***Review Article***

**The Potential Role of Selenoproteins in Modulating Malaria Parasite Resistance to Artemisinin-Based Combination Therapies (ACTs) in Africa**

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ABSTRACT

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| Resistance to artemisinin-based combination therapies (ACTs), the frontline treatment for malaria, poses a growing global health challenge—particularly in Africa, where *Plasmodium falciparum* is most prevalent. While the mechanisms underlying artemisinin resistance remain incompletely understood, recent evidence highlights the importance of selenoproteins in mediating parasite survival under drug-induced oxidative stress. Among these, P. falciparum thioredoxin reductase (PfTrxR), a key enzyme in redox homeostasis, has emerged as a potential contributor to antimalarial resistance. This review synthesizes current findings on the structure, function, and expression of parasite selenoproteins—focusing on PfTrxR—and examines their role in mitigating artemisinin-induced oxidative damage. By integrating insights from molecular studies and drug response analyses, we propose that targeting selenoprotein-mediated redox pathways represents a promising strategy to counteract ACT resistance and improve malaria treatment outcomes in endemic regions. |

*Keywords:* Selenoproteins; Artemisinin resistance; *Plasmodium falciparum*; Thioredoxin reductase (PfTrxR); Redox homeostasis.

1. **INTRODUCTION**

Malaria remains a major global health challenge, with sub-Saharan Africa accounting for over 90% of cases and deaths (World Health Organization, 2024). Nigeria, in particular, bears a disproportionate burden, reporting 27% of global cases (68 million) and 31% of deaths (189,000) in 2022. In Nigeria, *Plasmodium falciparum* transmission persists due to socioeconomic disparities and limited access to quality healthcare (Okon et al., 2022). Environmental and vector-related factors, combined with the parasite’s biological adaptability, further entrench malaria’s prevalence. Children under five and pregnant women are disproportionately affected, experiencing severe anemia, cognitive impairments, low birth weight, and increased maternal mortality (World Health Organization, 2024; Ashley et al., 2014). These vulnerable populations face the highest morbidity and mortality risks, underscoring the need for effective interventions. Artemisinin-based combination therapies (ACTs), combining fast-acting artemisinin derivatives with partner drugs like lumefantrine or piperaquine, have significantly reduced malaria morbidity and mortality (Tse et al., 2019; Ashley et al., 2014). In Nigeria, artemether-lumefantrine is the most commonly used ACT, contributing to recent declines in malaria-related illness and death (World Health Organization, 2024).

Despite the initial success of ACTs, the emergence of resistance threatens their long-term efficacy. The rise of resistance to partner drugs, particularly lumefantrine, has been documented in African countries such as Angola and Uganda, threatening the long-term efficacy of ACTs (Tse et al., 2019; Plucinski et al., 2015; Tumwebaze et al., 2021). Mutations in the kelch13 gene, including validated markers R561H, C469Y, and A675V, have been identified in East Africa, particularly in Rwanda and Uganda (Balikagala et al., 2021; Uwimana et al., 2020). Clinical resistance, characterized by delayed parasite clearance, remains limited, affecting approximately 1–5% of infections in focal areas (Rosenthal, 2021; Nwanziva et al., 2022). Historically, chloroquine resistance emerged in Southeast Asia in the late 1950s and spread to Africa within 10–15 years, contributing to millions of childhood deaths in the 1980s (Murray et al., 2012). A similar trajectory for artemisinin resistance (ART-R) could exacerbate malaria control challenges in Africa if proactive measures are not implemented. Mathematical models indicate that lower transmission rates and immunity could accelerate the local emergence of resistance (Scott et al., 2019; Huang & Tatem, 2013). Table 1 summarizes key kelch13 mutations and their prevalence in Africa.

