Chapter

Combating Antimalarial Drug Resistance: Recent Advances and Future Perspectives

Samuel Uzondu, Adaeze Echezona, Chinekwu Nwagwu, Adaeze Onugwu, Lydia Ugorji, Chinazom Agbo, Franklin Kenechukwu, John Ogbonna, Paul Akpa, Petra Nnamani, Audu Momoh and Anthony Attama

Abstract

This chapter X-rayed antimalarial drug resistance (ADR) by plasmodium species with a particular focus on *P. falciparum*, which is the most deadly species of the malaria parasite responsible for over 90% of the global malaria burden domiciled in Sub-Saharan Africa. The introduction intently looked at malaria therapeutics across the decades and the development of drug resistance by the parasite. With the malaria parasite (*P. falciparum*) as the focal point, the mechanisms by which they develop resistance to antimalarial drugs was looked at, including factors affecting drug resistance development. Armed with this knowledge, the chapter also highlighted the therapeutic interventions taken against this hydra-headed monster together with their limitations and recent advances towards addressing those limitations or opening new frontiers for research exploration. Future perspectives that will provide research strategy and direction as possible tools for combating drug resistance development by the malaria parasite were also discussed.

Keywords: antimalarial drug resistance (ADR), *P. Falciparum*. Malaria, mutation

1. Introduction

Malaria is a public health concern which has ravaged majorly Sub-Saharan Africa which accounts for over 90% of the global malaria burden [1]. This disease is caused by Plasmodium species, five of them are known to cause the disease in man. They *are Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, Plasmodium knowlesi. Plasmodium falciparum* is the responsible for the most deadly form of the disease found in Sub-Saharan Africa causing

the highest global morbidity and mortality rates in Africa. Children from 0 to 5 years and pregnant women are the most vulnerable to this disease. There has been a lot of therapeutic interventions by way of drugs targeted at eliminating or eradicating malaria. Prior to the introduction of the first synthetic drug chloroquine, cinchona alkaloids, quinine and quinidine have been used for the treatment of malaria. Chloroquine was introduced in 1940 as the mainstay for malaria treatment for about a decade plus until the parasite developed resistance to it. This led to the development and introduction of other drug classes consecutively as follows.

a. 4-Aminoquinolines (e.g. chloroquine, amodiaquine and piperaquine)

b. Aminoalcohols (e.g. mefloquine, halofantrine and lumefantrine)

c. Antifolates (e.g. sulphadoxine, pyrimethamine, proguanil)

d. Hydroxynaphthoquinone (e.g. atovaquone)

e. Endoperoxides (e.g. artemisinin and derivatives with their combination with other antimalarial drugs (ACTs) [2].

The following classes of drugs consecutively have been used clinically in the treatment of malaria; (1)4-aminoquinolines (e.g. chloroquine, amodiaquine and piperaquine) (2) aminoalcohols (e.g. mefloquine, halofantrine and lumefantrine) (3) antifolates (e.g. Sulphadoxine, pyrimethamine, proguanil) (4) hydroxynaphthoquinone (e.g. atovaquone) and (5) endoperoxides [e.g. artemisinin and derivatives with their combination with other antimalarial drugs (ACTs.)] Classes 1–4 are no longer used as first lines as a result of resistance development to them by the malaria parasite. Currently the endoperoxides' clinical efficacy against the malaria parasite is being threatened by emergence of artemisinin-resistant and ACT-resistant strains of the parasite particularly in the Greater Mekong Subregion (GMS) and recently in Africa [3].

The phenomenon of Antimalarial Drug Resistance (ADR) has led to the clinical retirement of Drug Classes 1–4 and is threatening the clinical efficacy of Drug Class 5-endoperoxides e.g. Artemisinins and their combinations. This is shown in the **Figure 1** below.

A critical look at **Figure 1** shows ADR as shown by the brown band generally causes a reduction in the clinical lifespan of the antimalarial drug as one moves interclass. This reduction in clinical lifespan has led to the retirement of drug classes 1–4 as first line treatment for malaria. Drug class 5; the Artemisinins and their combinations (ACTs) are currently under threat of resistance by the malaria parasite. ACTs are the WHO-recommended firstline and lastline (of some sorts) treatment for malaria. ACTs are one of the major factors responsible for the global successes recorded in the fight against malaria for about two decades now. The recent emergence of ACT-resistant strains of the malaria parasite in GMS and Africa has underlined the need for the discovery and development of novel therapeutic agents with novel mechanisms of action as one of the ways of tackling this hydra-headed monster. In tackling ADR, it is pertinent to zoom in on it and take a close look at it.

