Biointerface Research in Applied Chemistry
Open-Access Journal (ISSN: 2069-5837)

Review
Volume 13, Issue 6, 2023, 598
https://doi.org/10.33263/BRIAC136.598

The Best Preventive and Curative Approach in Treating Artemisinin Resistance Case

Royyan Adiwijaya [1], Fifi F. Masduki [2,*], Elfahmi Elfahmi [1]

[1] School of Pharmacy, Institut Teknologi Bandung, Bandung City, Indonesia; adiwijaya.royyan@gmail.com (R.A.); elfahmi@itb.ac.id (E.);
[2] Biochemistry Division, Faculty of Mathematic and Science, Institut Teknologi Bandung, Bandung City, Indonesia; fifimasduki@itb.ac.id (F.F.M.);
* Correspondence: fifimasduki@itb.ac.id (F.F.M.);

Scopus Author ID 55241707400
Received: 30.11.2022; Accepted: 5.01.2023; Published: 11.04.2023

Abstract: Malaria is one of the deadliest diseases. In 2020, there were 627,000 global deaths out of 241 million malaria cases. This mortality rate can be reduced by using artemisinin combination therapy (ACT). But there is a concern about the emergence of partial resistance to ACT in 2008. Therefore, rapid response is needed to tackle this problem. The method used is a narrative literature review. Four things must be conducted in managing malaria resistance: prevention, surveillance, access to quality diagnosis, and innovations. The innovations can be modifying conventional treatment and discovering new targets to develop new drugs rationally. The steps that must be taken in responding to cases of antimalarial resistance are the four steps of malaria resistance management based on the WHO protocol. Many new therapeutic targets can be exploited for new drug development, the most interesting of which are ATPase pumps, pyrimidine biosynthesis, and membrane biosynthesis. There are many new interesting drugs for these targets. For example, Cipargamin and E209 are effective against ACT-resistant strains; CDRI9778 and UCT943 are effective against MDR strains; Ganaplacid and AQ13 are effective against CQR strains.

Keywords: artemisinin; resistance; efforts; prevention; curative; countermeasures

1. Introduction

Malaria is one of the infectious diseases that has been faced by humanity since 30 million years ago [1–3]. For an 'ancient' disease, this disease still cannot be eradicated, like smallpox, due to the difficulty of developing an effective malaria vaccine [4,5]. A major bottleneck in developing a highly efficacious vaccine is a lack of reliable correlates of protection and limited application of assay to quantify functional immune response for vaccine evaluation [6]. The lack of an effective vaccine makes health workers rely on curative treatment to deal with malaria [7]. Over the centuries, humanity has developed remedies from natural sources such as the bark of the quinine tree (*Cinchona succirubra*) from South America and the *qing-hua* herb (*Artemisia annua*) from East Asia [8]. Then, isolates from the quinine bark were developed as a quinoline derivative, while the qing-hua herb isolate was developed as a sesquiterpenoid lactone derivative. Due to resistance to many types of quinoline derivatives, especially chloroquine, which was used as a first-line treatment half a century ago, sesquiterpenoid lactone derivatives are now the main therapy used to treat malaria cases [9]. Artemisinin is the first member of sesquiterpenoid lactone derivatives as a treatment for

malaria. Artemisinin and its derivatives are currently used as artemisinin combination therapy (ACT) as a first-line treatment with high efficacy and safety. The therapy administration in the form of a combination is intended to increase efficacy, reduce side effects, accelerate healing, and prevent the probability of resistance appears. This can be done because the combination of drugs used in ACT has pharmacokinetic and pharmacological characters that complement each other [10]. Although combinations are also intended to reduce the probability of the emergence of resistance, cases of partial resistance are still found in Southeast Asia and Africa [11–15]. This resistance is probably due to mutations in the Pfkelch13 domain associated with the endocytosis of hemoglobin to the parasite at the ring stage [15]. Mutations in Pfkelch13 cause a decrease in the degradation of hemoglobin which is required for artemisinin to be converted to its active form [16,17]. This resistance case is very serious because, without prompt and serious handling, this problem can become an epidemic and even a pandemic [4]. It is estimated that the material losses that must be borne to handle cases of uncontrolled malaria resistance are not small, around 276 million USD [18]. In addition, the species that developed resistance strains were *P. falciparum*. This species has the most severe and deadliest symptoms among all *Plasmodium* species, especially in Africa and Southeast Asia [19–22]. *P. vivax* has also developed resistance mainly to ACT partner drugs. It is even more concerning knowing these two species contribute to the vast majority of malaria cases globally [23]. Therefore, there is a need to manage resistance countermeasures and the latest innovations to overcome this case of malaria resistance. In addition to resistance, hypersensitivity to artemisinin derivatives is repeatedly documented in ACT adverse drug reactions [24]. So, non-artemisinin malaria drug development is recommended. Drug development should also be carried out rationally, starting from target identification to drug development by optimizing the structure and activity relationship. This rational drug development will be a new thing in the curative treatment of malaria and can facilitate the optimization of the efficacy, safety, and quality of treatment in the future.

2. Materials and Methods

The articles used were searched from the PubMed article database. The reason for using this database is because the articles published in this database focus on the health and medicine subject, so that searches can be more specific. Search in search engines using the MeSH term: "((antimalarial or antimalarial) AND (resistance) AND (new drugs development OR new treatments development OR novel target)" plus a language filter to English. From this MeSH term, 1734 articles were found. Because there are too many, the range of publication years was reduced from the last 10 years (2012-2022) to the last 2 years (2020-2022). From this, 173 related articles were found. From the 173 articles, articles were selected based on inclusion criteria and issued articles that matched the exclusion criteria. These criteria are as follows:

Inclusion Criteria: Articles contain relevant information (information published is irrefutable with more recent findings, maximum publication deadline is 10 years ago/October 2012, published in reputable journals (minimum Q4), has been cited at least 1x (for journals in 2-3 years). Last year except late 2021/2022), 5x (journal in the last 5 years), and 20x (journal in the last 10 years).

Exclusion Criteria: Articles that do not contain relevant information (refuted by information in more recent articles) were published more than 10 years ago and are not published in a reputable journal.

After applying the inclusion and exclusion criteria in the literature, 45 articles were screened that were used from 2020 to 2022. To complete the literature review, 4 reports and guidelines related to malaria were used from World Health Organization (WHO) and 2 reports. The total literature used at the beginning was 51 articles. From the review articles used among these 51 articles, 83 additional articles were found, the longest published in the last 10 years. Thus, the total number of articles used is 134 articles. The 134 articles used were then entered into the Mendeley application to be grouped for easy analysis and comparison. Articles are grouped by articles discussing new targets, new drugs, new targets, and drugs, as well as meta-analysis articles. The library search results' schema is described in the following flow chart.

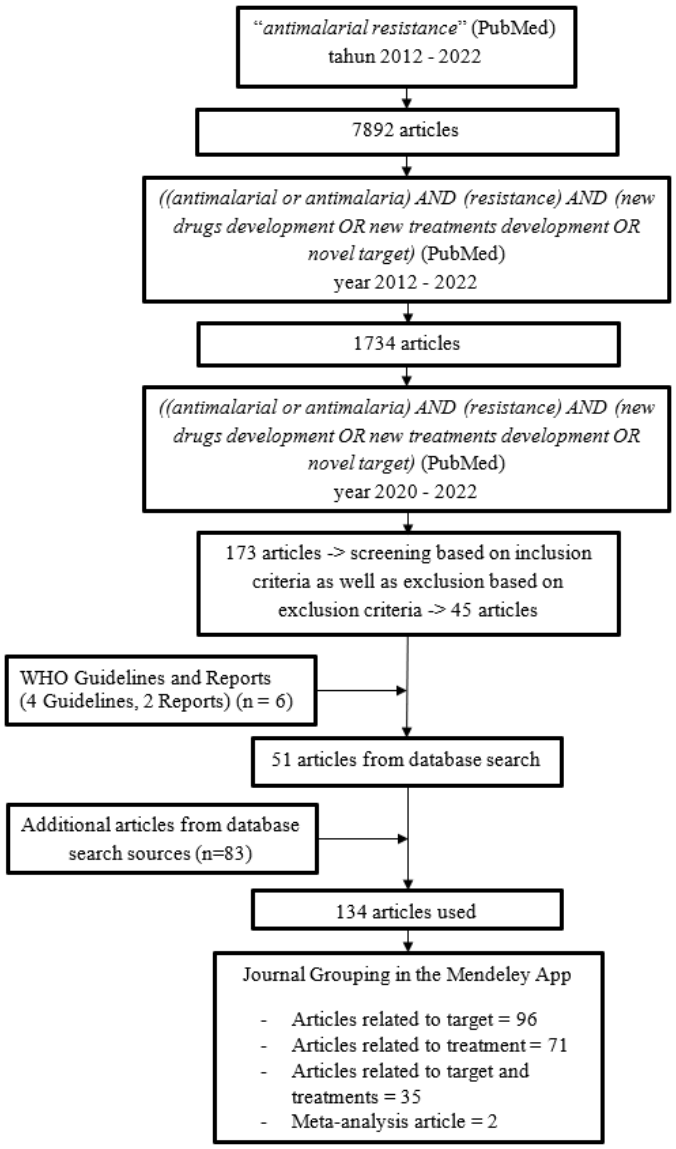

Figure 1. Articles search result scheme.

3. Results and Discussion

3.1. Drug-resistant malaria management outline.

3.1.1. Preventing the spread of resistance.

The first step to stopping the spread of resistance is to decrease the mosquito-human contact frequency. It is also referred to as vector control scale-up. These activities include

increasing the scope of personal protection and eradicating mosquitoes in areas with high resistance or transmission. Personal protection can be in the form of insecticide-treated nets (ITNs), long-lasting insecticide nets, and long-lasting insecticide hammock nets [25]. Mosquito eradication can be done by using smogging insecticides (indoor residual spraying/IRS) and controlling the mosquito life cycle.

In addition to vector control, preventive measures can be carried out using chemoprevention. This step utilizes chemoprophylaxis medicines to keep the parasite concentration in the blood below the threshold for disease onset. The use of chemoprophylaxis should be accompanied by monitoring drug resistance in the area. The use of chemoprophylaxis is supported, especially in vulnerable groups such as children and pregnant women [26]. Chemoprevention can also be given to travelers or as a seasonal malaria prevention [9]. Chemoprophylactic drugs WHO recommends doxycycline or atovaquone-proguanil, chloroquine (if *P. falciparum* is not present in the area), or primaquine [19]. Giving the type of drug depends on the situation and condition.

3.1.2. Improving monitoring for resistance evaluation.

Monitoring of antimalarial drug resistance can be monitored by various studies, ranging from in vivo and molecular studies to *in vitro* studies. Because therapeutic outcomes have clinical relevance to therapeutic efficacy, clinical studies have been established as the gold standard for global antimalarial resistance monitoring by WHO. According to the WHO protocol, national malaria surveillance programs should evaluate the efficacy of first and second-line antimalarial drugs at sentinel sites every 24 months. If there are more than 10% of cases of therapy failure, then responses and policy changes must be made as soon as possible [27]. If it is proven that there are new cases of resistance, the addition of new sentinel sites near the foci of resistant cases may be considered. Routine surveillance of malaria should also be strengthened especially in areas of high risk of resistance.

3.1.3. Improving access to quality diagnosis and therapy.

Increased access to affordable and quality diagnostic tests and therapies could limit the possibility of the spread of resistance to the antimalarial drugs being used. Accurate and affordable diagnosis is essential to prevent the unnecessary use of antimalarial drugs. This refers to the finding that 78% of patients receiving antimalarial drugs were not infected with malaria and just had a common fever. Increasing the manufacturing capacity and quality of rapid detection tests (RDT) can overcome this problem. In addition, increasing access to existing diagnoses as well as education to health workers about diagnosis is also very much needed [28].

In addition to diagnosis, the availability of quality and guaranteed therapy is also important to reduce resistance rates. This is done not only by increasing production capacity but also by eradicating suboptimal drugs. These suboptimal drugs are not only counterfeit drugs but also monotherapy drugs, which are less effective than ACT and can increase resistance rates. Eradication can be done by entering into agreements with the government and manufacturers to stop all activities related to non-optimal drugs and take regulatory action to stop the circulation of non-optimal drugs. Educating citizens about the dangers of counterfeit drugs and monotherapy is also important in reducing market demand [28].

3.2. Development and innovation to tackle drug resistance.

3.2.1. Conventional therapy development.

Developing new drugs from the outset takes time and a long process. In addition to taking a long time, this development also drains resources for a project with a high probability of failure. This modifies existing therapy as an alternative to responding to cases of resistance quickly. Since resistance cases are still partial resistance cases, increasing the duration of therapy from 3 days to 6 days is a rational solution. This strategy implies that more ACT components are needed. Artemisinin precursors used to make artemisinin derivatives can be produced through a microbial fermentation process with a fairly high titer (>40 g/L) [29]. This makes optimization of fermentation conditions and engineering to produce optimum yeast cells the best option to obtain higher titers [18,19]. It should also be noted that improving the therapeutic regimen must also be accompanied by ensuring patient compliance and therapeutic success. This strategy of increasing the therapy duration has proven effective in tackling cases of partial resistance in the Greater Mekong area [32].

