**Advances in Bioresearch**
Adv. Biores., Vol 16 (4) July 2025: 347-358

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.16.4.347358

Advances in Bioresearch

## REVIEW ARTICLE

# Recent Advances to Tame Malaria by Green Nanotechnology: Current Status and Future Perspectives

**Mayank Raj[1], Charu Bansal[1], Akash Sharma[1], Sushil Kumar Upadhyay[1], Manoj Singh[1*], Yogendra Prasad Pandey[2], Deepak Yadav[3] and Rajesh Kumar[4]**

[1]Department of Bio-Sciences and Technology, MMEC, Maharishi Markandeshwar (Deemed to be University), Mullana-Ambala (Haryana)-133207, India
[2]Department of Zoology, Government Model Science College, Rewa (MP), India
[3]Department of Zoology, Miranda House (University of Delhi), New Delhi, India
[4]Department of Zoology, S.S. Memorial P.G. College, Takha, Etawah (UP), India
***Corresponding author's Email:** manoj.singh@mmumullana.org

**ABSTRACT**

*Malaria represents a global issue that significantly affects personal health, resulting in millions of cases and thousands of deaths each year. It primarily affects nations that are still developing, particularly in tropical and subtropical regions. Malaria is a disease caused by Plasmodium species, mainly spread through the blood-feeding habits of female Anopheles mosquitoes. The main approaches to address malaria include eliminating the parasite using pharmacological treatments and preventing its spread through vector control strategies. However, the rise of resistance in vectors and parasites to current methods poses a considerable challenge. Given the diminishing efficacy of pharmaceuticals and the detrimental impact of pesticides on the environment, focus has turned to discovering biocompatible compounds as possible anti-malarial treatments. For many years, plant-derived compounds have been employed in conventional medicine, particularly in the management of malaria. The effects of these chemicals on both the parasite and the insect have been shown to be harmful. Furthermore, these are readily available and cost-effective. The limitation of this lies within the governance framework, as green chemical constituents degrade rapidly. The application of nanotechnology to these chemicals can improve their absorption in the body, increase solubility in liquids, and achieve the desired effects. Consequently, employing nanotechnology in the development of plant-based products is a crucial approach in the fight against malaria. This investigation aims to review and comprehend the effects of nanoparticles obtained from plant extracts on Anopheles mosquitoes and Plasmodium parasites. Additionally, the research finding of this review will be helpful for developing sustainable nanotechnology and advance the current strategies of malaria prevention for community health and social welfare.*

***Keywords:*** *Green nanotechnology; Plant extracts; Anopheles; Plasmodium; Malaria.*

Received 16.02.2025 Revised 07.04.2025 Accepted 16.06.2025

**How to cite this article:**
Mayank R, Charu B, Akash S, Sushil K U, Manoj S, Yogendra P P, Deepak Y and Rajesh K. Recent Advances to Tame Malaria by Green Nanotechnology: Current Status and Future Perspectives. Adv. Biores., Vol 16 (4) July 2025: 347-358.

## INTRODUCTION

In 2021, there were more than 247 million cases of malaria worldwide, leading to 619 thousand deaths. The data indicates a fatality rate of 14.8 per 100,000 individuals at risk. There was an increase of 2 million global malaria cases compared to the previous year [1]. The changes in the frequency and spread of malaria can be attributed to increased susceptibility to transmission, the genetic variation of the parasite, rising drug resistance, and the effects of the COVID-19 pandemic [2]. In the first year of the pandemic, the control of malaria faced significant challenges due to restricted access to Insecticide-Treated Nets (ITNs) and disruptions in malaria treatment and diagnosis, especially within the African Region of the World Health Organization (WHO) [1]. The pandemic caused a limitation on malaria preventive measures because of the lockdown, resulting in a reduction in the distribution of insecticide-treated bed nets. Moreover, the health systems encountered a considerable obstacle due to a shortage of healthcare personnel, which stemmed from a lack of protective equipment, the shutdown of clinics as a

