EURASIAN EXPERIMENT JOURNAL OF MEDICINE AND MEDICAL SCIENCES (EEJMMS)
ISSN: 2992-4103
©EEJMMS Publications Volume 7 Issue 1 2025

Artemisinin Resistance Mechanisms in Plasmodium falciparum: Molecular Pathways and Clinical Implications

Asiimawe Masika Agnovia

Department of Clinical Medicine and Dentistry Kampala International University Uganda
agnovia.asiimawe@studwc.kiu.ac.ug

ABSTRACT

Artemisinin-based combination therapies (ACTs) represent the cornerstone of contemporary falciparum malaria treatment worldwide. However, the emergence and spread of artemisinin-resistant Plasmodium falciparum strains pose significant threats to global malaria elimination efforts. This review examines current understanding of artemisinin resistance mechanisms in P. falciparum, focusing on molecular pathways, biomarkers, and clinical implications for therapeutic management. A comprehensive literature search was conducted using PubMed, Scopus, and Web of Science databases (2012-2025), with emphasis on peer-reviewed studies examining Kelch13 mutations, resistance mechanisms, and clinical outcomes. Artemisinin resistance primarily involves mutations in the Kelch13 (K13) protein, particularly in the propeller domain, leading to reduced hemoglobin endocytosis and altered parasite stress responses. The most prevalent resistance-conferring mutations include C580Y, R539T, and Y493H, which demonstrate variable geographic distribution and fitness costs. Resistance mechanisms encompass disrupted endocytic pathways, enhanced unfolded protein response activation, and modified phosphatidylinositol 3-phosphate signaling. Clinical manifestations include delayed parasite clearance times, with clearance half-life (t1/2) values exceeding 5 hours, indicating resistance. Understanding artemisinin resistance mechanisms is crucial for developing next-generation antimalarials and optimizing current therapeutic strategies. Continued molecular surveillance and development of alternative therapeutic approaches remain paramount for sustaining malaria control achievements.

Keywords: Artemisinin resistance, Plasmodium falciparum, Kelch13 mutations, Malaria therapeutics, Drug resistance mechanisms.

INTRODUCTION

Malaria remains a persistent global health challenge, with approximately 247 million cases and 619,000 deaths reported annually according to the World Health Organization [1-5]. Plasmodium falciparum, the most virulent malaria parasite, is responsible for the majority of severe malaria cases and deaths, particularly in Sub-Saharan Africa where disease burden remains disproportionately high [6-9]. The introduction of artemisinin-based combination therapies (ACTs) has dramatically improved malaria treatment outcomes over the past two decades, representing one of the most significant advances in antimalarial chemotherapy. However, the emergence and spread of artemisinin-resistant P. falciparum strains, initially documented in the Greater Mekong Subregion and subsequently detected in East Africa, threaten to undermine these therapeutic gains [10-14].

Artemisinin resistance manifests clinically as delayed parasite clearance following ACT treatment, with resistance defined by parasite clearance half-life values exceeding 5 hours. The molecular basis of this resistance centers primarily on mutations within the Kelch13 (K13) propeller domain, which fundamentally alters parasite physiology and drug susceptibility. These resistance mechanisms extend beyond simple drug binding alterations to encompass complex cellular processes, including endocytic dysfunction, stress response modifications, and metabolic reprogramming. Understanding these mechanisms is essential for developing rational therapeutic strategies and maintaining the efficacy of current antimalarial interventions [15-19].

This review systematically examines current knowledge regarding artemisinin resistance mechanisms in P. falciparum, beginning with molecular pathways underlying resistance phenotypes. We then discuss biomarkers and diagnostic approaches, followed by analysis of pharmacokinetic implications and therapeutic challenges. The review

concludes by addressing current limitations in resistance management and future directions for sustaining antimalarial efficacy in the face of evolving parasite resistance [20-25].