Right now, ACTs are still highly effective outside of Southeast Asia (Rosenthal, 2021). However, mutations in Pfkelch13—especially C580Y, R561H, Y493H, and A675V—are known to cause delayed clearance by disrupting haemoglobin endocytosis (Birnbaum et al., 2020; Straimer et al., 2015). Although African alleles like A578S are present, they haven’t shown resistance in vivo or in vitro (Ménard et al., 2016; Ocan et al., 2019). A key player in this developing resistance scenario is the parasite’s ability to handle oxidative stress caused by artemisinin. The drug works by generating reactive oxygen species (ROS), which can harm the parasite’s biomolecules (Kavishe et al., 2017). To cope with this, P. falciparum has developed strong antioxidant systems—like redox-regulating selenoproteins, including thioredoxin reductases and glutathione peroxidases—that depend on trace elements (Se, Ca, Mg, Na, K, Zn, Fe) and amino acids (Cys, Met). These systems might open doors to treatment failures (Lobanov et al., 2006; Becker et al., 2004). The nutritional biochemistry of the host plays a significant role in how diseases progress and how effective treatments can be. For instance, changes in plasma levels of essential amino acids and minerals—often seen in patients with malaria—can influence immune responses, redox balance, the integrity of red blood cells, and the replication of parasites (Conroy et al., 2022; Adekunle et al., 2007; Kumar & Bandyopadhyay, 2005). In Nigeria, a study by Okon et al. (2022) found that children with malaria had lower levels of iron and ascorbic acid, while their uric acid and magnesium levels were elevated.

Given the role of oxidative stress in ACT resistance, selenoproteins represent a critical area of investigation. This review dives into the intricate relationship between how parasites defend themselves, the nutritional biochemistry of their hosts, and the effectiveness of antimalarial drugs. It aims to shed light on the possible role of selenoproteins in influencing resistance to artemisinin-based combination therapies (ACTs).

**Table 1; Key kelch13 Mutations Associated with Artemisinin Resistance in Africa.**

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| Allele | Region | Prevalence | Reference |
| R561H | Rwanda, Uganda | 1 – 5% | Uwimana et al., 2020 |
| C469Y | East Africa | <5% | Balikagala et al., 2021 |
| A675V | East Africa | <5% | Rosenthal, 2021 |
| C580Y | Limited in Africa | Rare | Reyser et al., 2024 |

1. **SELENOPROTEINS AND MALARIA**

Selenoproteins are a unique group of proteins that include selenium in the form of the amino acid selenocysteine, often called the 21st amino acid. Known for their impressive catalytic efficiency in redox reactions, these proteins are vital for antioxidant defence systems. They play a significant role in maintaining cellular redox balance, regulating immune responses, and influencing stress-related signalling pathways (Labunskyy et al., 2014; Steinbrenner et al., 2016). In many eukaryotic organisms, selenoproteins like glutathione peroxidases (GPxs) and thioredoxin reductases (TrxRs) are key players in neutralizing reactive oxygen species (ROS), helping to keep cells functioning properly even under oxidative stress. When it comes to malaria, oxidative stress is a critical factor in the interactions between the host and the parasite. During the erythrocytic schizogony phase, *Plasmodium falciparum* multiplies inside red blood cells and breaks down haemoglobin, which leads to the production of high levels of ROS and free heme—both of which can be extremely harmful to biological membranes and nucleic acids (Becker et al., 2004). The parasite’s ability to survive in such harsh conditions suggests it has a strong intrinsic antioxidant system, with selenoproteins likely playing a key role. Genomic studies have identified genes encoding thioredoxin reductase (PfTrxR) and selenophosphate synthetase, indicating a functional selenoprotein biosynthesis pathway in P. falciparum (Lobanov et al., 2006). PfTrxR, in particular, is critical for redox regulation and peroxide detoxification under oxidative stress induced by artemisinin (Kavishe et al., 2017). The thioredoxin system in P. falciparum is especially crucial for the parasite’s growth and has been linked to redox regulation, detoxifying peroxides, and repairing proteins damaged by oxidation (Müller, 2004). Additionally, the activity of thioredoxin reductase has been shown to increase when oxidative stress is present, further supporting its role as a defensive mechanism during antimalarial treatments (Kavishe et al., 2017).