result of quarantine protocols, and the reallocation of all resources to manage the pandemic. This promptly obstructed the capacity to efficiently oversee and avert new instances of malaria [3]. In 2021, the World Health Organization (WHO) reported a significant increase in malaria infections, particularly in Africa and Asia. About 268 million people in these areas required assistance due to humanitarian crises, such as floods, famine, and political turmoil. Malaria is an infectious disease caused by the *Plasmodium* sp. parasite, transmitted through the blood-feeding activities of female mosquitoes belonging to the *Anopheles* sp. species. More than forty species of *Anopheles* mosquitoes are recognized for their role in transmitting malaria to humans, including *Anopheles stephensi, A. gambiae, A. coluzzii,* and *A. funestus* [4,5].

Anophelinae predominantly inhabits tropical areas, as warmer temperatures significantly enhance its survival and growth prospects [6]. Female organisms in a state of development lay their eggs in still water bodies, leading to the hatching of larvae thereafter. Following four distinct stages of growth referred to as instars, larvae experience metamorphosis, resulting in their transformation into pupae. Pupae represent a dormant stage where feeding stops, leading to the emergence of the adult mosquito from the water's surface after several days. In the adult stage, female mosquitoes acquire blood meals to facilitate egg production and may become infected with the malaria parasite if they feed on a host that carries the infection [7-9]. The life cycle of Plasmodium is intricate and requires the participation of two separate hosts to complete its development. Following human infection, the parasite enters the bloodstream and migrates to the liver, where it matures. The management of malaria is complex, influenced by the parasite's resistance to current pharmacological treatments, the mosquitoes' resilience to insecticides, and the environmental impacts associated with these insecticides. In light of these challenges, it is crucial to strengthen efforts in exploring innovative therapies, identifying pharmacological targets, improving vector control, and advancing more effective technologies for the implementation of these strategies.

**GREEN NANOTECHNOLOGY**

Nanotechnology involves the manipulation of matter at the atomic or molecular scale to produce new products and materials ranging from 1 to 100 nanometers in size. Nano systems can be classified into two categories: organic, originating from lipids or polymers frequently employed in the pharmaceutical industry, and inorganic, consisting of metals. Nanosystems display differences in composition, fabrication techniques, and structural arrangement [10,11]. The primary methods for synthesizing nanoparticles (NPs) utilize expensive and toxic hydrogen [12]. To mitigate toxicity, numerous nanocarriers are presently being assessed for the production of these particles. A promising approach includes the use of plant extracts for biogenic synthesis. Nanotechnology finds broad application across multiple medical domains, such as wound healing [13], cancer therapy [14–16], dental practices [17], and the cosmetics industry [18].

Plant extracts present a practical alternative owing to their cost-effectiveness, easy accessibility, and variety of choices [19]. Nanoparticles generated from plant extract exhibit appropriate dimensions and morphology, consistent with the characteristics of conventional nanoparticles. Furthermore, they demonstrate remarkable efficiency as a result of their capacity to produce a significant amount in a reduced synthesis timeframe. Additionally, employing plant extracts requires the implementation of a bottom-up approach for the synthesis of nanoparticles (NPs). This approach is characterized by the self-assembly of atoms and molecules via chemical interactions, leading to a simpler and more efficient process [20]. Silver (Ag) is often employed in the synthesis of nanoparticles (NPs) because of its antibacterial and anti-inflammatory characteristics. Consequently, employing plant extracts for the synthesis of AgNPs can enhance these activities owing to the beneficial properties demonstrated by polyphenols [21]. Moreover, silver nanoparticles (Ag NPs) adversely affect aquatic organisms and are recognized as a pollutant. Nonetheless, the environmentally conscious production of these nanoparticles has the potential to reduce the detrimental impacts of silver by improving the stability of molecules and decreasing the aggregation of particles [22].