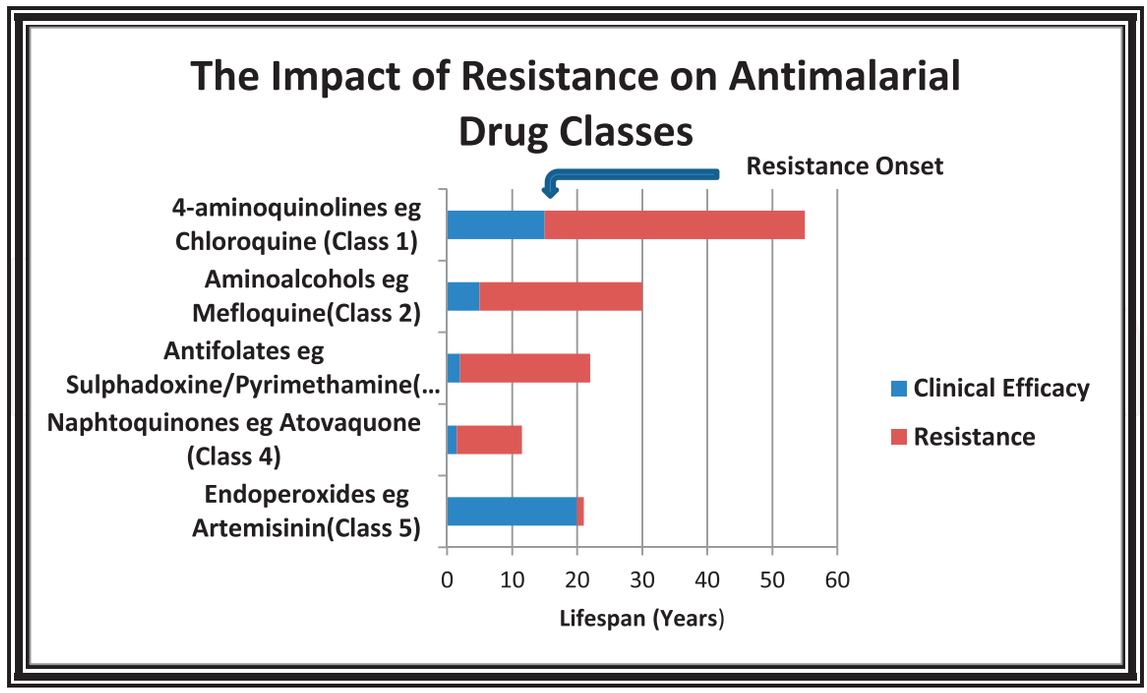

Figure 1.
The impact of resistance on antimalarial drug classes. (adapted from a journal article, drawn with Microsoft excel).

2. What is antimalarial drug resistance (ADR)?

Antimalarial Drug Resistance (ADR) can be best described as resistance to antimalarial drugs by the malaria parasite; Plasmodium species particularly *P. falciparum* which is responsible for the most deadly form of malaria - Falciparum malaria. *P. falciparum* is responsible for over 90% of the global malaria burden domiciled in Sub-Saharan Africa. It is the most virulent plasmodium species responsible for high morbidity and mortality rates of malaria observed in Africa particularly Sub-Saharan Africa. ADR has rendered most of the antimalarial drug classes clinically ineffective; these drug classes include 4-aminoquinolines, antifolates, mefloquine and atovaquone etc.

2.1 Development of ADR

When the malaria parasite is exposed to antimalarial drugs, initially it succumbs to the pharmacological action of the drug, over time develops resistance to it. Resistance development by the parasite is its adaptation to the new environment (with the presence of the drug) a complete departure from the old environment (absence of the drug). Continuous use of antimalarial drugs particularly at sub-therapeutic doses exposes them to the malaria parasite leading to the development of resistant strains of the parasite with several resistance phenotypes, some of these resistance genotypes might not necessarily have the resistance phenotypes. In Africa, the most frequent PfKelch13 mutation is A578S, this mutation does not confer Artemisinin resistance in vivo or in vitro [4]. The period between the first introduction of the antimalarial drug and the emergence of resistant strains of the parasite is laden with a variety of adaptive activities which may include genetic mutations which may include Gene Copy Number variations (CNV), Point mutations etc. An example of point mutation is the substitution of the Amino acid lysine with threonine at position 76 on the protein

(K76T). Gene copy number variants are deletions and amplification of a gene or a set of continuous genes and contribute to the great diversity of P.falciparum genome. *In vitro* studies have revealed their roles in parasite fitness phenotypes which include transmissibility, drug resistance, red cell invasion [5]. Resistance can also be imported into sensitive parasitic cells from neighboring resistant cells by R-plasmids transfer.