MOLECULAR MECHANISMS OF ARTEMISININ RESISTANCE

Kelch13 Mutations and Protein Function

The discovery of Kelch13 (K13) mutations as the primary molecular determinant of artemisinin resistance represents a pivotal advancement in understanding resistance mechanisms [3]. The K13 protein, encoded by the PfKelch13 gene, functions as a crucial component in parasite endocytic pathways and stress response mechanisms. Resistance-conferring mutations occur predominantly within the propeller domain, with over 20 validated mutations identified to date. The most clinically significant mutations include C580Y, R539T, Y493H, and I543T, which demonstrate varying degrees of resistance phenotypes and geographic distribution patterns [26-30].

Structural analysis reveals that K13 propeller domain mutations disrupt normal protein conformation, leading to functional alterations in cellular processes critical for artemisinin susceptibility. The C580Y mutation, most prevalent in Cambodia and Vietnam, confers the highest degree of resistance with clearance t1/2 values reaching 7-8 hours compared to <3 hours in sensitive parasites [31-37]. These mutations fundamentally alter K13 protein interactions with downstream cellular targets, particularly affecting endocytic machinery function and stress response pathway activation.

Hemoglobin Endocytosis and Drug Activation

Recent mechanistic studies have elucidated the central role of hemoglobin endocytosis in artemisinin action and resistance [6]. P. falciparum parasites acquire hemoglobin from host erythrocytes through specialized endocytic structures called cytostomes, where K13 protein localizes and regulates endocytic function. Artemisinin compounds require activation by ferrous iron (Fe^{2+}) released during hemoglobin digestion, generating reactive oxygen species (ROS) that damage parasite cellular components.

K13 mutations significantly reduce hemoglobin endocytosis efficiency, with mutant parasites demonstrating 40-60% decreased hemoglobin uptake compared to wild-type strains [7]. This reduced endocytosis directly correlates with decreased artemisinin activation, as lower hemoglobin degradation results in reduced Fe^{2+} availability for drug activation. Consequently, artemisinin-resistant parasites experience diminished oxidative stress, allowing enhanced survival during drug exposure periods.

Cellular Stress Response Pathways

Artemisinin resistance involves complex alterations in cellular stress response mechanisms, particularly the unfolded protein response (UPR) and autophagy pathways [8]. K13 mutations enhance UPR activation, leading to increased expression of protein chaperones and stress response genes. This enhanced stress tolerance enables mutant parasites to better survive artemisinin-induced cellular damage.

Transcriptomic analysis of resistant parasites reveals upregulation of genes involved in protein folding, oxidative stress response, and DNA repair mechanisms [9]. Key upregulated genes include protein disulfide isomerase, heat shock proteins, and glutathione-related enzymes, collectively contributing to enhanced cellular protection. Additionally, resistant parasites demonstrate altered phosphatidylinositol 3-phosphate (PI3P) metabolism, with elevated PI3P levels promoting autophagy activation and cellular survival during drug stress [38-42].

BIOMARKERS AND DIAGNOSTIC APPROACHES

Molecular Markers for Resistance Detection

Accurate detection of artemisinin resistance requires comprehensive molecular surveillance targeting K13 mutations and associated genetic markers. Current diagnostic approaches primarily focus on K13 propeller domain sequencing, which remains the gold standard for resistance detection. However, the complexity of resistance mechanisms necessitates broader genomic surveillance approaches to capture the full spectrum of resistance-associated genetic changes.

Quantitative polymerase chain reaction (qPCR) assays targeting specific K13 mutations provide rapid screening capabilities for field surveillance programs. These assays demonstrate high sensitivity and specificity, with detection limits reaching <1% for minority variant populations [11]. Additionally, next-generation sequencing approaches enable comprehensive analysis of resistance-associated genes beyond K13, including pfmdr1, pfcrt, and other genetic determinants of ACT partner drug resistance.

