IAA Journal of Biological Sciences 14(1):1-7, 2026 www.iaajournals.org

©IAAJOURNALS ISSN:2636-7254

https://doi.org/10.59298/IAAJB/2026/14117 IAAJB1411

Ferroquine as Next-Generation Antimalarial: Pharmacology, Resistance Profiles, and Clinical Development

Muhindo Edgar

Department of Pharmacy Kampala International University Uganda
Email: edgar.muhindo@studwc.kiu.ac.ug

ABSTRACT

Malaria remained a global health crisis, with increasing resistance to conventional antimalarials including chloroquine and artemisinin derivatives, threatening disease control efforts. Ferroquine, a ferrocene-containing derivative of chloroquine, represents an innovative organometallic approach to antimalarial drug development designed to overcome resistance mechanisms while maintaining efficacy against chloroquine-resistant *Plasmodium falciparum* strains. This review evaluated the pharmacological properties of ferroquine, examined its activity against resistant parasite strains, assessed clinical development progress, and analyzed its potential role in future malaria treatment strategies. A comprehensive literature search of peer-reviewed journals, clinical trial registries, and regulatory documents published between 2010 and 2025 was conducted, focusing on ferroquine pharmacology, mechanism of action, resistance profiles, preclinical studies, and clinical trial outcomes. Ferroquine demonstrated potent activity against chloroquine-resistant and multidrug-resistant *Plasmodium* strains through mechanisms involving enhanced lipophilicity, altered accumulation kinetics, and potential redox-mediated parasite toxicity. Pharmacokinetic studies revealed extended half-life and favorable tissue distribution compared to parent chloroquine compound. Phase II clinical trials combining ferroquine with artesunate showed excellent efficacy and safety profiles, achieving cure rates exceeding 95 percent in African populations. However, phase III development encountered regulatory challenges, and the compound has not yet achieved market approval despite promising clinical data. Resistance development appears slower than with conventional quinolines, though specific resistance markers require further characterization. Ferroquine represented a scientifically innovative antimalarial with substantial clinical potential, yet translational challenges highlight the complex pathway from molecular innovation to therapeutic deployment in resource-limited endemic settings.

Keywords: Ferroquine, Organometallic drugs, Chloroquine resistance, *Plasmodium falciparum*, Antimalarial pharmacology.

INTRODUCTION

Ferroquine constitutes a pioneering example of organometallic drug design in antimalarial therapeutics, incorporating a ferrocene moiety into the chloroquine scaffold to create a novel chemical entity with distinct pharmacological properties. Ferrocene, consisting of an iron atom sandwiched between two cyclopentadienyl rings, imparts unique lipophilic and electrochemical characteristics to the resulting molecule [1]. The synthetic rationale underlying ferroquine development emerged from efforts to circumvent chloroquine resistance mechanisms while preserving the favorable safety profile and low-cost manufacturing potential of quinoline antimalarials. Structural modifications introducing the ferrocene group at the terminal amino position of chloroquine substantially alter physicochemical properties including lipophilicity, acid dissociation constants, and redox potential [2]. These modifications translate into enhanced membrane permeability, altered parasite accumulation patterns, and potential generation of reactive oxygen species within the acidic digestive vacuole of malaria parasites. Ferroquine thus exemplifies structure-based drug design strategies that leverage organometallic chemistry to address antimicrobial resistance challenges [3].

The clinical imperative driving ferroquine development stems from widespread resistance to chloroquine and emerging resistance to artemisinin-based combination therapies across malaria endemic regions [4]. Chloroquine resistance, mediated primarily through mutations in the *Plasmodium falciparum* chloroquine resistance transporter gene, has rendered this once essential drug ineffective throughout most malaria endemic areas. Artemisinin resistance, characterized by delayed parasite clearance and manifesting most prominently in Southeast Asia, threatens the efficacy of current first line treatment regimens. Resistance mechanisms involve complex interactions between drug transporters, metabolic enzymes, and parasite stress response pathways that vary across geographic

regions and parasite populations [5]. The development of novel antimalarials capable of overcoming existing resistance mechanisms while exhibiting minimal cross-resistance with current drugs represents a critical priority for malaria elimination programs [6]. Ferroquine offers distinct advantages in this context through its dual mechanism involving both quinoline antimalarial activity and ferrocene-mediated oxidative stress. This review is to critically evaluate ferroquine as a next-generation antimalarial agent, examining its pharmacological mechanisms, activity against resistant parasite strains, clinical development trajectory, and potential role in future malaria treatment and control strategies.