In addition to the strategy of increasing the duration, changing the combination is also a way that can be taken to obtain new antimalarial preparations. One application of this combination strategy is triple artemisinin combination therapy (TACT) [33]. This strategy does not require more ACT components but adds another component so that the combination of drugs given to the patient becomes three combinations (one artemisinin derivative and two companion drugs) [33,34]. This strategy has proven to be effective in dealing with HIV and Tuberculosis cases [22,23]. To make TACT preparations, the half-life and side effects of the drug components must be considered [37]. At this time, the clinical trial of TACT's efficacy is undergoing phase 2 clinical trials [38]. In addition to the use of TACT, the use of a combination of non-artemisinin antimalarial drugs can also be used to treat cases of resistance to artemisinin. Examples of this new combination are Atovaquone-Proguanil, Chloroquine + Sulfadoxine-Pyrimethamine, and Mefloquine + Sulfadoxine-Pyrimethamine. As with TACT, the use of this combination must pay attention to the half-life of each component and the side effects of the combination. In addition, the use of quinoline-derived drugs (such as chloroquine) is not very effective in resistant strains, and antifolate drugs (such as sulfadoxine-pyrimethamine) have a fairly rapid risk of developing resistance [39]. So TACT is preferable to using a combination of non-artemisinin antimalarial drugs if a combination modification approach is chosen.

In addition to using TACT, it is possible to manufacture new artemisinin analogs to complement the TACT regimen or even replace it if the analog has a significantly higher half-life than conventional artemisinin derivatives. Artemisinin analogs have been used as conventional drugs because pure artemisinin has poor pharmaceutical properties. Artemisinin-derived drugs used in the ACT, such as artemether and artesunate, are first-generation artemisinin analogs. This first-generation derivative is designed to improve artemisinin's pharmaceutical problems and poor pharmacokinetics. In addition to these derivatives, there are many types of analogs that were developed afterward. The second generation of derivatives was carried out to increase the bioavailability and safety profile of the first generation. This derivative focuses on structural modifications at the C-10, C-16, C-11, and C-6 positions on artemisinin [27,28]. In addition, hybrid artemisinin can also be made to create species with synergistic interactions that have higher efficacy than the individual components [42]. Dimerization can also be done to overcome the obstacles in manufacturing hybrids. This is done by making various chemical linkers such as alkyl, aryl, and esters in symmetric and

asymmetric forms [43]. Trimer and tetramer forms have also been investigated. Even so, the results of the trimer and tetramer species were not satisfactory because they violated Lipinski's Rule of Five a lot. This makes the medicinal properties of this species less potent than other options [40].

Another conventional treatment modification approach is covalent bitherapy. Covalent bitherapy involves combining two chemical components that can interact with the same/different biological targets through different mechanisms [44]. An example of these compounds is Trioxaquine (a combination of 1,2,4-trioxane and 4-aminoquinoline) which can bind to targets by two different mechanisms: heme alkylation (with the trioxane moiety) and heme binding (via the quinoline moiety).

In addition to the modification of conventional antimalarial treatment, non-malarial antimicrobial treatment can be converted to treat malaria. Azithromycin, clindamycin, and doxycycline can have antimalarial activity by inhibiting the parasite's ribosomes. In the case of prevention, azithromycin can produce antimalarial activity when tested in Kenya and Indonesia [14,31].

3.2.2. Discovery of new targets for new drug development.

One of the drawbacks of conventional mainstay medications such as chloroquine and artemisinin is that they were developed from empirical natural medicine used in local traditional health practice. Although this non-rational development is effective, its mechanism, target, and structure-activity relationship are still uncertain. This makes it difficult for researchers to optimize drug compounds and evaluate the safety, efficacy, and quality aspects when needed [46]. Therefore, the development of new antimalarial drugs should ideally use the principles of rational drug development. Researchers usually use a variety of approaches that can be divided into two categories, namely the biological assay approach and the *in silico* approach to find potential targets for new drugs [47]. The combination of biological and in silico methods can provide more efficient and practical findings [47,48]. From this target discovery method, various potential antimalarial drug mechanisms, such as:

- Glycolisis Pathway Inhibitor

The erythrocytic phase of malaria is highly dependent on its anaerobic glycolysis for growth, development, and energy supply [26]. Glucose is transported into infected erythrocytes 100 times more than healthy erythrocytes. Glucose is transported from the blood to erythrocytes via GLUT1 and transported into the parasite by the *P. falciparum* hexose transporter (PFHT). There are structural differences between host GLUT1 and parasitic PFHT so that PFHT can be used as a target for new antimalarial drugs [49]. After the glucose is processed anaerobically, the parasite will produce lactic acid, which must be removed from the erythrocytes by the mechanism of lactate H + simport [50]. It is very important to maintain the intracellular pH and osmotic stability of the parasite. Therefore, inhibition of the parasite's lactate:H+ symport system could be a potential target for new antimalarial drugs. In addition to lactate transporters, the enzyme lactate dehydrogenase, which plays a role in the glycolysis process can also be a target for new antimalarial drugs due to its important role in parasite growth and development [39].

- Sikhimate Metabolism Inhibitor

The shikimate metabolic pathway is an important pathway for the synthesis of aromatic amino acids in parasitic cells. This pathway does not exist in humans, so it can be a specific target for developing new antimalarial drugs [51]. One of the most studied enzymes of the shikimate cycle is 5-enolpyruvil shikimate 3-phosphate synthase and chorismate synthase [39]. Many inhibitors can function on these two enzymes, even though these inhibitors are designed to be made into herbicides [51]. Further research is needed to develop this herbicide into an antimalarial drug that can target the metabolism of the parasite shikimate.

- Purine Salvage Pathway Inhibitor

Purines are used to synthesize nucleic acids used in malaria parasite replication. Purines cannot be biosynthesized by host cells, so they must be 'salvaged' from human host cells. Because this mechanism is only found in parasites, it is selective enough to be a target for the manufacture of new antimalarial drugs [51]. There are several target molecules that can be used as targets for new antimalarial drugs, namely 6-oxopurine phosphoribosyltransferase, purine nucleoside phosphorylase, adenylsuccinate synthetase, s-adenosylhomocysteine hydrolase, and adenosine deaminase [39]. In addition to enzymes, transporters used to transport purines can be used as potential targets. Equilibrative nucleoside transporter (ENT) is a transporter used to transport purines into parasitic cells. PFENT1 is the main transporter of *P. falciparum* and this transporter has only 17% homology with human host cell ENT1. Therefore, this PfENT1 pump can also be a fairly specific target to block parasitic purine gain [52].

- Pyrimidine Biosynthesis Inhibitor

Apart from purines, pyrimidines are also important components in the synthesis of nucleic acids for parasite replication. Unlike purines, pyrimidines can be produced by the host cell itself [51]. In addition, pyrimidines also play a role in the formation of phospholipids, glycoproteins, and folates [53]. The enzyme dihydroorotate dehydrogenase (DHODH) is an enzyme that determines the rate of *de novo* pyrimidine synthesis, which functions to catalyze the oxidation of dihydroorotate to orotate [51]. This target is selective in the host because human cells have a backup pathway other than the *de novo* pathway, so if this enzyme is blocked, healthy host cells can still synthesize pyrimidines, whereas parasites cannot [54]. In addition, ornitidine 5'-monophosphate decarboxylase (OMPDC) and orotate phosphoribosyltransferase also facilitate pyrimidine biosynthesis [55]. The three enzymes above have elucidated their 3D structures so that this target can be ideal in developing new antimalarial drugs [53].

- Plasmodium Special Transporter Inhibitor

Plasmodium has special transporters to supply additional substrate for its very fast metabolism. This transporter is the Plasmodium surface anion channel (PSAC) [26]. PSAC has the critical function of providing additional nutrients such as methionine, pantothenic acid, tyrosine, and cysteine for parasites. This transporter does not have similar homology to other proteins in the human host, so it can be a target for the development of new antimalarial drugs.

- P-type ATPase Inhibitor

Erythrocytes that have been penetrated by the parasite have a higher permeability to Na^+. If not controlled, it can be very toxic to the parasite. Therefore, the parasite has a Na^+ ion efflux pump to maintain the intracellular Na^+ level of the parasite, namely PfATP4 [56]. In addition, this pump mutation also causes the parasite to become resistant to several antimalarial drugs [51]. In addition, PfATP6 (sarco/endoplasmic reticulum Ca^{2+}-ATPase homolog [SERCA]) can be an ATPase pump target for the development of new antimalarial drugs [55]. Because the structure of these proteins has been elucidated, drug development can be carried out more effectively and rationally because the strategy to increase the interaction of drug and protein ligands can be optimized. PfATP4 is also one of the protein targets that has been validated as a new target [57].

- V-type ATPase Inhibitor

Plasmodium has an H^+ pump mechanism similar to the Na^+ pump mechanism. This pump is called the V-type ATPase transporter. This pump is very important to regulate the intracellular pH of the parasite to keep it at pH 7.3 [26]. Similar to PfATP4, this pump is a potential target for new antimalarial drugs [58]. Manipulation of this pump can result in rapid death of the parasite because the intracellular pH of the parasite will change drastically so that normal physiological processes that normally take place at pH 7.3 will be disrupted, even stopped. The structure of V-type ATPase has also been elucidated. This will facilitate the rational drug development process.

- Parasite Membrane Biosynthesis Inhibitor

Phospholipids play an important role as structural components and regulation of intraerythrocytic *P. falciparum*. Parasites require *de novo* phosphatidylcholine as a structural component after invading erythrocytes [51]. The rate-limiting step of *de novo* phosphatidylcholine biosynthesis is the enzyme cholinephosphate cytidyl transferase [26]. In addition, membrane biosynthesis is also needed to protect the parasite when it invades the host cell by enveloping the cell with parasitophorous vacuoles. This parasitophorous vacuole protects the parasite from the phagolysosomes of the host cell. The target molecules to target this parasitophorous vacuole are the GRA17 and GRA23 protein pores [59]. The importance of this membrane formation makes the parasite need a high supply of lipids when invading host cells to replicate more parasites and protect parasitic cells with parasitophorous vacuoles [60].

- Aquaporin-3 Inhibitor

Aquaporin-3 (AQP3) is an aquaglyceroporin facilitates the movement of water and glyceryl inside the mammalian cells. AQP3 3 was induced in hepatocytes infected by *Plasmodium*. AQP3 plays a role in providing glycerol for *Plasmodium* to be used in parasitic replication in the asexual intraerythrocytic stage [26]. AQP3 genetic depletion can significantly reduce the parasite load of the hepatocyte stage of *P. berghei*. What is even more interesting is that genetic disruption of AQP3 in mice has been shown to be non-lethal. This can be a new guideline for developing antimalarial drugs with gene-silencing mechanisms [58].

- Plasmodium Protein Kinase Inhibitor

Kinases are a group of enzymes involved in the phosphorylation of various specific amino acids in the body of organisms [51]. For parasites, this enzyme plays an important role in transcriptional control, post-transcriptional control, protein degradation, and phosphorylation. The most well-understood cyclin-dependent kinases (CDKs) in *P. falciparum* are *P. falciparum* cyclin-dependent protein kinase 4 (PfCDPK4), *P. falciparum* protein kinase 5 (PfPK5), as well as *P. falciparum* mitogen related kinase (PfMRK) [39]. PfCDPK4 plays a key role in the formation of infective sporozoites and exflagellation of male gametocytes of the parasite [51]. The enzymes phosphoinositide kinase (PI3K) and phosphatidylinositol kinase (PfVps34/PI4K) play important roles in membrane biosynthesis and autophagy. This mechanism affects the rate of drug-induced parasite death [61]. *Plasmodium* eukaryotic initiation factor-2α (eIF2α) kinase is an enzyme that is activated when parasites are under stress from artemisinin derivatives. Inhibition of this enzyme can impair parasite differentiation and reduce cases of recrudescence on artemisinin treatment [62].

- Isoprenoid Biosynthesis Inhibitor

Isoprenoids are essential for the post-translational modification of proteins and asexual replication of *Plasmodium*. In addition, isoprenoids are also important for synthesizing ubiquinones, which are mitochondrial electron carriers [51]. The 5-carbon precursor for isoprenoid preparation was prepared from two independent biosynthetic pathways, the mevalonate pathway (MEV) and the 2C-methyl-D-erythritol 4-phosphate (MEP) pathway. Bacteria and *P. falciparum* are highly dependent on the MEP pathway, whereas most eukaryotic organisms can use both pathways [26]. Therefore, enzymes in the MEP pathway can be used as targets for new antimalarial drugs. The rate-determining step in the MEP pathway is catalyzed by *P. falciparum* 1-deoxy-D-xylulose-5-phosphate reductoisomerase (pfDxr/DOXP)[14,51]. PfDXR inhibitors can inhibit the growth of *P. falciparum* without a significant reaction from human cells.

