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Nanoparticle-Based Antimalarials versus Conventional Therapy: Resistance Suppression in *Plasmodium falciparum* Clinical Studies

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ABSTRACT

Malaria caused by *Plasmodium falciparum* remains one of the most pressing public health challenges in sub-Saharan Africa and Southeast Asia. Artemisinin-based combination therapies (ACTs) have reduced mortality substantially over the past two decades, yet partial artemisinin resistance has emerged, threatening long-term control. Pharmacokinetic limitations of conventional antimalarials, such as rapid metabolism and short plasma half-life, create subtherapeutic exposure windows that accelerate resistance selection. Nanoparticle drug delivery systems are being explored to enhance pharmacokinetics, improve efficacy, and suppress resistance emergence. This review evaluates nanoparticle-based antimalarial formulations in comparison with conventional therapies, with emphasis on resistance suppression in *P. falciparum*, particularly in translational and clinical studies. This review synthesizes peer-reviewed studies retrieved from PubMed, Scopus, and Web of Science, focusing on in vitro, in vivo, pharmacokinetic, and clinical evidence related to nanoparticle-formulated artemisinin derivatives and partner drugs. Nanoparticle systems, including liposomes, polymeric nanoparticles, and solid lipid nanoparticles, extend systemic drug exposure by 2–5 fold, increase half-life by up to fourfold, and enhance bioavailability compared with free drug formulations. Preclinical studies show nanoparticle-encapsulated dihydroartemisinin lowers IC50 values against resistant *P. falciparum* strains by 30–70%. Clinical pilot data suggest faster parasite clearance, reduced recrudescence, and delayed resistance emergence. Sustained drug exposure narrows the pharmacological "selection window," reducing survival of resistant parasites. **Conclusion:** Nanoparticle-based antimalarials outperform conventional therapies in prolonging systemic exposure and suppressing resistance, though large-scale randomized trials, cost-effectiveness evaluations, and regulatory frameworks remain necessary before widespread adoption.

Keywords: Malaria, *Plasmodium falciparum*, Nanoparticles, Antimalarial therapy, Resistance suppression

INTRODUCTION

Malaria continues to impose a substantial health burden, with 249 million cases and 608,000 deaths reported worldwide in 2022 [1]. More than 95% of cases occur in sub-Saharan Africa, and children under five years of age account for over 70% of malaria-related mortality [2]. *Plasmodium falciparum*, the most virulent parasite species, is responsible for the majority of these deaths [1]. Global reviews emphasize that malaria remains pervasive, particularly in Africa, due to poverty, weak health systems, and limited access to effective treatments [2,3]. Traditional medicine continues to play a supplementary role in many endemic communities, with medicinal plants widely used to manage malaria symptoms in Uganda and other regions [4]. The introduction of ACTs dramatically reduced malaria morbidity and mortality in the early 2000s [5]. Yet, partial resistance to artemisinin has now been confirmed in Southeast Asia and Africa, characterized by delayed parasite clearance and mutations in the *kelch13* gene [6]. Resistance to ACT partner drugs, such as lumefantrine and piperaquine, has also emerged, further undermining treatment success [7]. The problem is exacerbated by the pharmacokinetic limitations of conventional artemisinin derivatives, which have short half-lives (0.5–2 hours), poor solubility, and variable bioavailability [8]. These limitations create subtherapeutic exposure windows, during which resistant parasites are selectively enriched [9]. Nanoparticle drug delivery systems are being developed to overcome these barriers. By encapsulating

antimalarials in lipid, polymeric, or inorganic carriers, nanoparticles can improve solubility, enhance oral absorption, prolong circulation, and allow controlled drug release [10]. Such modifications hold the potential to sustain therapeutic drug levels, improve efficacy, and suppress resistance selection. This review critically evaluates nanoparticle-based antimalarials compared with conventional therapies, focusing on their potential to suppress resistance in *P. falciparum*. The article explores mechanisms of resistance, nanoparticle delivery platforms, comparative efficacy, pharmacokinetics, safety considerations, translational challenges, and future clinical implications.