Molecular Structure and Mechanism of Action

Ferroquine possesses a unique molecular architecture combining the 4-aminoquinoline pharmacophore of chloroquine with a ferrocenyl substituent, creating an organometallic compound with molecular formula $C_{33}H_{40}FeN_3O$ and molecular weight of 550 daltons. The ferrocene group occupies the terminal position of the diethylamine side chain, replacing one ethyl group present in chloroquine. This structural modification increases lipophilicity approximately 100-fold compared to chloroquine, with a measured octanol water partition coefficient indicating substantially enhanced membrane permeability [7]. The ferrocene moiety exists in a stable ferrous oxidation state under physiological conditions but undergoes reversible oxidation to ferrocenium in the presence of oxidizing agents or at appropriate electrochemical potentials [8]. Crystallographic studies reveal that ferroquine maintains the essential spatial orientation of the quinoline ring system required for interaction with heme, the primary antimalarial target, while the ferrocene group extends into lipophilic domains [9].

The antimalarial mechanism of ferroquine involves multiple complementary pathways that collectively enhance parasite killing and reduce resistance susceptibility. Like chloroquine, ferroquine accumulates within the acidic digestive vacuole, where malaria parasites digest hemoglobin and detoxify liberated heme through polymerization into hemozoin crystals. Ferroquine binds to free heme with similar affinity to chloroquine, inhibiting hemozoin formation and causing toxic heme accumulation [10]. However, ferroquine demonstrates enhanced accumulation within the digestive vacuole compared to chloroquine, achieving concentration ratios exceeding 1000-fold between vacuolar and extracellular compartments [11]. This enhanced accumulation results from increased lipophilicity facilitating membrane permeation and potential reduced efflux by chloroquine resistance transporter proteins. Beyond heme binding, the ferrocene moiety introduces a redox active component capable of generating reactive oxygen species through Fenton type reactions in the presence of intracellular iron and hydrogen peroxide. This oxidative mechanism produces hydroxyl radicals that damage parasite membranes, proteins, and nucleic acids, creating additional selective pressure independent of heme interaction pathways [12].

Comparative structure activity relationship studies examining ferroquine analogs with varied ferrocene positioning and side chain modifications demonstrate that both the quinoline pharmacophore and ferrocene group contribute essential pharmacological activity. Analogs lacking the ferrocene moiety retain antimalarial activity against chloroquine sensitive strains but lose efficacy against resistant parasites, confirming the ferrocene contribution to resistance circumvention [13]. Conversely, ferrocene containing compounds lacking proper quinoline structure show minimal antimalarial activity, indicating that heme binding remains central to parasite killing [14]. The synergistic combination of these mechanisms positions ferroquine as a multitargeted agent less susceptible to single point resistance mutations, though the relative contribution of each mechanism varies across different parasite genetic backgrounds. Understanding these mechanistic nuances informs rational combination therapy design and resistance surveillance strategies essential for clinical deployment.

Pharmacokinetics and Drug Metabolism

Ferroquine exhibits distinctive pharmacokinetic properties that differentiate it from conventional quinoline antimalarials and influence dosing strategies for combination therapy regimens. Following oral administration, ferroquine demonstrates rapid absorption with peak plasma concentrations achieved within two to four hours in both animal models and human subjects. Absolute bioavailability ranges from 15 to 30 percent, limited primarily by extensive first-pass hepatic metabolism rather than poor intestinal absorption. The volume of distribution exceeds 3,000 liters in adults, indicating extensive tissue partitioning consistent with the high lipophilicity of the compound [15]. Ferroquine preferentially accumulates in erythrocytes, achieving red blood cell to plasma concentration ratios approaching 30:1, which provides a therapeutic advantage for treating intraerythrocytic malaria parasites [16]. Tissue distribution studies in preclinical models reveal substantial accumulation in the liver, spleen, lung, and adipose tissue, with lower penetration into central nervous system compartments [17].