- Pf translational Elongation Factor 2 Inhibitor

One of the promising targets in developing new antimalarial drugs is the blocking of *P. falciparum* ribosomes. *P. falciparum* ribosomes are an evolutionary intermediate between prokaryotic and eukaryotic ribosomes. This is good because it can provide selective toxicity between the parasite and host ribosomes. *P. falciparum* elongation factor 2 (pfEF2) is a ribosomal component that catalyzes GTP-dependent translocation of ribosomes along mRNA. These ribosomes are very important for Plasmodium protein synthesis [26].

- Farnesyltransferase Inhibitor

Prenylated proteins have important roles in cellular processes such as signal transduction, vesicular traffic, regulation of DNA replication, and cell division. These post-translational modifications help intracellular proteins to bind to membranes and promote interactions between proteins. Farnesyltransferase catalyzes the transfer of farnesyl groups from farnesyl pyrophosphate to the C-terminus protein with a Caax motif. Inhibition of this enzyme can kill Plasmodium parasites [26].

- Proteasom Inhibitor

Proteasomes are protein complexes that function to degrade proteins by breaking peptide bonds. *Plasmodium* parasites have three types of proteasomes, namely the eukaryotic proteasome (26S) in the cytoplasm and nucleus, the prokaryotic homologous proteasome (ClpQ) in the mitochondria, and the caseionolytic-like proteasome (ClpP) in the apicoplast [63]. Proteasome functions for protein homeostasis andvercoming disorders caused by the human immune system [64]. Unfortunately, identifying and exploiting parasitic and human proteasome differences is still difficult [47,49]. There is a difference in binding preference between the two proteasomes in which the parasitic proteasome prefers to bind to the aromatic resident at the P1 and P3 peptide positions. The ligand specifically binds to the β-2 subunit in the parasitic proteasome 20s [47,50].

- Apicoplast Inhibitor

Plasmodium has three genomes:he apicoplast genome, the nuclear genome, and the mitochondrial genome [27]. Apicoplasts are non-photosynthetic plastids present in apicomplex parasites such as *Plasmodium*. This organelle functions in carrying out biochemical metabolic pathways such as fatty acid biosynthesis, isoprenoid precursors, and heme synthesis for the survival of *Plasmodium* [27]. Target molecules that can potentially inhibit fatty acid biosynthesis in parasitic apicoplasts are β-ketoacyl-ACP synthase (Fab H) and enoyl-ACPreductase (FabI) enzymes [67]. For example, target molecules for inhibiting isoprenoid biosynthesis processesre β-ketoacyl-ACP reductase (FabG) and 1-deoxy-d-xylulose-5-phosphate-reductoisomerase [39]. Since this organelle is not possessed by human cells, it can be a target for new antimalarial drugs.

- Plasmodium Digestive Vacuole Inhibitor

Plasmodium digestive vacuole is responsible for degrading 60-80% of host hemoglobin. This process is a key process for obtaining amino acids in the growth and development of parasites [27]. The investigation of this pathway provides a promising method in the research and development of new antimalarial drugs. In addition, the glutathione-dependent degradation mechanism in the cytoplasm can also be used by the parasite to degrade hemoglobin [68]. Apart from hemoglobin degradation, there are many processes in the digestive vacuole, from heme polymerization to free radical generation [39].

- Parasite's Protease Inhibitor

Protease for *Plasmodium* parasites is a regulatory and catalytic enzyme that plays a very important role in its survival because of its function in hydrolyzing peptide bonds [26]. This effect works when *Plasmodium* penetrates host tissues, evades the immune system, digests hemoglobin, develops parasites, and activates inflammatory reactions [36,53]. Synthetic peptides that inhibit cysteine protease Pf68 have been shown to inhibit erythrocyte invasion and merozoite formation in *Plasmodium* [26]. In addition to cysteine proteases, serine proteases also play an important role in erythrocyte invasion and breakdown of *Plasmodium* schizonts. These two targets are very potential because no homologous enzymes exist in the human host [51].

- Aminopeptidase Inhibitor

Aminopeptidases catalyze the breakdown of amino acids from the amino ends of proteins as well as peptides. This enzyme is well distributed in prokaryotes and eukaryotes as a cytosolic and integral protein [27]. Bestain inhibits the growth of *P. falciparum in vitro* and *in vivo*. Bestain is active against the intraerythrocytic phase because of the inhibition of leucine aminopeptidase (PfLAP) and membrane alanine aminopeptidase (PfA-M1) by chelating the active metal ion at the metal binding center [27].

- Heat-Shock Protein (HSP) Inhibitor

Heat Shock Protein (HSP) is a chaperon that guides protein folding to become functional [55]. HSP90 is one of the most studied HSPs because it plays an important role in the growth and development of eukaryotic organisms. The cytosolic expression of PfHSP90 increases during the erythrocytic stage of life due to stress in the developmental process of the parasite. In the body of *Plasmodium*, HSP90 also plays a role in regulating sexual development and the transition from the ring stage to the trophozoite. Research has revealed that HSP90 can work as a drug target in many parasitic infections, including malaria [55].

- Protein Nieman-Pick Type C1 (PfNCR1) Inhibitor

PfNCR1 stands for *P. falciparum* Nieman-Pick type C-1 related protein. This protein was identified by selecting the parasite with three different antimalarial compounds using *In vitro* Evolution and Whole Genome Analysis (IVIEWGA) [70]. Subsequent investigations showed that PfNCR1 is located in the parasite's plasma membranand functions for food vacuole biogenesis [32,54]. This gene is critical for the asexual growth of the parasite, making it particularly suitable as a target for new drugs.

- Aminoacyl tRNA synthetase Inhibitor

Aminoacyl-tRNA synthetase (aaRS) plays a key role in protein biosynthesis in *Plasmodium*. *Plasmodium* parasites have 36 aaRS enzymes such as arginyl- (41), tryptophanyl- (42), isoleucyl- (32), prolyl (44), and tyrosyl- (45) aaRS. The pan-active bicyline azetidine, BRD3444, was identified to target this target by phenotypic screening [46,71–73].

- Acetyl-CoA synthetase Inhibitor

Acetyl-CoA is an important molecule for cellular metabolism because it plays an important role in the tricarboxylic acid cycle, lipids, histone acetylation, and phospholipid synthesis. *In vitro* Evolution and Whole Genome Analysis (IVIEWGA) identified a point mutation in the acetyl CoA synthetase *P. falciparum* that could potentially make this enzyme a drug target [74]. Advanced allele switching using CRISPR/Cas9 technology, conditional expression modulation, and enzymatic analysis of heterologically expressed proteins confirmed that this enzyme can be a target molecule and is essential for the survival of *Plasmodium* parasites. Drugs targeting this enzyme in parasites can have a dual action at the erythrocytic and hepatocyte stages simultaneouslyso they can be used as chemotherapy and chemoprophylaxis [46].

- Antiadhesive Polisaccharide Compound

One of the chemical groups that can be developed as a symptomatic drug for severe malaria is an antiadhesive polysaccharide. The main features of severe malaria are inflammation, microvascular obstruction, and a drastic reduction in parasite-infected erythrocytes. The *P. falciparum* uses heparan sulfate when it attaches to the host's endothelium and other blood cells during microvascular obstruction. Inhibition of abnormal cells and interactions of these pathogens will increase the success of therapy by improving blood flow damaged by parasites [26].

3.2.3. Development and discovery of new antimalarial drugs.

Most antimalarial drugs are small molecules designed to interact with biological targets. After the biological target is found and validated, Computer-Aided Drug Discovery (CADD) is used to identify hits, select leads, and optimize them by studying their physicochemical, pharmaceutical, and ADMET (absorption, distribution, metabolism, excretion, toxicity) characteristics [55]. The main focus of the CADD technique is to make it easier for researchers to find compounds with the most optimal medicinal characteristics and eliminate compounds that do not match the specified parameters. Drugs with unique targets and mechanisms of action than conventional treatment are much more likely to treat resistant malaria, just as artemisinin effectively eliminated chloroquine-resistant Plasmodium in the 1970s. Antimalarial drugs found and developed now based on their target of action can be divided into the following set of tables (Tables 1-25).

3.3. Discussion.

There are many treatment targets that have been identified and can be selected in the development of new antimalarial drugs. However, a good treatment target must meet several criteria, such as a confirmed target having a pathophysiological role, selective target expression only on treatment targets (such as only in pathogens), 3D structures available, assayable targets so that bycatch can be carried out, promising safety profile, and the target status. profitable intellectual property (important for pharmaceutical companies). From this, it can be concluded that pyrimidine biosynthesis, membrane biosynthesis, and ATPase pumps (P-type and V-type) are the most potential targets for developing new antimalarial drugs. This is because these three targets have clear pathophysiological properties and can affect many vital physiological systems of the parasite. This can provide a quick and complete effect in the elimination of parasites. In addition, the enzymes and proteins involved in this target have their 3D elucidated structure so that the SAR (structure and activity relationship) research process can be carried out easily to optimize the manufacture of new antimalarial drugs. These targets are also selective enough that their safety profile is guaranteed. In its development, there are many candidates created to target this target and have entered advanced clinical trials. Other characteristics such as high effectiveness against resistant strains, rapid elimination activity, and high half-life were also detected in many drugs targeting these three targets.

In addition to the three targets previously mentioned, heme detoxification and generation of oxidative species also have many well-developed and well-tested candidates for the treatment of malaria. However, these two mechanisms are very similar to conventional treatments that have been used, such as quinoline derivatives and sesquiterpenoid lactones.

Table 1. New drug candidate targeting P-type ATPase.

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
KAE609 (Cipargamin)	Synthetic Spiroindolone	PfATP4	2a	All stages, gametocytes	>Fast action speed >Effective against PfK13 mutation strains >Possibly hepatotoxic	[32,75–81]
OZ277 (Arterolane)	1,2,4-trioxolane	PfATP6/PfSERCA, inhibition of hemoglobin digestion	2-3	All stages	>Combination was marketed in India in 2012 and in Africa in 2014 in combination artolane/piperaquine for uncomplicated malaria	[26,27,75,82]
SC83288	Optimized Amicarbalide	PfATP6/PfSERCA	Preclinical	Erythrocytic stage, most active trophozoites	>Suitable for severe malaria >Fast action speed >Without significant toxic effects	[82,83]
SJ733	Dihydroisoquinolone	PfATP4	1	The biphasic effect on trophozoites and schizonts is rapid, followed by a residual ring stage.	>Bioavailability >30% >High safety profile	[78,81,84–86]

Table 2. New drug candidate targeting V-type ATPase.

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
KAF156 (Ganaplacid)	Imidazolpiperazine	PI4K, PfVP2	3	Sexual erythrocytic stage, asexual erythrocytic stage, pre-erythrocytic stage	>Possibly hepatotoxic >Very effective against QC and LF-resistant *P. falciparum*	[27,79,81,87–89]
MMV253 (AZ13721412)	Triaminopyrimidine	PfVP2	Preclinical	Erythrocytic stage	>High bioavailability >Good as a complementary medicine	[58,78,90]

Table 3. New drug candidates targeting phospholipid metabolism.

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
CDRI9778	1,2,4-trioxane	Phospholipid metabolism	2	Erythrocytic stage	>Effective against Pf MDR (multidrug resistant) >Good bioavailability >Good pharmacokinetics >Good safety profile >Reduce post-therapy recrudescence	[78,82,91]

Table 4. New Drug Candidate Targeting Phosphatidylinositol 4-kinase (PI4K).

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
KAF156 (Ganaplacid)	Imidazolpiperazine	PI4K, PfVP2	3	Sexual erythrocytic, asexual erythrocytic, and pre-erythrocytic stages	>Possibly hepatotoxic >Very effective against *Pf* resistant chloroquine and lumefantrine	[27,79,87–89]
UCT943	Piperazine Amide Derivatives	PI4K	Preclinical	Pre-erythrocytic, asexual erythrocytic, and gametocyte stages	>Can be used for Pf MDR (multidrug resistant) and CQS (chloroquine susceptible) >Effective at low doses >High safety profile	[92,93]
MMV048	Aminopyridine	PfP14K	2a	Asexual erythrocytic stage, and gametocytes	>Can be used for prophylaxis	[26,27,93,94]

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
MMV390048	2-aminopyridine	PfP14K	2a	All stages except the final hypnozoite	>Can be used for prophylaxis	[26,75,81,82,93]

Table 5. New drug candidates targeting choline transport.

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
SAR9727 (Albitiazolium)	Choline Analog	Choline Transport	2	Asexual erythrocytic stage	>Effective at low doses >IM for severe malaria >Not suitable for children	[26,27,82,95]

Table 6. New drug candidate targeting heat shock protein (HSP).

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
SNX-0723	Aminobenzamide	HSP90	Preclinical	Erythrocytic stage, pre-erythrocytic	>Works well in combination with PIK inhibitors (phosphatidylinositol 3 kinase)	[55,96]

Table 7. New drug candidates targeting lactate transporters.

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
MMV007839	Cyclic/linear hemiketal vinylogous acid	Lactate H^+ transporter	Preclinical	Erythrocytic stage	>Kills at micromolar concentrations	[76,97]

Table 8. New drug candidates targeting glutathione homeostasis.

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
Methylene Blue	Thiazine	Pf glutathione reductase, heme polymerization, produces oxidizing species	2	Erythrocytic stage	-	[26,39,41,98]

Table 9. New drug candidate targeting parasite protein transporters.