Although the advantages of nano systems are significant, it is crucial to recognize some drawbacks, such as potential toxicity, the materials' insufficient biocompatibility, and the relatively high expense associated with acquiring these systems for the treatment of neglected diseases. The environmentally friendly production of nanoparticles (NPs) entails the use of biological resources as capping agents to improve the shape, functionality, and stability of NPs [23]. Figure 1 illustrates the process of synthesizing nanoparticles through environmentally friendly methods. Capping agents consist of compounds characterized by a polar head and a non-polar tail, which gives them amphiphilic properties. The polar head group forms coordination interactions with the metal atoms found in nanocrystals that are produced during the agglomeration process. In the meantime, the tail region engages with the

surrounding environment. The selection of suitable reducing and capping agents is crucial in nanoparticle synthesis to ensure optimal effectiveness. The potential of bioactive chemicals present in plant-based products is often overlooked because of their degradation and volatilization in field conditions. A different strategy to address these drawbacks involves the creation of bioactive plant products through the utilization of polymers, plasticizers, stabilizers, and biodegradable antioxidants. A plant extract comprises a variety of metabolites and reductive biomolecules that play a crucial role in the reduction of metal ions. The components consist of terpenoids, flavones, ketones, aldehydes, amides, carboxylic acids, carbohydrates, proteins, and vitamins [24]. In the course of green synthesis, biocompounds attach to the surface of nanoparticles, resulting in the formation of a coating [25].

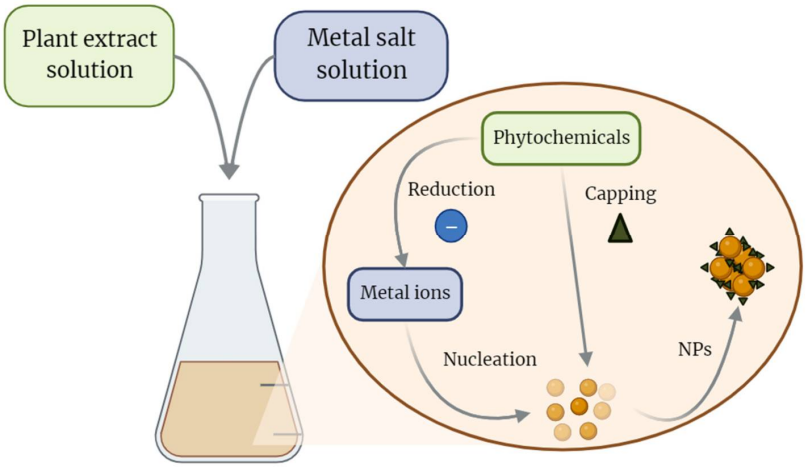


**Figure 1: Schematic diagram for the biosynthesis of nanoparticle *via* a green route using plant extract.**

This extra layer improves the biological properties of green nanoparticles in comparison to those generated through other chemical reduction methods. The traditional green synthesis reaction involves the direct combination of a natural extract with a metal salt solution, serving as the precursor for nanoparticles [26]. In the last ten years, this method has garnered significant interest, especially concerning Ag and Au NPs, which are viewed as safer alternatives compared to other metallic NPs [27]. Metals including nickel (Ni), manganese (Mn), titanium (Ti), titanium trichloride ($TiO_2$), palladium (Pd), cerium (Ce), platinum (Pt), and zinc oxide (ZnO) have been utilized in the creation of plant-derived nanoparticles (NPs) and the development of eco-friendly NPs [28-30].

**MALARIA PREVENTION STRATEGIES**

The main strategies for addressing mosquito populations, which act as carriers, include Indoor Residual Spraying (IRS) and Insecticide-Treated Nets (ITNs) [31]. Insecticide-Treated Nets are the primary strategy employed to prevent diseases in sub-Saharan Africa. Although there has been an increase in the ownership and usage of ITNs, the overall availability at the population level has decreased since 2017. Additionally, the proportion of individuals protected by the IRS in countries experiencing widespread disease has decreased, falling from 5.5% in 2010 to 2.4% in 2021 [32]. The implementation of IRS (Indoor Residual Spraying) and ITNs (pesticide-Treated Nets) has effectively reduced the prevalence of malaria; however, these strategies face challenges stemming from limited home accessibility [33] and the emergence of pesticide resistance in mosquito populations [34]. The dominant main recommendation from the World Health Organization (WHO) emphasizes the utilization of long-lasting insecticidal nets (LLINs) that are solely composed of pyrethroids. Nonetheless, the efficacy of these nets has diminished as a result of the emergence of mosquito resistance to pyrethroids. Pyrethroids are man-made substances derived from pyrethrins, which are naturally occurring insecticides sourced from the flowers of the Pyrethrum plant. The development of pyrethroids was driven by the molecular instability observed in pyrethrins [35]. Pyrethroids increase the activation of sodium channels in insects, resulting in the disruption of nerve impulse transmission and the over-stimulation of nerve cells [36]. This outcome leads to paralysis in mosquitoes, a phenomenon also noted in nanoformulated plant extracts, which is explored in greater detail in this review. There is a conditional recommendation for additional synthetic pesticides, given the uncertainties surrounding their cost effectiveness and the absence of supporting evidence. Pesticides are acknowledged as hazardous to the environment [37]. The toxicity of these substances