Mechanisms of Resistance in *Plasmodium falciparum*

Antimalarial resistance is a multifactorial process involving genetic, pharmacological, and epidemiological drivers. Artemisinin resistance is linked primarily to mutations in the *kelch13* gene, which confer survival advantages to ring-stage parasites under transient drug exposure [6]. These parasites exhibit delayed clearance phenotypes without complete loss of drug sensitivity, enabling survival in the presence of conventional dosing. Partner drug resistance arises from polymorphisms in genes such as *pfcrt* (chloroquine and piperaquine resistance) and *pfmdr1* (lumefantrine and mefloquine resistance) [7]. In high-transmission regions, selective pressure accelerates the spread of resistant alleles when treatment regimens fail to maintain consistent therapeutic drug levels. Pharmacokinetic profiles play a central role in resistance evolution. Conventional artemisinin derivatives are rapidly cleared, with plasma half-lives under two hours [8]. This rapid clearance leaves a prolonged period during which drug concentrations fall within the "selection window" the range in which sensitive parasites are eliminated but partially resistant parasites survive [9,11]. Incomplete adherence to dosing schedules further exacerbates resistance selection. By prolonging exposure above the minimum inhibitory concentration, nanoparticle-based formulations aim to eliminate this selection window. Encapsulation strategies enable sustained release and targeted delivery, ensuring consistent drug pressure that can eradicate both sensitive and tolerant parasite subpopulations.

Nanoparticle Platforms for Antimalarial Delivery

Liposomes

Liposomes are spherical vesicles with phospholipid bilayers that encapsulate both hydrophilic and lipophilic drugs. Liposomal artesunate extended plasma half-life from 1 hour to 5–6 hours in preclinical studies and maintained therapeutic concentrations for over 24 hours [11].

Polymeric Nanoparticles

PLGA nanoparticles are biodegradable carriers that allow controlled release. Encapsulation efficiencies of 80–90% have been reported, with release sustained for up to 48 hours. Artemisinin-loaded PLGA nanoparticles significantly improved stability and reduced burst release compared with free drug [12].

Solid Lipid Nanoparticles (SLNs)

SLNs enhance oral bioavailability through lymphatic absorption. Artemether-SLNs increased bioavailability by 3.5-fold in rats, with higher Cmax and prolonged systemic exposure compared with free drug [13].

Inorganic Nanoparticles

Gold nanoparticles conjugated with artemisinin derivatives improved ROS generation and parasite killing, even in resistant strains [14]. However, their long-term safety and clearance remain unresolved. Collectively, lipid-based and polymeric carriers are the most advanced platforms in translational development, while inorganic nanoparticles are still largely experimental.

Comparative Efficacy: Nanoparticle-Based versus Conventional Therapy

In vitro evidence demonstrates that nanoparticle formulations enhance potency against resistant parasites. Dihydroartemisinin (DHA)-PLGA nanoparticles reduced IC50 values from 12 nM for free DHA to 5–7 nM in resistant *P. falciparum* strains [15]. Liposomal artesunate decreased IC50 by 40–60% relative to free drug [16]. In vivo studies corroborate these findings. Artesunate-SLNs reduced parasitemia by 95% within 72 hours in murine models, compared with 70% for free artesunate [17]. In humanized mouse models, DHA nanoparticles extended survival by over 50% compared with unformulated DHA [18]. Early clinical data are encouraging. A Phase I trial of liposomal artemether-lumefantrine in humans demonstrated faster parasite clearance times (median 36 hours) compared with conventional therapy (median 48 hours) and reduced recrudescence rates [19]. Though sample sizes were small, these results highlight the translational promise of nanoformulations.

Pharmacokinetics and Biodistribution

Pharmacokinetic enhancement is one of the most significant benefits of nanoparticle formulations. Free DHA exhibits a half-life of approximately 1 hour [8]. PLGA nanoparticle encapsulation extended half-life to 3–4 hours and increased AUC by fourfold [15]. Liposomal artesunate increased half-life to 5–6 hours and provided sustained therapeutic concentrations beyond 24 hours [11]. SLNs improved oral absorption, increasing AUC three- to fivefold compared with free drug [13]. Tissue distribution studies revealed that nanoparticles preferentially accumulate in the liver and spleen, the major sites of parasite sequestration, thereby enhancing therapeutic targeting [20]. This altered pharmacokinetic profile addresses two critical shortcomings of conventional formulations: rapid clearance

and uneven tissue penetration. By ensuring consistent exposure, nanoparticles reduce the likelihood of treatment failure and resistance selection.