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
ACT-213615	Piperazine containing compounds	Possibly protein transporters	Preclinical	Asexual erythrocytic stage	>Fast effect	[61, 78]

Table 10. New drug candidate targeting acetyl CoA synthetase.

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
MMV693183 (Pantothenamide)	Pantothenamide	Acetyl-KoA sintetase	Preclinical	Erythrocytic and gametocyte stages	>Has effect on nanomolar concentration >Very high safety profile (>30 x safety margin)	[79, 80]

Table 11. New drug candidates targeting proteasomes.

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
Epoxomycin	Epoxide	20S proteasom	Preclinical	Erythrocytic and gametocyte stages	>Can block the production of oocysts in the mosquito's body	[26,100]
Lactacystin	Acetamide	20S proteasom	Preclinical	All stages	>No mild side effects	[101]
MG132 (Bortezomib)	Synthetic Aldehyd Peptides	Hemoglobin and proteasome degradation	Preclinical	Erythrocytic, gametocyte, and preerythrocytic stages	-	[65,102]

Table 12. New drug candidate targeting aaRS.

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
BRD7929	Azetidine Biscyclic	Phenylalanyl-tRNA synthetase	Preclinical	Pre-erythrocytic, asexual erythrocytic, and gametocyte stages	>80% bioavailability >High water solubility >Half-life 32 hours >Need further structure optimization to be more selective	[71,73]

Table 13. New drug candidates produce toxic oxidative species.

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
E209	Tetraoxane	Production of oxidative species	Preclinical	Erythrocytic and gametocyte stages	>Can overcome ART-resistant Pf mutation PfK13 >Good stability and half-life >Potential better than ACT in combination	[82,103]
Tafenoquine (Krintafel)	8-aminoquinoline	Oxidative stress and proteotoxicity	2b-3	Erythrocytic, pre-erythrocytic, and gametocyte stages	>Prevents relapse of *P. vivax* and *P. ovale* >Single dose of *P. vivax* radical drug >Risk of hemolytic anemia for patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency >High half-life	[78,104–106]
OZ439 (Artefenomel)	1,2,4-trioxolane 2nd generation	Possibly ART-like (produces oxidative species and inhibits heme detoxification)	2b	All stages, especially the erythrocytic stage	>Quick clearing activity >High safety profile >High half-life	[17,78,81,82,107,108]

Table 14. New drug candidates targeting pyrimidine biosynthesis.

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
DSM190	Triazolopirimidine	DHODH	Preclinical	Erythrocytic and pre-erythrocytic stages	>Binding to DHODH is still weak compared to other candidates	[78]
DSM265	Triazolopirimidine	DHODH	2	Erythrocytic and pre-erythrocytic stages	>Potential as a complementary medicine	[26,78,82,109,110]
DSM421	Triazolopirimidine	DHODH	Preclinical	Erythrocytic and pre-erythrocytic stages	>Modification of DSM265 with better physicochemical and pharmacokinetic properties	[78,111]
P218	P65 derivative (WR99210 analogue) Diaminopyridine	PfDHFR and DHODH	1	Erythrocytic and pre-erythrocytic stages	>Effective against pyrimethamine-resistant malaria	[26,75,81,82,109,112]

Table 15. New drug candidate targeting heme detoxification.

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
Methylene Blue	Thiazine	Pf glutathione reductase, heme polymerization, produces oxidizing species	2	Erythrocytic stage	-	[26,39,41,98]

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
AQ13	4-aminoquinoline	Possibility of heme detoxification	2	Asexual erythrocytic stage	>Effective against Pf CQS (chloroquine susceptible) and CQR (chloroquine resistant) >Needs testing on non-immune patients	[82,113,114]
SSR97193 (Ferroquine)	4-aminoquinoline	Heme detox	-(usually used in combination with artefenomel / artesunate)	Erythrocytic stage	>Very long half-life >Prophylaxis promises >Cardiovascular side effects >Hepatotoxic effects should also be monitored in combination use	[115–119]
OZ439 (Artefenomel)	1,2,4-trioxolane 2nd generation	Possibly ART-like (produces oxidative species and inhibits heme detoxification)	2b	All stages, especially the erythrocytic stage	>Quick clearing activity >High safety profile >High half-life	[78,82,107,108]

Table 16. New drug candidate targeting 80S ribosome and elongation factor.

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
M5717/ DDD107498 (Cabamiquine)	Quinoline-4-carboxamide	Ribosom 80s, PfEF2	1	Pre-erythrocytic, erythrocytic, and gametocyte stages	>Quick activity >High pharmacokinetics >More effective than artesunate >Can be single dose chemoprophylaxis	[81,98–100]

Table 17. New drug candidate targeting parasitic RNA transcription.

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
Benzoxaboroles	Heterocyclic boron	Polyadenylation specific factor subunit	Preclinical	All stages, the most active is the trophozoite stage	>High pharmacological and pharmacokinetic activity >High safety profile	[46, 101–103]

Table 18. New drug candidates targeting isoprenoid biosynthesis.

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
Fosmidomycin	Phosphonic acid derivative antibiotics	DOXP Reductoisomerase	2a and 2b	Erythrocytic stage (late schizont)	>Combined with Clindamycin >Can be used on children > 95% therapeutic success at day 28 in children	[14, 15, 104]

Table 19. New drug candidate targeting electron transfer.

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
MK-4815	Mannich base	Possible mitochondrial electron transport chain	Preclinical	Erythrocytic stage	>Half life high, >High safety profile >Good pharmacokinetic properties	[82,120]
ELQ-300	4-quinolone-3-diarileter	Cytochrome complex (cytochrome bc1 complex)	Preclinical	Erythrocytic stage and pre-erythrocytic stage	>Slow activity >Good oral bioavailability >Difficult to cause resistance >Poor pharmacokinetics, >Low plasma concentration	[121–123]

Table 20. New drug candidate targeting AQP3.

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
Auphen	Inorganic compounds containing gold	AQP3	Preclinical	Erythrocytic stage and pre-erythrocytic stage	-	[85]

Table 21. New drug candidate targeting plasmepsin.

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
WEHI-842	Carbamate	*Plasmodium export element* (PEXEL), Plasmepsin V	Preclinical	Asexual erythrocytic and gametocyte stages	>0.2 nanomolar inhibition concentration	[36]
WEHI-916	Carbamate	*Plasmodium export element* (PEXEL), Plasmepsin V	Preclinical	Erythrocytic stage and preerythrocytic stage	-	[36]

Table 22. New drug candidates targeting parasitic proteases.

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
Streptomyces LK3 Extract	Peptide	Parasitic proteases	Preclinical	-	-	[44,64]

Table 23. New symptomatic medicine candidate.

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
DF02 (Sevuparin)	Heparin	Antiadhesive polysaccharide	1 and I/II	Asexual erythrocytic stage	> Overcome microvascular obstruction >Given as IV	[26,124,125]
E6446	Nucleic acid-responding TLR synthetic antagonists	TLR9 and TLR8	Preclinical	Prevents excessive inflammatory reaction	>To reduce cerebral malaria lethality	[78]

Table 24. New antimalarial drug combination candidate.

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
Cipargamin-Ganaplacid	Cip = Spiroindolone Gan = Imidazolpiperazine	PfATP4, PI4K, PfVP2	Precilinical	All stages and gametocytes	-	[126–128]
Ganaplacid-Lumefantrine	Gan = Imidazole Piperazine Lum = aril amino alcohol	PfCARL, DHODH	2b	-	-	[82,109,129]
Artefenomel + Piperaquine	ART = trioxolane Pip = 4-aminoquinoline	ART= similar to ART Pip = bond with heme	2b	All stages	>Efficacy is still 71%, 68%, 79%, not yet eligible	[107,115]
Artefenomel-Ferroquine	ART = trioxolane Fer = 4-aminoquinoline	ART = similar to ART Fer = bond with heme	2b	All stages, especially erythrocytic	>Research stopped in 2018 >Combination efficacy is less effective in children under 5 yr. side effect = severe vomiting.	[115,130]

Table 25. New drug candidates from natural ingredients.

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
Bulbine frutescens root extract	Joziknipholones A and B (phenylanthraquinone)	Unknown	Preclinical	Unknown	Effective against CQR (chloroquine resistant) strains	[55,131]

Candidate	Class	Target	Clinical Test	Life Cycle Target	Note(s)	Source(s)
Methylated flavonoids	Flavonoid	HSP90	Preclinical	Unknown, probably erythrocytic and preerythrocytic		[55]
Nauclea pobeguinii bark extract	Strictosamide (similar to spiroindolone)	Possibility of Ptpn 4 (P type Na^+ ATPase)	2b	Unknown, probably all stages including gametocytocidal	The active substance must be activated in the digestive tract before it becomes the active form	[75,132]
Argemone mexicana extract	Various alkaloids	Unknown	2	Unknown	-	[75,133]
Artocarpus champedes Bark Extract	Methylated flavonoids	Increases immune system activity (inflammatory cytokines, IFN-γ, TNF-α)	Preclinical	-	>Also involves inhibition of malaria heme detoxification	[134]
Arylmethylamino Steroids	Sarachine steroid derivatives	Glutathione Homeostasis	Preclinical	Unknown	>Fast action >Low plasma stability	[82]

This causes drugs developed with mechanisms similar to conventional drugs to be at risk of cross-resistance due to resistance that arises from conventional treatment. Although proven effective in in vitro and in vivo tests, treatment with these two mechanisms is still less than ideal compared to the three newer mechanisms: membrane biosynthesis, pyrimidine biosynthesis, and ATPase pumps. The use of drugs with this new mechanism should be prioritized in areas with high resistance, such as the Greater Mekong region, while for areas with low resistance, conventional drugs or new drugs with mechanisms similar to conventional drugs should be used. This is intended to further reduce the possibility of new resistance to drugs with new mechanisms.

The development of new antimalarial drugs has found many drugs with interesting, specific efficacy. There are even malaria drugs that work to reduce malaria-related mortality. Drugs such as Cipargamin and E209 have been shown to be effective against artemisinin-resistant *Plasmodium falciparum*. Candidates such as CDRI9778 and UCT943 also showed satisfactory activity against *P. falciparum* MDR (multidrug-resistant) strains. Ganaplacid and AQ13 also showed high activity against *P. falciparum* CQR (chloroquine-resistant). Three drugs targeting the parasite ATPase pump Arterolane, Cipargamin, and Ganaplacid have a high potential to be developed as the main therapy for malaria in the future, especially for areas with high ACT transmission and resistance. Even so, it is still necessary to optimize the side effects and safety profile of this drug candidate. For severe malaria, candidates such as SC83288 and Albitiazolim show satisfactory potency. Tafenoquine has also been found as an alternative to radical drugs other than primaquine. In addition to drugs that seek to eliminate parasite numbers, there are drugs being developed to reduce lethality associated with severe malaria cases. Examples are Sevuparin and E6446. Each of these two drugs is used to treat microvascular obstruction and to treat immune hyperactivity in cerebral malaria. Treatment using natural ingredients with the highest potential is a drug from the bark extract of *Nauclea pobeguinii*, which has entered phase 2 clinical trials. However, this natural treatment does not have a clear mechanism and target, so its development is irrational. This can complicate the optimization and modification process if it is found that there are obstacles when administering malaria therapy in the future. Even so, this natural treatment still has hope. Identifying specific compounds that have activity can make the herbal treatment much more reliable, as can the identification of quinine bark isolates (quinine) and qing-hua herbs (artemisinin).

4. Conclusions

Cases of infective disease resistance are serious cases that must be responded to quickly, responsively, and carefully by health agencies around the world. Steps that must be taken to respond to resistance to conventional antimalarial drugs are to stop the spread of resistance (by increasing vector control and chemoprophylaxis), increase surveillance for evaluation of resistance, increase access to quality diagnosis and therapy, and develop new therapies. The development of new therapies can be done by developing conventional therapies (change in therapeutic regimens, different combinations, or use of non-antimalarial drugs) or by finding new targets that can be inhibited by the use of new drugs (rational drug development).

New targets of new antimalarial drugs that have been identified are parasitic glycolysis pathway, parasitopore vacuole, shikimate metabolism, purine salvage pathway, pyrimidine biosynthesis, *Plasmodium* specific transporter, carbonic anhydrase, P-type ATPase, V-type ATPase, parasite membrane biosynthesis, aquaporin 3, parasitic protein kinase, isoprenoid

biosynthesis, Pf translational elongation factor 2, farnesyltransferase, proteasome, apicoplast, food vacuole, parasitic protease, aminopeptidase, heat shock protein, PfNCR1, aaRS, and acetyl CoA synthetase. The most potential targets for further development are ATPase pumps, pyrimidine biosynthesis, and parasite membrane biosynthesis. Of the many targets that have been found, new drugs have been rationally developed and have shown promising efficacy, safety, and quality through clinical and preclinical trials that have been carried out. Interesting new antimalarial drugs for further development are Cipargamine and E209 (suitable for artemisinin derivative-resistant *Plasmodium*), CDRI9778 and UCT943 (suitable for *Plasmodium* multidrug-resistant strains), and Ganaplacid and AQ13 (suitable for chloroquine-resistant *Plasmodium*). Albitiazolium and SC83288 are suitable to be developed for the treatment of severe malaria. Sevuparin and E6446 can reduce lethality in microvascular obstruction and cerebral malaria cases. The Ganaplacid-Lumefantrine combination entering phase 2b clinical trials, has promising activity, including for artemisinin-resistant *Plasmodium*.

