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Antimalarial drug resistance and drug discovery: learning from the past to innovate the future

Liana Theodoridis, Teresa G. Carvalho *

Department of Microbiology, Anatomy, Physiology, and Pharmacology, School of Agriculture, Biomedicine and Environment, La Trobe University, Melbourne, Australia

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ABSTRACT

The emergence and spread of artemisinin-resistant malaria over the past 15 years has led to a recent rise in global malaria cases and represents a major public health concern. Following decades of intense research efforts, the first malaria vaccine has been approved for clinical use in October of 2021. However, its 36 % efficacy highlights the ongoing need for novel and effective drugs to combat malaria. The majority of current antimalarials are derivatives of previous efficient compounds whilst new treatments with diverse chemical scaffolds have not been implemented into clinical practice since 1996. We argue that current research efforts should focus on developing novel chemical classes of compounds to help fight drug resistant malaria. Here we provide a comprehensive review of the antimalarial treatments currently in clinical use and discuss their significant limitations due to parasite drug resistance. Further, we discuss various approaches to antimalarial drug discovery and offer new perspectives on the topic, informing on current methods, both rarely and extensively used. Collating the most recent and up-to-date drug discovery strategies will not only maximise current global research efforts but will ensure all possible drug development avenues are trialed. This review provides innovative insights to circumvent antimalarial drug resistance and diversify malaria therapeutics.

1. Introduction

Categorised as one of the "Big Three" infectious diseases by the World Health Organisation, malaria is a major global burden that has plagued humans for millennia (Tishkoff et al., 2001). Malaria parasite antigens have been detected in human Egyptian remains as early as 3200 BCE. Symptoms of malaria disease have been found in the works of Greek poets and philosophers, including Aristophanes, Aristotle and Hippocrates, and in Homer's *Iliad*. In northern India, Vedic scriptures from approximately 1500 BCE refer to malaria as the "king of diseases". Similarly, the Chinese Canon of Medicine determined malaria-like symptoms and links between fevers and epidemic occurrences in 270 BCE. Impressively, *Plasmodium* parasites have been detected around the globe across multiple civilisations. However, despite centuries worth of historical citings and medicinal advancements (Miller et al., 1994), malaria remains an ever-present health concern, continuing to impact a third of the global population today.

Human-infecting protozoan malaria parasites (*Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, Plasmodium knowlesi* and *Plasmodium falciparum*) can be transmitted via female *Anopheles* mosquitoes. To combat rising infection rates, prominent antimalarial therapeutics are widely distributed amongst malaria-affected regions, with optimal drug selection depending on *Plasmodium* species and disease severity (Organization, 2015). However, the currently available malaria vaccines (RTS,S and R21/Matrix-M) have limitations (Lancet, 2024), and disease management efforts rely on vector control, prompt diagnosis and efficient treatment. Significant reductions in malaria mortality have occurred since 2000, raising hopes for disease elimination and eventual eradication by 2050 (Feachem et al., 2019). However, *Plasmodium* drug resistance has emerged against all existing antimalarial treatments (Table 1). As malaria control and elimination relies on effective drug administration, the prevalence of antimalarial resistance severely hinders disease prevention efforts. Here, we review the current knowledge behind the inefficiency of major malaria chemotherapeutics such as chloroquine and artemisinin, and we discuss promising antimalarial drug discovery strategies that could enhance global research efforts.

2. Chloroquine

Chloroquine (CQ) has been used for the treatment of malaria over the

* Corresponding author.
E-mail address: t.carvalho@latrobe.edu.au (T.G. Carvalho).

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past 70 years and is the current drug of choice for *P. vivax* infections (Nomura et al., 2001). Classified by WHO as an essential medicine, CQ is also a therapeutic for auto-immune diseases such as systemic lupus erythematosus and rheumatoid arthritis (Rainsford et al., 2015). Following World War II, CQ was mass distributed worldwide and used as the primary antimalarial in WHO's global malaria eradication campaign (Ginsburg, 2005). This 4-aminoquinoline compound is a relatively safe, inexpensive and readily available treatment option for blood-stage infection (Martin et al., 2009). In addition, it is used as a prophylactic treatment for international travel to malaria endemic regions in the Middle East and Central America (Batchelor and Gherardin, 2007; Connor, 2001). CQ is well-tolerated in humans and provides a long-lasting antimalarial response due to its prolonged half-life of 45–55 days (Gustafsson et al., 1987).

2.1. Mode of action of chloroquine

The mechanism of action of chloroquine is intertwined with haemoglobin digestion in mature erythrocytic parasites. To ensure intracellular parasite survival, toxic haem is converted to hemozoin within the parasite digestive vacuole (DV), a process inhibited by CQ. This weak base accumulates within the acidic DV, altering the internal pH and inhibiting membrane diffusion. CQ is active during haemoglobin-to-hemozoin conversion by firstly impeding falcipain 2 binding to haemoglobin, thereby affecting haem detoxification (Chugh et al., 2013). In addition, CQ binds to toxic haem to form a complex and inhibits the crystallization of hemozoin, hindering parasite detoxification (Martin et al., 2009). As parasites continue to feed on haemoglobin, potential CQ binding sites are increased and thereby its overall effectivity. CQ-induced partial permeabilisation of the DV triggers a programmed cell death cascade, resulting in mitochondrial disfunction, DNA fragmentation and parasite death (Ch'Ng et al., 2011).

2.2. Chloroquine resistance: PfCRT mutation

Despite CQ's lengthy period of antimalarial efficacy, emergence of

Table 1
List of prominent antimalarial therapeutics, their current status and resistance mechanisms.