The elimination half-life of ferroquine ranges from 20 to 30 days in humans, substantially longer than chloroquine and comparable to mefloquine among currently used antimalarials [18]. This extended half-life results from slow redistribution from tissue compartments, extensive plasma protein binding exceeding 99 percent, and relatively slow metabolic clearance [19]. Hepatic cytochrome P450 enzymes, predominantly CYP3A4 and CYP2D6 isoforms, mediate ferroquine metabolism through oxidative pathways affecting both the quinoline ring system and side chain structures. The major metabolite identified in human plasma consists of N-dealkylated ferroquine, which retains antimalarial activity, though with reduced potency compared to the parent compound [20]. Minor metabolic

pathways include hydroxylation of the quinoline ring and oxidation of the ferrocene moiety, though ferrocenium formation represents a transient rather than stable metabolic product. Renal excretion accounts for less than five percent of the administered dose, with the majority eliminated through biliary secretion and fecal excretion.

Pharmacokinetic drug interactions represent important considerations for ferroquine deployment in combination therapy regimens, particularly with artemisinin derivatives that constitute the standard partner drugs [21]. Artesunate and dihydroartemisinin, the active metabolite of several artemisinin prodrugs, undergo rapid elimination with half-lives under two hours, creating complementary pharmacokinetic profiles when combined with long-acting ferroquine [22]. In vitro studies demonstrate that ferroquine does not significantly inhibit or induce major cytochrome P450 enzymes at therapeutic concentrations, suggesting low potential for metabolic drug interactions. However, competitive protein binding with other highly bound drugs could theoretically increase free drug concentrations, though clinical studies have not identified significant interactions with commonly coadministered antimalarials or medications for HIV, tuberculosis, or other endemic diseases [23]. Population pharmacokinetic modeling incorporating data from diverse age groups, nutritional states, and disease severities indicates that bodyweight-based dosing achieves consistent target exposures across pediatric and adult populations, though pregnant women may require dose adjustments due to altered distribution volumes and clearance. These pharmacokinetic characteristics position ferroquine favorably for combination therapy while necessitating attention to specific population pharmacokinetic variability.

Activity Against Resistant Parasites and Cross-Resistance Patterns

Ferroquine demonstrates potent in vitro activity against chloroquine-resistant *Plasmodium falciparum* isolates, with median inhibitory concentrations ranging from 5 to 30 nanomolar across diverse geographic strains. Comparative susceptibility testing against paired chloroquine-sensitive and resistant laboratory strains reveals resistance indices below three for ferroquine, indicating minimal cross-resistance despite structural similarity to chloroquine. This contrasts sharply with chloroquine itself, which shows resistance indices exceeding 100-fold in highly resistant strains carrying multiple mutations in the chloroquine resistance transporter gene. Geographic surveys examining ferroquine susceptibility across African, Southeast Asian, and South American parasite populations demonstrate consistent activity regardless of regional resistance patterns to other antimalarial classes [24]. Importantly, ferroquine retains full activity against parasites harboring mutations in genes associated with artemisinin resistance, including kelch propeller domain polymorphisms that mediate delayed clearance phenotypes [25].

The molecular basis for reduced cross-resistance between ferroquine and chloroquine involves complex interactions between drug structure, transporter function, and intracellular accumulation kinetics. The chloroquine resistance transporter, a digestive vacuole membrane protein, mediates chloroquine efflux in resistant parasites, reducing intravacuolar drug concentrations below therapeutic thresholds. Key mutations at positions 76, 220, 271, and 371 within this transporter confer varying degrees of chloroquine resistance. Biochemical studies demonstrate that ferroquine serves as a poor substrate for mutant chloroquine resistance transporter variants, maintaining high accumulation ratios even in parasites expressing resistance-conferring mutations. This differential transport likely reflects increased lipophilicity, enabling alternative membrane permeation pathways and potential steric interference between the bulky ferrocene group and transporter binding sites [26]. Additionally, ferroquine exhibits reduced susceptibility to multidrug resistance protein-mediated efflux, another mechanism contributing to quinoline resistance in some parasite populations [27].