Phenotypic Resistance Assessment

The ring-stage survival assay (RSA) represents the primary phenotypic method for measuring artemisinin resistance in vitro [12]. This assay measures the survival rate of early ring-stage parasites following brief exposure to dihydroartemisinin at 700 nM concentration. Resistant parasites typically demonstrate survival rates >1%, while sensitive strains show <1% survival.

Clinical assessment relies on parasite clearance kinetics, with clearance t1/2 >5 hours indicating artemisinin resistance. Advanced modeling approaches utilizing frequent parasite density measurements enable precise clearance rate calculations, providing quantitative resistance measurements for clinical surveillance. These methods require

specialized expertise and equipment, limiting their application in resource-constrained settings where resistance monitoring is most critical.

PHARMACOKINETIC AND PHARMACODYNAMIC IMPLICATIONS

Drug Exposure and Resistance Development

Artemisinin pharmacokinetics significantly influence resistance development and therapeutic outcomes. Artemisinin compounds demonstrate short elimination half-life values ($t1/2$ = 1-3 hours), requiring frequent dosing or combination with longer-acting partner drugs to maintain therapeutic efficacy [13]. Suboptimal drug exposure, resulting from inadequate dosing, poor adherence, or pharmacokinetic variability, creates selective pressure favoring resistant parasite survival.

Population pharmacokinetic studies reveal substantial inter-individual variability in artemisinin exposure, with coefficient of variation values reaching 40-60% for maximum concentration (Cmax) and area under the curve (AUC) parameters [14]. This variability, combined with resistance-associated alterations in parasite susceptibility, complicates dose optimization strategies and contributes to treatment failure risks.

Partner Drug Interactions and Resistance

ACT efficacy depends critically on partner drug activity, as artemisinin compounds provide rapid parasite reduction while partner drugs eliminate residual parasites. The emergence of partner drug resistance, particularly to piperaquine and mefloquine, threatens ACT effectiveness in regions with established artemisinin resistance [15]. Resistant parasites surviving artemisinin exposure face selection pressure from partner drugs, potentially accelerating resistance development to both components.

Pharmacodynamic modeling indicates that artemisinin resistance reduces the initial parasite killing rate by 2-3 fold, placing greater reliance on partner drug activity for treatment success [16]. This altered pharmacodynamic profile necessitates careful consideration of partner drug selection and dosing optimization to maintain therapeutic efficacy in resistance-endemic areas.

THERAPEUTIC STRATEGIES AND CLINICAL MANAGEMENT

Current Treatment Approaches

WHO guidelines recommend artemisinin-based combination therapies as first-line treatment for uncomplicated P. falciparum malaria, with specific ACT selection based on local resistance patterns and drug efficacy data [17]. In areas with confirmed artemisinin resistance, treatment approaches focus on optimizing partner drug selection and ensuring adequate drug exposure through improved adherence and dosing strategies.

Extended ACT treatment courses, typically 5-7 days instead of the standard 3-day regimen, may improve treatment outcomes in resistant areas. However, this approach requires careful consideration of safety profiles and patient compliance factors. Additionally, combination approaches utilizing multiple partner drugs or sequential therapy regimens show promise for overcoming resistance challenges.

Alternative Therapeutic Approaches

The limitations of current ACTs in resistance-endemic areas drive the development of alternative therapeutic strategies. Triple combination therapies, incorporating two partner drugs with artemisinin, demonstrate enhanced efficacy against resistant parasites in clinical trials [18]. The artemisinin-piperaquine-mefloquine combination shows particular promise, with cure rates exceeding 95% even in multidrug-resistant areas.

Novel antimalarial compounds targeting different cellular pathways offer potential solutions for artemisinin resistance. Compounds targeting parasite protein synthesis, such as cycloheximide derivatives, demonstrate activity against artemisinin-resistant strains. Additionally, combination approaches utilizing artemisinin with resistance-reversing agents, such as chloroquine or other compounds that restore drug susceptibility, represent innovative therapeutic strategies under investigation.