Antimalarial	Drug Class	Mode of Action	Drug Limitations	Resistance Mechanisms	Ref.
Amodiaquine	4-Aminoquinoline	Inhibition of haem/hemozoin polymerisation and detoxification	Resistance observed in South America, Asia and East Africa and has been linked to severe cases of acute hepatitis	Mutations in *P. falciparum* chloroquine resistance transporter and multi-drug resistance 1 genes	(Khaliq et al., 1987; Kremsner et al., 1988; Mutabingwa et al., 2005; Venkatesan et al., 2014)
Artemisinin	Sesquiterpene Lactone	ROS damages vital cellular necessities following haem-catalysed activation	Resistance in South-East Asia and recently confirmed in Africa	Mutations in the *P. falciparum* kelch propeller domain protein K13	(Cui and Su, 2009; Witkowski et al., 2013)
Atovaquone	Hydroxynaphthoquinone	Competitive inhibitor of ubiquinol leading to mitochondrial membrane disruption	High recrudescence rates and drug failure in monotherapy. Only used in combination with proguanil, however is expensive and not widely used	Mutations in the cytochrome bc_1 complex of the mitochondrial electron transport chain	(Looareesuwan et al., 1996; Vaidya and Mather, 2000)
Chloroquine	4-Aminoquinoline	Inhibition of haem/hemozoin polymerisation and detoxification	Resistance first detected in Thailand, and soon after lost its antimalarial efficacy in most endemic countries	Mutations in the *P. falciparum* chloroquine resistance transporter gene	Martin et al. (2009)
Halofantrine	Aryl-amino alcohol	Disrupts detoxification of haem following haemoglobin digestion	Lethal drug-associated cardiac effects associated with use. Additionally, resistance has been observed in Africa	Mutations in the *P. falciparum* multi-drug resistance 1 gene	(Carme et al., 1993; Peel et al., 1994)
Lumefantrine	Benflumetol	Inhibition of haem/hemozoin polymerisation and detoxification	Low efficacy in monotherapy, used in combination with artemether for higher efficiency	Susceptibility linked to overexpression of *P. falciparum* multi-drug resistance 1	Sidhu et al. (2006)
Mefloquine	Aryl-amino alcohol	Inhibits protein synthesis in parasite cytoplasm, however underlying mechanisms of action are unknown	Resistance observed in several South-East Asian countries, South America and some African regions	Overexpression of *P. falciparum* multi-drug resistance 1	Cowman et al. (1994)
Primaquine	8-Aminoquinoline	Hyponozoiticidal (*P. vivax and P. ovale*) & gametocytocidal (*P. falciparum*)	Haematotoxicity and haemolytic anaemia in glucode-6-phosphate dehydrogenase (G6PD) deficient individuals	Needs to be used in combination with a blood schizonticidal agent, potential treatment failure associated with the inability to differentiate relapse and re-infection	(Fernando et al., 2011; Ferone et al., 1969)
Proguanil	Biquanides	Inhibition of parasite dihydrofolate reductase, thereby disrupting DNA synthesis and parasite replication	Rapid resistance following its introduction. Now only used in combination with atovaquone, however is expensive and not widely used	Mutations in *P. falciparum* dihydrofolate reductase	(Hyde, 2007; Painter et al., 2007; Skinner-Adams et al., 2019)
Pyrimethamine	Diaminopyrimidine	Inhibition of folate biosynthesis pathway in schizont stage parasites	Resistance in Africa after widespread administration, followed by Asia and South America	Mutations in *P. falciparum* dihydrofolate reductase	(Gatton et al., 2004; Vinetz et al., 2011)
Sulfadoxine	Antifolate	Hinders dihydropteroate synthase, thereby interrupting folate biosynthesis	Resistance seen in Asia, which later emerged in Africa and South America	Mutations in *P. falciparum* dihydropteroate synthase gene	(Hyde, 2007; Mita et al., 2011; Triglia et al., 1998)
Quinine	Arly-amino alcohol	Schizonticidal and gametocytocidal (*P. vivax* and *P. malariae*) and inhibition of haem polymerisation	Resistance first observed in Brazil in 1910, and later seen in Asia and South America	Mutations in *P. falciparum* Na^+/H^+ exchanger Nhe. Additional mutations in *P. falciparum* multi-drug resistance 1 can further decrease drug activity	(Chou and Fitch, 1993; Legrand et al., 2008; Mayxay et al., 2007)

drug-resistant *Plasmodium* was first detected in Thailand in 1957 (Hyde, 2007). CQ resistance soon spread across South-East Asia, South America and Africa, which resulted in a loss of antimalarial efficacy in most endemic countries (Sidhu et al., 2002). Mutations of *P. falciparum* chloroquine resistance transporter gene (*Pf*CRT) have been associated with CQ resistance. Located within the parasite DV membrane, *Pf*CRT belongs to a superfamily of drug and metabolite transporters and is known to affect parasite sensitivity to various pharmacophores (Bellanca et al., 2014). *Pf*CRT operates as a channel or pore, expelling CQ from the parasite food vacuole and away from its binding target, haem (Hyde, 2007). This efflux allows CQ to remain inactive and unable to provide an effective antimalarial response. Like CQ, *Pf*CRT can also inhibit the effects of prominent antimalarial partner drugs such as quinine, quinidine and verapamil, indicating its key role in multi-drug resistance (Bellanca et al., 2014).

