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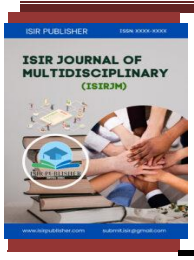

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ANTIMALARIAL DRUGS AND DRUG RESISTANCE *IN PLASMODIUM FALCIPARUM*

By

Bala Abubakar[1], Muhammad Fatima Yakubu[2], Hauwa'u Abdulkadir Usman[3], Ismail Muhammad[4]

[1]School of health Science and Technology Kaltingo, Gombe State

[2]Federal College of Education (Tech) Gombe, School of Secondary Education (Sciences) Department of Biology Education

[3]Federal College of Horticultural Technology Dadin-kowa, Gombe State

[4]Department of Zoology, Gombe State University, Gombe,

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Abstract

Plasmodium falciparum remains the most virulent parasite that causes high rate of morbidity and mortality among children and pregnant women. Prevention and treatment of malaria mainly rely on the use of synthetic drugs. Unfortunately, the parasite has developed resistance to all classes of antimalarial drugs. Therefore this review aimed at describing various antimalarial drugs and their resistance status, together with the common biomarkers of resistance. Apart from some physiological survival strategies adopted by the parasite to avoid the action of most drugs, there are several genetic mutations that are associated with resistant development by the parasite in some of the adverse drug reaction genes of the parasite which include, Multidrug Resistance Protein (PFMDR1),P.falciparum Chloroquine Resistance Transporter (PfCRT), Dihydropteroate Synthase (DHPS), Dihydrofolate Reductase (DHFR) and K13 Propeller gene.

Keywords: *Plasmodium falciparum, Antimalarial drug, Drug resistance, Malaria,*

INTRODUCTION

Malaria is a blood-borne protozoan parasitic infection that is transmitted by female anopheles mosquito that causes high rate of morbidity and mortality (Kweyamba, Zofou, Efange, Assob, & Kitau, 2019). Malaria control in Sub-Saharan Africa (SSA) is difficult, and despite concerted efforts, progress has stopped. It is estimated that a total of 241 million cases of malaria (up from 227 million cases estimated in 2019) occurred in 2020 in 85 endemic countries, with the majority of these cases occurring in members of the World Health Organization (WHO) African Region. Malaria-related fatalities also rose from 558,000 to 627,000 (Chemwor et al., 2023).Five species of *Plasmodium sp*. known to cause malaria in humans are *Plasmodium falciparum, P. vivax, P. malariae, P. ovale, and P. knowlesi*. The disease remains serious medical and public health concern in tropical and sub-tropical, and about 95% of cases and deaths are in sub-Saharan Africa, with young children and pregnant women and elderly people are at particular risk. *Plasmodium falciparum*, the most virulent human malaria parasite, is responsible for almost all of these cases of mortality and deaths (Rosenthal et al., 2024).

Shivering, body aches, abdominal pain, fever paroxysms, and other flu-like symptoms are common signs of malaria. Acute respiratory distress syndrome (ARDS), placental malaria, cerebral malaria, anemia, liver failure, and renal failure are some clinical signs of severe malaria. In high risk groups(Ceravolo, Aguiar, Adebayo, & Krettli, 2021), including infants, young children, pregnant women and their unborn children, older adults, and visitors from non-endemic malaria countries, these symptoms can be fatal if not identified and treated promptly. In regions where malaria is endemic, *P. falciparum* is the human malaria parasite that causes the greatest death rate. Cerebral malaria, pulmonary edema, jaundice, respiratory distress or acidosis, and other deadly signs are among the severe clinical manifestations of infection with this parasite (Azmi et al., 2023).