GEOGRAPHIC DISTRIBUTION AND EPIDEMIOLOGICAL PATTERNS

Regional Resistance Patterns

Artemisinin resistance demonstrates distinct geographic distribution patterns, with the highest prevalence in Southeast Asia, particularly Cambodia, Vietnam, and Myanmar [19]. The C580Y mutation predominates in this region, with frequencies exceeding 60% in some areas. Recent surveillance data indicate resistance spread to neighboring countries, including Thailand, Laos, and southern China, raising concerns about regional expansion.

East African emergence of artemisinin resistance, confirmed in Rwanda, Uganda, and Tanzania, represents a significant threat to malaria control efforts in high-burden regions [20]. The resistance mutations detected in Africa include both Southeast Asian variants and novel mutations, suggesting independent evolution of resistance mechanisms. This geographic expansion necessitates enhanced surveillance and rapid response strategies to prevent further spread.

Factors Influencing Resistance Spread

Multiple factors contribute to artemisinin resistance emergence and spread, including drug pressure, population genetics, and malaria transmission intensity. Areas with intensive antimalarial use, particularly those with

widespread artemisinin monotherapy use before ACT implementation, show higher resistance prevalence. Additionally, low transmission settings may favor resistance development by reducing competition from sensitive parasites and allowing resistant variants to establish and spread.

Human population movement, particularly in border regions with active trade and migration, facilitates resistance gene flow between parasite populations [21]. Mathematical modeling studies indicate that resistance spread rates depend critically on migration patterns, local transmission dynamics, and intervention coverage levels. These findings emphasize the importance of coordinated regional approaches to resistance management.

LIMITATIONS AND CHALLENGES IN RESISTANCE MANAGEMENT

Diagnostic and Surveillance Constraints

Current artemisinin resistance surveillance faces significant technical and logistical challenges, particularly in resource-limited settings where resistance monitoring is most critical. Molecular diagnostics require sophisticated laboratory infrastructure and technical expertise, limiting widespread implementation. Additionally, the complexity of resistance mechanisms, extending beyond simple K13 mutations, necessitates comprehensive genomic surveillance approaches that exceed current diagnostic capabilities in many endemic regions.

Phenotypic resistance assessment through RSA and clearance kinetics measurement requires specialized training and equipment, further constraining surveillance capacity. The lack of rapid, point-of-care resistance detection methods hampers real-time resistance monitoring and limits the ability to adapt treatment strategies promptly to emerging resistance patterns [22].

Therapeutic Development Challenges

The development of next-generation antimalarials faces substantial scientific and economic challenges. The complex nature of artemisinin resistance mechanisms complicates target identification and drug design strategies. Additionally, the requirement for compounds to retain activity against diverse resistance mechanisms while maintaining safety profiles suitable for endemic populations presents significant development hurdles.

Economic constraints limit investment in antimalarial research and development, particularly for compounds targeting resistance mechanisms specific to P. falciparum. The relatively small market size compared to other therapeutic areas, combined with the need for affordable pricing in resource-limited settings, creates challenging economic dynamics for pharmaceutical development programs.

FUTURE DIRECTIONS AND CLINICAL IMPLICATIONS

Novel Therapeutic Approaches

Future antimalarial development focuses on targeting cellular pathways distinct from artemisinin action mechanisms, potentially circumventing established resistance mechanisms. Compounds targeting parasite protein translation, such as translation elongation factor inhibitors, demonstrate promising activity against artemisinin-resistant strains [23]. Additionally, host-directed therapy approaches, targeting host cellular processes essential for parasite survival, offer innovative strategies less susceptible to resistance development.

Combination therapy optimization through pharmacokinetic modeling and personalized dosing approaches may improve treatment outcomes while minimizing resistance selection pressure. Advanced modeling techniques incorporating resistance mechanism data enable rational combination design and dosing optimization for diverse patient populations and resistance backgrounds.

