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Artemisinin-Based Combination Therapy: Resistance Mechanisms and Treatment Outcomes in *Plasmodium falciparum* Malaria

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ABSTRACT

Malaria remained a major global health challenge, with *Plasmodium falciparum* responsible for the most severe and fatal forms of the disease. Artemisinin-based combination therapy has been the cornerstone of *P. falciparum* malaria treatment for over two decades due to its rapid parasite clearance and high clinical efficacy. However, the emergence and spread of artemisinin resistance threatened recent gains in malaria control and elimination. The purpose of this review was to examine the biochemical and molecular mechanisms underlying artemisinin resistance in *P. falciparum* and to evaluate treatment outcomes associated with artemisinin-based combination therapy in both resistant and non-resistant settings. This article was developed through a critical narrative review of published experimental, molecular, and clinical studies on artemisinin pharmacology, resistance markers, and therapeutic outcomes. Current evidence indicates that resistance is mediated primarily through mutations in the kelch13 gene, altered parasite stress responses, and changes in hemoglobin metabolism, leading to delayed parasite clearance. Despite these challenges, artemisinin-based combination therapy continued to demonstrate high cure rates in most endemic regions, although declining efficacy has been reported in parts of Southeast Asia, and emerging signals are being observed in Africa. Sustained surveillance, molecular monitoring, and the development of novel combination strategies were essential to preserve the clinical effectiveness of artemisinin-based therapies and support global malaria elimination efforts.

Keywords: Artemisinin, Combination therapy, *Plasmodium falciparum*, Drug resistance, Malaria treatment.

INTRODUCTION

Malaria is a life-threatening parasitic disease that continues to impose a substantial public health and socioeconomic burden, particularly in sub-Saharan Africa and parts of Southeast Asia [1, 2]. Among the five species of *Plasmodium* known to infect humans, *Plasmodium falciparum* is responsible for the majority of severe malaria cases and malaria-related deaths due to its high replication rate and capacity to cause microvascular obstruction [3]. The introduction of artemisinin-based combination therapy marked a turning point in malaria treatment, dramatically reducing morbidity and mortality worldwide through rapid parasite clearance and improved treatment outcomes.

Artemisinin-based combination therapy combines a fast-acting artemisinin derivative with a longer-acting partner drug, a strategy designed to enhance therapeutic efficacy and delay the emergence of resistance [4, 5]. For many years, these combinations were highly effective across endemic regions. However, the emergence of artemisinin resistance, first documented in Southeast Asia, has raised serious concerns regarding the long-term sustainability of

current malaria treatment strategies. Resistance manifests clinically as delayed parasite clearance and is increasingly linked to specific molecular and biochemical adaptations within the parasite.

The problem of artemisinin resistance poses a significant threat to global malaria control and elimination programs, particularly if resistant strains spread to high transmission regions. Understanding the biochemical basis of artemisinin action, the molecular mechanisms driving resistance, and the clinical implications for treatment outcomes is therefore of critical importance. This review examines the pharmacological rationale of artemisinin-based combination therapy, explores the molecular and cellular mechanisms underlying resistance in *P. falciparum*, evaluates clinical treatment outcomes in resistant and non-resistant settings, and discusses public health implications and future therapeutic strategies. The purpose of this article is to provide an integrated biochemical and clinical perspective that informs research, policy, and malaria treatment practice.

Biochemical Basis and Pharmacological Rationale of Artemisinin-Based Combination Therapy

Artemisinin and its derivatives, including artesunate, artemether, and dihydroartemisinin, are sesquiterpene lactones derived from the plant *Artemisia annua* [6]. Their antimalarial activity is attributed primarily to the presence of an endoperoxide bridge, which is activated within the parasite by iron derived from hemoglobin digestion. This activation generates reactive oxygen species and carbon-centered radicals that damage vital parasite proteins, lipids, and membranes, leading to rapid parasite death.

The pharmacokinetic profile of artemisinin derivatives is characterized by rapid absorption and short plasma half-life [7]. While this property contributes to the swift reduction of parasite biomass, it also necessitates a combination with a longer-acting partner drug to ensure complete parasite clearance. Partner drugs such as lumefantrine, amodiaquine, mefloquine, or piperaquine provide sustained antimalarial activity, eliminating residual parasites and reducing the likelihood of recrudescence.

From a biochemical perspective, combination therapy reduces selective pressure on the parasite by requiring simultaneous resistance to two mechanistically distinct drugs [8]. Artemisinin targets multiple cellular pathways through oxidative damage, while partner drugs often interfere with heme detoxification, nucleic acid synthesis, or membrane transport processes. This complementary pharmacological action underpins the rationale for artemisinin-based combination therapy as a resistance containment strategy and has contributed significantly to its clinical success.