To overcome resistance, medicinal chemistry efforts have increasingly focused on the development of novel CQ analogues (Cortopassi et al., 2022). One such strategy involves molecular hybridisation, leading to the synthesis of harmiquins. The fusion of a CQ scaffold with a β-carboline ring capable of binding to *P. falciparum* heat shock protein 90 (*Pf*Hsp90) provide a singular therapeutic with a dual inhibition activity. Harmiquins have demonstrated potent activity against erythrocytic stages of both CQ-sensitive and CQ-resistant *P. falciparum* strains, with nanomolar IC_{50} values (Poje et al., 2022). Concurrently, research has turned towards rescuing prominent antimalarials like CQ. Pairing CQ with natural bile acids to form CQ-derived bile salts has yielded compounds active against the hepatic, blood and gametocyte stages of *Plasmodium* spp. (Silva et al., 2024), offering a promising strategy to overcome drug resistance and extend the utility of legacy drugs.

3. Artemisinin

Derived from *Artemisia annua* L., a plant used in Chinese herbal medicine, artemisinin (ART) is the current leading antimalarial drug and is effective for treating severe malaria. Although ART provides prompt erythrocytic parasite relief, its major hindrance is its short half-life of only 1 hr (Tilley et al., 2016). Whilst rapid drug deterioration rates prevent residual drug resistance, short-lived efficacy results in increased parasite recovery rates (Cui and Su, 2009). To combat this, partner drugs with longer half-lives are co-administered as artemisinin-based combination therapies (ACTs), such as artemether-lumefantrine and artesunate-mefloquine (Cui and Su, 2009), currently used as the primary defence strategy in endemic countries (Flannery et al., 2013).

3.1. Mode of action of artemisinin

The precise mechanisms of ART remain unknown and numerous hypotheses are currently proposed. The most widely accepted theory lies with the iron-catalysed cleavage of the endoperoxide bridge in the presence of haem (Dogovski et al., 2015; Straimer et al., 2015). Upon haemoglobin digestion, toxic haem concentrations increase within infected erythrocytes, allowing the iron-containing compounds to initiate ART activation (Dondorp et al., 2009). As a result, haemoglobin uptake is suppressed, allowing newly generated free haem, if not rapidly polymerised into non-toxic hemozoin, to activate reactive oxygen species (ROS) production (Straimer et al., 2015). These ROS molecules impact proteins and antioxidants, such as glutathione used to alleviate ROS damage (Cui and Su, 2009). The accumulation of damaged molecules overwhelms the protein repair system, ultimately resulting in parasite death. ART has no effect on mature gametocytes and liver stages due to the lack of haemoglobin digestion during the development of these parasite forms (Tilley et al., 2016).

3.2. Artemisinin resistance: PfKelch13 mutation

Despite its antimalarial efficacy, the emergence of ART resistance in the Greater Mekong subregion and several regions in Africa is a significant hurdle for malaria eradication (Bwire et al., 2020; Ouji et al., 2018). Mutation of the kelch propeller domain protein K13 located on *P. falciparum* chromosome 13 (*Pf*Kelch13) lead to its interaction with multiple proteins that mediate protein degradation and oxidative stress responses (Straimer et al., 2015). Consequently, resistant strains exhibit upregulated metabolic-related gene expression relating to protein metabolism, signal recognition particles and the proteasome, all of which impact repair or degradation of damaged proteins (Mok et al., 2015). *Pf*Kelch13 mutations are associated with reduced parasite clearance (Straimer et al., 2015), downregulation of DNA replication genes and reduced developmental rates (Tucker et al., 2012) due to reduced haemoglobin digestion. Decelerated parasite development complemented with upregulated protein repair expression allows for drug circumvention of short-lived ARTs and drug damage repairment (Witkowski et al., 2013).

As artemisinin remains the current antimalarial “magic bullet”, reducing the inefficiency of ACTs is essential. ART-induced dormancy of *P. falciparum* parasites remains a concern and has been shown to reduce the sensitivity of prominent partner drugs (Tripathi et al., 2024). Recent investigations have highlighted the need for triple artemisinin-based combination therapies (TACTs). *P. falciparum* transmission and resistance simulation models (“MORU” 20 and “PSU” 16.33) highlighted that the introduction of artesunate-mefloquine-piperaquine or artemether-lumefantrine-amodiaquine can delay artemisinin drug resistance and reduce treatment failures (Nguyen et al., 2023). However, antimalarial drug resistance and resulting treatment failures is inevitable, and global malaria eradication cannot solely rely on ACTs or TACTs. Considering the alarming spread of ART-resistant parasites worldwide, including most recently in Africa (Rosenthal et al., 2024), compounds with novel modes of action are in urgent demand.

4. Widespread antimalarial resistance

Similar to CQ and ART, resistance has emerged against all major antimalarial therapies, often driven by the widespread use of combination treatments. A key contributor to this resistance is the *P. falciparum* multi-drug resistance 1 gene (*Pf*MDR1), an ATP-binding cassette transporter involved in intracellular drug transport (Gil and Krishna, 2017). Mutations in *Pf*MDR1 have been linked to resistance against multiple antimalarials, including amodiaquine, halofantrine, lumefantrine, mefloquine and quinine (Reed et al., 2000) (Table 1). In addition, mutations in the mitochondrial electron transport chain and in *P. falciparum* dihydrofolate reductase (*Pf*DHFR), both of which are critical for DNA synthesis and parasite replication, have been identified as key mechanisms underlying resistance to atovaquone, and proguanil and pyrimethamine, respectively (Table 1).