Drug Resistance

According to World Health Organization, drug resistance is the ability of a parasite strain (*P. falciparum*) to survive and/or proliferate/multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within the subject's tolerance. Resistance of *Plasmodium falciparum* to antimalarial drugs is

*Corresponding Author: **Ismail Muhammad***

one of the greatest obstacles in the fight against malaria, especially in terms of prevention and eradication of the parasites (Bhagavathula, 2020; Fenta & Kahaliw, 2019). Certain factors that caused the parasites to be resistant include the following: Genetic mutation, and use of substandard or counterfeit antimalarial drugs. For thousands of years, malaria was treated with natural products found in bark, roots, or leaves of plants like Annua and Cinchona plants. Their active ingredients however, were identified and used as isolated drug compounds only in the last century. Perhaps the most successful of these medicines was quinine, a quinoline-containing alkaloid from the bark of cinchona trees (Wicht, Mok, & Fidock, 2020).

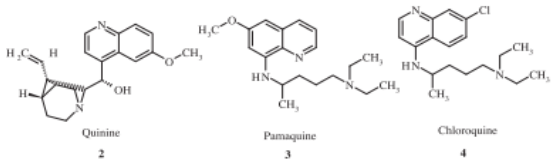
Resistance to Quinoline

Plasmodium falciparum parasite has long been endemic in African countries such as the Democratic Republic of the Congo (DRC), Burkina Farso, Malawi, South Africa and Nigeria. Due to its limited supply and high importation costs from South-East Asia, quinine the first medication used to treat and prevent malaria was not provided by widespread programs until the middle of the 20th century(Olukosi et al., 2014). During World War II, colonial authorities began manufacturing the drug domestically and introducing newly created synthetic antimalarial drugs, such as pyrimethamine and chloroquine. Chloroquine's rapid rise to prominence as a prominent antimalarial medication due to its low cost and great efficacy allowed for extensive distribution programs via a few industrial and urban cities in the 1940s and 1950s (Kayiba et al., 2023;Plowe et al., 2007).

Quinoline or benzo pyridine is a heterocyclic aromatic chemical that contains nitrogen. It is a weak tertiary base with the chemical formula C_9H_7N. It exhibits reactions resembling those of pyridine and benzene and can combine with acids to create salt. It exhibits substitution reactions that are both nucleophilic and electrophilic. It is not harmful to people when taken orally or inhaled. Friedrich Ferdinand Runge identified quinoline as a heterocyclic aromatic organic molecule in 1834. Quinolone derivatives, including Piperaquine, Amodiaquine, Mefloquine, and Quinine and Chloroquine, are used in a variety of medications, including those that treat *Plasmodium falciparum* malaria

Quinoline nuclei are found in a variety of pharmacologically active chemicals with a wide spectrum of biological activity as well as natural compounds (Cinchona Alkaloids). Antimalarial, antibacterial, antifungal, anthelmintic, cardiotonic, anticonvulsant, anti-inflammatory, and analgesic properties have all been discovered in Quinoline. The drugs belonging to the quinoline family are thought to harm the parasite in two ways: by limiting the growth of hemozoin crystals, which delays the deposition of heme onto the crystal surface, and by complexing with free heme in the digestive vacuole lumen, though this process should be secondary to the inhibition of crystal growth. According to both theories, the parasite suffers harm as a result of heme that is liberated from hemoglobin but is unable to solidify. Therefore, it is essential to ascertain the crystal structure of hemozoin in order to elucidate the mechanism of antimalarial action by quinoline drugs (Kapishnikov et al., 2019).

Multidrug Resistance Protein (PFMDR1) was linked to *Plasmodium falciparum's* quinoline resistance; mutations of PFMDR1 enhance the efflux of drugs based on quinolines(Yah & Fatumo, 2010). The Greater Mekong Subregion, which includes Cambodia, Vietnam, Thailand, Laos, Myanmar, southern China, and African nations like Nigeria, is where resistance to quinoline derivatives like chloroquine (CQ), sulfadoxine-pyrimethamine (SP), piperaquine (PPQ), and mefloquine (MFQ) first appeared in Southeast Asia. One possible contributing aspect is Southeast Asia's low transmission rates, which can facilitate the propagation of relatively unsuitable mutations due to the absence of within-host asexual parasite competition in humans and the absence of other parasite genomes for recombination during sexual mosquito stages. In addition to having far lower overall infection rates than sub-Saharan Africa, Southeast Asia also has less robust acquired immunity, which leads to a larger reliance on treatments, which in turn puts more selection pressure on parasite populations (Abdulkadir, Jatau, Abdussalam, & Bichi, 2022).