Molecular and Cellular Mechanisms of Artemisinin Resistance in *Plasmodium falciparum*

Artemisinin resistance in *P. falciparum* is a complex phenotype that does not involve complete loss of drug efficacy but rather a reduction in parasite susceptibility, manifested as delayed clearance during treatment [9, 10]. At the molecular level, resistance has been strongly associated with mutations in the kelch13 propeller domain gene. These mutations alter parasite responses to artemisinin-induced oxidative stress, enabling survival during early ring stages of the erythrocytic cycle.

Biochemical studies suggest that resistant parasites enter a quiescent or dormant state upon artemisinin exposure, reducing metabolic activity and limiting drug-induced damage [11]. This adaptive stress response involves upregulation of unfolded protein response pathways, enhanced proteostasis mechanisms, and altered redox homeostasis. As a result, parasites are better equipped to repair damaged proteins and resume growth once drug concentrations decline. Additionally, changes in hemoglobin endocytosis and digestion have been observed in resistant strains, leading to reduced availability of free iron required for artemisinin activation [12]. This biochemical adaptation diminishes radical formation and attenuates drug toxicity. Together, these cellular and molecular mechanisms illustrate how *P. falciparum* exploits metabolic plasticity to survive artemisinin exposure without complete resistance in the classical sense.

Genetic Markers and Biochemical Pathways Associated with Resistance Development

The identification of kelch13 mutations has provided a valuable molecular marker for surveillance of artemisinin resistance [13]. Specific mutations such as C580Y, R539T, and Y493H are strongly associated with delayed parasite clearance and have been widely reported in Southeast Asia [14]. These genetic changes appear to influence ubiquitin-mediated protein degradation pathways, enhancing parasite capacity to manage oxidative and proteotoxic stress.

Beyond kelch13, additional genetic factors are increasingly recognized as contributors to resistance phenotypes. Alterations in genes involved in phosphatidylinositol signaling, autophagy, and mitochondrial metabolism have been implicated in modulating parasite susceptibility [15]. From a biochemical standpoint, these pathways converge on cellular survival mechanisms that mitigate the lethal effects of artemisinin-induced damage.

Importantly, resistance is not solely determined by a single mutation but reflects a multifactorial process shaped by parasite genetics, drug exposure patterns, and host immunity [16]. Ongoing genomic and metabolomic studies

continue to refine the understanding of resistance networks, highlighting the need for integrated molecular surveillance approaches in endemic regions.

Treatment Outcomes and Clinical Efficacy of Artemisinin-Based Combination Therapy

Despite the emergence of resistance, artemisinin-based combination therapy remains highly effective in most malaria-endemic regions. In Africa, where malaria transmission intensity is high, clinical trials continue to demonstrate cure rates exceeding ninety-five percent for recommended combinations [17]. This sustained efficacy is attributed to partial immunity in exposed populations and the continued effectiveness of partner drugs.

In contrast, parts of Southeast Asia have reported declining treatment efficacy of ACT, with increased rates of delayed parasite clearance and treatment failure [18]. These outcomes are closely linked to the high prevalence of kelch13 mutations and resistance to partner drugs such as piperaquine. Clinical consequences include prolonged illness, increased transmission potential, and greater risk of severe disease.

From a treatment perspective, delayed clearance does not always equate to immediate clinical failure, but it signals reduced therapeutic robustness. Monitoring treatment outcomes, adjusting national treatment guidelines, and deploying alternative combinations are essential to mitigate the impact of resistance. The clinical experience underscores the importance of integrating molecular data with therapeutic efficacy studies to guide evidence-based malaria control strategies.

Public Health Implications and Future Therapeutic Strategies

The emergence of artemisinin resistance has profound implications for malaria control and elimination efforts. Resistance threatens to reverse gains achieved through the widespread deployment of effective therapy and places additional strain on already limited health systems [19, 20]. Surveillance programs integrating therapeutic efficacy studies and molecular marker monitoring are, therefore, critical components of resistance containment.

Future strategies must prioritize the development of new antimalarial compounds with novel mechanisms of action, as well as optimization of existing combination therapies. From a biochemical research standpoint, targeting parasite stress response pathways and metabolic vulnerabilities offers promising avenues for drug discovery. Strengthening health systems, ensuring rational drug use, and maintaining high treatment coverage are equally important in limiting resistance spread.

CONCLUSION

Artemisinin-based combination therapy has played a pivotal role in reducing the global burden of *Plasmodium falciparum* malaria through its potent biochemical activity and favorable treatment outcomes. However, the emergence of artemisinin resistance, driven by molecular adaptations and altered parasite stress responses, represents a significant challenge to malaria control efforts. While current therapies remain largely effective, particularly in high transmission regions, declining efficacy in some settings highlights the need for sustained vigilance. Integrating biochemical research, molecular surveillance, and clinical outcome data is essential for informed decision-making and timely intervention. Continued investment in novel antimalarial development and resistance monitoring will be critical to safeguarding the effectiveness of malaria treatment strategies. It is recommended that coordinated global surveillance and research efforts be strengthened to detect resistance early and guide the rational deployment of current and future antimalarial therapies.

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