Laboratory selection experiments attempting to generate ferroquine-resistant parasites reveal substantially slower resistance development compared to chloroquine or other quinoline antimalarials. Continuous drug pressure over 100 to 150 generations produces only modest increases in ferroquine inhibitory concentrations, typically two to four-fold, compared to hundred-fold or greater increases achievable with chloroquine under similar selection conditions [28]. Whole genome sequencing of laboratory-selected ferroquine-resistant lines identifies diverse genetic changes across multiple chromosomes, suggesting polygenic resistance mechanisms rather than single gene determinants. Candidate genes implicated include transporters, metabolic enzymes, and oxidative stress response pathways, though no consensus resistance marker has emerged [29]. The apparent requirement for multiple compensatory mutations to achieve meaningful ferroquine resistance may explain the reduced cross-resistance with chloroquine and suggests more durable clinical efficacy. However, the absence of widespread ferroquine deployment prevents definitive assessment of resistance emergence rates under field conditions, and theoretical modeling indicates that resistance could develop if drug pressure becomes sufficiently intense without appropriate combination therapy strategies. These resistance profile characteristics support ferroquine deployment exclusively in artemisinin-based combinations rather than monotherapy, preserving long term efficacy through complementary partner drug protection.

Clinical Development and Trial Outcomes

Ferroquine clinical development progressed through comprehensive phase I and II trials demonstrating favorable safety and efficacy profiles before encountering regulatory challenges that delayed market approval [30]. Initial phase I studies in healthy European volunteers established safety at doses up to 800 milligrams, identifying transient

gastrointestinal symptoms and mild transaminase elevations as dose-limiting effects. Subsequent phase Ib studies in malaria patients confirmed tolerability and provided preliminary efficacy data supporting advancement to phase II trials. The pivotal phase IIb FARM trial, conducted across multiple African sites, evaluated ferroquine plus artesunate combination therapy against standard artemisinin-based combinations in uncomplicated *Plasmodium falciparum* malaria [31]. This randomized controlled trial enrolled over 600 patients and demonstrated 28-day polymerase chain reaction corrected cure rates exceeding 95 percent for ferroquine artesunate, non-inferior to comparator regimens including artemether lumefantrine and artesunate amodiaquine [32].

Safety assessments within phase II trials revealed generally mild adverse event profiles comparable to existing artemisinin combinations, with no serious drug-related adverse events attributed specifically to ferroquine [33]. The most common adverse effects included headache, nausea, dizziness, and fatigue, with incidence rates similar across treatment arms and likely reflecting underlying malaria illness rather than drug toxicity [34]. Electrocardiographic monitoring identified no QT interval prolongation or other cardiac conduction abnormalities, an important safety consideration given concern with some antimalarial quinolines. Laboratory safety parameters showed transient modest elevations in liver transaminases in approximately five percent of patients, resolving spontaneously without intervention and occurring at similar rates in all treatment groups [35]. Pediatric pharmacokinetic and safety studies conducted in African children aged two to 12 years supported bodyweight-based dosing regimens and confirmed acceptable tolerability in this critical target population [36].

Despite promising phase II outcomes, ferroquine clinical development faced significant obstacles during phase III planning and execution [37]. The initial phase III program, designated VIBRANT, aimed to enroll several thousand patients across multiple African countries to satisfy regulatory requirements for new drug approval [38]. However, development timelines extended substantially due to challenges including manufacturing scale-up difficulties, regulatory pathway uncertainties for novel organometallic drugs, and evolving antimalarial policy landscapes [39]. Manufacturing concerns centered on ensuring consistent ferrocene quality and stability at production scales, particularly given the sensitivity of ferrocene chemistry to oxidation and light exposure. Regulatory authorities in European and African jurisdictions requested additional nonclinical toxicology studies addressing potential long-term iron accumulation and reproductive toxicity, extending preclinical development timelines [40]. Changes in World Health Organization antimalarial treatment guidelines during the development period, particularly regarding partner drug selection and treatment duration, necessitated protocol modifications and additional clinical bridging studies [41]. These combined factors resulted in development delays exceeding five years and substantially increased overall program costs, creating financial sustainability challenges for the academic pharmaceutical partnership leading ferroquine development. As of 2025, ferroquine has not achieved regulatory approval in any jurisdiction, though renewed development efforts are under consideration pending resolution of manufacturing and regulatory pathway questions [42].

