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# Antimalarial Drug Resistance Mechanisms and Emerging Therapeutic Strategies in Plasmodium falciparum Infection

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## ABSTRACT

Plasmodium falciparum remained the deadliest malaria parasite, causing over 600,000 deaths annually, with antimalarial drug resistance threatening global control efforts. Multiple resistance mechanisms have emerged against quinolines, antifolates, and artemisinin-based combinations, compromising therapeutic efficacy across endemic regions. This review examined the molecular mechanisms underlying antimalarial drug resistance in Plasmodium falciparum and evaluates emerging therapeutic strategies to combat resistant parasites. A comprehensive literature search of PubMed, Web of Science, and Cochrane databases identified peer-reviewed articles published between 2014 and 2025, prioritizing studies on resistance genetics, biochemical mechanisms, and novel drug development. Resistance mechanisms involved genetic mutations in drug target proteins (PfCRT, PfMDR1, PfDHFR, PfDHPS, kelch13), altered drug metabolism through efflux transporters, enhanced DNA repair pathways, and metabolic adaptations. Chloroquine resistance mediated by PfCRT mutations remains widespread, while kelch13 polymorphisms confer artemisinin resistance through enhanced oxidative stress responses and cell cycle modulation. Emerging strategies included triple artemisinin-based combinations, synthetic peroxides, spiroindolones targeting PfATP4, aminoacyl-tRNA synthetase inhibitors, proteasome inhibitors, and monoclonal antibodies. Combination therapies exploiting synergistic mechanisms and targeting multiple parasite stages demonstrate promising efficacy against resistant strains. Multifaceted resistance mechanisms necessitate integrated approaches combining genomic surveillance, rational drug design, combination therapies, and transmission-blocking interventions. Strategic deployment of emerging therapeutics alongside enhanced pharmacovigilance offers renewed hope for malaria elimination despite escalating resistance challenges.

**Keywords:** Plasmodium falciparum, Antimalarial resistance, kelch13 mutations, Artemisinin resistance, Emerging therapeutics

## INTRODUCTION

Plasmodium falciparum represents the most virulent human malaria parasite, accounting for approximately 95% of malaria mortality worldwide, predominantly affecting sub-Saharan Africa and Southeast Asia [1, 2]. The parasite exhibits a complex life cycle involving hepatic schizogony, erythrocytic multiplication, and sexual gametocyte development, with each stage presenting distinct biochemical vulnerabilities for therapeutic intervention [3]. Antimalarial drugs historically targeted critical metabolic pathways including heme detoxification, folate synthesis, and mitochondrial electron transport, achieving remarkable reductions in disease burden during the mid-20th century [4]. However, the remarkable genetic plasticity of Plasmodium falciparum, characterized by high mutation rates, chromosomal rearrangements, and clonal selection under drug pressure, has facilitated rapid evolution of resistance mechanisms [5, 6].

The emergence and geographic spread of drug-resistant parasites have systematically compromised successive antimalarial regimens, from chloroquine and sulfadoxine-pyrimethamine to contemporary artemisinin-based combination therapies. Resistance mechanisms involve multifaceted molecular adaptations including point mutations in drug target genes, amplification of resistance-conferring loci, upregulation of drug efflux transporters, and metabolic reprogramming that collectively reduce intracellular drug concentrations or diminish target susceptibility [7]. Chloroquine resistance, mediated primarily by mutations in the Plasmodium falciparum chloroquine resistance transporter gene (pfcrt), emerged in Southeast Asia during the 1950s and subsequently spread to Africa, rendering this once highly effective drug obsolete in most endemic regions. Similarly, mutations in dihydrofolate reductase (pfdhfr) and dihydropteroate synthase (pfdhps) genes confer resistance to antifolate

combinations, while recent identification of kelch13 propeller domain mutations associated with artemisinin resistance in the Greater Mekong Subregion threatens the efficacy of frontline artemisinin-based combination therapies [8]. Understanding the biochemical and genetic foundations of antimalarial resistance is essential for developing surveillance strategies, optimizing therapeutic regimens, and designing next-generation antimalarials. This review critically examines the molecular mechanisms underlying drug resistance in Plasmodium falciparum and evaluates emerging therapeutic strategies that hold promise for overcoming resistance and advancing toward malaria elimination.