Funding

This research received no external funding

Acknowledgments

The literature review and research behind this would not have been possible without the guidance of my supervisor, Dr. Elfahmi. apt. as the main supervisor and Dr. rer. nat Fifi F. Masduki as accompanying supervisor. Because of their insights, help, guidance, direction, and patience, I was able to write this paper to its final form. I also extend my gratitude to the Dean of the ITB School of Pharmacy, Prof. I Ketut Adnyana, and all ITB lecturers, academic staff, and non-academic staff who supported my studying process so that I could gain sufficient knowledge to discuss this topic as my last project. Apart from that, of course, I have to express my gratitude to my family, friends, and all those who have supported me both materially and mentally during this time of pandemic and hardship so that the process of writing this thesis runs smoothly.

Conflicts of Interest

The funders had no role in the study's design; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

References

1. Poinar, G. Evolutionary History of Terrestrial Pathogens and Endoparasites as Revealed in Fossils and Subfossils. *Adv Biol* **2014**, *2014*, 1–29, https://doi.org/10.1155/2014/181353.
2. Sato, S. Plasmodium—a Brief Introduction to the Parasites Causing Human Malaria and Their Basic Biology. *J Physiol Anthropol* **2021**, *40*, 1–13, https://doi.org/10.1186/s40101-020-00251-9.
3. Li, X.H.; Zhou, H.N.; Xu, J.W.; Lin, Z.R.; Sun, X.D.; Li, J.Y.; Lin, X.X.; Xie, Y.; Alonso, P.; Yang, H.L. Seven Decades towards Malaria Elimination in Yunnan, China. *Malar J* **2021**, *20*, 1–16, https://doi.org/10.1186/s12936-021-03672-8.
4. Bonam, S.R.; Rénia, L.; Tadepalli, G.; Bayry, J.; Kumar, H.M.S. Plasmodium Falciparum Malaria Vaccines and Vaccine Adjuvants. *Vaccines (Basel)* **2021**, *9*, 1–35, https://doi.org/10.3390/vaccines9101072.
5. Nevagi, R.J.; Good, M.F.; Stanisic, D.I. Plasmodium Infection and Drug Cure for Malaria Vaccine Development. *Expert Rev Vaccines* **2021**, *20*, 163–183, https://doi.org/10.1080/14760584.2021.1874923.

6. Opi, D.H.; Kurtovic, L.; Chan, J.A.; Horton, J.L.; Feng, G.; Beeson, J.G. Multi-Functional Antibody Profiling for Malaria Vaccine Development and Evaluation. *Expert Rev Vaccines* **2021**, *20*, 1257–1272, https://doi.org/10.1080/14760584.2021.1981864.
7. Talapko, J.; Škrlec, I.; Alebić, T.; Jukić, M.; Včev, A. Malaria: The Past and the Present. *Microorganisms* **2019**, *7*, https://doi.org/10.3390/microorganisms7060179.
8. Tiwari, M.K.; Chaudhary, S. Artemisinin-Derived Antimalarial Endoperoxides from Bench-Side to Bed-Side: Chronological Advancements and Future Challenges. *Med Res Rev* **2020**, *40*, 1220–1275, https://doi.org/10.1002/med.21657.
9. Ippolito, M.M.; Moser, K.A.; Kabuya, J.-B.B.; Cunningham, C.; Juliano, J.J. Antimalarial Drug Resistance and Implications for the WHO Global Technical Strategy. *Curr Epidemiol Rep* **2021**, *8*, 46–62, https://doi.org/10.1007/s40471-021-00266-5.
10. Zou, Y.; Julie, N.; Guo, S.; Tang, Y.; Zhang, H.; Xu, Z.; Wu, W.; Yuan, Y.; Wu, Z.; Guo, W.; et al. The Effect of Artemisinin-Based Drugs vs Non-Artemisinin-Based Drugs on Gametophyte Carrying in the Body After the Treatment of Uncomplicated Falciparum Malaria: A Systematic Review and Meta-Analysis. *Front Pharmacol* **2022**, *12*, 1–12, https://doi.org/10.3389/fphar.2021.707498.
11. Lu, F.; Culleton, R.; Zhang, M.; Ramaprasad, A.; von Seidlein, L.; Zhou, H.; Zhu, G.; Tang, J.; Liu, Y.; Wang, W.; et al. Emergence of Indigenous Artemisinin-Resistant Plasmodium Falciparum in Africa . *New England Journal of Medicine* **2017**, *376*, 991–993, https://doi.org/10.1056/nejmc1612765.
12. Fairhurst, R.M.; Nayyar, G.M.L.; Breman, J.G.; Hallett, R.; Vennerstrom, J.L.; Duong, S.; Ringwald, P.; Wellems, T.E.; Plowe, C. V.; Dondorp, A.M. Artemisinin-Resistant Malaria: Research Challenges, Opportunities, and Public Health Implications. *American Journal of Tropical Medicine and Hygiene* **2012**, *87*, 231–241, https://doi.org/10.4269/ajtmh.2012.12-0025.
13. De Villiers, K.A.; Egan, T.J. Heme Detoxification in the Malaria Parasite: A Target for Antimalarial Drug Development. *Acc Chem Res* **2021**, *54*, 2649–2659, https://doi.org/10.1021/acs.accounts.1c00154.
14. Muhseen, Z.T.; Hameed, A.R.; Al-Bhadly, O.; Ahmad, S.; Li, G. Natural Products for Treatment of Plasmodium Falciparum Malaria: An Integrated Computational Approach. *Comput Biol Med* **2021**, *134*, 104415, https://doi.org/10.1016/j.compbiomed.2021.104415.
15. Dhorda, M.; Amaratunga, C.; Dondorp, A.M. Artemisinin and Multidrug-Resistant Plasmodium Falciparum - a Threat for Malaria Control and Elimination. *Curr Opin Infect Dis* **2021**, *34*, 432–439, https://doi.org/10.1097/QCO.0000000000000766.
16. Heller, L.E.; Roepe, P.D. Artemisinin-Based Antimalarial Drug Therapy: Molecular Pharmacology and Evolving Resistance. *Trop Med Infect Dis* **2019**, *4*, https://doi.org/10.3390/tropicalmed4020089.
17. Egwu, C.O.; Augereau, J.M.; Reybier, K.; Benoit-Vical, F. Reactive Oxygen Species as the Brainbox in Malaria Treatment. *Antioxidants* **2021**, *10*, 1–20, https://doi.org/10.3390/antiox10121872.
18. Lubell, Y.; Dondorp, A.; Guerin, P.J.; Drake, T.; Meek, S.; Ashley, E.; Day, N.P.J.; White, N.J.; White, L.J. Artemisinin Resistance-Modelling the Potential Human and Economic Costs. *Malar J* **2014**, *13*, https://doi.org/10.1186/1475-2875-13-452.
19. WHO Report *Report on Antimalarial Drug Efficacy, Resistance and Response*; **2020**, https://www.google.com/books?hl=en&lr=&id=oMFqEAAAQBAJ&oi=fnd&pg=PR5&dq=WHO+Report+Report+on+Antimalarial+Drug+Efficacy,+Resistance+and+Response%3B+2020%3B&ots=Hgm1JlHoFr&sig=TlJ8GE-fU_CAJqZcTg8eZVKnres.
20. Sena-Dos-santos, C.; Braga-Da-silva, C.; Marques, D.; dos Santos Pinheiro, J.A.; Ribeiro-Dos-santos, Â.; Cavalcante, G.C. Unraveling Cell Death Pathways during Malaria Infection: What Do We Know so Far? *Cells* **2021**, *10*, 1–29, https://doi.org/10.3390/cells10020479.
21. de Villiers, K.A.; Egan, T.J. Heme Detoxification in the Malaria Parasite: A Target for Antimalarial Drug Development. *Acc Chem Res* **2021**, *54*, 2649–2659, https://doi.org/10.1021/acs.accounts.1c00154.
22. Al-Awadhi, M.; Ahmad, S.; Iqbal, J. Current Status and the Epidemiology of Malaria in the Middle East Region and Beyond. *Microorganisms* **2021**, *9*, 1–20, https://doi.org/10.3390/microorganisms9020338.
23. Buyon, L.E.; Elsworth, B.; Duraisingh, M.T. The Molecular Basis of Antimalarial Drug Resistance in Plasmodium Vivax. *Int J Parasitol Drugs Drug Resist* **2021**, *16*, 23–37, https://doi.org/10.1016/j.ijpddr.2021.04.002.
24. Nordmann, T.; Borrmann, S.; Ramharter, M. Drug-Induced Hypersensitivity to Artemisinin-Based Therapies for Malaria. *Trends Parasitol* **2022**, *38*, 136–146, https://doi.org/10.1016/j.pt.2021.08.011.
25. WHO WHO Guidelines for Malaria - 3 June 2022. *World Health Organization* **2022**, https://www.google.com/books?hl=en&lr=&id=oMFqEAAAQBAJ&oi=fnd&pg=PR5&dq=WHO+Report

+Report+on+Antimalarial+Drug+Efficacy,+Resistance+and+Response%3B+2020%3B&ots=Hgm1JlHoFr&sig=TlJ8GE-fU_CAJqZcTg8eZVKnres.
26. Belete, T.M. Recent Progress in the Development of New Antimalarial Drugs with Novel Targets. *Drug Des Devel Ther* **2020**, *14*, 3875–3889, https://doi.org/10.2147/DDDT.S265602.
27. Shibeshi, M.A.; Kifle, Z.D.; Atnafie, S.A. Antimalarial Drug Resistance and Novel Targets for Antimalarial Drug Discovery. *Infect Drug Resist* **2020**, *13*, 4047–4060, https://doi.org/10.2147/IDR.S279433.
28. World Health Organization Emergency Response to Artemisinin Resistance in the Greater Mekong Subregion. *WHO Publications* 2013, https://apps.who.int/iris/handle/10665/79940.
29. Paddon, C.J.; Westfall, P.J.; Pitera, D.J.; Benjamin, K.; Fisher, K.; McPhee, D.; Leavell, M.D.; Tai, A.; Main, A.; Eng, D.; et al. High-Level Semi-Synthetic Production of the Potent Antimalarial Artemisinin. *Nature* **2013**, *496*, 528–532, https://doi.org/10.1038/nature12051.
30. Carsanba, E.; Pintado, M.; Oliveira, C. Fermentation Strategies for Production of Pharmaceutical Terpenoids in Engineered Yeast. *Pharmaceuticals* **2021**, *14*, https://doi.org/10.3390/ph14040295.
31. Guirimand, G.; Kulagina, N.; Papon, N.; Hasunuma, T.; Courdavault, V. Innovative Tools and Strategies for Optimizing Yeast Cell Factories. *Trends Biotechnol* **2021**, *39*, 488–504, https://doi.org/10.1016/j.tibtech.2020.08.010.
32. Ashley, E.A.; Dhorda, M.; Fairhurst, R.M.; Amaratunga, C.; Lim, P.; Suon, S.; Sreng, S.; Anderson, J.M.; Mao, S.; Sam, B.; et al. Spread of Artemisinin Resistance in Plasmodium Falciparum Malaria . *New England Journal of Medicine* **2014**, *371*, 411–423, https://doi.org/10.1056/nejmoa1314981.
33. Tindana, P.; de Haan, F.; Amaratunga, C.; Dhorda, M.; van der Pluijm, R.W.; Dondorp, A.M.; Cheah, P.Y. Deploying Triple Artemisinin-Based Combination Therapy (TACT) for Malaria Treatment in Africa: Ethical and Practical Considerations. *Malar J* **2021**, *20*, 1–7, https://doi.org/10.1186/s12936-021-03649-7.
34. van der Pluijm, R.W.; Amaratunga, C.; Dhorda, M.; Dondorp, A.M. Triple Artemisinin-Based Combination Therapies for Malaria – A New Paradigm? *Trends Parasitol* **2021**, *37*, 15–24, https://doi.org/10.1016/j.pt.2020.09.011.
35. WHO Consolidated Guidelines on The Use of Antiretroviral Drugs for Treating and Preventing HIV Infection. *WHO Publications* 2016, *2*, https://www.who.int/publications/i/item/9789241549684.
36. WHO, W.H.O. *World Malaria Report: 20 Years of Global Progress and Challenges*; 2020; Vol. WHO/HTM/GM; ISBN 978-92-4-001579-1, https://www.who.int/publications/i/item/9789240015791.
37. Sureshkumar, B.; Mary, Y.S.; Panicker, C.Y.; Suma, S.; Armaković, S.; Armaković, S.J.; Van Alsenoy, C.; Narayana, B. Quinoline Derivatives as Possible Lead Compounds for Anti-Malarial Drugs: Spectroscopic, DFT and MD Study. *Arabian Journal of Chemistry* **2020**, *13*, 632–648, https://doi.org/10.1016/j.arabjc.2017.07.006.
38. Wicht, K.J.; Mok, S.; Fidock, D.A. Molecular Mechanisms of Drug Resistance in Plasmodium Falciparum Malaria. *Annu Rev Microbiol* **2020**, *74*, 431–454, https://doi.org/10.1146/annurev-micro-020518-115546.
39. Mishra, M.; Mishra, V.K.; Kashaw, V.; Iyer, A.K.; Kashaw, S.K. Comprehensive Review on Various Strategies for Antimalarial Drug Discovery. *Eur J Med Chem* **2016**, *125*, 1300–1320, https://doi.org/10.1016/j.ejmech.2016.11.025.
40. Patel, O.P.S.; Beteck, R.M.; Legoabe, L.J. Exploration of Artemisinin Derivatives and Synthetic Peroxides in Antimalarial Drug Discovery Research. *Eur J Med Chem* **2021**, *213*, https://doi.org/10.1016/j.ejmech.2021.113193.
41. Pinheiro, L.C.S.; Feitosa, L.M.; da Silveira, F.F.; Boechat, N. Current Antimalarial Therapies and Advances in the Development of Semi-Synthetic Artemisinin Derivatives. *An Acad Bras Cienc* **2018**, *90*, 1251–1271, https://doi.org/10.1590/0001-3765201820170830.
42. Sampath Kumar, H.M.; Herrmann, L.; Tsogoeva, S.B. Structural Hybridization as a Facile Approach to New Drug Candidates. *Bioorg Med Chem Lett* **2020**, *30*, 127514, https://doi.org/10.1016/j.bmcl.2020.127514.
43. Patel, O.P.S.; Beteck, R.M.; Legoabe, L.J. Exploration of Artemisinin Derivatives and Synthetic Peroxides in Antimalarial Drug Discovery Research. *Eur J Med Chem* **2021**, *213*, https://doi.org/10.1016/j.ejmech.2021.113193.
44. Aguiar, A.C.C.; da Rocha, E.M.M.; de Souza, N.B.; França, T.C.C.; Krettli, A.U. New Approaches in Antimalarial Drug Discovery and Development - A Review. *Mem Inst Oswaldo Cruz* **2012**, *107*, 831–845, https://doi.org/10.1590/S0074-02762012000700001.
45. Croft, S.L.; Duparc, S.; Arbe-Barnes, S.J.; Craft, J.C.; Shin, C.S.; Fleckenstein, L.; Borghini-Fuhrer, I.; Rim, H.J. Review of Pyronaridine Antimalarial Properties and Product Characteristics. *Malar J* **2012**, *11*, 1, https://doi.org/10.1186/1475-2875-11-270.