2.2 Resistance phenotypes

ADR by *P. falciparum* manifests with several resistance phenotypes which include; delayed parasite clearance, increased transmissibility, decreased schizont susceptibility, decreased gametocyte susceptibility, Ring stage resistance. Clinically, delayed parasite clearance is the phenotype used to establish resistance to antimalarial drugs. Parasite clearance rate can be used to measure delayed parasite clearance. It is quantified as the time taken by the antimalarial drug to reduce parasitaemia by half: for sensitive strains of *P. falciparum*, it is usually between 1 and 3 h, for resistant strains >5 h [6].

3. Mechanisms of drug resistance development

ADR by *P. falciparum* occurs through various mechanisms which include;

a. Reduction of the drug concentration at the site of action (Efflux mechanism): This is the mechanism of resistance by *P. falciparum* to chloroquine, a 4-aminoquinoline. Point mutation in the *P.falciparum* chloroquine resistance transporter gene (PfCRT) results in the transporter effluxing more of the chloroquine out of the digestive vacuole reducing its effective intravacuolar concentration. Point mutation in the *P. falciparum* multidrug resistance-1 transporter (Pfmdr1) gene is responsible for the resistance of *P. falciparum* to amodiaquine, piperaquine and pyronaridine [7].

b. Structural changes in the drug-binding receptors which could be part of an enzyme or enzymes or part of a cascade system-electron transport chain. Mutations in two key enzymes of the parasite"s folate synthesis pathway - Dihydropteroate Synthethase (DHPS) and Dihydrofolate Reductase (DHFR) is responsible for resistance to the antifolates - sulphadoxine, pyrimethamine etc. A single point mutation in the cytochrome b (CYTb) subunit of the bc1 complex confers resistance to atovaquone [7]. Mutations in Kelch-13(K13) Propeller domains are responsible for resistance to the artemisinins and Artemisinin Combination Therapy (ACTs).

3.1 Factors affecting drug resistance development

Having looked at the mechanisms of drug resistance, it is pertinent to also look at the enabling factors which include:

3.1.1 Spontaneous mutations

This occurs as a natural survival strategy of the parasite independent of the presence of the drug, Mutations occur *de novo*. The parasite's genome replication rate,

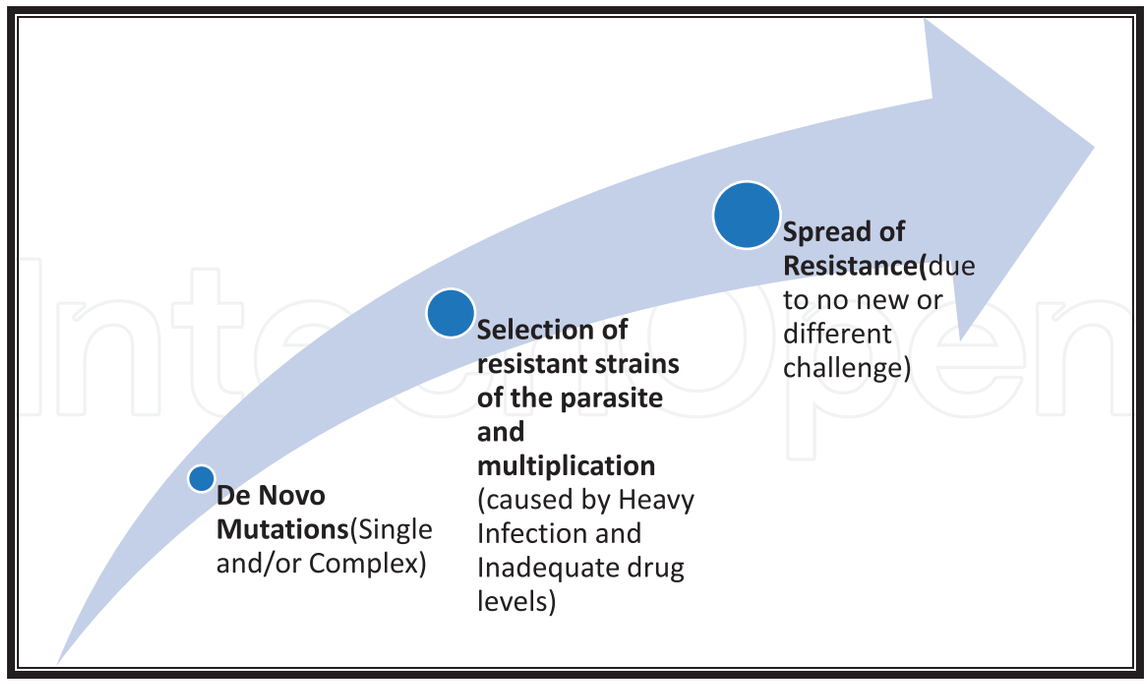

Figure 2.
Showing factors enabling resistance development and spread (adapted from www.malariasite.com with the aid of www.biorender.com).

mutation rate per base pair per parasite generation are the principal determinants of spontaneous mutation [8].