**Molecular Mechanisms of Chloroquine and Quinoline Resistance**

Chloroquine resistance represents the most extensively characterized antimalarial resistance mechanism, providing fundamental insights into parasite adaptation strategies [9]. The primary determinant of chloroquine resistance involves mutations in the pfcrt gene, which encodes a digestive vacuole membrane transporter responsible for drug efflux. The critical K76T mutation, along with additional compensatory mutations at positions 72 to 76 (CVMNK to CVIET haplotype), significantly reduces chloroquine accumulation within the acidic digestive vacuole where the drug inhibits heme polymerization [10]. Biochemical studies demonstrate that mutant PfCRT proteins exhibit enhanced capacity for transporting protonated chloroquine out of the digestive vacuole, reducing effective drug concentrations below therapeutic thresholds. Importantly, the fitness cost associated with pfcrt mutations, manifested as reduced parasite growth rates in the absence of drug pressure, explains the partial reversion to chloroquine susceptibility observed in Malawi following chloroquine withdrawal.

The pfmdr1 gene, encoding the Plasmodium falciparum multidrug resistance protein 1, modulates chloroquine resistance and influences susceptibility to multiple antimalarials including mefloquine, lumefantrine, and quinine. Amplification of pfmdr1 copy number correlates with mefloquine and lumefantrine resistance, while specific point mutations (N86Y, Y184F, D1246Y) modulate drug transport efficiency and alter the parasites' susceptibility profile across different quinoline compounds. The interplay between pfcrt and pfmdr1 genotypes creates complex resistance phenotypes, with certain mutation combinations conferring multidrug resistance while others generate reciprocal susceptibility patterns [11]. Recent structural studies employing cryo-electron microscopy have elucidated the three-dimensional architecture of PfCRT, revealing drug binding pockets and conformational changes associated with resistance mutations, thereby facilitating rational design of resistance-circumventing compounds.

Metabolic adaptation represents an additional resistance mechanism, wherein parasites upregulate alternative heme detoxification pathways or enhance antioxidant defenses to mitigate chloroquine-mediated oxidative stress [12]. Transcriptomic analyses of resistant isolates reveal coordinated upregulation of glutathione biosynthesis genes and stress response pathways that contribute to the resistance phenotype independently of transport mutations. These findings underscore the multifactorial nature of quinoline resistance and highlight the necessity for combination approaches targeting multiple resistance pathways simultaneously.

**Antifolate Resistance: Genetic Determinants and Metabolic Consequences**

Resistance to antifolate antimalarials exemplifies how sequential accumulation of point mutations progressively diminishes drug efficacy through incremental reductions in target enzyme affinity. Sulfadoxine-pyrimethamine, which inhibits folate biosynthesis by targeting dihydropteroate synthase and dihydrofolate reductase respectively, represented a critical second-line therapy following chloroquine failure. However, the relatively low genetic barrier to resistance facilitated rapid emergence of resistant parasites throughout endemic regions. The pfdhfr S108N mutation alone confers low-level pyrimethamine resistance, while additional mutations at positions 51, 59, and 164 progressively enhance resistance, with the quintuple mutant (pfdhfr N51I/C59R/S108N combined with pfdhps A437G/K540E) exhibiting complete clinical resistance [13].

Structural studies demonstrate that resistance mutations sterically hinder drug binding while preserving sufficient catalytic activity for folate metabolism, representing an elegant evolutionary solution that maintains enzyme function while evading inhibition. The S108N mutation, present in nearly all resistant isolates, reduces pyrimethamine binding affinity approximately 1000-fold while decreasing enzyme efficiency only modestly, illustrating the selective advantage conferred by this mutation under drug pressure [14]. Geographic distribution patterns reveal that antifolate resistance originated independently in multiple foci, with subsequent spread facilitated by human migration and parasite gene flow, contrasting with the more restricted origins of chloroquine resistance.

The clinical implications of antifolate resistance extend beyond treatment failure to impact intermittent preventive treatment strategies in pregnancy and childhood. High-grade sulfadoxine-pyrimethamine resistance in eastern and southern Africa has necessitated exploration of alternative chemoprevention regimens, including dihydroartemisinin-piperaquine for intermittent preventive treatment, although concerns regarding artemisinin resistance emergence temper enthusiasm for widespread deployment [15]. Metabolic studies reveal that antifolate-resistant parasites exhibit altered nucleotide metabolism and enhanced salvage pathway utilization, adaptations that partially compensate for impaired de novo folate synthesis. The molecular epidemiology of antifolate resistance has been extensively mapped using molecular markers, enabling real-time surveillance and informing policy decisions regarding sulfadoxine-pyrimethamine utility in specific geographic contexts [16]. These insights demonstrate how

understanding resistance mechanisms directly translates to evidence-based therapeutic recommendations and resistance containment strategies.