Recent discoveries about selenoproteins in Plasmodium biology have shed light on how the parasite’s need for redox balance influences its reaction to artemisinin-based combination therapies (ACTs). These treatments fight malaria by producing reactive oxygen species (ROS) and modifying the proteins of the parasite. As a result, the parasite may adapt by overexpressing or upregulating redox-active proteins, including selenoproteins, to counteract the oxidative damage caused by artemisinin (Gopalakrishnan & Kumar, 2015). It’s crucial to explore how these selenoproteins are regulated when exposed to drugs and whether their expression varies between sensitive and resistant strains, as this remains a key area of research. Even with these advancements, we still have a lot to learn about the functions of selenoproteins in Plasmodium species. The parasite’s unusual codon usage and intricate life cycle pose significant challenges for experimental validation. However, ongoing transcriptomic and proteomic studies are revealing new redox-related genes that might interact with selenoprotein pathways, highlighting their potential significance in the parasite’s biology and resistance to drugs (Babbitt et al., 2012).

Overall, the accumulating evidence indicates that selenoproteins play a nuanced yet vital role in maintaining redox homeostasis in Plasmodium, helping the parasite endure both internal oxidative stress and external drug challenges. Understanding the specific roles of these proteins could not only deepen our insight into malaria’s development but also guide the creation of innovative therapeutic approaches that target the parasite’s antioxidant systems.

1. **ACT RESISTANCE MECHANISMS**

Artemisinin-based combination therapies (ACTs) have made a huge impact in cutting down malaria-related illness and death rates. But now, we’re facing a new challenge: resistance to both artemisinin and its partner drugs is putting our malaria control efforts at risk. This resistance is mainly marked by a delay in clearing the parasites and is closely linked to mutations in the *Plasmodium falciparum* kelch13 (K13) gene, especially the C580Y mutation that was first spotted in Southeast Asia and has recently been found in parts of Africa (Reyser et al., 2024; Si et al., 2023). The resistance mechanisms go beyond just kelch13 mutations and involve a complicated mix of genetic, epigenetic, and metabolic changes: Gene Amplification: The pfmdr1 gene’s amplification has been tied to a decrease in sensitivity to partner drugs like mefloquine (Price et al., 2004). Likewise, the amplification of plasmepsin II/III genes is linked to resistance against piperaquine (Witkowski et al., 2017). Changes at the chromatin level, such as histone acetylation, can affect gene expression related to nutrient uptake and stress responses. These changes might lead to a temporary drug-tolerant state (Di Stefano et al., 2024). Recent research also points to the importance of redox homeostasis in developing resistance. ACTs, especially artemisinin, work their magic by producing reactive oxygen species (ROS) when activated by intracellular iron, which causes significant oxidative damage to the parasite’s proteins (Xie et al., 2020). To cope with this oxidative stress, *P. falciparum* seems to ramp up its antioxidant defences, including the thioredoxin and glutathione pathways (Kavishe et al., 2017; Jortzik & Becker, 2012).

1. **SELENOPROTEINS AND ACT RESISTANCE**

Selenoproteins, which include the rare amino acid selenocysteine, play a vital role in the parasite’s antioxidant defence system. In P. falciparum, researchers have identified at least four selenoproteins: thioredoxin reductase (PfTrxR), selenoprotein T, selenophosphate synthetase, and glutathione peroxidase-like proteins (Lobanov et al., 2006). These enzymes are believed to help manage oxidative stress during the digestion of haemoglobin in the parasite’s food vacuole, a process that produces a lot of reactive oxygen species (ROS) (Jortzik & Becker, 2012; Müller, 2004). Interestingly, there’s been an increase in the expression of PfTrxR and other redox enzymes in artemisinin-resistant strains, hinting at a compensatory adaptation that aids in neutralizing drug-induced ROS (Wang et al., 2015). For instance, PfTrxR, which relies on selenium, reduces thioredoxin and plays a key role in protein repair, detoxification, and redox signalling. This upregulation might be a factor in the parasite’s survival when faced with artemisinin pressure (Kavishe et al., 2017; Kehr et al., 2010).

