrugs of albitalizolium (T3/SAR97276): Synthesis and biological activities. *J Med Chem* 2012;55:4619-28.
39. ClinicalTrials. First-in-Human Trial of Single Ascending Dose, Multiple Ascending Dose and maLaria Challenge Model in Healthy Subjects NCT03261401. U. S. National Library of Medicine; 2017. Available online from: <https://clinicaltrials.gov/ct2/show/study/NCT03261401?view=results>. [Last accessed on 2020 Sep 05].
40. ClinicalTrials. First-in-Humans Study of an Oral *Plasmodium falciparum* Plasma Membrane Protein Inhibitor. St. Jude Children's Research Hospital; 2016. Available from: <https://clinicaltrials.gov/ct2/show/NCT02661373>. [Last accessed on 2020 Sep 05].
41. Rutgers University. Promising Malaria Drug to Undergo Clinical Trials. *Medical Xpress*; 2016. Available from: <https://medicalxpress.com/news/2016-03-malaria-drug-clinical-trials.html>. [Last accessed on 2020 Sep 05].
42. Gaur A, Panetta J, Dallas R, Tang Li, Stewart T, Branum K, *et al.* St. Jude Experimental Anti-Malarial Drug Shows Promise in First Clinical Trial. St. Jude Children's Research Hospital. Memphis, Tennessee; 2020. Available from: <https://www.stjude.org/media-resources/news-releases/2020-medicine-science-news/experimental-anti-malarial-drug-shows-promise-in-first-clinical-trial.html>. [Last accessed on 2020 Sep 05].
43. National Institutes of Health. Early Stage Clinical Trial of Antimalarial Drug Begins. U.S. Department of Health & Human Services, News releases; 2018.
44. Njeru G. Malaria Breakthrough as Scientists Find 'Highly Effective' Way to Kill Parasite; *The Guardian*; 2019. Available from: <https://www.theguardian.com>. [Last accessed on 2020 Sep 05].
45. Burrows JN, Duparc S, Gutteridge WE, Hooft van Huijsduijnen R, Kaszubska W, Macintyre F, *et al.* New developments in anti-malarial target candidate and product profiles. *Malar J* 2017;16:26.
46. Fontelles-Drabek S, Reddy D, Wells TN. Managing intellectual property to develop medicines for the world's poorest. *Nat Rev Drug Discov* 2017;16:223-4.
47. Birrell GW, Heffernan GD, Schiehsler GA, Anderson J, Ager AL, Morales P, *et al.* Characterization of the preclinical pharmacology of the new 2-aminomethylphenol, JPC-3210, for malaria treatment and prevention. *Antimicrob Agents Chemother* 2018; 62 (4):e01335-17.
48. Pegoraro S, Duffey M, Otto TD, Wang Y, Rösemann R, Baumgartner R, *et al.* SC83288 is a clinical development candidate for the treatment of severe malaria. *Nat Commun* 2017;8:14193.
49. Jiménez-Díaz MB, Ebert D, Salinas Y, Pradhan A, Lehane AM, Myrand-Lapierre ME, *et al.* (+)-SJ733, a clinical candidate for malaria that acts through ATP4 to induce rapid host-mediated clearance of *Plasmodium*. *Proc Natl Acad Sci U S A* 2014;111:E5455-62.
50. Kang M, Lisk G, Hollingworth S, Baylor SM, Desai SA. Malaria parasites are rapidly killed by dantrolene derivatives specific for the plasmodial surface anion channel. *Mol Pharmacol* 2005;68:34-40.
51. Biagini GA, Fisher N, Berry N, Stocks PA, Meunier B, Williams DP, *et al.* Acridinediones: Selective and potent inhibitors of the malaria parasite mitochondrial bc1 complex. *Mol Pharmacol* 2008;73:1347-55.
52. Beteck RM, Smit FJ, Haynes RK, N'Da DD. Recent progress in the development of anti-malarial quinolones. *Malar J* 2014;13:339.
53. Gaillard T, Madamet M, Tsombeng FF, Dormoi J, Pradines B. Antibiotics in malaria therapy: Which antibiotics except tetracyclines and macrolides may be used against malaria? *Malar J* 2016;15:556.
54. Wilson DW, Goodman CD, Sleebs BE, Weiss GE, de Jong NW, Angrisano F, *et al.* Macrolides rapidly inhibit red blood cell invasion by the human malaria parasite, *Plasmodium falciparum*. *BMC Biol* 2015;13:52.
55. Rowe JA, Claessens A, Corrigan RA, Arman M. Adhesion of *Plasmodium falciparum*-infected erythrocytes to human cells: Molecular mechanisms and therapeutic implications. *Expert Rev Mol Med* 2009;11:e16.
56. Dana S, Prusty D, Dhayal D, Gupta MK, Dar A, Sen S, *et al.* Potent antimalarial activity of acriflavine *in vitro* and *in vivo*. *ACS Chem Biol* 2014;9:2366-73.
57. Dohutia C, Chetia D, Gogoi K, Bhattacharyya DR, Sarma K. Molecular docking, synthesis and *in vitro* antimalarial evaluation of certain novel curcumin analogues. *Braz J Pharm Sci* 2017;53:e00084.
58. Lilach S. Parasite' Could Mean More Effective Treatment For Toxoplasmosis And Malaria. An Unexpected Breakthrough Looks Promising for Finding New Drugs to Treat Two Diseases. *The Conversation*; 2018.