5. Approaches to antimalarial drug development

Drug resistance mutations can be inherited or appear in response to drug pressure (Tilley et al., 2016). Broad administration of counterfeit treatments and inappropriately distributed doses allow selective drug pressure from low antimalarial potency (Diagana, 2015; Dondorp et al., 2011). Resistance mutations can alter parasite drug susceptibility, creating multi-drug resistance and rendering entire drug classes redundant (Bellanca et al., 2014). The prevalence of parasite resistance against prominent antimalarial therapeutics presents an urgent need for novel treatment options, with new drug candidates being of priority. As of 2025, there are 21 antimalarial compounds currently endorsed by the Medicines for Malaria Venture (MMV) (Table 2). Alongside MMV, other examples of product development partnerships with a focus on antimalarial drug discovery and development include Novartis Institute for Tropical Diseases (KAF156, KAE609, INE963, IWY357), GlaxoSmithKline Tres Cantos (GSK484, GSK701) and Drugs for Neglected Diseases (see Table 2).

Table 2
Current antimalarial pipeline supported by MMV and other product development partnerships at all stages of drug development.

Preclinical Development	Human Volunteers	Patient Exploratory	Patient Confirmatory	Regulatory Review
GSK484 IWY357 MMV183 MMV055 MMV167 MMV609 Lotilaner	GSK701 INE963 MMV533 MMV371	Cipargamin (KAE609) M5717 + pyronaridine Piperaquine + pyronaridine ZY19489 + ferroquine	DHA-piperaquine dispersible Ganaplacide (KAF156)-lumefantrine Artemether-lumefantrine Artemether-lumefantrine-amodiaquine FDC Primaquine dispersible	Sulfadoxine-pyrimethamine

Prerequisites have been established to facilitate the development of these therapeutics, including MMV Target Candidate Profile (TCP) and Target Product Profile (TPP) (Fig. 1). The new generation of antimalarials should show rapid activity in a parasite reduction ratio assay, reduced rates of resistance in MIR assays, as well as activity against multiple parasite stages (Siqueira-Neto et al., 2023). Here, we discuss recent state-of-the-art drug discovery approaches that have the potential to generate novel antimalarial candidates that address the current criteria for next-generation therapies (see Table 3).

5.1. Phenotypic screening

Over the past decade, phenotypic screening methods have been used as the primary method for lead antimalarial drug discovery. This approach allows for the screening of vast chemical libraries against live whole cells at the desired parasite life cycle stage *in vitro*. This method can allow for the identification of active molecules with cell permeability and cytotoxic capabilities as well as potentially novel modes of action. The analysis of observable characteristics (e.g. live *versus* dead) and morphological changes (e.g. cell division *versus* quiescence) (Swinney, 2013) in response to drug exposure provides an unbiased screening of candidate compounds. This approach has been extensively used against asexual blood stage parasite cultures. For example, a recent screening of 766,000 compounds identified 29 compounds that inhibited the growth of asexual erythrocytic *P. falciparum* parasites (Molina et al., 2025). Phenotypic analysis revealed that two compounds target CLAG3 of the plasmodial surface anion channel, vital for parasite nutrient acquisition.

In addition to large-scale screenings against asexual blood stage parasites, gametocyte and liver stage parasites have now been incorporated in phenotypic drug discovery pipelines. Trisubstituted imidazole MMV030084 was screened against multiple *P. falciparum* life cycle stages which uncovered the *P. falciparum* cGMP-dependent protein kinase (*Pf*PKG) as the drug target. MMV030084 treatment inhibited sporozoite invasion of hepatocytes and interfered with male gametogenesis, highlighting promising multi-stage activity (Vanaerschot et al., 2020). Although widely used, phenotypic methods of target-free screening do not uncover drug mechanisms of action and can be challenging for downstream drug lead development. To counter this, phenotypic screenings can be used in combination with genetic or proteomic analysis, or along side target-based approaches.

5.2. In silico chemical screens and target-based approaches

Advances in computational biology and molecular screening technologies have accelerated antimalarial drug discovery through the integration of *in silico* modelling and target-based strategies. *In silico*