3.1.2 The antimalarial drug pharmacokinetics

The selection of resistant mutants in the presence of the drug as shown in **Figure 2** is principally dependent on its pharmacokinetics (Slowly eliminated drugs with a long tail of sub-lethal dose generally select faster) and magnitude of drug use within the parasite population (the higher the drug pressure per parasite the faster the selection).

4. Measures to tackle antimalarial drug resistance (ADR)

ADR has retired drug classes 1–4 (**Figure 1**) clinically. Currently Drug class 5 (**Figure 1**) faces a big threat of being retired too by ADR. What measures has been taken to checkmate this hydra-headed monster and their limitations?

4.1 Combination therapy

The advent of chloroquine resistance led the World Health Organization (WHO) to approve some combination therapies which included various combinations of Antifolates e.g. Sulphadoxine 500 mg + Pyrimethamine 25 mg (SP), SP + Chloroquine (CQ), SP + Amodiaquine etc. The rationale for combination therapy is combining at least two drugs with different mechanisms of action against the malaria parasite. The aforementioned combination therapies are no longer in use as a result of resistance development to one or both drugs in the combination by the malaria parasite, secondly due to adverse effects of one or both drugs in the combination. With the introduction of Artemisinins as the mainstay for the treatment of uncomplicated *P. falciparum* malaria and the subsequent development of resistance to artemisinin

monotherapy, WHO approved Artemisinin-based Combination therapy (ACT) as the first line of treatment for uncomplicated and resistant *P. falciparum* malaria. The following ACTs approved by WHO are currently in clinical use;

a. Artemether plus Lumefantrine (AL)

b. Dihydroxyartemisinin plus Piperaquine (DHA-PPQ)

c. Artesunate plus Amodiaquine (AS-AQ)

d. Artesunate-Pyronaridine (AS-P)

e. Artesunate-Sulphadoxine-pyrimethamine (AS-SP)

f. Artesunate-Mefloquine (AS-MF).

The rationale for ACTs is combining a short-acting artemisinin with a long-acting partner drug whose duration of action provides the much-needed antimalarial cover long after the action of artemisinins has withered. This strategy was meant to overcome the phenomenon of ADR but sadly in 2009, there were reports of a deadly strain of *P. falciparum* (artemisinin-resistant P. *falciparum*) in the Greater Mekong Subregion (GMS) comprising Laos, Cambodia, Vietnam, Thailand, Myanmar and Yunnan Province in Southern China. The magnitude of this resistance threat in the GMS was to the extent of resistance to four out of the five WHO-approved ACTs for use in the region. This led to the setting up of the Regional Artemisinin-resistance Initiative (RAI) by the Global fund to address this emerging global health threat in the GMS in 2013. The outcomes of the RAI strategy in the GMS will be discussed under the section; Recent Advances against ADR.

4.2 Continuous discovery of chemically and mechanistically novel antimalarial agents

The need for unrelenting search for chemically and mechanistically novel antimalarial agents has been underscored by the growing threat of ACT-resistant malaria in the GMS. The past decade has seen an unprecedented renewed focus on the discovery of new antimalarial entities through extraordinary collaboration between academia (parasitologists, medicinal chemists, pharmacologists, clinicians) and industrial/private partnerships e.g. Medicines for Malaria Venture (MMV). The following promising antimalarial drug leads are products of such collaborations and are in the product development (patient exploratory) stages (**Figure 3**).