46. Yang, T.; Ottilie, S.; Istvan, E.S.; Godinez-Macias, K.P.; Lukens, A.K.; Baragaña, B.; Campo, B.; Walpole, C.; Niles, J.C.; Chibale, K.; et al. MalDA, Accelerating Malaria Drug Discovery. *Trends Parasitol* **2021**, *37*, 493–507, https://doi.org/10.1016/j.pt.2021.01.009.
47. Agamah, F.E.; Damena, D.; Skelton, M.; Ghansah, A.; Mazandu, G.K.; Chimusa, E.R. Network-Driven Analysis of Human–Plasmodium Falciparum Interactome: Processes for Malaria Drug Discovery and Extracting in Silico Targets. *Malar J* **2021**, *20*, 1–20, https://doi.org/10.1186/s12936-021-03955-0.
48. Shangguan, Z. A Review of Target Identification Strategies for Drug Discovery: From Database to Machine-Based Methods. *J Phys Conf Ser* **2021**, *1893*, https://doi.org/10.1088/1742-6596/1893/1/012013.
49. Heitmeier, M.R.; Hresko, R.C.; Edwards, R.L.; Prinsen, M.J.; Ilagan, M.X.G.; Odom John, A.R.; Hruz, P.W. Identification of Druggable Small Molecule Antagonists of the Plasmodium Falciparum Hexose Transporter PfHT and Assessment of Ligand Access to the Glucose Permeation Pathway via FLAG-Mediated Protein Engineering. *PLoS One* **2019**, *14*, 1–20, https://doi.org/10.1371/journal.pone.0216457.
50. Marchetti, R. V.; Lehane, A.M.; Shafik, S.H.; Winterberg, M.; Martin, R.E.; Kirk, K. A Lactate and Formate Transporter in the Intraerythrocytic Malaria Parasite, Plasmodium Falciparum. *Nat Commun* **2015**, *6*, 1–7, https://doi.org/10.1038/ncomms7721.
51. Tibon, N.S.; Ng, C.H.; Cheong, S.L. Current Progress in Antimalarial Pharmacotherapy and Multi-Target Drug Discovery. *Eur J Med Chem* **2020**, *188*, https://doi.org/10.1016/j.ejmech.2019.111983.
52. Keough, D.T.; Špaček, P.; Hocková, D.; Tichý, T.; Vrbková, S.; Slavětínská, L.; Janeba, Z.; Naesens, L.; Edstein, M.D.; Chavchich, M.; et al. Acyclic Nucleoside Phosphonates Containing a Second Phosphonate Group Are Potent Inhibitors of 6-Oxopurine Phosphoribosyltransferases and Have Antimalarial Activity. *J Med Chem* **2013**, *56*, 2513–2526, https://doi.org/10.1021/jm301893b.
53. Krungkrai, S.R.; Krungkrai, J. Insights into the Pyrimidine Biosynthetic Pathway of Human Malaria Parasite Plasmodium Falciparum as Chemotherapeutic Target. *Asian Pac J Trop Med* **2016**, *9*, 525–534, https://doi.org/10.1016/j.apjtm.2016.04.012.
54. Llanos-Cuentas, A.; Casapia, M.; Chuquiyauri, R.; Hinojosa, J.C.; Kerr, N.; Rosario, M.; Toovey, S.; Arch, R.H.; Phillips, M.A.; Rozenberg, F.D.; et al. Antimalarial Activity of Single-Dose DSM265, a Novel Plasmodium Dihydroorotate Dehydrogenase Inhibitor, in Patients with Uncomplicated Plasmodium Falciparum or Plasmodium Vivax Malaria Infection: A Proof-of-Concept, Open-Label, Phase 2a Study. *Lancet Infect Dis* **2018**, *18*, 874–883, https://doi.org/10.1016/S1473-3099(18)30309-8.
55. Kushwaha, P.P.; Vardhan, P.S.; Kumari, P.; Mtewa, A.G.; Kumar, S. *Bioactive Lead Compounds and Targets for the Development of Antimalarial Drugs*; Elsevier Inc., 2019; ISBN 9780128178911, https://doi.org/10.1016/B978-0-12-817890-4.00020-2.
56. Kumar, S.; Bhardwaj, T.R.; Prasad, D.N.; Singh, R.K. Drug Targets for Resistant Malaria: Historic to Future Perspectives. *Biomedicine and Pharmacotherapy* **2018**, *104*, 8–27, https://doi.org/10.1016/j.biopha.2018.05.009.
57. Flannery, E.L.; McNamara, C.W.; Kim, S.W.; Kato, T.S.; Li, F.; Teng, C.H.; Gagaring, K.; Manary, M.J.; Barboa, R.; Meister, S.; et al. Mutations in the P-Type Cation-Transporter ATPase 4, PfATP4, Mediate Resistance to Both Aminopyrazole and Spiroindolone Antimalarials. *ACS Chem Biol* **2015**, *10*, 413–420, https://doi.org/10.1021/cb500616x.
58. Ashley, E.A.; Phyo, A.P. Drugs in Development for Malaria. *Drugs* **2018**, *78*, 861–879, https://doi.org/10.1007/s40265-018-0911-9.
59. Gold, D.A.; Kaplan, A.D.; Lis, A.; Bett, G.C.L.; Emily, E.; Cirelli, K.M.; Bougdour, A.; Sidik, S.M.; Beck, J.R.; Lourido, S.; et al. The Toxoplasma Dense Granule Proteins GRA17 and GRA23 Mediate the Movement of Small Molecules between the Host and the Parasitophorous Vacuole. *Cell Host Microbe* **2015**, *17*, 642–652, https://doi.org/10.1016%2Fj.chom.2015.04.003.
60. Itoe, M.A.; Sampaio, J.L.; Cabal, G.G.; Real, E.; Zuzarte-Luis, V.; March, S.; Bhatia, S.N.; Frischknecht, F.; Thiele, C.; Shevchenko, A.; et al. Host Cell Phosphatidylcholine Is a Key Mediator of Malaria Parasite Survival during Liver Stage Infection. *Cell Host Microbe* **2014**, *16*, 778–786, https://doi.org/10.1016/j.chom.2014.11.006.
61. Gaviria, D.; Paguio, M.F.; Turnbull, L.B.; Tan, A.; Siriwardana, A.; Ghosh, D.; Ferdig, M.T.; Sinai, A.P.; Roepe, P.D. A Process Similar to Autophagy Is Associated with Cytocidal Chloroquine Resistance in Plasmodium Falciparum. *PLoS One* **2013**, *8*, 8–11, https://doi.org/10.1371/journal.pone.0079059.
62. Zhang, Min.; Gallego-Delgado, Julio.; Fernandez-Arias, Cristina.; Waters, Norman.C.; Rodriguez, Ana.; Tsuji, Moriya.; Wek, Ronald.C.; Nussenzweig, Victor.; Sullivan Jr., W.J. Inhibiting the Plasmodium EIF2α

Kinase PK4 Prevents Artemisinin-Induced Latency. *Cell Host Microbe* **2017**, *22*, 766–776, https://doi.org/10.1016/j.chom.2017.11.005.
63. Krishnan, K.Mosur.; Williamson, K.C. The Proteasome as a Target to Combat Malaria: Hits and Misses. *Transl Res.* **2018**, *198*, 40–47, https://doi.org/10.1016/j.trsl.2018.04.007.
64. Anas, M.; Kumari, V.; Gupta, N.; Dube, A.; Kumar, N. Protein Quality Control Machinery in Intracellular Protozoan Parasites: Hopes and Challenges for Therapeutic Targeting. *Cell Stress Chaperones* **2019**, *24*, 891–904, https://doi.org/10.1007/s12192-019-01016-9.
65. Aminake, M.N.; Arndt, H.D.; Pradel, G. The Proteasome of Malaria Parasites: A Multi-Stage Drug Target for Chemotherapeutic Intervention? *Int J Parasitol Drugs Drug Resist* **2012**, *2*, 1–10, https://doi.org/10.1016/j.ijpddr.2011.12.001.
66. Li, H.; Bogyo, M.; da Fonseca, P.C.A. The Cryo-EM Structure of the Plasmodium Falciparum 20S Proteasome and Its Use in the Fight against Malaria. *FEBS J.* **2016**, *283*, 4238–4243, https://doi.org/10.1111/febs.13780.
67. Solomon Tesfaye; Bhanu Prakash; Prati Pal Singh Apicoplast Biosynthetic Pathways as Possible Targets for Combination Therapy of Malaria. *Journal of Pharmacy and Pharmacology* **2015**, *3*, 101–115, https://doi.org/10.17265/2328-2150/2015.03.001.
68. Coronado, L.M.; Nadovich, C.T.; Spadafora, C. Malarial Hemozoin: From Target to Tool. *Biochim Biophys Acta Gen Subj* **2014**, *1840*, 2032–2041, https://doi.org/10.1016/j.bbagen.2014.02.009.
69. Roy, K.K. Targeting the Active Sites of Malarial Proteases for Antimalarial Drug Discovery: Approaches, Progress and Challenges. *Int J Antimicrob Agents* **2017**, *50*, 287–302, https://doi.org/10.1016/j.ijantimicag.2017.04.006.
70. Istvan, E.S.; Das, S.; Bhatnagar, S.; Beck, J.R.; Owen, E.; Llinas, M.; Ganesan, S.M.; Niles, J.C.; Winzeler, E.; Vaidya, A.B.; et al. Plasmodium Niemann-Pick Type C1- Related Protein Is a Druggable Target Required for Parasite Membrane Homeostasis. *Elife* **2019**, *8*, 1–23, https://elifesciences.org/articles/40529.
71. Kato, N.; Comer, E.; Sakata-Kato, T.; Sharma, A.; Sharma, M.; Maetani, M.; Bastien, J.; Brancucci, N.M.; Bittker, J.A.; Corey, V.; et al. Diversity-Oriented Synthesis Yields Novel Multistage Antimalarial Inhibitors. *Nature* **2016**, *538*, 344–349, https://doi.org/10.1038/nature19804.
72. Manickam, Y.; Malhotra, N.; Mishra, S.; Babbar, P.; Dusane, A.; Laleu, B.; Bellini, V.; Hakimi, M.A.; Bougdour, A.; Sharma, A. Double Drugging of Prolyl-TRNA Synthetase Provides a New Paradigm for Anti-Infective Drug Development. *PLoS Pathog* **2022**, *18*, 1–17, https://doi.org/10.1371/journal.ppat.1010363.
73. Sharma, M.; Malhotra, N.; Yogavel, M.; Harlos, K.; Melillo, B.; Comer, E.; Gonse, A.; Parvez, S.; Mitasev, B.; Fang, F.G.; et al. Structural Basis of Malaria Parasite Phenylalanine TRNA-Synthetase Inhibition by Bicyclic Azetidines. *Nat Commun* **2021**, *12*, https://doi.org/10.1038/s41467-020-20478-5.
74. Schalkwijk, J.; Allman, E.L.; Jansen, P.A.M.; Vries, L.E. De; Verhoef, J.M.J.; Jackowski, S.; Botman, P.N.M.; Beuckens-schortinghuis, C.A.; Koolen, K.M.J.; Bolscher, J.M.; et al. Antimalarial Pantothenamide Metabolites Target Acetyl – Coenzyme A Biosynthesis in Plasmodium Falciparum. *Science Tranlational Medicine* **2019**, *9917*, https://pubmed.ncbi.nlm.nih.gov/31534021/.
75. Flannery, E.L.; Chatterjee, A.K.; Winzeler, E.A. Antimalarial Drug Discovery-Approaches and Progress towards New Medicines. *Nat Rev Microbiol* **2013**, *11*, 849–862, https://doi.org/10.1038/nrmicro3138.
76. Rosling, J.E.O.; Ridgway, M.C.; Summers, R.L.; Kirk, K.; Lehane, A.M. Biochemical Characterization and Chemical Inhibition of PfATP4-Associated Na-ATPase Activity in Plasmodium Falciparum Membranes. *Journal of Biological Chemistry* **2018**, *293*, 13327–13337, https://doi.org/10.1074/jbc.RA118.003640.
77. Bouwman, S.A.; Zoleko-Manego, R.; Renner, K.C.; Schmitt, E.K.; Mombo-Ngoma, G.; Grobusch, M.P. The Early Preclinical and Clinical Development of Cipargamin (KAE609), a Novel Antimalarial Compound. *Travel Med Infect Dis* **2020**, *36*, https://doi.org/10.1016/j.tmaid.2020.101765.
78. Imrat, A.K.V. and P.R.M. Recent Advances in Antimalarial Drug Discovery: Challenges and Opportunities. *IntechOpen* **2021**, http://dx.doi.org/10.5772/intechopen.97401.
79. White, N.J.; Duong, T.T.; Uthaisin, C.; Nosten, F. Antimalarial Activity of KAF156 in Falciparum and Vivax Malaria. *N Engl J Med* **2016**, *375*, 1152–1160, https://doi.org/10.1056/NEJMoa1602250.Antimalarial.
80. Pacheco, P.A.F.; Santos, M.M.M. Recent Progress in the Development of Indole-Based Compounds Active against Malaria, Trypanosomiasis and Leishmaniasis. *Molecules* **2022**, *27*, https://doi.org/10.3390/molecules27010319.
81. Birkholtz, L.M.; Alano, P.; Leroy, D. Transmission-Blocking Drugs for Malaria Elimination. *Trends Parasitol* **2022**, *38*, 390–403, https://doi.org/10.1016/j.pt.2022.01.011.