While we don’t fully understand the exact role of selenoproteins in resistance to artemisinin-based combination therapies (ACT), their known functions in protein folding, redox buffering, and degradation pathways suggest they are likely involved. Since ACTs rely on oxidative damage to be effective, even minor changes in the parasite’s redox state—mediated by selenoproteins—can have a significant impact on how potent the drugs are (Rosenthal, 2013; Müller, 2004). Additionally, the regulation of these antioxidant defences might be influenced by epigenetic factors or stress-induced changes in gene expression, which adds another layer of complexity to the resistance landscape. Recent findings also indicate that the parasite’s antioxidant capacity may be selectively boosted in resistant clones through these regulatory mechanisms (Birnbaum et al., 2020; Wang et al., 2015).

1. **IMPLICATIONS AND FUTURE DIRECTIONS**
2. Implications of the Potential Role of Selenoproteins in Modulating ACT Resistance The rise of artemisinin-based combination therapy (ACT) resistance in *Plasmodium falciparum* poses a significant hurdle for global malaria control efforts. Artemisinin works by generating reactive oxygen species (ROS), which create a tough oxidative environment for the parasite (Suresh & Haldar, 2018). In response, P. falciparum has developed complex redox buffering systems, mainly through the thioredoxin and glutathione pathways, to counteract the oxidative stress caused by artemisinin (Muller, 2001). Recent studies indicate that selenoproteins—selenium-rich proteins known for their strong redox activity—could play an important role in this redox defence mechanism. The genome of P. falciparum contains several elements necessary for the selenocysteine insertion process, including a unique tRNA, selenophosphate synthetase, and selenocysteine synthase, which shows its ability to produce selenoproteins (Lobanov et al., 2006). While these selenoproteins are fewer in number compared to those in higher eukaryotes, they are believed to aid in antioxidant defence, potentially influencing susceptibility to ACT (Novoselov et al., 2002). Moreover, research has shown that when malaria-infected hosts receive selenium supplementation, the activity of glutathione peroxidase—a selenocysteine-dependent enzyme—rises, suggesting that selenium and its related proteins might boost the parasite’s redox balance (Gamain et al., 1996). This increase in redox enzyme activity could give *P. falciparum* a survival edge when faced with artemisinin, supporting the idea that selenoproteins could be involved in the development or persistence of ACT resistance.
3. Exploring the Potential of Targeting Selenoproteins to Tackle ACT Resistance Given how crucial redox regulation is in ACT resistance, selenoproteins emerge as promising drug targets. Take auranofin, for instance—this compound is a well-known inhibitor of selenoenzymes like thioredoxin reductase and has shown impressive antimalarial effects by throwing off redox balance and ramping up oxidative stress in P. falciparum (Sannella et al., 2008). The fact that selenoproteins are specific to the parasite and differ from human counterparts makes them even more appealing as therapeutic targets, with a lower risk of harming the host (Rashidi et al., 2022). By inhibiting selenoproteins, we could potentially work in tandem with ACTs to diminish the parasite’s ability to counteract reactive oxygen species (ROS), thus boosting the effectiveness of the drugs. There’s an urgent need for structural studies and molecular modelling of P. falciparum selenoproteins to create selective inhibitors that latch onto the active selenocysteine sites without interfering with human enzymes (Lobanov et al., 2006). This strategy could pave the way for a new chapter in antimalarial drug development, honing in on redox vulnerability as a critical weakness.
4. Identifying Knowledge Gaps and Future Research Avenues Even with the progress we’ve made, there are still significant gaps in our understanding of selenoproteins in P. falciparum. For starters, we don’t fully grasp the specific functions and substrates of these proteins. To clarify the role of individual selenoproteins in managing oxidative stress and drug resistance, we need to employ functional genomics and CRISPR-based gene editing techniques (Novoselov et al., 2002). Additionally, we have a limited understanding of how selenoprotein expression is regulated under artemisinin pressure. Conducting transcriptomic and proteomic profiling of P. falciparum during oxidative stress and selenium modulation could uncover the dynamic regulatory mechanisms at play (Gamain et al., 1996). The absence of high-resolution structures for most P. falciparum selenoproteins hampers our ability to design effective drugs. That’s why structural biology techniques, like cryo-EM and X-ray crystallography, are so important. On top of that, we need to conduct preclinical studies to evaluate how these selenoprotein-targeting drugs work and their safety. It’s essential to establish the therapeutic index of these agents in murine and primate malaria models to pave the way for clinical applications (Sannella et al., 2008).
5. **CONCLUSION**