4.3 Limitations

Despite the above measures taken against ADR, limitations abound and they include development of resistance by *P. falciparum* to ACTs which presents as delayed parasite clearance. The huge cost involved in drug discovery and development projects is a great limitation to the search for novel antimalarial agents with novel mechanism(s) of action [9]. Some of the candidates have not gone beyond Phase II clinical trials because of safety concerns. The ones that crossed Phase II clinical trials do not

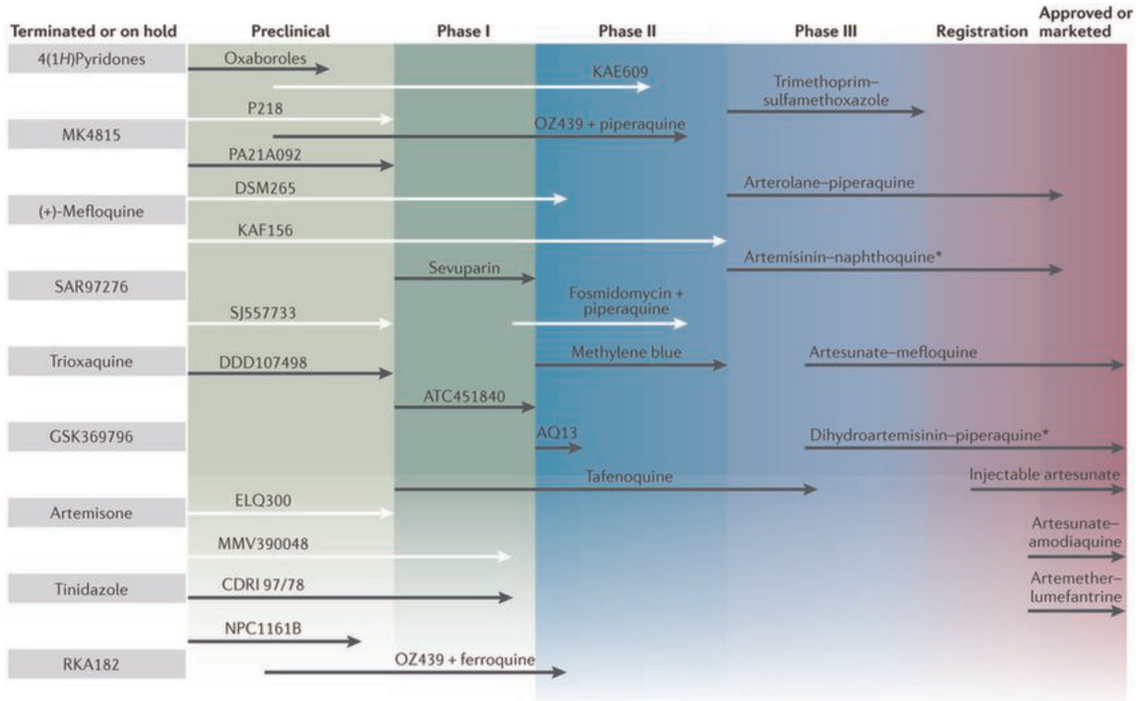

Figure 3.
Showing progression of the clinical development of new antimalarial candidates over the past five years (source: www.researchgate.net, date accessed: 28th June, 2022).

have significant antimalarial action due to resistance development and may exhibit unexplained loss of potency necessitating stoppage of such multi-billion dollar drug discovery and development projects.

5. Recent advances

Advances in the fight against ADR should among other challenges and areas of need address major limitations mentioned above. There has been renewed drive in terms of research to tackle head-on ADR using a multi-pronged approach, this has led to some recent advances which includes but not limited to the following:

5.1 Regional artemisinin-resistance initiative (RAI)

Launched in 2013 by the Global Fund to tackle Artemisinin resistance in the GMS (with the exception of Yunnan province in Southern China) [10] using a multi-pronged approach which included treatment and prophylactic strategies resulted in 88% reduction in indigenous malaria cases and 95% reduction in *P. falciparum* cases [1]. Partly responsible for the success story of malaria control in the GMS is the policy of Drug Rotation-exposure of the malaria parasite to different cycles of ACTs.

5.2 Nanomimics

This era of an emerging global threat (ACT-resistant malaria), an emerging, very promising strategy is the concept of nanomimics, an ingenious strategy developed by Najer et al. [11]. Researchers in Switzerland have successfully designed and tested host cell nanomimics. They developed a single procedure to produce polymer vesicles-