poses significant risks to aquatic species and may adversely affect human development if exposure occurs during pregnancy, particularly through the disruption of hormone signaling. Currently, the World Health Organization (WHO) does not support the application of insecticide space-spraying due to the insufficient data on its impact on malaria and the short-lived nature of the chemicals used [38]. This analysis offers a succinct examination of the effects of various environmentally friendly alternatives to synthetic pesticides, emphasizing the role of nanotechnology in improving their efficacy (Table 1).

The coils derived from *Senna occidentalis* and *Ocimum basilicum* demonstrated significant toxicity towards *A. stephensi*, leading to mortality rates of 38% and 52% respectively. The observed rates were similar to the 42% mortality rate caused by the pyrethrin-based control coil [39]. The use of *Pteridium aquilinum* AgNPs coils, synthesized from different plant parts, resulted in mortality rates comparable to those observed with pyrethrin-based coils [40]. Moreover, in both trials, the smoke from the plants was observed to diminish the transmission of parasites by lowering the percentage of mosquitoes that had taken a blood meal. The coils crafted from *Ulva lactuca* exhibited superior efficacy against *A. stephensi,* achieving a mortality rate of 66%, in contrast to the pyrethrin-based coil, which recorded a mortality rate of 41% [41]. Moreover, the application of the green nanotechnology strategy can significantly improve a biological approach to vector control. This occurs because most plant extracts can enhance the predatory behavior of non-target species during the early growth stages of the mosquito. For instance, the application of chitosan-synthesized silver nanoparticles (AgNPs) at a concentration of 1 ppm improved the predatory efficiency of *Danio rerio* fish on *A. stephensi* mosquito larvae [42]. The introduction of *Citrus limon* gold-palladium (Au-Pd) nanoparticles did not adversely impact the predatory behavior of flying insects. Indeed, the predatory behavior of these insects intensified over time [43]. Furthermore, the application of *Lagenaria siceraria* zinc oxide (ZnO) nanoparticles led to an enhancement in the predation efficacy of *P. reticulata*, rising from 45.8% in the aqueous extract to 61.13% [44].

Furthermore, the application of *Cymbopogon citratus* Au NPs enhanced the predation efficiency of *Mesocyclops aspericornis* on *A. stephensi,* leading to an increase from 26.8% to 45.6% [45]. The increased efficiency of predation can be linked to the diminished mobility of larvae, which are typically nimble, after being exposed to the green-synthesized nanoparticles [46]. Furthermore, silver nanoparticles synthesized from *Ichnocarpus frutescens* [47], *Rubus ellipticus* [48], *Naregamia alata* [49], and *Hugonia mystax* [50] exhibited low toxicity levels towards non-target aquatic organisms, such as *G. affinis*, *Diplonychus indicus*, and *Anisops bouvieri*. Silver nanoparticles (AgNPs) synthesized from *Solanum xanthocarpum* [51] and titanium dioxide nanoparticles ($TiO_2$ NPs) derived from *Momordica charantia* leaf extract [52] demonstrated no toxicity *to P. reticulata* at doses lethal to mosquitoes. Specifying the selection of material used for synthesizing NPs is crucial, given the observed toxicity of CdS to non-target aquatic species [53]. These organisms feed on regions where mosquitoes proliferate, making it essential to develop pesticides that specifically affect the intended species to maintain ecological equilibrium. An assessment was conducted on the toxicity of *Malva sylvestris* silver nanoparticles (AgNPs) towards *D. indicus* and *G. affinis*. The investigation revealed that exposure to NPs had no impact on the lifespan and swimming behaviors of the organisms. Nonetheless, the suitability index revealed that the treatment with NPs exhibited a greater degree of toxicity on the mosquito larvae in comparison to other organisms [54]. The investigations discussed align with the recently established preferred product characteristics for vector-control agents as specified by the World Health Organization. The aim of PPCs was to promote the investigation and development of novel strategies for managing *Anopheles* mosquitoes. These methods must take into account various elements, including the management of transmission in both indoor and outdoor settings, enhancing current treatments, and prioritizing safety for both humans and the environment [55]. Green-synthesized nanotechnology fulfills most of the necessary criteria, positioning it as a strong candidate in the fight against malaria.