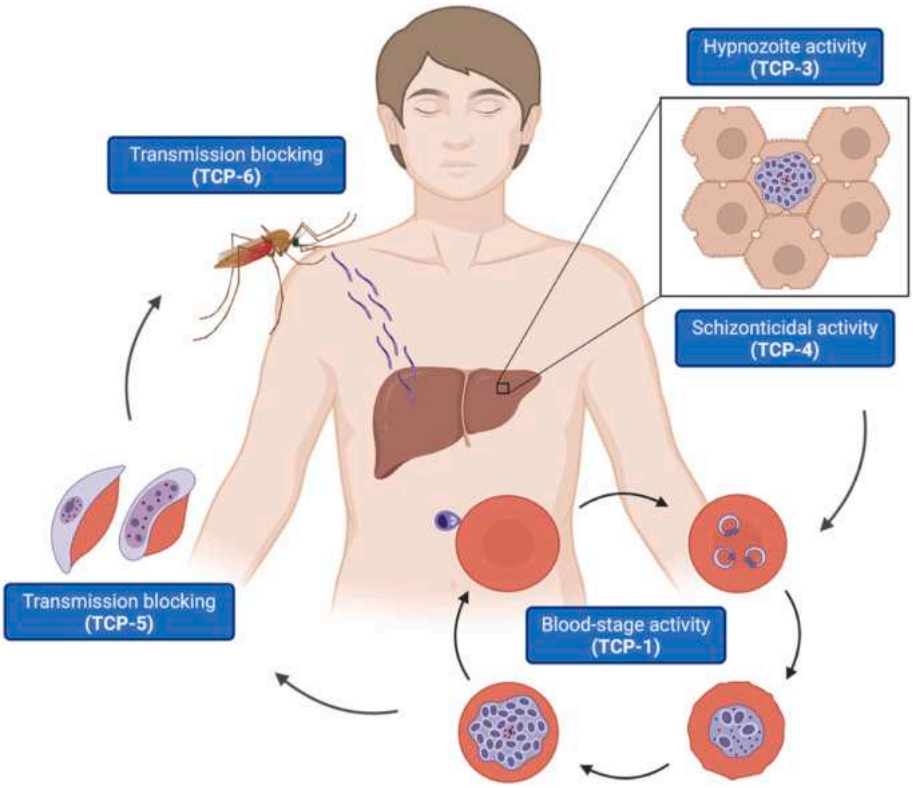

Fig. 1. Target Candidate Profiles (TCP) within the *Plasmodium* parasite lifecycle. MMV's TCPs include asexual erythrocytic parasite clearance (TCP-1), antimalarial activity against hypnozoites primarily in *P. vivax* (TCP-3), schizonticidal compounds (TCP-4), compounds active against parasite gametocytes for transmission blocking (TCP-5), and candidates that target insect vector for transmission blocking (TCP-6). (This figure has been created using BioRender).

Table 3
Approaches to antimalarial drug development and examples.

Approach	Considerations	Category	Example	Ref.
Phenotypic screening	High-throughput analysis of drug-induced phenotypic changes at desired parasite life cycle stages	Late-stage development and merozoite egress	MMV030084 displayed potency against blood and liver stage *P. falciparum* parasites by targeting cGMP-dependent protein kinase *Pf*PKG	Vanaerschot et al. (2020)
			Screening of molecules MV020670 and MMV026356 highlighted *P. falciparum* schizont inhibition and induced DNA damage in merozoites	Patra et al. (2020)
			R,S-WEHI/Merck4, *R,S*-WEHI/Merck5 and WM382 inhibit *P. falciparum* growth and egress by targeting aspartic protease, plasmepsin X	Favuzza et al. (2020)
		Protein synthesis and aggregation	Known human polo-like kinase 1 inhibitor BI-2536 impaired *P. falciparum* growth through the inhibition of NIMA related kinase 3 *Pf*NEK3, however genomic analysis suggested methionyl-tRNA synthetase *Pf*MRS as a second target	Bohmer et al. (2023)
			Bis(styrylpyridinium) salt YAT2150 displayed activity against *P. falciparum* trophozoite parasites through the inhibition of protein aggregation	Bouzón-Arnáiz et al. (2022)
		Haem detoxification	Screening of 530 compounds found 171 β-hematin inhibitors against *P. falciparum* parasites, and 25 compounds with nanomolar potency *in vitro*	Sandlin et al. (2014)
			Six pyrido[1,2-*a*]benzimidazole derivatives were active against *P. falciparum* gametocytes and inhibited hemozoin formation in asexual erythrocytic parasites	Leshabane et al. (2021)
			Novel tetrazole-based series showed rapid activity against *P. falciparum* parasites *in vitro* through the inhibition of haem polymerisation and hemozoin formation	Lawong et al. (2021)
		Host cell transport	Screening of vast chemical library against *P. falciparum* asexual parasites *in vitro* highlighted 2 compounds that target CLAG3 of the plasmodial surface anion channel	Molina et al. (2025)
			Analysis of GSK Tres Cantos Anti-malarial Set against *P. falciparum* identified 3 compounds with the ability to disrupt calcium distribution	Chia et al. (2021)
In silico and target-based approaches	Allows for high-throughput computational screening of drug candidates followed by experimental validation	Docking analysis	Molecular docking showed high binding affinities of 2 compounds from *Nauclea latifolia* roots targeting *P. falciparum* erythrocyte membrane protein 1 and *P. falciparum* cGMP-dependent protein kinase	Asanga et al. (2024)
			Screening against *P. falciparum* cyclin-dependent kinase-like protein highlighted FDA-approved Lurasidone and Donovex inhibit *Pf*mrk *in silico*	Sahu et al. (2023)
			Talniflumate and Sulfaphenazole compounds showed high binding affinities to *P. falciparum* dihydroorotate dehydrogenase	Joshi et al. (2024)
			2509 FDA-approved drugs screened against *P. falciparum* serine hydroxymethyltransferase showed antifungal Amphotericin B to be the lead inhibitor	Mee-Udorn et al. (2023)
			Computational *P. falciparum* phosphatidylinositol-3-kinase inhibitor screening found FDA-approved Oxetacaine, Simvastatin, Repaglinide, Aclidinium and Propafenone as inhibitors	Verma et al. (2021)
		Experimental validation	ZINC12900664 displayed activity against cysteine proteases falcipain-2 and falcipain-3. Confirmed to impair growth of CQ-resistant *P. falciparum* and reduced *P. berghei* parasite load *in vivo*	Uddin et al. (2022)
			Molecular screening of natural quinoline derivatives found 2 compounds inhibit *P. falciparum* protease plasmepsine II	En-Nahli et al. (2023)
			Screening of repurposed chaperone inhibitors against *Pf*GRP78 found Apoptozole displayed activity in the micromolar range and prevented *P. falciparum* growth *in vitro*	Chen et al. (2018)
Host-directed therapeutics	Targets host molecules or pathways vital for infection and prevents parasite genetic manipulation. Remains largely unsuccessful due to lack of knowledge of parasite-host molecular interactions	Erythrocytic	Anti-apoptotic B-cell lymphoma 2 inhibitors impaired *P. falciparum* growth through eryptosis of infected red blood cells	Boulet et al. (2022)
			Inhibition of human GTPase Rac1 using EHop-016 affected erythrocytic *P. falciparum* growth without inhibiting red blood cell invasion	Parapini et al. (2022)
			Ferrochelatase inhibitor *N*-methylprotophorphyrin impaired erythrocytic *P. falciparum* growth *in vitro*	Smith et al. (2015)
			Peroxiredoxin 6 inhibition by Darapladib hindered *P. yoelii* blood stage growth *in vitro* with no evidence of human off-target effects	Wagner et al. (2022)