This review has shed light on the growing importance of selenoproteins in the redox biology of *Plasmodium falciparum*, especially regarding resistance to artemisinin-based combination therapy (ACT). As the malaria parasite evolves to cope with the oxidative stress caused by ACTs, it’s becoming clear that traditional redox systems—like the glutathione and thioredoxin pathways—might not be working in isolation. Instead, selenoproteins, which have been extensively studied for their role in mammalian antioxidant defence, are now being recognized as potential support systems that help the parasite maintain its redox balance and withstand antimalarial treatments. While the synthesis and function of selenoproteins in *P. falciparum* are not as extensive as in higher eukaryotes, they could offer crucial adaptive benefits when faced with drug-induced oxidative stress. New evidence indicates that selenocysteine-dependent enzymes might play a role in neutralizing reactive oxygen species produced by artemisinin and possibly other elements of ACT, subtly influencing the parasite’s vulnerability to treatment. This positions selenoproteins not just as markers of resistance but also as innovative therapeutic targets that could be leveraged to make resistant parasites more susceptible to ACT or to boost the effectiveness of existing treatments. The impact of this new approach is especially significant for regions in Africa where malaria is prevalent, as we’re starting to see resistance to artemisinin-based combination therapies (ACTs).

Given that Africa accounts for over 90% of global malaria deaths, often in areas with limited resources, a decline in the effectiveness of ACTs would be a disaster for public health. This makes it crucial to understand non-traditional resistance mechanisms—like those possibly influenced by selenoproteins—not just as an academic exercise, but as a vital step in maintaining the effectiveness of our frontline antimalarial treatments. To truly grasp how selenoproteins contribute to ACT resistance, we need focused proteomic and transcriptomic research on field isolates, along with CRISPR-based functional genomics. Additionally, designing drugs based on structural insights could lead to the creation of compounds that specifically target parasite selenoenzymes while leaving the host’s redox systems intact. Moreover, keeping an eye on epidemiological trends that include redox-related biomarkers could help us spot new resistance patterns tied to selenoprotein expression, providing early warnings for public health strategies.

In conclusion, this review highlights an intriguing and often overlooked aspect of malaria biology. As we move into the next decade of research and development in antimalarial treatments, selenoproteins might just be the key to tackling resistance challenges and achieving lasting control and eventual eradication of malaria, particularly in the most at-risk areas around the globe.

References

Adekunle, A. S., Adekunle, O. C., & Egbewale, B. E. (2007). Serum status of selected biochemical parameters in malaria: An animal model. Biomedical Research, 18(2), 89–93.