**ANTIMALARIAL EFFECTS OF GREEN NPs**

Numerous studies have evaluated the effectiveness of plant extracts in addressing malaria by focusing on parasite elimination and vector management. The principal criteria assessed in vector population management included the death rates of larvae, pupae, and adult mosquitoes, alongside the inhibition of oviposition and the viability of produced eggs. Figure 2 depicts the principal effects of green-synthesized nanoparticles on mosquitoes and parasites. A eucalyptus nanoemulsion demonstrated larvicidal efficacy against *A. stephensi* in laboratory and semi-field conditions. The breeding sites treated with the nanoemulsion demonstrated a continuously low larval density throughout duration of 6 days. In contrast to the breeding sites treated with standard eucalyptus oil, which exhibited a rise in larvae within merely two days [56]. Leaf extract of *Aristolochia indica*-derived silver nanoparticles (AgNPs) demonstrated toxicity against *A. stephensi* larvae and pupae under controlled laboratory conditions, with a fatal

concentration ($LC_{50}$) between 3.94 and 15.65 parts per million (ppm). Field tests demonstrated that both the crude extract and nanoparticles displayed similar larvicidal activity, achieving around 50% larval mortality within 24 hours and 100% mortality within 72 hours [57]. The larvae of *A. stephensi* were demonstrated to be detrimental when subjected to nanoemulsion and nanogel formulations of *Artemisia dracunculus* essential oil. The nanogel formulation had more toxicity than the nanoemulsion, as indicated by LC50 values of 6.6 and 13.5 µg/mL, respectively [58]. Nano liposomes containing *A. dracunculus* essential oil exhibited a more significant larvicidal effect against *A. stephensi* mosquitoes than other Artemisia species, specifically *A. annua* and *A. sieberi*, while all three species displayed toxicity towards the larvae. The nano liposomes of *A. dracunculus* essential oil caused 100% mortality at concentrations of 50, 100, and 200 µg/mL. Conversely, *A. annua* attained an equivalent death rate alone at a concentration of 200 µg/mL, whilst *A. sieberi* induced a mortality rate of 77% [59]. The essential oil nanoemulsion of *Acroptilon repens* had restricted efficacy in eliminating *A. stephensi* larvae, with $LC_{50}$ and LC90 values of 7 and 35 ppm, respectively. The bimetallic AuPd nanoparticles derived from *C. limon* shown considerable larvicidal efficacy against *A. stephensi*. The research additionally investigated the death rates of *A. aegypti* larvae and determined that they were lower in comparison *to A. stephensi*. A mortality rate of 100% was observed in the first larvae of *A. stephensi*, although *A. aegypti* did not demonstrate a comparable mortality rate. *A. cordifolia* AgNPs demonstrated heightened toxicity towards *A. stephensi* larvae relative to other mosquito species [60].