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Table 3 (*continued*)

Approach	Considerations	Category	Example	Ref.
		Hepatocytic	Blocking the SLC7a11-GPX4 pathway using P53 reduced liver stage *P. yoelii* infection through ferroptosis-like cell death	Kain et al. (2020)
			Inhibition of nuclear hormone receptor NR1D1 with modulators MMV1088447 and MMV1346624 disturbed hepatic growth of *P. berghei* through host lipid metabolism impairment	Mittal et al. (2023)
			Kinase inhibitors VX-680, Roscovitine and Sunitinib reduced parasitaemia in *P. yoelii*-infected hepatocytes	Arang et al. (2017)
Drug repurposing	Implementation of pre-existing drugs with known side effects and proven safety profiles	Antibiotic	Antibiotics Moxifloxacin and Roxithromycin showed activity against *P. falciparum* parasites and repressed parasite multiplication	Yadav et al. (2021)
			Ciprofloxacin showed low IC_{50} against CQ-susceptible and CQ-resistant strains *P. falciparum* FFC_1 and VNS	Divo et al. (1988)
			Trimethoprim-Sulfamethoxazole reduced hepatic *P. yoelii* parasites *in vivo* and impeded *P. falciparum* liver stage development *in vitro*	Hobbs et al. (2012)
		Anticancer	Derivatives of clinical histone deacetylase inhibitor Quisinostat displayed a lytic effect against blood, liver and gametocyte stage parasites and several drug-resistant *P. falciparum* strains	(Le Govic et al., 2021; Wang et al., 2022)
			5-fluorouracil showed significant *P. yoelii* parasite inhibition *in vivo*	Yadav et al. (2021)
		Antidiabetic	Metformin impaired hepatic parasite development of *P. falciparum* and *P. berghei* and reduced parasite load *in vivo* when used in combination therapy	Vera et al. (2019)
		Antihistaminic	Cyproheptadine showed erythrocytic schizonticidal activity in multi-drug resistant *Plasmodium yoelii nigeriensis*	Agrawal et al. (2002)
			Astemizole inhibited *P. falciparum* strains 3D7, DD2 and ItG at sub-micromolar concentrations and reduced burden of *P. vinckei* and *P. yoelii* infection *in vivo*	Chong et al. (2006)
		Diuretic	Triamterene showed activity against *P. cynomolgi* in rhesus macaque model	Deye et al. (2012)
		Immunosuppressive	Cyclosporin A impeded *P. falciparum* growth *in vitro*	(Azouzi et al., 2011; Bell et al., 1994)
Natural compounds	Represents a plethora of bioactive extracts that may translate to novel antimalarial modes of action	Animal extracts	Crotoxin B from *Crotalus durissus cumanensis* Columbian rattlesnake venom showed no cytotoxicity *in vitro* and *in vivo* and possessed activity against *P. falciparum* FcB1	Quintana et al. (2012)
			Polypeptide cromatine from South American *Crotalus durissus terrificus* venom highlighted dose-dependent inhibition of *P. falciparum in vitro* whilst compromising parasite metabolism	Maluf et al. (2016)
			Psalmopeotoxins I and II from Trinidad chevron tarantula venom (*Psalmopoeus cambridgei*) displayed IC_{50} values in the low micromolar range against *P. falciparum* FcB1 and lacked cytotoxic activity	Choi et al. (2004)
			Phylloseptin-1 from skin secretion of the amphibian *Phyllomedusa azurea* showed *P. falciparum* growth inhibition at low concentrations with minimal effects on erythrocytes	Kückelhaus et al. (2009)
			Peptide cruzioseptin-4 derived from Ecuadorian frog skin (*Cruziohyla calcarifer*) showed IC_{50} values in the low micromolar range when tested against *P. falciparum* strains NF54 and drug resistant C2B	Proaño-Bolaños et al. (2024)
			Melittin, TP10, Vida3, Mastoparan X and Anophlin peptides from wasp and bee toxins affected *P. berghei* ookinetes *in vitro* without harming mosquito fitness	Carter et al. (2013)
			Bufadienolides from *Rhinella marina* and *Rhaebo guttatus* toad paratoid glands from the Brazilian Amazon hindered CQ-resistant *P. falciparum* W2 growth *in vitro*	Banfi et al. (2016)
		Plant derivatives	Aqueous extract of *Strychnos ligustrina* samples from Indonesia when used in combination treatment significantly reduced parasitaemia of *P. berghei in vivo*	Cahyaningsih et al. (2022)
			Leaf extracts and fractions from *Persea americana* and *Dacryodes edulis* fruit trees showed antiplasmodial activity *in vivo* against *P. berghei* mouse models	Uzor et al. (2021)
			Quercetin extracted from *Dioscorea bulbifera* L. bulbils shown to inhibit *P. falciparum* lactate dehydrogenase	Chaniad et al. (2021)
			Xanthohumol, main chalcone of *Humulus lupulus* L., interfered with haemin degradation of *P. falciparum* with evidence of additional modes of action	Frölich et al. (2005)
			Caged *Garcinia* xanthones impaired mitochondrial structure and function in *P. falciparum* at sub-micromolar concentrations	Ke et al. (2017)

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Table 3 (*continued*)