Resistance Reversal Strategies

Research into artemisinin resistance reversal focuses on compounds that restore drug susceptibility in resistant parasites. Chloroquine, surprisingly, demonstrates synergistic activity with artemisinin against resistant strains, possibly through interference with resistance mechanisms [24]. This finding suggests that previously abandoned antimalarials may find renewed utility in combination approaches targeting resistant parasites.

Epigenetic approaches targeting parasite gene expression regulation offer additional resistance reversal strategies. Compounds modifying histone acetylation or DNA methylation patterns may reverse resistance-associated gene expression changes, restoring artemisinin susceptibility in resistant parasites.

Enhanced Surveillance and Response Systems

Future resistance management requires integrated surveillance systems combining molecular diagnostics, phenotypic assessment, and epidemiological monitoring. Real-time resistance mapping utilizing mobile health technologies and point-of-care diagnostics could enable rapid response to emerging resistance threats. Additionally, predictive modeling approaches incorporating genetic, epidemiological, and intervention data may anticipate resistance emergence patterns, enabling proactive management strategies.

International coordination mechanisms for resistance monitoring and response require strengthening to address the global nature of resistance threats. Standardized protocols for resistance detection, reporting, and response could facilitate coordinated international efforts to contain resistance spread and maintain antimalarial efficacy.

CONCLUSION

Artemisinin resistance in P. falciparum represents a multifaceted challenge encompassing complex molecular mechanisms, diverse clinical manifestations, and significant public health implications. The primary resistance determinant, Kelch13 mutations, disrupts fundamental parasite cellular processes, including hemoglobin endocytosis and stress response pathways, leading to reduced artemisinin susceptibility and delayed parasite clearance. Current evidence indicates that resistance mechanisms extend beyond simple K13 mutations to encompass broader genetic and epigenetic changes affecting multiple cellular pathways. The clinical implications of artemisinin resistance are profound, threatening the therapeutic efficacy of ACTs and potentially undermining decades of malaria control progress. Geographic expansion of resistance from Southeast Asia to East Africa demonstrates the urgent need for enhanced surveillance, improved therapeutic approaches, and coordinated international response strategies. Current management approaches focus on optimizing existing ACTs through partner drug selection and dosing modifications, while novel therapeutic strategies under development offer promise for addressing resistance challenges. Future research priorities must emphasize comprehensive resistance mechanism characterization, development of resistance-circumventing therapeutics, and implementation of robust surveillance systems capable of detecting and responding to emerging resistance threats. The complexity of resistance mechanisms necessitates multidisciplinary approaches integrating molecular biology, pharmacology, epidemiology, and public health perspectives to develop effective countermeasures. The successful management of artemisinin resistance requires sustained investment in research and development, strengthened health systems capacity, and continued commitment to malaria elimination goals despite evolving resistance challenges. Clinicians and researchers must prioritize the development of rapid diagnostic tools for artemisinin resistance detection combined with the implementation of novel therapeutic strategies to preserve the gains achieved through decades of malaria control efforts.