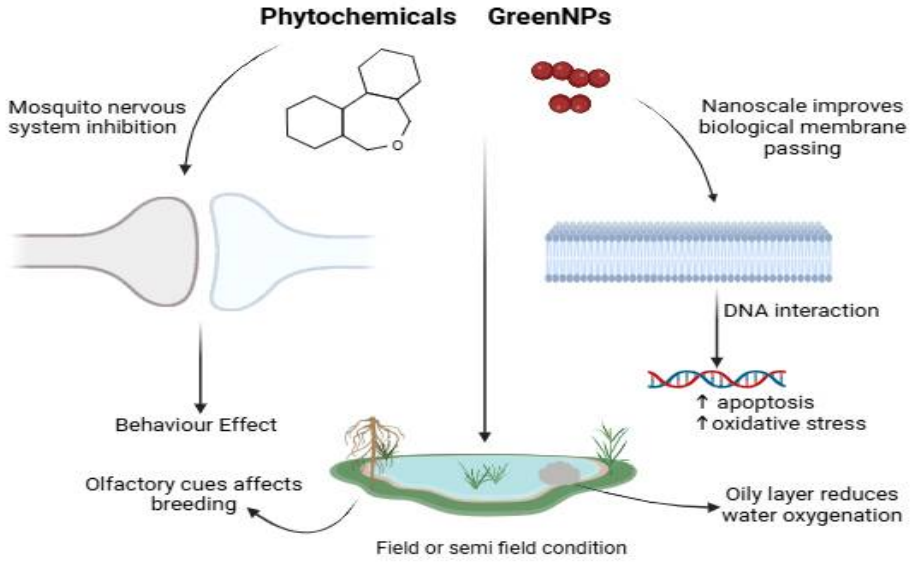


**Figure 2: Action mechanisms of phytochemicals in plant extracts and plant-derived nanoparticles.**

The $LC_{50}$ values of *Annona squamosa* AgNPs were higher for *A. stephensi* than for *A. aegypti* and *C. quinquefasciatus* [61]. Titanium dioxide nanoparticles derived from *Mangifera indica* demonstrated significant efficacy in managing *Aedes subpictus* larvae. Larvae exposed to $TiO_2$ nanoparticles at a minimal concentration of 5 mg/L exhibited a higher mortality rate than those exposed to TiO(OH) solution ($TiO_2$ NPs: 37%; TiO(OH): 11%). The $TiO_2$ nanoparticles demonstrated the maximum mortality rate at a concentration of 25 mg/L, whereas the TiO(OH) solution revealed a mortality rate of 89% at the same concentration [62]. The silver nanoparticles (AgNPs) produced by *I. frutescens* demonstrated a detrimental impact on the larvae of *A. subpictus*, which was contingent upon the dosage administered. The NPs attained a peak death rate of 100% at a concentration of 35 µg/mL, whereas the crude extract exhibited a mortality rate of 99.2% at 450 µg/mL [63]. The use of plant-based therapies in water reservoirs led to the total eradication of the larval population within 72 hours of exposure [64]. Silver nanoparticles produced from *R. ellipticus* demonstrated deadly effects on eggs ($LC_{50}$: 60 µg/mL) and adults ($LD_{50}$: 21.10 µg/mL), and blocked 89% of oviposition at a concentration of 60 ppm [65]. Moreover, researchers extracted essential oil from *C. deodara* and encapsulated it within pectin nanocapsules. They subsequently subjected cotton-bag fibers to this aqueous solution containing *A. culicifacies* third instar larvae. After five days, the larval population diminished by 90%, and after 28 days, it decreased by 98% [66].