Resistance Suppression with Nanoparticle-Based Delivery

The primary mechanism by which nanoparticles suppress resistance is through elimination of subtherapeutic exposure windows. Serial passage experiments revealed that DHA nanoparticles delayed resistance emergence beyond 30 generations, compared with 15–20 generations for free DHA [21]. Co-encapsulation of artemisinin derivatives with partner drugs further strengthens resistance suppression. DHA and lumefantrine encapsulated together in liposomes exhibited superior synergy, reducing recrudescence and maintaining therapeutic exposure compared with separate administration [22]. Mathematical models of drug resistance predict that prolonging half-life from 1 to 5 hours reduces the probability of resistance emergence by 40–60% in high-transmission settings [23]. These data highlight the pharmacological potential of nanoparticle formulations to extend the useful lifespan of existing antimalarials.

Safety and Translational Challenges

Preclinical safety studies of lipid and polymeric nanoparticles demonstrate acceptable tolerability, with no significant hepatic or renal toxicity at therapeutic doses [24]. Mild, transient elevations in liver enzymes have been reported but without long-term effects [25]. Inorganic systems such as gold nanoparticles present unresolved safety challenges, including risk of accumulation and immunogenicity [14]. Translational barriers remain substantial. Manufacturing reproducibility is a challenge due to variability in nanoparticle size and drug loading [26]. Stability in tropical conditions is critical, yet many nanoparticle formulations require refrigeration [27]. Production costs are higher than conventional formulations, potentially limiting accessibility [28]. Regulatory frameworks for nanomedicines are evolving but remain incomplete, especially for infectious diseases in low-resource settings [27].

Future Directions and Clinical Implications

Future research must focus on Phase II and III clinical trials in endemic regions to validate efficacy, safety, and resistance suppression benefits of nanoparticle formulations. Pediatric trials are especially important given the disproportionate malaria burden in children under five [2]. Technological innovations should prioritize thermostable nanoparticle formulations for use in tropical regions without robust cold-chain infrastructure. Advances in microfluidic nanoparticle manufacturing offer scalable, cost-efficient production methods [28]. Pharmacoeconomic studies will be essential to establish cost-effectiveness compared with ACTs. Integration into national malaria control programs requires alignment with existing distribution and surveillance networks. By extending drug half-lives and reducing recrudescence, nanoparticles could decrease treatment frequency, improve adherence, and slow resistance spread. If successfully implemented, nanoparticle-based formulations could extend the clinical lifespan of current antimalarials and reduce the urgent pressure for new drug discovery, thereby supporting long-term malaria elimination strategies.

CONCLUSION

Resistance in *Plasmodium falciparum* threatens global malaria control efforts and undermines the gains achieved by ACTs. Conventional artemisinin therapies are hampered by pharmacokinetic weaknesses, including short half-lives and inconsistent oral absorption, which create subtherapeutic exposure windows that enable resistant parasites to survive. Nanoparticle-based delivery systems offer a promising strategy to address these limitations by improving solubility, extending systemic exposure, enhancing bioavailability, and enabling preferential targeting of infected tissues. Preclinical studies consistently demonstrate that nanoparticle-encapsulated antimalarials achieve superior pharmacokinetics, lower IC50 values, improved clearance of parasitemia, and delayed resistance emergence compared with free drug formulations. Early clinical data suggest faster clearance times and reduced recrudescence, although large-scale validation in endemic populations is urgently needed. Safety studies indicate favorable tolerability for lipid and polymeric platforms, though challenges remain with manufacturing reproducibility, thermostability, regulatory adaptation, and affordability. Nanoparticle-based therapies represent an innovative adjunct to conventional ACTs and hold promise as a resistance-suppressing intervention in malaria-endemic regions. If barriers to scalability and affordability can be overcome, these technologies may become integral to malaria elimination strategies. Researchers should prioritize randomized controlled trials of nanoparticle-based antimalarials in endemic pediatric and adult populations to confirm their role in resistance suppression.

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