REFERENCES

1. 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
2. Kungu, E., Inyangat, R., Ugwu, O.P.C. and Alum, E. U. (2023). Exploration of Medicinal Plants Used in the Management of Malaria in Uganda. Newport International Journal of Research In Medical Sciences 4(1):101-108.
3. Ndwiga, L., Kimenyi, K. M., Wamae, K., Osoti, V., Akinyi, M., Omedo, I., Ochola-Oyier, L. I, et al. (2021). A review of the frequencies of Plasmodium falciparum Kelch 13 artemisinin resistance mutations in Africa. *International Journal for Parasitology: Drugs and Drug Resistance*, *16*, 155-161.
4. Ariey, F., Witkowski, B., Amaratunga, C., Beghain, J., Langlois, A. C., Khim, N., et al. (2014). A molecular marker of artemisinin-resistant Plasmodium falciparum malaria. Nature, 505(7481), 50-55. doi: 10.1038/nature12876.
5. Ashley, E. A., Dhorda, M., Fairhurst, R. M., Amaratunga, C., Lim, P., Suon, S., et al. (2014). Spread of artemisinin resistance in Plasmodium falciparum malaria. N Engl J Med, 371(5), 411-423. doi: 10.1056/NEJMoa1314981.
6. Birnbaum, J., Scharf, S., Schmidt, S., Jonscher, E., Hoeijmakers, W. A., Flemming, S., et al. (2020). A Kelch13-defined endocytosis pathway mediates artemisinin resistance in malaria parasites. Science, 367(6473), 51-59. doi: 10.1126/science.aax4735.
7. Yang, T., Xie, S. C., Cao, P., Giannangelo, C., McCaw, J., Creek, D. J., et al. (2019). Comparison of the exposure time dependence of the activities of synthetic ozonide antimalarials and dihydroartemisinin against K13 wild-type and mutant Plasmodium falciparum strains. Antimicrob Agents Chemother, 63(4), e02484-18. doi: 10.1128/AAC.02484-18.
8. Mok, S., Ashley, E. A., Ferreira, P. E., Zhu, L., Lin, Z., Yeo, T., et al. (2015). Drug resistance. Population transcriptomics of human malaria parasites reveals the mechanism of artemisinin resistance. Science, 347(6220), 431-435. doi: 10.1126/science.1260403.
9. Rocamora, F., Zhu, L., Liong, K. Y., Dondorp, A., Miotto, O., Mok, S., et al. (2018). Oxidative stress and protein damage responses mediate artemisinin resistance in malaria parasites. PLoS Pathog, 14(3), e1006930. doi: 10.1371/journal.ppat.1006930.
10. Demas, A. R., Sharma, A. I., Wong, W., Early, A. M., Redmond, S., Bopp, S., et al. (2018). Mutations in Plasmodium falciparum actin-binding protein coronin confer reduced artemisinin susceptibility. Proc Natl Acad Sci U S A, 115(50), 12799-12804. doi: 10.1073/pnas.1812317115.
11. Talundzic, E., Okoth, S. A., Congpuong, K., Plucinski, M. M., Morton, L., Goldman, I. F., et al. (2015). Selection and spread of artemisinin-resistance associated haplotypes over the greater mekong subregion. PLoS One, 10(8), e0134190. doi: 10.1371/journal.pone.0134190.