82. Okombo, J.; Chibale, K. Recent Updates in the Discovery and Development of Novel Antimalarial Drug Candidates. *Medchemcomm* **2018**, *9*, 437–453, https://doi.org/10.1039/c7md00637c.
83. Pegoraro, S.; Duffey, M.; Otto, T.D.; Wang, Y.; Rösemann, R.; Baumgartner, R.; Fehler, S.K.; Lucantoni, L.; Avery, V.M.; Moreno-Sabater, A.; et al. SC83288 Is a Clinical Development Candidate for the Treatment of Severe Malaria. *Nat Commun* **2017**, *8*, https://doi.org/10.1038/ncomms14193.
84. Zhang, R.; Suwanarusk, R.; Malleret, B.; Cooke, B.M.; Nosten, F.; Lau, Y.L.; Dao, M.; Lim, C.T.; Renia, L.; Tan, K.S.W.; et al. A Basis for Rapid Clearance of Circulating Ring-Stage Malaria Parasites by the Spiroindolone KAE609. *Journal of Infectious Diseases* **2016**, *213*, 100–104, https://doi.org/10.1093/infdis/jiv358.
85. SheelaNair, A.; Romanczuk, A.S.; Aogo, R.A.; Haldar, R.N.; Lansink, L.I.M.; Cromer, D.; Salinas, Y.G.; Guy, R.K.; McCarthy, J.S.; Davenport, M.P.; et al. Similarly Efficacious Anti-Malarial Drugs SJ733 and Pyronaridine Differ in Their Ability to Remove Circulating Parasites in Mice. *Malar J* **2022**, *21*, 1–11, https://doi.org/10.1186/s12936-022-04075-z.
86. Jiménez-Díaz, M.B.; Ebert, D.; Salinas, Y.; Pradhan, A.; Lehane, A.M.; Myrand-Lapierre, M.E.; O'Loughlin, K.G.; Shackleford, D.M.; De Almeida, M.J.; Carrillo, A.K.; 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–E5462, https://doi.org/10.1073/pnas.1414221111.
87. Kuhen, K.L.; Chatterjee, A.K.; Rottmann, M.; Gagaring, K.; Borboa, R.; Buenviaje, J.; Chen, Z.; Francek, C.; Wu, T.; Nagle, A.; et al. KAF156 Is an Antimalarial Clinical Candidate with Potential for Use in Prophylaxis, Treatment, and Prevention of Disease Transmission. *Antimicrob Agents Chemother* **2014**, *58*, 5060–5067, https://doi.org/10.1128/AAC.02727-13.
88. McCarthy, J.S.; Abd-Rahman, A.N.; Collins, K.A.; Marquart, L.; Griffin, P.; Kümmel, A.; Fuchs, A.; Winnips, C.; Mishra, V.; Csermak-Renner, K.; et al. Defining the Antimalarial Activity of Cipargamin in Healthy Volunteers Experimentally Infected with Blood-Stage Plasmodium Falciparum. *Antimicrob Agents Chemother* **2021**, *65*, https://doi.org/10.1128/AAC.01423-20.
89. Mwai, L.; Diriye, A.; Masseno, V.; Muriithi, S.; Feltwell, T.; Musyoki, J.; Lemieux, J.; Feller, A.; Mair, G.R.; Marsh, K.; et al. Genome Wide Adaptations of Plasmodium Falciparum in Response to Lumefantrine Selective Drug Pressure. *PLoS One* **2012**, *7*, https://doi.org/10.1371/journal.pone.0031623.
90. Hameed P., S.; Solapure, S.; Patil, V.; Henrich, P.P.; Magistrado, P.A.; Bharath, S.; Murugan, K.; Viswanath, P.; Puttur, J.; Srivastava, A.; et al. Triaminopyrimidine Is a Fast-Killing and Long-Acting Antimalarial Clinical Candidate. *Nat Commun* **2015**, *6*, 1–11, https://doi.org/10.1038/ncomms7715.
91. Wahajuddin, M.; Singh, S.P.; Taneja, I.; Raju, K.S.R.; Gayen, J.R.; Siddiqui, H.H.; Singh, S.K. Development and Validation of an LC-MS/MS Method for Simultaneous Determination of Piperaquine and 97-63, the Active Metabolite of CDRI 97-78, in Rat Plasma and Its Application in Interaction Study. *Drug Test Anal* **2016**, *8*, 221–227, https://doi.org/10.1002/dta.1807.
92. Le Manach, C.; Nchinda, A.T.; Paquet, T.; Gonzàlez Cabrera, D.; Younis, Y.; Han, Z.; Bashyam, S.; Zabiulla, M.; Taylor, D.; Lawrence, N.; et al. Identification of a Potential Antimalarial Drug Candidate from a Series of 2-Aminopyrazines by Optimization of Aqueous Solubility and Potency across the Parasite Life Cycle. *J Med Chem* **2016**, *59*, 9890–9905, https://doi.org/10.1021/acs.jmedchem.6b01265.
93. Brunschwig, Christel.; Wirjanata, G.; Marsh, K.C.; Duffy, J.; Noviyanti, R.; Rochford, R.; McPhail, J.A.; Njoroge, M.; Smith, D.A.; Birkholtz, L.-M.; et al. "UCT943, a Next-Generation Plasmodium Falciparum PI4K Inhibitor Preclinical Candidate for the Treatment of Malaria." *Antimicrob Agents Chemother* **2018**, *62*, 1–16, https://doi.org/10.1128/aac.00012-18.
94. Odom John, A.R.; Mathews, E.S. Tackling Resistance: Emerging Antimalarials and New Parasite Targets in the Era of Elimination. *F1000Res* **2018**, *7*, 1–11, https://doi.org/10.12688/f1000research.14874.1.
95. Schiafino-Ortega, S.; Baglioni, E.; Pérez-Moreno, G.; Marco, P.R.; Marco, C.; González-Pacanowska, D.; Ruiz-Pérez, L.M.; Carrasco-Jiménez, M.P.; López-Cara, L.C. 1,2-Diphenoxiethane Salts as Potent Antiplasmodial Agents. *Bioorg Med Chem Lett* **2018**, *28*, 2485–2489, https://doi.org/10.1016/j.bmcl.2018.05.060.
96. Posfai, D.; Sylvester, K.; Reddy, A.; Ganley, J.G.; Wirth, J.; Cullen, Q.E.; Dave, T.; Kato, N.; Dave, S.S.; Derbyshire, E.R. Plasmodium Parasite Exploits Host Aquaporin-3 during Liver Stage Malaria Infection. *PLoS Pathog* **2018**, *14*, 1–26, https://doi.org/10.1371/journal.ppat.1007057.
97. Hapuarachchi, S. V.; Cobbold, S.A.; Shafik, S.H.; Dennis, A.S.M.; McConville, M.J.; Martin, R.E.; Kirk, K.; Lehane, A.M. The Malaria Parasite's Lactate Transporter PfFNT Is the Target of Antiplasmodial