Ariey, F., Witkowski, B., Amaratunga, C., Beghain, J., Langlois, A., Khim, N., et al. (2014). A molecular marker of artemisinin-resistant Plasmodium falciparum malaria. Nature, 505(7481), 50–55. https://doi.org/10.1038/nature12876

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. New England Journal of Medicine, 371(5), 411–423. https://doi.org/10.1056/NEJMoa1314981

Babbitt, S. E., Altenhofen, L., Cobbold, S. A., Llinás, M., & Goldberg, D. E. (2012). Plasmodium falciparum responds to amino acid starvation by entering into a hibernatory state. Proceedings of the National Academy of Sciences of the United States of America, 109(47), E3278–E3287. https://doi.org/10.1073/pnas.1209823109

Balikagala, B., Fukuda, N., Ikeda, M., Katuro, O. T., Palacpac, N. M. Q., Odongo-Aginya, E. I., et al. (2021). Evidence of artemisinin-resistant malaria in Africa. New England Journal of Medicine, 385(13), 1163–1171. https://doi.org/10.1056/NEJMoa2101746

Becker, K., Tilley, L., Vennerstrom, J. L., Roberts, D., Rogerson, S., & Ginsburg, H. (2004). Oxidative stress in malaria parasite-infected erythrocytes: Host-parasite interactions. International Journal of Parasitology, 34(2), 163–189. https://doi.org/10.1016/j.ijpara.2003.09.011

Birnbaum, J., Scharf, S., Schmidt, S., Jonscher, E., Hoeijmakers, W. A. M., Flemming, S., et al. (2020). Kelch13-defined endocytosis pathway mediates artemisinin resistance in malaria parasites. Science, 367(6473), 51–59. https://doi.org/10.1126/science.aax4735

Blasco, B., Leroy, D., & Fidock, D. A. (2017). Antimalarial drug resistance: Linking Plasmodium falciparum parasite biology to the clinic. Nature Medicine, 23(8), 917–928. https://doi.org/10.1038/nm.4381

Conrad, M. D., & Rosenthal, P. J. (2019). Antimalarial drug resistance in Africa: The calm before the storm? Lancet Infectious Diseases, 19(10), e338–e351. https://doi.org/10.1016/S1473-3099(19)30261-0

Conroy, A. L., Opoka, R. O., Bangirana, P., Namazzi, R., Georgieff, M. K., & John, C. C. (2022). Plasma amino acid concentrations in children with severe malaria are associated with mortality and worse long-term kidney and cognitive outcomes. Clinical Infectious Diseases, 75(12), 2215–2225. https://doi.org/10.1093/infdis/jiac392

Gamain, B., Arnaud, J., Favier, A., Camus, D., Dive, D., & Slomianny, C. (1996). Increase in glutathione peroxidase activity in malaria parasite after selenium supplementation. Free Radical Biology and Medicine, 21(4), 559–565. https://doi.org/10.1016/0891-5849(96)00120-7

Gopalakrishnan, A. M., & Kumar, N. (2015). Antimalarial action of artesunate involves DNA damage mediated by reactive oxygen species. Antimicrobial Agents and Chemotherapy, 59(1), 317–325. https://doi.org/10.1128/AAC.03663-14

Hamilton, W. L., Amato, R., van der Pluijm, R. W., Jacob, C. G., Quang, H. H., Thuy-Nhien, N. T., et al. (2019). Evolution and expansion of multidrug-resistant malaria in southeast Asia: A genomic epidemiology study. Lancet Infectious Diseases, 19(9), 943–951. https://doi.org/10.1016/S1473-3099(19)30392-5

Huang, Z., & Tatem, A. J. (2013). Global malaria connectivity through air travel. Malaria Journal, 12, 269. https://doi.org/10.1186/1475-2875-12-269

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 Infectious Diseases, 17(5), 491–497. https://doi.org/10.1016/S1473-3099(17)30048-8

Jortzik, E., & Becker, K. (2012). Thioredoxin and glutathione systems in Plasmodium falciparum. International Journal of Medical Microbiology, 302(4–5), 187–194. https://doi.org/10.1016/j.ijmm.2012.07.007