12. Witkowski, B., Amaratunga, C., Khim, N., Sreng, S., Chim, P., Kim, S., et al. (2013). Novel phenotypic assays for the detection of artemisinin-resistant Plasmodium falciparum malaria. Proc Natl Acad Sci U S A, 110(9), 3618-3623. doi: 10.1073/pnas.1218576110.
13. Alum, E. U. (2024). Phytochemicals in Malaria Treatment: Mechanisms of Action and Clinical Efficacy. KIU J. Health Sci., 4(2):71-84. https://doi.org/10.59568/KJHS-2024-4-2-06.
14. Stepniewska, K., Ashley, E., Lee, S. J., Anstey, N., Barnes, K. I., Binh, T. Q., et al. (2010). In vivo parasitological measures of artemisinin susceptibility. J Infect Dis, 201(4), 570-579. doi: 10.1086/650301.
15. 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
16. White, N. J. (2013). Pharmacokinetic and pharmacodynamic considerations in antimalarial chemotherapy. Antimicrob Agents Chemother, 57(12), 5792-5807. doi: 10.1128/AAC.1363-12.
17. World Health Organization. (2021). Guidelines for the treatment of malaria. 3rd edition. Geneva: World Health Organization.
18. van der Pluijm, R. W., Tripura, R., Hoglund, R. M., Pyae Phyo, A., Lek, D., ul Islam, A., et al. (2020). Triple artemisinin-based combination therapies versus artemisinin-based combination therapies for uncomplicated Plasmodium falciparum malaria: a multicentre, open-label, randomised clinical trial. Lancet, 395(10233), 1345-1360. doi: 10.1016/S0140-6736(20)30552-3.
19. Imwong, M., Suwannasin, K., Kunasol, C., Sutawong, K., Mayxay, M., Rekol, H., et al. (2017). The spread of artemisinin-resistant Plasmodium falciparum in the Greater Mekong subregion: a molecular epidemiology observational study. Lancet Infect Dis, 17(5), 491-497. doi: 10.1016/S1473-3099(17)30048-8.
20. Uwimana, A., Legrand, E., Stokes, B. H., Ndikumana, J. M., Warsame, M., Umulisa, N., et al. (2020). Emergence and clonal expansion of in vitro artemisinin-resistant Plasmodium falciparum kelch13 R561H mutant parasites in Rwanda. Nat Med, 26(10), 1602-1608. doi: 10.1038/s41591-020-1005-2.
21. Miotto, O., Sekihara, M., Tachibana, S. I., Yamauchi, M., Pearson, R. D., Amato, R., et al. (2019). Emergence of artemisinin-resistant Plasmodium falciparum with kelch13 C580Y mutations on the island of New Guinea. PLoS Pathog, 15(12), e1008074. doi: 10.1371/journal.ppat.1008074.
22. Conrad, M. D., & Rosenthal, P. J. (2019). Antimalarial drug resistance in Africa: the calm before the storm? Lancet Infect Dis, 19(10), e338-e351. doi: 10.1016/S1473-3099(19)30261-0.
23. Leroy, D., Doerig, C., & Schneweis, S. (2013). Antimalarial drug discovery: academic vs industry approaches. Curr Opin Microbiol, 16(4), 488-495. doi: 10.1016/j.mib.2013.06.007.
24. Sondo, P., Derra, K., Lefevre, T., Diallo-Nakanabo, S., Tarnagda, Z., Zampa, O., et al. (2016). Artesunate-amodiaquine and artemether-lumefantrine therapies and selection of pfcrt and pfmdr1 alleles in Nanoro, Burkina Faso. PLoS One, 11(3), e0151565. doi: 10.1371/journal.pone.0151565.
25. Nsanzabana, C. (2019). Resistance to artemisinin combination therapies (ACTs): do not forget the partner drug! Trop Med Int Health, 24(1), 26-35. doi: 10.1111/tmi.13168.
26. Orji OU, Ibiam UA, Aja PM, Ugwu P, Uraku AJ, Aloke C, Obasi OD, Nwali BU. Evaluation of the phytochemical and nutritional profiles of Cnidoscolus aconitifolius leaf collected in Abakaliki South East Nigeria. World J Med Sci. 2016;13(3):213-217.
27. Enechi OC, Okpe CC, Ibe GN, Omeje KO, Ugwu Okechukwu PC. Effect of Buchholzia coriacea methanol extract on haematological indices and liver function parameters in *Plasmodium berghei*-infected mice. Glob Veterinaria. 2016;16(1):57-66.
28. Alum EU, Uti DE, Ugwu Okechukwu PC, Alum BN. Toward a cure–Advancing HIV/AIDS treatment modalities beyond antiretroviral therapy: A review. Med. 2024;103(27):e38768.
29. Obeagu EI, Bot YS, Obeagu GU, Alum EU, Ugwu Okechukwu PC. Anaemia and risk factors in lactating mothers: A concern in Africa. Int J Innov Appl Res. 2024;11(2):15-17.
30. Alum EU, Ibiam UA, Ugwuja EI, Aja PM, Igwenyi IO, Offor CE, Orji UO, Ezeani NN, Ugwu OP, Aloke C, Egwu CO. Antioxidant effect of Buchholzia coriacea ethanol leaf extract and fractions on Freund's adjuvant-induced arthritis in albino rats: A comparative study. 2022;59(1):31-45.
31. Offor CE, Ugwu Okechukwu PC, Alum EU. Determination of ascorbic acid contents of fruits and vegetables. Int J Pharm Med Sci. 2015;5:1-3..
32. Amusa MO, Adepoju AO, Ugwu Okechukwu PC, Alum EU, Obeagu EI, Okon MB, Aja PM, Samson AOS. Effect of ethanol leaf extract of *Chromolaena odorata* on lipid profile of streptozotocin-induced diabetic Wistar albino rats. IAA J Biol Sci. 2024;10(1):109-117.
33. Enechi YS, Ugwu OC, Ugwu Okechukwu PC, Omeh K. Evaluation of the antinutrient levels of *Ceiba pentandra* leaves. IJRRPAS. 2013;3(3):394-400.