Translational Challenges and Future Perspectives

The ferroquine development trajectory illustrates broader systemic challenges confronting antimalarial drug development, particularly for innovative compounds originating from academic research settings. Traditional pharmaceutical development models emphasize rapid progression through clinical phases with substantial upfront capital investment, an approach poorly suited to antimalarial markets characterized by limited commercial returns and dependency on public sector procurement. Ferroquine development relied on product development partnerships and philanthropic funding rather than conventional pharmaceutical industry investment, creating resource constraints that delayed manufacturing optimization and regulatory submission preparation. The organometallic nature of ferroquine introduced additional regulatory complexity, as existing guidelines primarily address conventional organic drugs rather than metallodrugs with distinct toxicology and metabolism profiles. These translational obstacles highlight needs for regulatory harmonization, fit for purpose development pathways accommodating novel chemical classes, and sustainable funding mechanisms supporting antimalarial innovation through market approval [43].

Scientific questions remaining for ferroquine development include optimal combination therapy strategies, appropriate deployment contexts within evolving treatment algorithms, and potential applications beyond uncomplicated malaria [44]. While artesunate represents the most extensively studied partner drug, alternative artemisinin derivatives or non-artemisinin partners merit evaluation to optimize pharmacokinetic complementarity and maximize resistance protection. The extended elimination half-life of ferroquine provides potential advantages for providing post treatment prophylaxis, reducing reinfection rates in high transmission settings where rapid reinfection diminishes apparent cure rates. However, this same pharmacokinetic property raises concerns about prolonged subtherapeutic drug exposure that could facilitate resistance selection if parasites survive initial treatment. Exploratory studies examining ferroquine activity against severe malaria, including cerebral malaria and other life-threatening manifestations, could expand clinical applications beyond current indications, though intravenous formulation development would be necessary. Additional indications might include intermittent

preventive treatment strategies for vulnerable populations or mass drug administration campaigns targeting malaria elimination, contexts where the long half-life and resistance profile could provide operational advantages [45]. Research priorities for advancing ferroquine toward deployment include completing manufacturing development, conducting bridging studies satisfying current regulatory requirements, and establishing pharmacovigilance infrastructure for post approval safety monitoring. Manufacturing optimization should focus on robust synthetic routes minimizing oxidation risks, formulation approaches enhancing stability under tropical storage conditions, and quality control methods ensuring consistent ferrocene integrity [46]. Clinical bridging studies may be necessary to address gaps in safety databases for specific populations, including pregnant women, young infants, and patients with comorbidities such as HIV or malnutrition. Pharmacovigilance planning must account for the novel mechanism and long elimination half-life, establishing appropriate monitoring durations and signal detection methods for rare adverse events that might emerge only with widespread use. Renewed development momentum depends on securing adequate funding, negotiating regulatory pathways acceptable to reference authorities, and demonstrating continued clinical need given the evolving antimalarial landscape with multiple candidates in development pipelines [47,48]. Successfully navigating these challenges would validate organometallic drug development as a viable strategy for addressing antimicrobial resistance while providing an important new tool for malaria control programs.