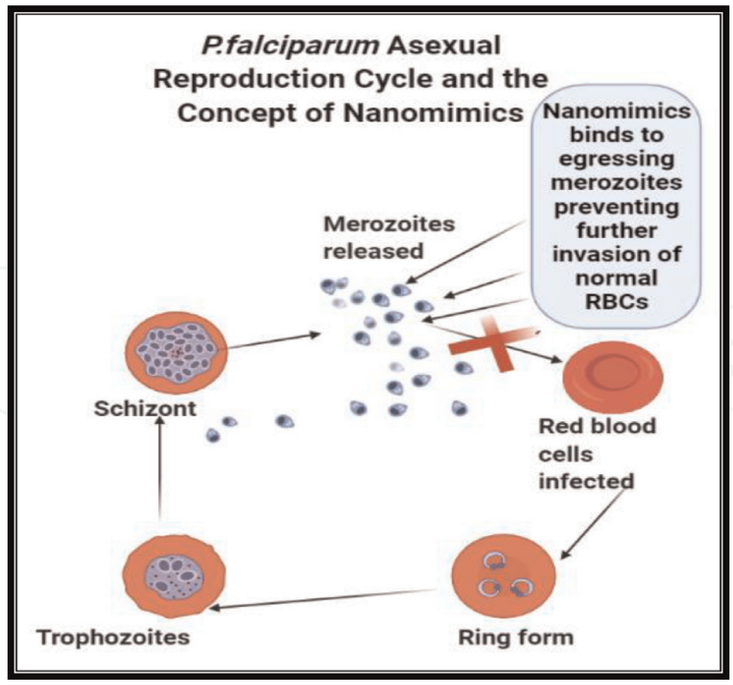

Figure 4.
Polymer-based RBC membrane nanomimics (source: Self-drawn with www.biorender.com).

small artificial bubbles with host cell receptors on the surface [11]. The concept of nanomimics is shown in **Figure 4**.

In **Figure 4**, an infected red blood cell undergoes various stages of the life cycle of the malaria parasite, mature schizonts rupture to release merozoites (light-blue) which are bound by nanomimics (nanoscaled polymer vesicles) preventing them from further invading normal red blood cells trapping them within the blood which exposes them to the immune system of the host.

Usually, the malaria parasites destroy their host cell after 48 h and then infect new red blood cells. At this stage they have to bind to specific cell receptors. Nanomimics as a result of their size and composition bind egressing parasites thus blocking the invasion of new cells [11]. The parasites are no longer able to invade cells and are consequently exposed to the host immune system, which kills them. Nanomimics exhibit a dual action; a therapeutic-like and vaccine-like effects. By preventing further invasion of red blood cells, it stops the progression of the disease (therapeutic-like action) and by exposing the bound merozoites to the host immune system for destruction (vaccine-like action) [12]. The intelligence of this strategy is that there is no payload (drug), malaria parasites are not exposed to any payload (exposure is key for resistance development). Non exposure of malaria parasites to drugs using this strategy could bring back exposure-caused, resistance-retired antimalarial drugs like chloroquine, SP, etc. as frontline antimalarial drugs [13]. This strategy is potentially resistance-proof and should be explored for possible translation into products for clinical trials.

5.3 Targeted drug delivery

This is one approach that inhibits resistance development by ensuring that adequate concentration of the antimalarial drug is delivered at the desired site of action ensuring rapid clearance of the parasite. The majority of antimalarial drugs under

development are lipophilic with poor plasma solubility and large biodistribution volumes which ultimately results in low accumulation in RBCs [9, 10]. This buttresses the need for targeted drug delivery to deliver optimum concentrations of drug within RBCs.

Targeted drug delivery using antibodies is a promising strategy that could be harnessed to combat resistant malaria. Antibodies have successfully been used to target pRBCs [14]. Antibody-targeted liposomes having on their surface $F(ab)_2$ fragments of mouse monoclonal antibody raised against *P. berghei*-infected mouse erythrocytes significantly increased the therapeutic efficacy of chloroquine implying that target-specific liposomes can cure CQ-resistant malarial infections [15]. A tenfold increase in the therapeutic effect of CQ was observed when delivered in liposomes covalently functionalized with oriented, specific half antibodies against *P. falciparum* late form-infected RBCs [14]. Antibody-functionalized liposomes can discriminate pRBCs from non-infected RBCs specifically delivering antimalarial drugs to pRBCs in sufficient concentration to clear parasitaemia, however their use as targeting molecule in antimalarial therapy is limited by their high cost of production [16], high immunogenicity and the potential decrease in targeting efficiency due to variability in plasmodium protein expressed on the surface of pRBCs [17].