**Artemisinin Resistance: Kelch13 Mutations and Cellular Adaptations**

Artemisinin resistance represents the most concerning contemporary threat to malaria control, given that artemisinin-based combination therapies constitute frontline treatment globally. Unlike resistance to other antimalarials, artemisinin resistance manifests as delayed parasite clearance rather than complete treatment failure, characterized by ring-stage parasites surviving brief artemisinin exposure. The landmark discovery that mutations in the kelch13 propeller domain (k13) gene associate strongly with artemisinin resistance revolutionized understanding of this phenomenon and enabled molecular surveillance. Validated resistance mutations, including C580Y, R539T, I543T, and Y493H, concentrate in the kelch13 propeller domain and occur predominantly in the Greater Mekong Subregion, although recent reports document independent emergence in Africa and South America [17].

The biochemical mechanism underlying kelch13-mediated artemisinin resistance involves enhanced cellular responses to oxidative stress and modifications to the parasite cell cycle that reduce artemisinin susceptibility during the ring stage. Kelch13 functions as a substrate adaptor for a cullin E3 ubiquitin ligase complex, regulating protein degradation and cellular homeostasis [18]. Resistance mutations impair this function, resulting in accumulation of phosphatidylinositol-3-kinase and reduced hemoglobin endocytosis, thereby limiting artemisinin activation through decreased exposure to heme-derived iron. Additionally, resistant parasites exhibit cell cycle alterations characterized by developmental arrest at the ring stage, the developmental phase inherently least susceptible to artemisinin, effectively creating a temporal sanctuary from drug action [19].

Metabolic profiling reveals that artemisinin-resistant parasites display enhanced unfolded protein response activation and upregulated antioxidant defenses, adaptations that mitigate artemisinin-induced proteotoxic stress. The fitness costs associated with kelch13 mutations remain controversial, with some studies demonstrating reduced growth rates in resistant parasites while others detect minimal impact, potentially explaining variable competitive dynamics between sensitive and resistant populations [20]. Concerning epidemiological trends indicate that partial artemisinin resistance has emerged independently multiple times and continues spreading geographically, with documented cases in Rwanda and Uganda threatening African malaria control programs. Genomic surveillance employing whole-genome sequencing has identified additional genetic modifiers, including mutations in ferredoxin, apicoplast ribosomal proteins, and ubiquitin hydrolase, that modulate artemisinin resistance phenotypes in kelch13 mutant backgrounds [21]. These findings emphasize the polygenic nature of artemisinin resistance and complicate molecular surveillance strategies that rely solely on kelch13 genotyping.

**Partner Drug Resistance and Combination Therapy Failure**

The efficacy of artemisinin-based combination therapies depends critically on partner drug effectiveness, as the short artemisinin half-life necessitates a longer-acting companion drug to eliminate residual parasites. Emergence of resistance to partner drugs, particularly piperaquine and mefloquine, in combination with artemisinin resistance threatens therapeutic longevity and raises the specter of untreatable malaria [22]. Piperaquine resistance involves amplification of plasmepsin 2 and 3 genes along with mutations in the exonuclease E415G variant, resulting in treatment failures with dihydroartemisinin-piperaquine across Cambodia and Vietnam. The molecular mechanism remains incompletely elucidated, although plasmepsins function in hemoglobin degradation and their amplification may alter digestive vacuole hemoglobin processing, potentially reducing piperaquine accumulation or activity [23].

Mefloquine resistance, prevalent in Southeast Asia, involves pfmdr1 amplification and specific mutations that enhance drug efflux, limiting therapeutic efficacy of artesunate-mefloquine combinations. Mathematical modeling demonstrates that the sequential emergence of artemisinin resistance followed by partner drug resistance significantly accelerates treatment failure rates, with double-resistant parasites exhibiting selective advantages that facilitate rapid population replacement [24]. Clinical studies document alarming treatment failure rates exceeding 50% for dihydroartemisinin-piperaquine in western Cambodia, necessitating therapeutic regimen changes and heightened surveillance [25].

The phenomenon of collateral sensitivity, wherein resistance to one drug increases susceptibility to another, offers potential strategies for therapeutic cycling and combination optimization [26]. For instance, pfmdr1 mutations conferring lumefantrine resistance paradoxically enhance susceptibility to mefloquine and vice versa, suggesting that strategic deployment of different artemisinin-based combination therapies might delay or reverse resistance. However, practical implementation faces challenges including limited drug availability, cost considerations, and the need for real-time molecular surveillance to guide therapeutic choices. Triple artemisinin-based combination therapies, incorporating two partner drugs with distinct mechanisms, represent a promising strategy to overcome resistance, with artemisinin-naphthoquine-piperaquine demonstrating superior efficacy in regions with piperaquine resistance [27]. Population genetic analyses reveal that combination therapies exert strong selective pressure on parasite populations, necessitating careful consideration of deployment strategies to maximize therapeutic lifespan while minimizing resistance evolution.