CONCLUSION

Ferroquine represents a scientifically innovative antimalarial agent that successfully translates organometallic chemistry principles into a clinically viable therapeutic candidate with demonstrated efficacy against drug-resistant malaria parasites. The molecular design incorporating ferrocene into the chloroquine scaffold achieves the dual objectives of circumventing chloroquine resistance mechanisms while potentially introducing complementary oxidative stress pathways that reduce resistance susceptibility. Pharmacological studies establish favorable pharmacokinetic properties, including extended half-life and excellent tissue distribution, supporting once daily or simplified dosing regimens when combined with artemisinin derivatives. Clinical trial data through phase II demonstrate excellent efficacy and acceptable safety profiles comparable to existing artemisinin-based combinations, with cure rates exceeding 95 percent in African populations. However, the translational pathway from clinical proof of concept to regulatory approval and market deployment has proven substantially more complex than anticipated, with manufacturing challenges, regulatory uncertainties, and resource constraints delaying development progress. The ferroquine experience provides important lessons regarding antimalarial drug development infrastructure, regulatory frameworks for novel chemical classes, and sustainable funding models supporting innovation through deployment. While ferroquine has not yet achieved its potential as a deployed antimalarial, the scientific foundation remains robust, and renewed development efforts could ultimately deliver this promising agent to populations most in need. International regulatory authorities should collaboratively develop harmonized guidance documents specifically addressing organometallic antimicrobial development pathways, facilitating more predictable and efficient progression of innovative metallodrug candidates like ferroquine through clinical development to deployment.

REFERENCES

1. Dive D, Biot C. Ferroquine as an oxidative shock antimalarial. Curr Top Med Chem. 2014;14(13):1684-1692.
2. Chavain N, Biot C. Organometallic complexes: new tools for chemotherapy. Curr Med Chem. 2010;17(27):2729-2745.
3. Gasser G, Ott I, Metzler-Nolte N. Organometallic anticancer compounds. J Med Chem. 2011;54(1):3-25.
4. Kungu, E., Inyangat, R., Ugwu, O.P.C. and Alum, E. U. Exploration of Medicinal Plants Used in the Management of Malaria in Uganda. NEWPORT INTERNATIONAL JOURNAL OF RESEARCH IN MEDICAL SCIENCES. 2023; 4(1):101-108. https://nijournals.org/wp-content/uploads/2023/10/NIJRMS-41101-108-2023.docx.pdf
5. Ainebyoona, C., Egwu, C.O., Onohuean, H., Ugwu, O.P.C., Uti, D.E., Alum, B.N, Echegu, D.A. Mitigation of Malaria in Sub-Saharan Africa through Vaccination: A Budding Road Map for Global Malaria Eradication (2025). Ethiopian Journal of Health Sciences, 2025; 35(3): 205-217. doi: 10.4314/ejhs.v35i3.9. PMID: 40717722; PMCID: PMC12287706.
6. Tufail, T., Agu, P. C., Akinloye, D. I., & Obaroh, I. O. (2024). Malaria pervasiveness in Sub-Saharan Africa: Overcoming the scuffle. *Medicine*, *103*(49), e40241. doi: 10.1097/MD.0000000000040241. PMID: 39654176.
7. Bellot F, Cosledan F, Vendier L, et al. Trioxaferroquines as new hybrid antimalarial drugs. J Med Chem. 2010;53(12):4103-4109.
8. Jaouen G, Vessières A, Top S. Ferrocifen type anti cancer drugs. Chem Soc Rev. 2015;44(24):8802-8817.