An interesting alternative to antibody-mediated targeted delivery is the use of certain glycosaminoglycans like heparin, heparan sulphate and chondroitin sulphate [18], which are found in the human body and are being recognized as one of the main pRBC-binding molecules [17]. Heparin bound to liposomes has a dual action as a pRBC-targeting molecule acts mainly on trophozoites of some pfEMP1-expressing lines [19] and on schizont stages [20] and as an antimalarial drug (Nanomimic polymer constructs) blocks the merozoites from invading red blood cells [21]. Heparin is cheaper than monoclonal antibodies resulting in heparin-bound liposomes having ten times less cost than immunoliposomes of similar targeting activity [18]. In addition, resistance to heparin as antimalarial drug have not been reported [21]. Heparin when covalently bound to liposomes has substantially reduced anticoagulant activity [18]. Heparin maybe limited in its application as a targeting ligand as a result of its anticoagulant actions but when used at non-anticoagulant concentration, it increased the efficacy of encapsulated primaquine threefold in *in vitro P. falciparum* cultures [18]. Heparin when compared with immunoliposomes for targeted drug delivery is cheaper, has lower or no immunogenicity and may potentiate the effect of the payload when used at non-anticoagulant concentrations. Heparin-related polysaccharides such as heparan sulphate, chondroitin sulphate can be used as targeting moieties, in comparison with heparin have much lower anticoagulant action [18].

5.4 Triple artemisinin-based combination therapy (TACT)

This is a combination of an artemisinin with two partner drugs as against the conventional one partner drug. This strategy is being proposed (in the face of the growing threat of artemisinin-resistant P.falciparum malaria which is causing delayed parasite clearance by ACTs) as a measure to tackle to artemisinin-resistant *P. falciparum* malaria. The result of a multicentre, open-label, randomized clinical trial of triple artemisinin-based combination therapy versus artemisinin-based combination therapy conducted in the GMS showed overall that 42-day Polymerase Chain Reaction (PCR) corrected efficacy of dihydroartemisinin-piperaquine plus mefloquine (97%; 95% CI 93–99) was higher than for dihydroartemisinin-piperaquine

(60%; 52–67) with a risk difference of 37%, 29–45; p< 0.0001 [22]. There was no difference in efficacy between Artemether-Lumefantrine plus amodiaquine and Artemether-Lumefantrine-treated groups suggesting no relative advantage of having a triple combination of Artemether-Lumefantrine in treating resistant P.falciparum malaria [22]. Parasite half-lives in patients with Pfkelch 13 C580Y mutated infections were shorter in those treated with dihydroartemisinin-piperaquine plus mefloquine [mean = 6.93, SD = 1.77] than those treated with dihydroartemisinin-piperaquine [7.39 h (1.46); p = 0.019] [22]. This suggests albeit strongly that dihydroartemisinin-piperaquine plus mefloquine as a promising TACT candidate against artemisinin-resistant *P. falciparum* malaria. Extensive clinical trials involving TACTs has to be done to really establish and justify a possible switch from ACTs to TACTs.

5.5 Drug development

There are promising drug candidates which are at various product development stages in researches conducted by some of the global pharmaceutical companies and some Research Institutions (Universities) or partnerships between the two resulting in drugs licensed for use with market authorization (refer to **Table 1**). The drug tafenoquine was recently licensed for radical cure of *P. vivax* malaria [23]. Medicines for Malaria Ventures (MMV) is at the forefront n novel drug discovery and development research.

6. Future perspectives

The way of the future is that of malaria eradication. The strategy to drive this should be anchored on the development of novel, smart, resistance-proof, antimalarial nanoformulations that with a single exposure lead to cure and prophylaxis (transmission-blocking ability). To this end, the application of nanotechnology in combating drug resistance in plasmodium species holds a lot of promises. Future strategies should target delivering antimalarial drugs via non-receptor-mediated pathways which are not under the genetic control of the parasite [24]. To this end, liposomal delivery holds a lot in stock since liposomes deliver drugs to their intracellular targets by fusing with the parasite's cell membrane. This technique can be used to deliver drugs whose resistance mechanisms are receptor-mediated e.g. chloroquine [25]. The parasite is less likely to modify the chemical composition of its cell membrane as that may affect its survival in terms of nutrient acquisition from its host. Future research should target what would be called a "Starving Strategy" whereby the parasite is starved of its nutrient supply from the red blood cell by developing Plasmodium surface anion channel blockers whose channel-blocking ability is by nanoadhesion - a phenomenon where nanocarriers block the nutrient pore channels by forming strong bonds with the negatively charged nutrient channels.

Nanomimics development and optimization is another smart move in beating the resistance trap of the parasite and should be explored [12]. Nanocarriers such as dendrimers present diverse opportunities of formulating combination drug products with novel mechanism of action that with a single exposure may possibly eradicate the parasite. Discovery and development of host-derived factors with therapeutic activity against the parasite are possible research options that will eradicate the parasite since the host-derived factors are not under the genetic control of the parasite.