**Emerging Therapeutic Strategies and Novel Drug Development**

The antimalarial drug development pipeline has expanded substantially, with multiple compounds in clinical trials targeting novel parasite pathways and circumventing established resistance mechanisms [28]. Synthetic peroxides, including arterolane and artefenomel, maintain activity against artemisinin-resistant parasites while offering improved pharmacokinetic properties and single-dose treatment potential. These compounds generate reactive oxygen species through a similar mechanism to artemisinins but exhibit distinct structure-activity relationships that may delay resistance emergence [29]. Spiroindolones, exemplified by cipargamin, target the parasite sodium pump PfATP4 and demonstrate rapid parasite clearance with activity against multiple life cycle stages including liver and transmission stages. Phase II trials demonstrate excellent tolerability and efficacy, with cipargamin advancing toward registration as a component of novel combination therapies [30].

Imidazolopiperazines, such as KAF156, inhibit phosphatidylinositol 4-kinase and exhibit broad-spectrum activity against drug-resistant parasites, although recent reports document reduced susceptibility associated with mutations in PfCARL and UDP-galactose transporter genes. Aminoacyl-tRNA synthetase inhibitors represent another promising class, with compounds targeting prolyl-tRNA synthetase and other translation machinery components demonstrating potent antimalarial activity and acceptable safety profiles in early clinical development [31]. Proteasome inhibitors exploit the parasites' dependence on protein degradation pathways for hemoglobin catabolism and cell cycle regulation, although clinical development has been limited by concerns regarding host cell toxicity.

Monoclonal antibodies targeting merozoite surface proteins offer an immunotherapeutic approach, with several candidates demonstrating parasite neutralization in vitro and protection in animal models [32]. The development of bispecific antibodies that simultaneously engage multiple parasite antigens and host immune effectors represents an innovative strategy that may enhance efficacy and delay resistance. Host-directed therapies that modulate human pathways essential for parasite survival, such as Plasmodium falciparum kinase inhibitors that target erythrocyte membrane modifications, provide an alternative approach less vulnerable to parasite resistance evolution. Transmission-blocking vaccines and drugs targeting gametocyte development offer complementary strategies to reduce malaria transmission and limit resistance spread, although their impact depends on achieving high population coverage [33]. The strategic combination of these diverse approaches, informed by pharmacokinetic-pharmacodynamic modeling and evolutionary considerations, offers renewed optimism for sustainable malaria control despite continuing resistance challenges [34].

## CONCLUSION

Antimalarial drug resistance in Plasmodium falciparum represents a multifaceted challenge involving diverse molecular mechanisms that collectively threaten global malaria control achievements. Chloroquine and quinoline resistance, mediated primarily through PfCRT and PfMDR1 mutations altering drug transport, established the paradigm for understanding resistance evolution. Antifolate resistance exemplifies how sequential target site mutations progressively compromise therapeutic efficacy, while artemisinin resistance, associated with kelch13 mutations and complex cellular adaptations, presents the most immediate threat to frontline therapies. The emergence of partner drug resistance, particularly piperaquine resistance in artemisinin-resistant backgrounds, creates potentially untreatable malaria scenarios in Southeast Asia. Current evidence demonstrates variable quality, with robust genetic association studies contrasted by incomplete mechanistic understanding for some resistance phenotypes. Emerging therapeutic strategies encompass synthetic peroxides, spiroindolones, aminoacyl-tRNA synthetase inhibitors, and immunotherapeutic approaches that target novel parasite pathways and circumvent established resistance mechanisms. The clinical translation of these compounds, deployed rationally in triple combination therapies and informed by real-time genomic surveillance, offers promise for overcoming resistance. However, sustainable success requires integrated approaches combining novel drug development, optimized combination strategies, enhanced pharmacovigilance, transmission reduction interventions, and continued investment in resistance monitoring infrastructure. The evolutionary pressure exerted by antimalarial drugs demands continuous innovation and adaptive strategies to maintain therapeutic efficacy and advance toward malaria elimination. National malaria control programs should implement routine molecular surveillance for validated resistance markers, including kelch13 genotyping and partner drug resistance determinants, to enable evidence-based therapeutic policy decisions and facilitate early detection of resistance emergence in new geographic regions.

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