Compounds Identified in Whole Cell Phenotypic Screens. *PLoS Pathog* **2017**, *13*, 1–24, https://doi.org/10.1371/journal.ppat.1006180.
98. Ehrhardt, K.; Davioud-Charvet, E.; Ke, H.; Vaidya, A.B.; Lanzer, M.; Deponte, M. The Antimalarial Activities of Methylene Blue and the 1,4-Naphthoquinone 3-[4-(Trifluoromethyl)Benzyl]-Menadione Are Not Due to Inhibition of the Mitochondrial Electron Transport Chain. *Antimicrob Agents Chemother* **2013**, *57*, 2114–2120, https://doi.org/10.1128/AAC.02248-12.
99. Brunner, R.; Aissaoui, H.; Boss, C.; Bozdech, Z.; Brun, R.; Corminboeuf, O.; Delahaye, S.; Fischli, C.; Heidmann, B.; Kaiser, M.; et al. Identification of a New Chemical Class of Antimalarials. *Journal of Infectious Diseases* **2012**, *206*, 735–743, https://doi.org/10.1093/infdis/jis418.
100. Dogovski, C.; Xie, S.C.; Burgio, G.; Bridgford, J.; Mok, S.; McCaw, J.M.; Chotivanich, K.; Kenny, S.; Gnädig, N.; Straimer, J.; et al. Targeting the Cell Stress Response of Plasmodium Falciparum to Overcome Artemisinin Resistance. *PLoS Biol* **2015**, *13*, 1–26, https://doi.org/10.1371/journal.pbio.1002132.
101. Ōmura, S.; Crump, A. Lactacystin: First-in-Class Proteasome Inhibitor Still Excelling and an Exemplar for Future Antibiotic Research. *Journal of Antibiotics* **2019**, *72*, 189–201, https://doi.org/10.1038/s41429-019-0141-8.
102. Arkwright, R.; Pham, T.M.; Zonder, J.A.; Dou, Q.P. The Preclinical Discovery and Development of Bortezomib for the Treatment of Mantle Cell Lymphoma. *Expert Opin Drug Discov* **2017**, *12*, 225–235, https://doi.org/10.1080/17460441.2017.1268596.
103. O'Neill, P.M.; Amewu, R.K.; Charman, S.A.; Sabbani, S.; Gnädig, N.F.; Straimer, J.; Fidock, D.A.; Shore, E.R.; Roberts, N.L.; Wong, M.H.L.; et al. A Tetraoxane-Based Antimalarial Drug Candidate That Overcomes PfK13-C580Y Dependent Artemisinin Resistance. *Nat Commun* **2017**, *8*, 1–10, https://doi.org/10.1038/ncomms15159.
104. Kuan-Yi Lu Tafenoquine: A Step toward Malaria Elimination. *Biochemistry* **2020**, *59*, 911–920, https://doi.org/10.1021/acs.biochem.9b01105.
105. Lacerda, M.V.G.; Llanos-Cuentas, A.; Krudsood, S.; Lon, C.; Saunders, D.L.; Mohammed, R.; Yilma, D.; Batista Pereira, D.; Espino, F.E.J.; Mia, R.Z.; et al. Single-Dose Tafenoquine to Prevent Relapse of Plasmodium Vivax Malaria . *New England Journal of Medicine* **2019**, *380*, 215–228, https://doi.org/10.1056/nejmoa1710775.
106. Vijayan, K.; Wei, L.; Glennon, E.K.K.; Mattocks, C.; Bourgeois, N.; Staker, B.; Kaushansky, A. Host-Targeted Interventions as an Exciting Opportunity to Combat Malaria. *Chem Rev* **2021**, *121*, 10452–10468, https://doi.org/10.1021/acs.chemrev.1c00062.
107. Ogeto, T.; Ndubi, F.; Murithi, M.; Kagia, R.; Wambugu, E.; Suge, T.; Chepkirui, C.; Tonui, J.; Maiyo, F.; Momanyi, L.; et al. Malaria Vaccines Targeting the Pre-Erythrocytic Stage: A Scoping Review. *F1000Res* **2020**, *9*, 680, https://doi.org/10.12688/f1000research.24320.1.
108. Phyo, A.P.; Jittamala, P.; Nosten, F.H.; Pukrittayakamee, S.; Imwong, M.; White, N.J.; Duparc, S.; Macintyre, F.; Baker, M.; Möhrle, J.J. Antimalarial Activity of Artefenomel (OZ439), a Novel Synthetic Antimalarial Endoperoxide, in Patients with Plasmodium Falciparum and Plasmodium Vivax Malaria: An Open-Label Phase 2 Trial. *Lancet Infect Dis* **2016**, *16*, 61–69, https://doi.org/10.1016/S1473-3099(15)00320-5.
109. Reis, R.A.G.; Calil, F.A.; Feliciano, P.R.; Pinheiro, M.P.; Nonato, M.C. The Dihydroorotate Dehydrogenases: Past and Present. *Arch Biochem Biophys* **2017**, *632*, 175–191, https://doi.org/10.1016/j.abb.2017.06.019.
110. Phillips, M.A.; Lotharius, J.; Marsh, K.; White, J.; Dayan, A.; White, K.L.; Njoroge, J.W.; El Mazouni, Fa.; Lao, Ya.; Kokkonda, S.; et al. A Long-Duration Dihydroorotate Dehydrogenase Inhibitor (DSM265) for Prevention and Treatment of Malaria. *Sci Transl Med.* **2015**, *7*, 296, https://doi.org/10.1126/scitranslmed.aaa6645.
111. Phillips, M.A.; White, K.L.; Kokkonda, S.; Deng, X.; White, J.; El Mazouni, F.; Marsh, K.; Tomchick, D.R.; Manjalanagara, K.; Rudra, K.R.; et al. A Triazolopyrimidine-Based Dihydroorotate Dehydrogenase Inhibitor (DSM421) with Improved Drug-like Properties for Treatment and Prevention of Malaria. *ACS Infect Dis* **2016**, *2*, 945–957, https://doi.org/10.1021/acsinfecdis.6b00144.
112. Chughlay, M.F.; El Gaaloul, M.; Donini, C.; Campo, B.; Berghmans, P.J.; Lucardie, A.; Marx, M.W.; Cherkaoui-Rbati, M.H.; Langdon, G.; Angulo-Barturen, I.; et al. Chemoprotective Antimalarial Activity of P218 against Plasmodium Falciparum: A Randomized, Placebo-Controlled Volunteer Infection Study. *American Journal of Tropical Medicine and Hygiene* **2021**, *104*, 1348–1358, https://doi.org/10.4269/ajtmh.20-1165.

113. Ewer, K.J.; Sierra-Davidson, K.; Salman, A.M.; Illingworth, J.J.; Draper, S.J.; Biswas, S.; Hill, A.V.S. Progress with Viral Vectored Malaria Vaccines: A Multi-Stage Approach Involving "Unnatural Immunity." *Vaccine* **2015**, *33*, 7444–7451, https://doi.org/10.1016/j.vaccine.2015.09.094.
114. Koita, O.A.; Sangaré, L.; Miller, H.D.; Sissako, A.; Coulibaly, M.; Thompson, T.A.; Fongoro, S.; Diarra, Y.; Ba, M.; Maiga, A.; et al. AQ-13, an Investigational Antimalarial, versus Artemether plus Lumefantrine for the Treatment of Uncomplicated Plasmodium Falciparum Malaria: A Randomised, Phase 2, Non-Inferiority Clinical Trial. *Lancet Infect Dis* **2017**, *17*, 1266–1275, https://doi.org/10.1016/S1473-3099(17)30365-1.
115. Koehne, E.; Adegnika, A.A.; Held, J.; Kreidenweiss, A. Pharmacotherapy for Artemisinin-Resistant Malaria. *Expert Opin Pharmacother* **2021**, *22*, 2483–2493, https://doi.org/10.1080/14656566.2021.1959913.
116. Held, J.; Supan, C.; Salazar, C.L.O.; Tinto, H.; Bonkian, L.N.; Nahum, A.; Moulero, B.; Sié, A.; Coulibaly, B.; Sirima, S.B.; et al. Ferroquine and Artesunate in African Adults and Children with Plasmodium Falciparum Malaria: A Phase 2, Multicentre, Randomised, Double-Blind, Dose-Ranging, Non-Inferiority Study. *Lancet Infect Dis* **2015**, *15*, 1409–1419, https://doi.org/10.1016/S1473-3099(15)00079-1.
117. Salim, M.; Ramirez, G.; Peng, K.Y.; Clulow, A.J.; Hawley, A.; Ramachandruni, H.; Beilles, S.; Boyd, B.J. Lipid Compositions in Infant Formulas Affect the Solubilization of Antimalarial Drugs Artefenomel (OZ439) and Ferroquine during Digestion. *Mol Pharm* **2020**, *17*, 2749–2759, https://doi.org/10.1021/acs.molpharmaceut.0c00475.
118. Haeusler, I.L.; Chan, X.H.S.; Guérin, P.J.; White, N.J. The Arrhythmogenic Cardiotoxicity of the Quinoline and Structurally Related Antimalarial Drugs: A Systematic Review. *BMC Med* **2018**, *16*, 1–13, https://doi.org/10.1186/s12916-018-1188-2.
119. Supan, C.; Mombo-Ngoma, G.; Kombila, M.; Salazar, C.L.O.; Held, J.; Lell, B.; Cantalloube, C.; Djeriou, E.; Ogutu, B.; Waitumbi, J.; et al. Phase 2a, Open-Label, 4-Escalating-Dose, Randomized Multicenter Study Evaluating the Safety and Activity of Ferroquine (SSR97193) plus Artesunate, versus Amodiaquine plus Artesunate, in African Adult Men with Uncomplicated Plasmodium Falciparum Malaria. *American Journal of Tropical Medicine and Hygiene* **2017**, *97*, 514–525, https://doi.org/10.4269/ajtmh.16-0731.
120. Powles, M.A.; Allocco, J.; Yeung, L.; Nare, B.; Liberator, P.; Schmatz, D. MK-4815, a Potential New Oral Agent for Treatment of Malaria. *Antimicrob Agents Chemother* **2012**, *56*, 2414–2419, https://doi.org/10.1128/AAC.05326-11.
121. Nilsen, A.; LaCrue, A.N.; White, K.L.; Forquer, I.P.; Cross, R.M.; Marfurt, J.; Mather, M.W.; Delves, M.J.; Shackleford, D.M.; Saenz, F.E.; et al. Quinolone-3-Diarylethers: A New Class of Antimalarial Drug. *Sci Transl Med* **2013**, *5*, https://doi.org/10.1126/scitranslmed.3005029.
122. Frueh, L.; Li, Y.; Mather, M.W.; Li, Q.; Pou, S.; Nilsen, A.; Winter, R.W.; Forquer, I.P.; Pershing, A.M.; Xie, L.H.; et al. Alkoxycarbonate Ester Prodrugs of Preclinical Drug Candidate ELQ-300 for Prophylaxis and Treatment of Malaria. *ACS Infect Dis* **2017**, *3*, 728–735, https://doi.org/10.1021/acsinfecdis.7b00062.
123. Miley, G.P.; Pou, S.; Winter, R.; Nilsen, A.; Li, Y.; Kelly, J.X.; Stickles, A.M.; Mather, M.W.; Forquer, I.P.; Pershing, A.M.; et al. ELQ-300 Prodrugs for Enhanced Delivery and Single-Dose Cure of Malaria. *Antimicrob Agents Chemother* **2015**, *59*, 5555–5560, https://doi.org/10.1128/AAC.01183-15.
124. Leitgeb, A.M.; Charunwatthana, P.; Rueangveerayut, R.; Uthaisin, C.; Silamut, K.; Chotivanich, K.; Sila, P.; Moll, K.; Lee, S.J.; Lindgren, M.; et al. Inhibition of Merozoite Invasion and Transient De-Sequestration by Sevuparin in Humans with Plasmodium Falciparum Malaria. *PLoS One* **2017**, *12*, 1–19, https://doi.org/10.1371/journal.pone.0188754.
125. Telen, M.J.; Batchvarova, M.; Shan, S.; Bovee-Geurts, P.H.; Zennadi, R.; Leitgeb, A.; Brock, R.; Lindgren, M. Sevuparin Binds to Multiple Adhesive Ligands and Reduces Sickle Red Blood Cell-Induced Vaso-Occlusion. *Br J Haematol* **2016**, *175*, 935–948, https://doi.org/10.1111/bjh.14303.
126. Joel Leong, F.; Jain, J.P.; Feng, Y.; Goswami, B.; Stein, D.S. A Phase 1 Evaluation of the Pharmacokinetic/Pharmacodynamic Interaction of the Antimalarial Agents KAF156 and Piperaquine. *Malar J* **2018**, *17*, 1–11, https://doi.org/10.1186/s12936-017-2162-8.
127. Kublin, J.G.; Murphy, S.C.; Maenza, J.; Seilie, A.M.; Jain, J.P.; Berger, D.; Spera, D.; Zhao, R.; Soon, R.L.; Czartoski, J.L.; et al. Safety, Pharmacokinetics, and Causal Prophylactic Efficacy of KAF156 in a Plasmodium Falciparum Human Infection Study. *Clin Infect Dis* **2021**, *73*, e2407–e2414, https://doi.org/10.1093/cid/ciaa952.
128. Yipsirimetee, A.; Chiewpoo, P.; Tripura, R.; Lek, D.; Day, N.P.J.; Dondorp, A.M.; Pukrittayakamee, S.; White, N.J.; Chotivanich, K. Assessment In Vitro of the Antimalarial and Transmission- Blocking Activities

of Cipargamin and Ganaplacide in Artemisinin-Resistant Plasmodium Falciparum. *Antimicrob Agents Chemother* **2022**, *66*, 1–10, https://doi.org/10.1128/aac.01481-21.

129. Erhunse, N.; Sahal, D. Protecting Future Antimalarials from the Trap of Resistance: Lessons from Artemisinin-Based Combination Therapy (ACT) Failures. *J Pharm Anal* **2021**, *11*, 541–554, https://doi.org/10.1016/j.jpha.2020.07.005.
130. Adoke, Y.; Zoleko-Manego, R.; Ouoba, S.; Tiono, A.B.; Kaguthi, G.; Bonzela, J.E.; Duong, T.T.; Nahum, A.; Bouyou-Akotet, M.; Ogutu, B.; et al. A Randomized, Double-Blind, Phase 2b Study to Investigate the Efficacy, Safety, Tolerability and Pharmacokinetics of a Single-Dose Regimen of Ferroquine with Artefenomel in Adults and Children with Uncomplicated Plasmodium Falciparum Malaria. *Malar J* **2021**, *20*, 1–25, https://doi.org/10.1186/s12936-021-03749-4.
131. Bekono, B.D.; Ntie-Kang, F.; Onguéné, P.A.; Lifongo, L.L.; Sippl, W.; Fester, K.; Owono, L.C.O. The Potential of Antimalarial Compounds Derived from African Medicinal Plants: A Review of Pharmacological Evaluations from 2013 to 2019. *Malar J* **2020**, *19*, 1–35, https://doi.org/10.1186/s12936-020-03231-7.
132. Xu, Y.J.; Foubert, K.; Dhooghe, L.; Lemière, F.; Cimanga, K.; Mesia, K.; Apers, S.; Pieters, L. Chromatographic Profiling and Identification of Two New Iridoid-Indole Alkaloids by UPLC-MS and HPLC-SPE-NMR Analysis of an Antimalarial Extract from Nauclea Pobeguinii. *Phytochem Lett* **2012**, *5*, 316–319, https://doi.org/10.1016/j.phytol.2012.02.010.
133. Simoes-Pires, C.; Hostettmann, K.; Haouala, A.; Cuendet, M.; Falquet, J.; Graz, B.; Christen, P. Reverse Pharmacology for Developing an Antimalarial Phytomedicine. The Example of Argemone Mexicana. *Int J Parasitol Drugs Drug Resist* **2014**, *4*, 338–346, https://doi.org/10.1016/j.ijpddr.2014.07.001.
134. Uzor, P.F.; Prasasty, V.D.; Agubata, C.O. Natural Products as Sources of Antiprotozoal Drugs. *Evidence-Based Complementary and Alternative Medicine* **2020**, *2*, 2, https://doi.org/10.1155/2020/9385125.