Quinoline ring compounds.

Resistance to Chloroquine

Chloroquine is a synthetic antimalarial medication and was synthesized in 1934 by German chemist Hans Andersag. Control and treatment of malaria have become considerably more challenging due to the development of *Plasmodium falciparum* resistance to commonly used antimalarial medications like chloroquine (CQ). In the early 1960s, reports of P. *falciparum* resistance to CQ were initially reported almost simultaneously from South America and South-East Asia, where mass drug administration (MDA) had been used either directly or indirectly (by using medicated cooking salt)(Muhammad, Sale, Salisu, & Muhammad, 2022). In Africa, where *P. falciparum resistance* to CQ was initially identified from the eastern region in the late 1970s and gradually moved west. Although some states have switched to sulphadoxine-pyrimethamine (SP) as the first-line medication, the majority of African nations remain mostly rely on CQ as the first-line treatment despite varying degrees of resistance.

In the digestive vacuole, *Plasmodium falciparum* parasites convert host hemoglobin into peptides and amino acids, which are then exported to the parasite cytoplasm for development. A number of antimalarial medications work by blocking this process. *Plasmodium falciparum* acquires CQ resistance by mutations in the chloroquine (CQ) resistance transporter, Pfcrt, which is found in the digestive vacuole membrane of the parasites. These genes mutations usually have an impact on the fitness of the parasite. Its digestive vacuoles (DV) have membranes that express the mutant transporter, which

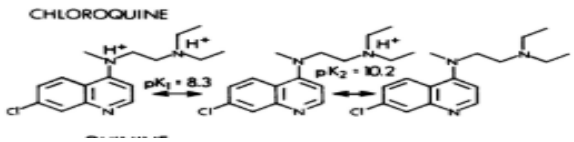
*Corresponding Author: **Ismail Muhammad**

excretes CQ from the vacuole and confers resistance. In addition to creating resistance to CQ, the reduction in intravesicular CQ concentration encourages the conversion of extremely poisonous hematin to hemozoin. To combat drug resistance in malaria parasites, it is crucial to elucidate the transport mechanism of PfCRT. However, it is still unknown how CQ-resistant PfCRT acquires the capacity to transport CQ and what function CQ-sensitive PfCRT transports under physiological settings. Chloroquine frequently inhibits the growth and multiplication of parasites and messes with *Plasmodium falciparum*'s heme detoxification. It is unknown, nevertheless, how other parasite loci contributed to the development of CQ resistance (Amambua-Ngwa et al., 2023). One mutation, K76T, was perfectly associated with in vitro resistance in all progeny of a genetic cross between chloroquine-sensitive and -resistant parental clones and among a set of geographically diverse parasite isolates(Kublin et al., 2003)

By breaking down hemoglobin in its acidic feeding vacuoles, the asexual malaria parasite creates heme (ferriprotoporphyrin IX/FPIX), amino acids, and free radicals as it feeds and develops in host erythrocytes. Because FPIX is poisonous and toxic to parasites, it is changed into hemozoin, a polymer that is also referred to as malaria pigment. After diffusing into the food vacuole, the chloroquine base gets protonated and becomes stuck there. The poisonous FPIX-Chloroquine complex, which is formed when chloroquine binds firmly to FPIX, prevents the synthesis of hemozoin, poisons the acidic food vacuoles, and causes the parasite to starve. Chloroquine buildup also raises the vacuole's pH, which lowers the rate at which FPIX polymerizes.

Mutations in Pfcrt, which encodes the *P.falciparum chloroquine resistance transporter (PfCRT*), are linked to resistance of P. falciparum to chloroquine and may be amodiaquine. Chloroquine can be moved out of the digestive vacuole and away from the drug's anti-plasma goals (heme detoxification) by transporters thanks to mutations in pfcrt (Fitri et al., 2023).