*Mimusops elengi* AgNP has demonstrated toxicity to mosquito larvae, pupae, and adult mosquitoes, even at minimal concentrations. It is notable that the application of minimal quantities of green-synthesized silver nanoparticles (AgNPs) resulted in a reduction of mosquito larvae movement, thereby improving the efficacy of natural mosquito predators like mosquito fish [67]. The leaf extract of *Datura metell*, containing alkaloids and atropine, is employed for therapeutic purposes [68]. Furthermore, the extract of *Aloe vera* [159] exhibited acute toxicity towards the larvae and pupae of *A. stephensi*, while simultaneously enhancing predation on larval populations. In practical scenarios, the use of *A. vera* AgNP led to a notable reduction of 97.7% in the larvae population within 72 hours [69]. *Annona muricata* extract exhibits a range of activities, such as antiviral, anticancer, antifungal, and particularly larvicidal effects. The silver nanoparticles (AgNPs) obtained from *A. muricata* demonstrated toxicity towards third instar larvae of *A. stephensi*, with $LC_{50}$ and $LC_{90}$ values recorded at 15.28 and 31.91 μg $mL^{-1}$ [70]. Moreover, *Chrysanthemum indicum*, a flower rich in pyrethrin, is recognized for its effectiveness in exterminating insects by impacting the integrity of cell membranes. This results in damage to both the lipid and aqueous components of the gill membrane. Notably, silver nanoparticles generated from *C. indicum* demonstrated remarkable mortality rates when evaluated against the larvae and pupae of *A. stephensi* [71]. Preventing hemozoin production is crucial in the pursuit of novel antimalarial therapies. Recent studies provide compelling evidence that green nanoparticles could be effectively employed in the fight against malaria.

## PLANT EXTRACTS AND GREEN NPs ACTION MECHANISMS

The mechanisms of NP activity remain ambiguous, with existing research confined to the morphological, molecular, biochemical, and physiological aspects of mosquitoes [72]. Table 1 defines the effects of plant extracts across various levels, together with the associated type and size of the nanoparticles. The elevated mortality rates caused by NPs in mosquito larvae can be attributed to the diminutive size of the particles, allowing them to traverse the respiratory tubes and/or insect cuticle, infiltrating cells where they disrupt molting and other physiological functions [73].

**Table 1: Larvicidal activity of green nanoparticles**

| Plant extract | Plant Use | Type of NPs | Effects | Size of NPs | Ref. |
|---|---|---|---|---|---|
| *Arachis hypogaea* peel | Cattle food | AgNPs | Larvicidal and impact on larvae morphology | 20–50 nm (TEM) | [74] |
| *Solanum xanthocarpum* leaf | Anti-cancer, antioxidant, anti-HIV, antibacterial, and insecticidal | AgNPs | Larvicidal and biocompatible with non-target organisms | 10–20 nm (TEM) | [75] |
| *Malva sylvestris* leaf | Antioxidant, anti–inflammatory, and antimicrobial | AgNPs | Larvicidal and biocompatible with non-target organisms | 10–25 nm (TEM) | [76] |
| *Ulva lactuca* | Antioxidant, antibacterial, and antiviral | AgNPs | Larvicidal, pupicidal, antiplasmodial, and repellent smoke | 20–35 nm (SEM) | [77] |
| *Eclipta prostrata* leaf | Lipidemia and snake-venom poisoning | Pd NPs | Antiplasmodial and cytotoxic | 18–64 nm (TEM) | [78] |
| *Citrus limon* leaf | Natural pesticide, insect repellent, and antimicrobial | Au-Pd NPs | Larvicidal and predation booster | 15–18.5 nm (TEM) | [79] |
| *Eucalyptus globulus* oil | Natural pesticide | Nanoemulsion | Larvicidal in laboratory and semi-field | 22–40 nm (TEM) | [80] |
| *Mangifera indica* leaf | Antioxidant and antibacterial | $TiO_2$ NPs | Larvicidal and acaricidal | 30 nm (TEM) | [81] |
| *Vitex negundo* leaf | Bactericidal, diabetes, inflammation | ZnO NPs | Larvicidal, pupicidal, antioxidant, and photocatalytic | 28–42 nm (TEM) | [82] |
| *Vitex negundo* leaf | Antimicrobial, anti–inflammatory, | ZnO NPs | Larvicidal and antioxidant | 28.48–42.14 nm | [83] |

| | | | | | |
|---|---|---|---|---|---|
| | diabetes, cytotoxic, and larvicidal | | | (TEM) | |
| *Momordica charantia* leaf | Antidiabetic, antiviral, | ZnO NPs | Larvicidal and acaricidal | 21.32 nm (SEM) | [84] |