Research		Translational		Product development			Access
Lead Optimization	**Candidate Profiling** →	**Preclinical**	**Human Volunteers** →	**Patient Exploratory**	**Patient Confirmatory**	**Regulatory Review** →	**Approved/ERP**
Phenotypic Lead Mitsubishi Tanabe	**MMV072** Eisai	**MMV371** Janssen	**Atoguanil** Ipca	**Ganaplacide-Lumefantrine** Novartis	**Dihydroartemisinin-piperaquine dispersible** Alfasigma	**Sulphadoxine-Pyrimethamine** Universal Corporation	**Artemether-Lumefantrine dispersible** Novartis
Pf Carl series Calibr		**MMV183** TropIQ	**MMV533** Sanofi	**Cipargamin** Novartis	**Artemether-Lumefantrine < 5 kg** Novartis	**Sulphadoxine-Pyrimethamine** Swipha/ Biogaran	**Artesunate for Injection** Fosun Pharma
GWT 1 Eisai		**GSK 701** GSK	**INE963** Novartis	**ZY19489+ ferroquine** Zydus	**Sulphadoxine-Pyrimethamine** Emzor Pharmaceutical		**Artesunate for Injection** Ipca
Molecular Target DDU Dundee		**MMV609** Univ. of Kentucky		**M5717 + Pyronaridine** Merck KGaA/Shin Poong	**Primaquine dispersible** B & O Pharm.		**Dihydroartemisinin-Piperaquine** Alfasigma
Azabenzimidazole UNICAMP		**GSK 484** GSK			**Artemether-Lumefantrine-Amodiaquine FDC** Tridem/MORU		**Pyronaridine-artesunate** Shi Poong
Mini portfolio Novartis		**IWY 357** Novartis					**Pyronaridine-artesunate granules** Shi Poong
4-aminoquinoline LSTM and University of Liverpool							**Artesunate-Amodiaquine** Sanofi
Molecular target UCB							**Artesunate-Mefloquine** Cipla
DHODH Broad							**Suphadoxine-Pyrimethamine + Amodiaquine dispersible** Fosun Pharma

Research		Translational		Product development			Access
Lead Optimization	**Candidate Profiling →**	**Preclinical**	**Human Volunteers →**	**Patient Exploratory**	**Patient Confirmatory**	**Regulatory Review →**	**Approved/ERP**
DHODH UTSW/UW/ Monash							**Sulphadoxine-Pyrimethamine + Amodiaquine dispersible** S Kant
Phenotypic Lead Merck KGaA-UCT							**Artesunate rectal capsules** Cipla
Whole Cell Actives H3D							**Artesunate rectal capsules** Strides Pharma
Irresistibles GHDD1							**Tafenoquine** GSK
YRS Takeda							**Tafenoquine Pediatric** GSK
ATP 4 Series Drexel							

Table 1.
Showing drug candidates in clinical development and their progression, accessed from www.mmv.org/research-development/mmv-supported-projects, date accessed: 29th June, 2022.

In all, nano-smart delivery of antimalarial drugs is the key to tackling and preventing resistance development in plasmodium species bringing global efforts steps closer to the actualization of the WHO ideal goal of malaria eradication by 2030.

7. Conclusion

This chapter introduced malaria and Antimalarial Drug Resistance (ADR), its impact on global health, therapeutic interventions and their resistance by the malaria parasite. The mechanisms of resistance development by the parasite and factors causing it were discussed in detail. Armed with the knowledge of the foregoing, measures including nanotechnological approaches to combat the resistance trap of the parasite and their limitations were looked at and also the future perspectives in the fight against drug resistance by *P. falciparum.* It is envisaged that application of nanotechnology tools to develop antimalarial nanomedicines would help bring back antimalarial drugs that have been retired because of resistance of malaria parasites to these drugs and possibly lead to the development of novel, smart, resistance-proof formulations that will eliminate and possibly eradicate malaria globally.

Conflict of interest

The Authors declare no conflict of interest.

Nomenclature

ACT	Artemisinin-based Combination Therapy
CRT	Chloroquine Resistance Transporter
WHO	World Health Organization
TACT	Triple Artemisinin-based Combination Therapy

Author details

Samuel Uzondu*, Adaeze Echezona, Chinekwu Nwagwu, Adaeze Onugwu, Lydia Ugorji, Chinazom Agbo, Franklin Kenechukwu, John Ogbonna, Paul Akpa, Petra Nnamani, Audu Momoh and Anthony Attama
NanoMalaria Research Unit, Drug Delivery and Nanomedicines Research Laboratory, Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Nigeria

*Address all correspondence to: samuel.uzondu@unn.edu.ng

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