It is undoubtedly cause for grave concern that *Plasmodium falciparum* in East Africa has just recently been found to be resistant to chloroquine, initially in the non-immune population and more recently in the semi-immune. Most nations, including Nigeria, Malawi, have stopped using chloroquine. However, a rapid decrease in the prevalence of point mutation resistance was noted after a lengthy period of its absence, and the drug is now regarded as efficacious once more. Due to widespread resistance to Chloroquine (CQ), dihydroartemisinin-piperaquine (DHA-PPQ), artesunate-pyronaridine (ASPYR), and Artemether-Lumefantrine (AL) are recommended as first-line therapies for uncomplicated malaria in Nigeria, Burkina Faso and some other African countries. Sulfadoxine-pyrimethamine (SP) is used for intermittent preventive treatment of malaria during pregnancy (IPTp) in conjunction with Amodiaquine (SP-AQ) and for seasonal malaria chemo-prevention in children under five (SMC) (Tarama et al., 2023).

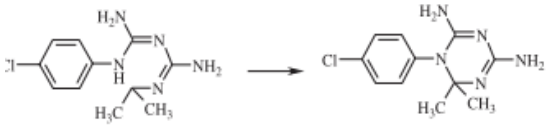


Resistance to Antifolates Drug

Antifolate malaria drugs are a class of medications that target folate synthesis in *Plasmodium falciparum.* The use of antimalarial antifolates, particularly the synergistic combination sulfadoxine/pyrimethamine (S/P), which targets the enzymatic synthesis of folate co-factors through dihydropteroate synthase (DHPS) and dihydrofolate reductase (DHFR), has become necessary in nearly all African nations due to chloroquine resistance (Muhammad, Sale, Khadija, et al., 2022). These important folate pathway enzymes do not yet have crystal structures. Tetrahydrofolate (THF), which serves as a methyl group carrier for the thymidylate synthase process during DNA synthesis, is produced by a crucial metabolic route that is inhibited by antifolates. Since the 1960s, sulfadoxine-pyrimethamine (SP), an antifolate medication, has also been used extensively in many African nations. Due to many DHPS and DHFR mutations, *Plasmodium falciparum* rapidly developed partial resistance to SP (Ebel et al., 2021).

Resistance to Sulfadoxine/Pyrimethamine has a well understood chemical basis. Before the widespread emergence of resistant parasites diminished their effectiveness, pyrimethamine (Pyr) and cycloguanil (Cyc), two strong inhibitors of *Plasmodium falciparum* DHFR (PfDHFR), were employed to treat *P. falciparum* malaria. The DHFR gene from isolates of *P. falciparum* that were resistant to Pyr and Cyc was recently sequenced, and the results showed a correlation between the parasites' level of drug resistance and point mutations in the gene (Rahmasari et al., 2022).

Drug resistance increased as a result of the *PFDHFR* and *PFDHPS* mutations, which frequently happened in a stepwise progressive way. Antifolate resistance has also been linked to gene amplification of P. falciparum guanosine triphosphate cyclohydrolase 1 (pfgch1), an enzyme that codes for a crucial enzyme in the folate pathway. Parasites with pfgch1 amplification were reported to be less susceptible to antifolates because increased expression of enzymes help antifolate resistance by competing with the drugs and compensating for the loss of fitness caused by mutations in pfdhfr and pfdhps by increasing the flux of metabolic products in the folate pathway (Sugaram et al., 2020).



Resistance to Artemisinin

Strong medications renowned for their capacity to quickly lower the level of *Plasmodium falciparum* parasites in the blood of malaria patients include artemisinin, which was extracted from the plant *Artemisia annua*, and its semi-

*Corresponding Author: **Ismail Muhammad**

synthetic derivatives, artesunate, dihydroartemisinin, and artemethether. Artemisinins have the distinct ability to eradicate parasitemia faster than any other antimalarial, including quinine. These chemicals are effective because, like the majority of antimalarial medications, they target both the early and late stages of erythrocytic parasites. Artemisinins prevent the parasite stages from developing and sequestering in the vessels by killing the ring stage forms, which allows the parasite to be ripped out of the host red blood cells and removed from circulation. Since chloroquine has become widely resistant, artemisinin-based combination treatment (ACT) has taken its place. In accordance to World Health Organization's (WHO) recommendations, ACT was introduced in 20 African nations between 2001 and 2004. As a first-line treatment for uncomplicated falciparum malaria, ACT is now utilized in South America, Asia, and Africa (Maiga et al., 2021).