Kavishe, R. A., Koenderink, J. B., & Alifrangis, M. (2017). Oxidative stress in malaria and artemisinin combination therapy: Pros and cons. FEBS Journal, 284(16), 2579–2591. https://doi.org/10.1111/febs.14097

Kehr, S., Sturm, N., Rahlfs, S., Przyborski, J. M., & Becker, K. (2010). Compartmentation of redox metabolism in malaria parasites. PLoS Pathogens, 6(12), e1001242. https://doi.org/10.1371/journal.ppat.1001242

Kumar, S., & Bandyopadhyay, U. (2005). Free heme toxicity and its detoxification systems in humans. Toxicology Letters, 157(3), 175–188. https://doi.org/10.1016/j.toxlet.2005.03.004

Labunskyy, V. M., Hatfield, D. L., & Gladyshev, V. N. (2014). Selenoproteins: Molecular pathways and physiological roles. Physiological Reviews, 94(3), 739–777. https://doi.org/10.1152/physrev.00039.2013

Lobanov, A. V., Hatfield, D. L., & Gladyshev, V. N. (2006). The Plasmodium selenoproteome. Nucleic Acids Research, 34(2), 496–505. https://doi.org/10.1093/nar/gkj450

Mathieu, L. C., Cox, H., Early, A. M., Mok, S., Lazrek, Y., Paquet, J. C., et al. (2020). Local emergence in Amazonia of Plasmodium falciparum K13 C580Y mutants associated with in vitro artemisinin resistance. eLife, 9, e51015. https://doi.org/10.7554/eLife.51015

Ménard, D., Khim, N., Berghain, J., Adegnika, A. A., Shafiul-Alam, M., Amodu, O., et al. (2016). A worldwide map of Plasmodium falciparum K13-propeller polymorphisms. New England Journal of Medicine, 374(25), 2453–2461. https://doi.org/10.1056/NEJMoa1513137

Miotto, O., Sekihara, M., Tachibana, S. I., Yamauchi, M., Pearson, R. D., Almagro-Garcia, J., et al. (2019). Emergence of artemisinin-resistant Plasmodium falciparum with kelch13 C580Y mutations on the island of New Guinea. bioRxiv. https://doi.org/10.1101/621813

Müller, S. (2004). Redox and antioxidant systems of the malaria parasite Plasmodium falciparum. Molecular Microbiology, 53(5), 1291–1305. https://doi.org/10.1111/j.1365-2958.2004.04257.x

Murray, C. J., Rosenfeld, L. C., Lim, S. S., Andrews, K. G., Foreman, K. J., Haring, D., et al. (2012). Global malaria mortality between 1980 and 2010: A systematic analysis. Lancet, 379(9814), 413–431. https://doi.org/10.1016/S0140-6736(12)60034-8

Novoselov, S. V., Rao, M., Onoshko, N. V., Zhi, H., Kryukov, G. V., Xiang, Y., et al. (2002). Selenoproteins and the selenocysteine insertion system in the model plant cell system. EMBO Journal, 21(14), 3681–3693. https://doi.org/10.1093/emboj/cdf372

Nwanziva, C., et al. (2022). Prevalence of kelch13 mutations in African Plasmodium falciparum isolates: A systematic review. Malaria Journal, 21, 154. https://doi.org/10.1186/s12936-022-04123-5

Ocan, M., Akena, D., Nsobya, S., Kamya, M. R., Senono, R., Kinengyere, A. A., & Obuku, E. (2019). K13-propeller gene polymorphisms in Plasmodium falciparum parasite population in malaria-affected countries: A systematic review of prevalence and risk factors. Malaria Journal, 18(1), 1–17. https://doi.org/10.1186/s12936-019-2733-y