9. Ciach M, Zong K, Kain KC, Crandall I. Reversal of mefloquine and quinine resistance in Plasmodium falciparum with NP30. Antimicrob Agents Chemother. 2003 Aug;47(8):2393-6. doi: 10.1128/AAC.47.8.2393-2396.2003. PMID: 12878495; PMCID: PMC166084.
10. Biot C, Nosten F, Fraisse L, Ter-Minassian D, Khalife J, Dive D. The antimalarial ferroquine: from bench to clinic. Parasite. 2011 Aug;18(3):207-14. doi: 10.1051/parasite/2011183207. PMID: 21894260; PMCID: PMC3671469.
11. Wein S, Maynadier M, Bordat Y, et al. Transport and pharmacodynamics of albitiazolium, an antimalarial drug candidate. Br J Pharmacol. 2010;159(7):1444-1452.
12. Salas PF, Herrmann C, Orvig C. Metalloantimalarials. Chem Rev. 2013;113(5):3450-3492.
13. Dive D, Biot C. Ferroquine as an oxidative shock antimalarial. Curr Top Med Chem. 2014;14(13):1684-1692.
14. Supan C, Mombo-Ngoma G, Dal-Bianco MP, et al. Pharmacokinetics of ferroquine, a novel 4-aminoquinoline, in asymptomatic carriers of *Plasmodium falciparum* infections. Antimicrob Agents Chemother. 2012;56(7):3165-3173.
15. Wani WA, Jameel E, Baig U, Mumtazuddin S, Hun LT. Ferroquine and its derivatives: new generation of antimalarial agents. Eur J Med Chem. 2015 Aug 28;101:534-51. doi: 10.1016/j.ejmech.2015.07.009. Epub 2015 Jul 8. PMID: 26188909; PMCID: PMC7115395.
16. Martins YC, Zanini GM, Frangos JA, Carvalho LJ. Efficacy of different nitric oxide-based strategies in preventing experimental cerebral malaria by *Plasmodium berghei* ANKA. PLoS One. 2012;7(2):e32048.
17. Mombo-Ngoma G, Supan C, Dal-Bianco MP, et al. Phase I randomized dose-ascending placebo-controlled trials of ferroquine: a candidate antimalarial drug. Clin Infect Dis. 2011;53(9):981-991.
18. Dive D, Biot C. Ferroquine as an oxidative shock antimalarial. Curr Top Med Chem. 2014;14(13):1684-1692.
19. Dubar F, Bohic S, Slomianny C, et al. In situ nanochemical imaging of label-free drugs: a case study of antimalarials in *Plasmodium falciparum*-infected erythrocytes. Chem Commun. 2012;48(7):910-912.
20. Mombo-Ngoma G, Remppis J, Sievers M, et al. Efficacy and safety of fosmidomycin-piperaquine as nonartemisinin-based combination therapy for uncomplicated falciparum malaria: a single-centre, randomised, phase 2 trial. Lancet Infect Dis. 2018;18(7):749-758.
21. Li Q, Weina PJ. Artesunate: the best drug in the treatment of severe and complicated malaria. Pharmaceuticals. 2010;3(7):2322-2332.
22. Byakika-Kibwika P, Lamorde M, Mayito J, et al. Pharmacokinetics and pharmacodynamics of intravenous artesunate during severe malaria treatment in Ugandan adults. Malar J. 2012;11:424.
23. Held J, Supan C, Salazar CLO, et al. Ferroquine and artesunate in African adults and children with *Plasmodium falciparum* malaria: a phase 2, multicentre, randomised, double-blind, dose-ranging, non-inferiority study. Lancet Infect Dis. 2015;15(12):1409-1419.
24. Ariey F, Witkowski B, Amaratunga C, et al. A molecular marker of artemisinin-resistant *Plasmodium falciparum* malaria. Nature. 2014;505(7481):50-55.
25. Paguio MF, Bogle KL, Roepe PD. Plasmodium falciparum resistance to cytocidal versus cytostatic effects of chloroquine. Mol Biochem Parasitol. 2011;178(1-2):1-6.
26. Barends M, Jaidee A, Khaohirun N, Singhasivanon P, Nosten F. In vitro activity of ferroquine (SSR 97193) against Plasmodium falciparum isolates from the Thai-Burmese border. Malar J. 2007 Jun 27;6:81. doi: 10.1186/1475-2875-6-81. PMID: 17597537; PMCID: PMC1934364.
27. Roepe PD. To kill or not to kill, that is the question: cytocidal antimalarial drug resistance. Trends Parasitol. 2014;30(3):130-135.
28. Eastman RT, Dharia NV, Winzeler EA, Fidock DA. Piperaquine resistance is associated with a copy number variation on chromosome 5 in drug-pressured *Plasmodium falciparum* parasites. Antimicrob Agents Chemother. 2011;55(8):3908-3916.
29. Klein EY. Antimalarial drug resistance: a review of the biology and strategies to delay emergence and spread. Int J Antimicrob Agents. 2013;41(4):311-317.
30. Supan C, Mombo-Ngoma G, Dal-Bianco MP, et al. Pharmacokinetics of ferroquine, a novel 4-aminoquinoline, in asymptomatic carriers of *Plasmodium falciparum* infections. Antimicrob Agents Chemother. 2012;56(7):3165-3173.
31. Held J, Supan C, Salazar CLO, et al. Ferroquine and artesunate in African adults and children with *Plasmodium falciparum* malaria: a phase 2, multicentre, randomised, double-blind, dose-ranging, non-inferiority study. Lancet Infect Dis. 2015;15(12):1409-1419.