34. Ugwu Okechukwu PC, Nwodo OFC, Joshua EP, Odo CE, Ossai EC. Effect of ethanol leaf extract of *Moringa oleifera* on lipid profile of malaria-infected mice. Res J Pharm Biol Chem Sci. 2014;4(1):1324-1332.
35. Ugwu OPC, Alum EU, Uhama KC. Dual burden of diabetes mellitus and malaria: Exploring the role of phytochemicals and vitamins in disease management. Res Inven J Res Med Sci. 2024;3(2):38-49.
36. Alum EU, Ugwu Okechukwu PC, Aja PM, Obeagu EI, Inya JE, Onyeije AP, Agu E, Awuchi CG. Restorative effects of ethanolic leaf extract of *Datura stramonium* against methotrexate-induced hematological impairments. Cogent Food Agric. 2013;9(1):2258774.
37. Offor CE, Nwankwegu FC, Joshua EP, Ugwu Okechukwu PC. Acute toxicity investigation and anti-diarrhoeal effect of the chloroform-methanol extract of the leaves of *Persea americana*. Iran J Pharm Res. 2014;13(2):651-658. PMID: 25237361; PMCID: PMC4157041.
38. Afiukwa CA, Oko AO, Afiukwa JN, Ugwu Okechukwu PC, Ali FU, Ossai EC. Proximate and mineral element compositions of five edible wild grown mushroom species in Abakaliki, southeast Nigeria. Res J Pharm Biol Chem Sci. 2013;4:1056-1064.
39. Ugwu OP, Alum EU, Ugwu JN, Eze VH, Ugwu CN, Ogenyi FC, Okon MB. Harnessing technology for infectious disease response in conflict zones: Challenges, innovations, and policy implications. Med. 2024;103(28):e38834.
40. Obeagu EI, Ugwu OPC, Alum EU. Poor glycaemic control among diabetic patients; A review on associated factors. Newport Int J Res Med Sci (NIJRMS). 2023;3(1):30-33.
41. Nwaka AC, Ikechi-Agba MC, Okechukwu PU, Igwenyi IO, Agbafor KN, Orji OU, Ezugwu AL. The effects of ethanol extracts of *Jatropha curcas* on some hematological parameters of chloroform intoxicated rats. Am-Eur J Sci Res. 2015;10(1):45-49.
42. Ezeani NN, Ibiam UA, Orji OU, Igwenyi IO, Aloke C, Alum E, Aja PM, Ugwu OP. Effects of aqueous and ethanol root extracts of *Olax subscopioidea* on inflammatory parameters in complete Freund's adjuvant-collagen type II induced arthritic albino rats. Pharmacogn J. 2019;11(1)

CITE AS: Asiimawe Masika Agnovia (2025). Artemisinin Resistance Mechanisms in Plasmodium falciparum: Molecular Pathways and Clinical Implications. EURASIAN EXPERIMENT JOURNAL OF MEDICINE AND MEDICAL SCIENCES, 7(1):11-17