Haem-artemisinin adducts are created in the parasitic feeding vacuole when artemisinins react with haem, which is produced during the breakdown of hemoglobin and is poisonous to the parasite. Inhibiting hemoglobin polymerization, which results in hemoglobin buildup, these adducts appear to interact with *P. falciparum* hemoglobin detoxification proteins. Alkylation of parasite proteins is another function of artemisinins, when combined, these occurrences result in oxidative stress, which damages and kills parasites permanently. This clarifies the mechanism behind artemisinins' higher efficacy in treating malaria and explains their life-saving advantage. With both direct anti-gametocyte activity and indirect action through the reduction of the asexual parasite population, which is the source of new gametocytes, artemisinins also lessen the number of gametocytes (sexual-stage parasites) that transmit the disease to the vector, the Anopheles mosquito (Ouji et al., 2018).

Artemether-lumefantrine (AL), artesunate-amodiaquine (ASAQ), artesunate-mefloquine (AS-MQ), artesunate-sulfadoxine-pyrimethamine (AS-SP), dihydroartemisinin-piperaquine (DHA-PPQ), and artesunate-pyronaridine (AS-PND) are the six first-line ACTs now recommended by the World Health Organization (Happi et al., 2009). While AL and ASAQ are the primary ACTs utilized in Africa and are responsible for almost 98% of doses administered globally, AS-MQ and DHA-PPQ have been the most often used ACTs in Southeast Asia. In the Greater Mekong Subregion (GMS), which has historically been a hotbed for the development of antimalarial resistance(Vijaykadga et al., 2004), ART-resistant *P. falciparum* first appeared more than ten years ago. Point mutations in *P. falciparum K13* (also called Kelch13), which mostly, though not entirely, lie in the beta-propeller domain, are the principal genetic drivers of ART resistance both in vitro and in vivo (Ward et al., 2022). K13 is found in the endoplasmic reticulum, vesicular compartments, and peripheral compartments of the parasite plasma membrane. K13 seems to be concentrated at the neck of hemoglobin-filled cytostomes at the plasma membrane, which transport the majority of the host hemoglobin from the cytoplasm of red blood cells to the parasite's lysosome-like digestive vacuole (DV).When ART is no longer present at inhibitory concentrations, a subgroup of early ring-stage parasites with K13 mutations can withstand cell-cycle arrest caused by ART exposure, allowing them to resume transcription and finish their intraerythrocytic growth cycle.

A list of verified K13 variants linked to ART resistance has also been released by the WHO. These include F446I, N458Y, M476I, Y493H, R539T, I543T, P553L, R561H, P574L, and C580Y (WHO, 2020; Siddiqui et al., 2021). In 2009, the first reports of artemisinin resistance were made in the Pailin province of western Cambodia. The sluggish parasite clearance phenotype was initially linked to more than 20 distinct PfK13 mutations (Muhammad, Sale, & Midala, 2022 ;Zhu et al., 2022).

Conclusion

In conclusion, the emergence and spread of antimalarial drugs resistance in *Plasmodium falciparum* mainly due to various genetic mutations (Polymorphisms) and some other physiological survival strategies exhibited by the parasite pose a highly significant threat to universal malaria control, prevention and elimination effort. Resistance to key antimalarial drugs including: Chloroquine, Sulfadoxine-Pyrimethamine, Artemisinin based combination therapies (ACTS), has compromised their effectiveness and hindered progress in reducing malaria related morbidity. Therefore, to complete and to succeed in elimination and subdue *Plasmodium falciparum*, malaria vaccine is the only solution.

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*Corresponding Author: **Ismail Muhammad**