Approach	Considerations	Category	Example	Ref.
			99 species of medicinal plants from Kenya shown to exhibit *in vitro* plasmodial activity, with *Maytenus obtusifolia* root bark extract highlighted to have lowest inhibitory concentration	Muthaura et al. (2015)
			Harmine and harmaline alkaloids from *Peganum harmala* L. seeds displayed moderate activity against *in vitro P. falciparum*	Astulla et al. (2008)
			Limonoid from *Chisocheton ceramicus* bark (ceramicine) displayed potent activity against *P. falciparum in vitro*	Nugroho et al. (2024)
			Tapirira guianensis seed extracts from the Amazon rainforest showed high antiplasmodial activity when used against CQ-sensitive and CQ-resistant *P. falciparum*	Crispim et al. (2025)
		Microbial products	Benzoquinones isolated from endophytic fungus *Xylaria* spp. displayed IC_{50} values against *P. falciparum* in the low micromolar range	Tansuwan et al. (2007)
			Fusaripeptide from *Fusarium* spp. fungus revealed higher *P. falciparum* inhibition when compared to artemisinin treatment	Ibrahim et al. (2018)
			9-methoxystrobilurins from basidiomycetes fungus *Favolaschia* spp. was potent against *P. falciparum* and exhibited low cytotoxicity in Vero cells *in vitro*	Kornsakulkarn et al. (2020)
			Synthetic analogue of NK-lysin displayed activity against intraerythrocytic *P. falciparum* parasites	Gelhaus et al. (2008)
			Chemical isolated derived from deep-sea bacterium *Marinactinospora thermotolerans* SCSIO 00652 inhibited growth of *P. falciparum* 3D7 and Dd2 strains	Huang et al. (2011)
			Cyclic pentapeptide isolated from deep-sea anemone-derived fungi *H. ingelheimensis* MSC5 displayed potent inhibitory activity against *P. falciparum* 3D7	Li et al. (2024)

approaches enable the virtual screening and computational design of novel chemical scaffolds by simulating compound interactions with biological targets. These methods allow for structural refinement of known antimalarial agents and the identification of novel chemical entities, which are subsequently added to drug discovery pipelines as potential leads (Flannery et al., 2013; Tahghighi et al., 2020). MMV have two curated compound libraries (the "Malaria Box" and the "Pathogen Box" chemical libraries), which offer globally accessible collections of chemical structures to be used for early-stage screening.

Complementing these efforts, target-based approaches have facilitated drug discovery using high-throughput screenings (HTS). These methods focus on identifying small molecules that specifically interact with validated parasite molecular targets (Flannery et al., 2013). However, target-based approaches often exhibit lower success in identifying candidates with novel modes of action, partly due to parasitic complexities such as mechanisms of drug absorption and stage-specific drug susceptibility (Swinney, 2013). Such hurdles often contribute to drop-off rates in late drug trial stages and reduced treatment efficacy.

Recent antimalarial discovery initiatives have increasingly combined *in silico* techniques with target-based strategies to improve hit identification. Virtual HTS of the ZINC database of natural molecules against cysteine proteases falcipain-2 and -3 identified a potential lead compound, ZINC12900664 (Uddin et al., 2022). These proteases are essential for haem detoxification, therefore inhibition of falcipain activity led to impaired parasite growth in CQ-sensitive and CQ-resistant *P. falciparum in vitro*, and reduced parasite load in *P. berghei*-infected mice (Uddin et al., 2022). Such studies highlight the synergistic potential of integrating *in silico* with molecular targeting strategies in the development of next-generation antimalarial therapies.

5.3. Host-directed therapeutics

Host-directed therapies (HDT) have recently emerged as an innovative and thought-provoking strategy to fight malaria (Boulet et al., 2018; Glennon et al., 2018). They aim to target and interfere with host molecules or pathways that play an integral part of the disease. HDTs have been broadly investigated in viral and bacterial infections and have strong potential against *Plasmodium* parasites. The innovation of HDTs is evident in their utilisation of drug targets that remain unaffected by parasite genetic adaptation. Therefore, considering that *Plasmodium* has developed resistance against all clinical antimalarials, HDT emerges as a potent strategy to avoid resistance mutations of the target molecule, allowing for prolonged antimalarial efficiency.

To date, HDTs against severe erythrocytic malaria and liver stage infection have been largely unsuccessful (Varo et al., 2018) due to the lack of extensive knowledge of parasite-host molecular interactions (Glennon et al., 2018). However, recent analysis of inhibitors of anti-apoptotic members of the B-cell lymphoma 2 (BCL-2) family has been shown to impair parasite growth through host mechanisms. Indeed, BCL-x_L inhibitors impair *P. falciparum* growth by binding to human SHOC2 leucine rich repeat scaffold proteins in infected red blood cells, inducing eryptosis of infected red blood cells (Boulet et al., 2022). Such studies highlight the potential of parasite inhibition by targeting host molecules, reinforcing the need for further exploration in the emerging field of HDT. Additional insights into cellular and molecular parasite-host interactions will provide opportunities to revisit the potential of host-directed antimalarial strategies.

5.4. Drug repurposing

Using pre-existing drugs to develop new medical applications, beyond their original approved purpose, is an appealing approach with many benefits (Baker et al., 2018). The development of novel drugs is time consuming and expensive. Therefore, drug repurposing has gained particular traction in "diseases of poverty" such as malaria. Other advantages of this strategy include prior knowledge of drug side effects and proven safety profiles (Baker et al., 2018).