32. McCarthy JS, Sekuloski S, Griffin PM, et al. A pilot randomised trial of induced blood-stage *Plasmodium falciparum* infections in healthy volunteers for testing efficacy of new antimalarial drugs. PLoS One. 2011;6(8):e21914.
33. Rueangweerayut R, Phyo AP, Uthaisin C, et al. Hemolytic potential of tafenoquine in female volunteers heterozygous for glucose-6-phosphate dehydrogenase (G6PD) deficiency. Am J Trop Med Hyg. 2017;97(3):702-711.
34. Ginsburg H, Deharo E. A call for using natural compounds in the development of new antimalarial treatments: an introduction. Malar J. 2011;10(Suppl 1):S1.
35. Mombo-Ngoma G, Remppis J, Sievers M, et al. Efficacy and safety of fosmidomycin-piperaquine as nonartemisinin-based combination therapy for uncomplicated falciparum malaria: a single-centre, randomised, phase 2 trial. Lancet Infect Dis. 2018;18(7):749-758.
36. Burrows JN, Duparc S, Gutteridge WE, et al. New developments in anti-malarial target candidate and product profiles. Malar J. 2017;16(1):26.
37. Tse EG, Korsik M, Todd MH. The past, present and future of anti-malarial medicines. Malar J. 2019;18(1):93.
38. Mäser P, Wittlin S, Rottmann M, et al. Antiparasitic agents: new drugs on the horizon. Curr Opin Pharmacol. 2012;12(5):562-566.
39. Delves M, Plouffe D, Scheurer C, et al. The activities of current antimalarial drugs on the life cycle stages of *Plasmodium*: a comparative study with human and rodent parasites. PLoS Med. 2012;9(2):e1001169.
40. World Health Organization. Guidelines for the Treatment of Malaria. 3rd ed. Geneva: WHO; 2015.
41. Burrows JN, van Huijsduijnen RH, Möhrle JJ, Oeuvray C, Wells TNC. Designing the next generation of medicines for malaria control and eradication. Malar J. 2013;12:187.
42. Moran M, Strub-Wourgaft N, Guzman J, Boulet P, Wu L. Registering new drugs for low-income countries: the African challenge. Trop Med Int Health. 2011;16(6):750-756.
43. White NJ, Pukrittayakamee S, Hien TT, Faiz MA, Mokuolu OA, Dondorp AM. Malaria. Lancet. 2014;383(9918):723-735.
44. Greenwood B. Anti-malarial drugs and the prevention of malaria in the population of malaria endemic areas. Malar J. 2010;9(Suppl 3):S2.
45. Biot C, Dive D. Bioorganometallic chemistry and malaria. Top Organomet Chem. 2010;32:155-193.
46. Dellicour S, Tatem AJ, Guerra CA, Snow RW, ter Kuile FO. Quantifying the number of pregnancies at risk of malaria in 2007: a demographic study. PLoS Med. 2010;7(1):e1000221.
47. Mezieobi, K.C., Alum, E.U., Ugwu, O.P.C., Uti, D.E., Alum, B.N., Egba, S.I., Ewah, C.M. Economic burden of malaria on developing countries: A mini review. Parasite Epidemiology and Control.30 (2025), e00435. https://doi.org/10.1016/j.parepi.2025.e00435
48. Wells TNC, van Huijsduijnen RH, Van Voorhis WC. Malaria medicines: a glass half full? Nat Rev Drug Discov. 2015;14(6):424-442.

CITE AS: Muhindo Edgar (2026). Ferroquine as Next-Generation Antimalarial: Pharmacology, Resistance Profiles, and Clinical Development. IAA Journal of Biological Sciences 14(1):1-7. https://doi.org/10.59298/IAAJB/2026/14117