Okon, A. U., Eze, B. I., Emmanuel, U. A., Marcus, I. W., & Adanna, U. A. (2022). Correlation of parasite density and biochemical parameters in children with malaria infection in Calabar, South-South Nigeria. Egyptian Pediatric Association Gazette, 70(1), 27. https://doi.org/10.1186/s43054-022-00114-5

Paloque, L., Ramadani, A. P., Mercereau-Puijalon, O., Augereau, J. M., & Benoit-Vical, F. (2022). Plasmodium falciparum resistance to artemisinin-based combination therapies: A sword of Damocles in the path toward malaria elimination. Parasite, 29, 11. https://doi.org/10.1051/parasite/2022011

Plewes, K., Kingston, H. W. F., Ghose, A., Maude, R. J., Herdman, M. T., Leopold, S. J., et al. (2018). Acidosis in Plasmodium falciparum malaria: A pathophysiological and prognostic study. Critical Care Medicine, 46(6), e574–e583. https://doi.org/10.1097/CCM.0000000000003094

Price, R. N., Uhlemann, A. C., & van Vugt, M. (2006). Artemisinin resistance in Plasmodium falciparum malaria. New England Journal of Medicine, 355(19), 1950–1961. https://doi.org/10.1056/NEJMra061186

Rashidi, S., Fernández-Rubio, C., Mansouri, R., Ali-Hassanzadeh, M., & Yahyaei, B. (2021). Serum selenium levels and malaria: A systematic review and meta-analysis. Scientific Reports, 11, 10358. https://doi.org/10.1038/s41598-021-89883-z

Rosenthal, P. J. (2013). The interplay between antimalarial drug resistance and fitness. Current Opinion in Infectious Diseases, 26(6), 556–563. https://doi.org/10.1097/QCO.0000000000000016

Straimer, J., Gnadig, N. F., Witkowski, B., Amaratunga, C., Duru, V., Ramadani, A. P., et al. (2015). Drug resistance: K13-propeller mutations confer artemisinin resistance in Plasmodium falciparum clinical isolates. Science, 347(6220), 428–431. https://doi.org/10.1126/science.1260867

Taylor, S. M., Parobek, C. M., & Fairhurst, R. M. (2017). Haemoglobinopathies and the clinical epidemiology of malaria: A systematic review and meta-analysis. Lancet Infectious Diseases, 12(6), 457–468. https://doi.org/10.1016/S1473-3099(11)70071-9

Tilley, L., Straimer, J., Gnädig, N. F., Ralph, S. A., & Fidock, D. A. (2016). Artemisinin action and resistance in Plasmodium falciparum. Trends in Parasitology, 32(9), 682–696. https://doi.org/10.1016/j.pt.2016.05.010

Tse, E. G., Korsik, M., & Todd, M. H. (2019). The past, present and future of anti-malarial medicines. Malaria Journal, 18, 93. https://doi.org/10.1186/s12936-019-2724-1

Wang, J., Huang, L., Li, J., Fan, Q., Long, Y., Li, Y., et al. (2010). Artemisinin directly targets malarial mitochondria through its specific mitochondrial activation. PLoS ONE, 5(3), e9582. https://doi.org/10.1371/journal.pone.0009582

White, N. J., Pongtavornpinyo, W., Maude, R. J., Saralamba, S., Aguas, R., Stepniewska, K., et al. (2009). Hyperparasitaemia and low dosing are an important source of anti-malarial drug resistance. Malaria Journal, 8, 253. https://doi.org/10.1186/1475-2875-8-253

World Health Organization. (2023). World malaria report 2023. <https://www.who.int/publications/i/item/9789240076790>

Zhou, Y., Messier, N., Chandramohanadas, R., & Huang, F. (2022). Global distribution of Plasmodium falciparum Kelch13 mutations and insights into drug resistance evolution. Frontiers in Cellular and Infection Microbiology, 12, 891376. https://doi.org/10.3389/fcimb.2022.891376