Broad-spectrum antibiotics and FDA-approved chemotherapeutics have been well-studied for antimalarial drug repurposing. Preliminary analysis of fluoroquinolone antibiotics, such as levofloxacin and moxifloxacin, highlighted dose-dependent inhibition of parasite growth, with the latter displaying increased repression of parasite multiplication (Yadav et al., 2021). Additionally, analysis of macrolide antibiotics, including roxithromycin and erythromycin, has also revealed the former to have increased activity against *P. falciparum* parasites (Yadav et al., 2021). As these macrolides inhibit red blood cell invasion (Wilson et al.,

2015), they offer a possibility to impede disease progression. Drug repurposing studies highlight the potential of redirecting antibiotics, and potentially other approved chemotherapeutics and immunomodulators, as antimalarials. Furthermore, it provides rationale for chemical modification of approved compounds to increase efficacy against *Plasmodium* parasites.

5.5. Exploring natural compounds as anti-parasitic drugs

Natural products have been used as therapeutics since the ancient civilisations, with medicinal products found in both frequented and remote locations. Notably, over 50 % of FDA-approved drugs have been directly or indirectly derived from natural compounds (Newman and Cragg, 2020), illustrating the plethora of bioactive extracts and chemical constituents that nature harbours.

5.5.1. Plant extracts

The plant kingdom has, and continues to, provide an array of medicinal products. It is the most widely explored starting point for drug discovery due to compound abundance, easy access, and large diversity of chemical structures. Approximately 25 % of drugs prescribed worldwide have originated from plants (Rates, 2001). Noteworthy, the prominent antimalarial artemisinin (qinghaosu) was purified from leaf extracts of *Artemisia annua* (or 'sweet wormwood'). Today, artemisinin remains listed as the 'gold standard' of antimalarial therapeutics.

More recent analysis of plant derived extracts has begun on caged *Garcinia* xanthones (CGXs). CGXs are naturally produced by tropical and subtropical *Garcinia* trees and have been documented in traditional Eastern medicine. CGXs extracts have shown anti-cancer, antiviral, antimicrobial and antimalarial potential, as well as potent cytotoxicity at low micromolar concentrations (Ke et al., 2017). CGXs appear to affect mitochondrial structure and function, which is an effective antimalarial target as demonstrated by the antimalarial atovaquone. Although further analysis into the antiplasmodial activity of CGXs is required, the promising anti-microbial activity of CGXs is a testament to exploring plant extracts for drug development.

5.5.2. Deep-sea extracts

Majority of antimalarial agents known to date are derived from plant and leaf extracts. However deep-sea organisms have been suggested as potential new sources for drug discovery in recent years. The deep-sea encompasses 75 % of the total ocean volume and has an average depth of approximately 3800 m, potentially harbouring a plethora of functional samples for medicinal purposes (Jannasch and Taylor, 1984). Natural resources that would otherwise never be exposed to parasites have shown to display antimalarial properties. Deep-sea organisms experience high pressure, low oxygen levels with the absence of light (Skropeta and Wei, 2014) and as a result of these conditions, produce unique metabolites and compounds that would not be found in frequented environments. A recent example of a deep-sea derived compound is the actinomycete strain, SCSIO 00652. Collected from South China Sea marine sediments at a depth of 3865 m, chemical isolates of the *Marinactinospora thermotolerans* strain SCSIO 00652 exhibited *in vitro* antiplasmodial potency against *P. falciparum* 3D7 and Dd2 strains (Huang et al., 2011). Further analysis is needed to gain broader insight into the anti-parasitic properties and specific mechanism of action of these isolates.

Interestingly, analysis of deep-sea invertebrates has identified a crustacean to exhibit antimalarial properties (Lino et al., 2015). The Azores region in the North Atlantic Ocean harbours many deep-sea environments, including hydrothermal vents and seamount ecosystems. Found in these hydrothermal vents are *Mirocaris fortunate* shrimp, which displayed an IC_{50} of 76.64 ± 6.33 μg/mL against *P. falciparum* Dd2, the highest antimalarial activity of all deep-sea extracts analysed (Lino et al., 2015). These studies highlight the potential of deep-sea extracts as possible novel antimalarials.

5.5.3. Amazon extracts

Located in South America, the Amazon forest spans 5.5 million km^2 across multiple countries and houses an array of unique plants, animals and fungi that can and have been used as a basis for medicinal development. Due to the prevalence of malaria within the Amazon region, traditional populations sought out therapeutics to help treat the disease, with plants being the most frequented option.

Much like plants, animals can host an array of structurally unique secondary metabolites that can provide scaffolds for drug discovery and development. *Rhinella marina* (or *Bufo marinus*) amphibians, also known as cane toads, are frequently found in the Amazon basin. Amphibians of the *Rhinella* genus have venom-secreting poison glands, or parotoid glands, which are initiated when under threat. These toxins have been identified as bufadienolides, cardioactive steroids reported to possess antiparasitic and antiviral properties (Cui et al., 2010; Tempone et al., 2008). Analysis of toad venom extracts have shown a large decrease in *Plasmodium* parasitaemia *in vitro*, and IC_{50} values lower than 5 μg/mL against the CQ-resistant *P. falciparum* W2. This study highlights the potential of Amazonian natural products as a source of unique bioactive prototypes with antimalarial properties (Banfi et al., 2016).

6. Conclusion

Global malaria eradication is dependent on identifying novel treatment options that act on multiple parasite stages and strains. It can be argued that each of the above-mentioned drug discovery approaches have their merits and disadvantages. However, in order to advance antimalarial drug discovery as timely as possible, several approaches should be used simultaneously. A firm focus on novel therapeutic options and new generations of antimalarials are essential to fight this ancient disease and curb the growing drug resistance.

CRediT authorship contribution statement

Liana Theodoridis: Writing – original draft. **Teresa G. Carvalho:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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