Upon breaching the exoskeleton, the Ag NPs influence the intracellular environment, directly interacting with proteins or DNA and inducing genotoxic consequences. The reduction of antioxidants triggers oxidative stress, the oxidative degradation of Ag NPs, and mitochondrial disruption [85]. It can also cause apoptosis by activating procaspase-3, down regulating the pro-survival protein Bcl-2, enhancing the production of pro-apoptotic gene products, and releasing cytochrome c into the cytosol [86]. The toxicity of nanoparticles is closely associated with their tendency to collect in different organs. Upon entering the bloodstream, nanoparticles demonstrate the ability to disseminate throughout the body, collecting in organs like the liver, spleen, lungs, and kidneys. The distribution of nanoparticles within the body is predominantly determined by their surface area-to-volume ratio, which influences their propensity to collect in specific tissues and organs [87]. The mechanisms by which nanoparticles (NPs) induce toxicity in organs involve numerous key components, including the generation of reactive oxygen species (ROS), DNA damage, alterations in protein structures and functions, and the disruption of membrane integrity. Significantly, the properties of nanoparticles that appear to augment these mechanisms include their extensive surface areas, which facilitate molecular interactions at designated target regions [88]. Toxicity extends beyond the target species to encompass the environment, particularly in the management of vectors under field settings. Nanoparticles discharged into aquatic environments impact organisms, leading to documented instances of blood acidity, circulatory failure, bioaccumulation, hepatotoxicity, oxidative stress, and impaired embryonic development. Nevertheless, similar effects were noted at heightened doses [89], in contrast to the modest quantities employed in nanoparticles. The drawback of inorganic nanoparticles is the toxicity of metal ions to the environment, underscoring the necessity for an environmentally sustainable and contemporary solution. Consequently, nanoparticles produced from biomolecules serve as a pertinent instrument in combating malaria while exerting low environmental influence. As the Figure 2 illustrates the effects and potential action mechanisms, hence authors propose that the toxicity of green nanoparticles may be attributed to the established effects of phytochemicals [90]. These compounds are acknowledged for their larvicidal and mosquitocidal attributes, influencing the mosquito nervous system by either overstimulation or inhibition. This neuro-modulation leads to noticeable behavioral alterations, including less swimming and increased restlessness in larvae. Nanoparticles of optimum size seamlessly traverse the membranes of mosquitoes. Their mode of action entails interactions with DNA, leading to increased apoptosis and oxidative stress in the target species. Significantly, when utilized in field or semi-field situations, these nanoparticles create an oily coating, a characteristic associated with decreased water oxygenation. Moreover, both phytochemicals and green nanoparticles affect parameters including the attractiveness of female mosquitoes to breeding locations, which are directed by olfactory signals influenced by water quality [91-93]. The effects of green-synthesized nanoparticles may be attributed to the established properties of biomolecules found in plant extracts.

**FUTURE PERSPECTIVES**

The lack of evidence regarding the mechanism of action of the plant extracts presents a significant issue in this review. The complex chemical composition of plants can hinder the evolution of resistance because of the diverse range of toxic compounds found in various plant species. The authors firmly advocate for comprehensive studies regarding the enduring presence of green nanoparticles, their potential adverse effects, the feasibility of large-scale production, and their practical applications. The extensive life cycle of the *Plasmodium parasite*, which necessitates both human and mosquito hosts, exacerbates treatment and prevention challenges [80]. The parasite experiences various developmental stages, each possessing distinct biological traits, complicating efforts to target numerous phases of its life cycle.

The antigenic variety and immune evasion mechanisms of *Plasmodium* complicate the development of universally effective treatments [94]. The biological obstacles are exacerbated by inadequate health infrastructure in numerous malaria-endemic areas, especially in sub-Saharan Africa and Southeast Asia. Insufficient health infrastructure hampers the provision of effective malaria treatment and prevention, characterized by restricted healthcare access, a shortage of trained medical professionals, and inadequate supply chains for medications and diagnostics, which present considerable obstacles to malaria control initiatives. Emerging challenges, including climate change, urbanization, and alterations in land use

patterns, are modifying the distribution and behavior of malaria vectors, potentially resulting in the establishment of malaria in novel regions [95]. These environmental alterations may hinder current malaria control initiatives and require novel tactics to address evolving epidemiological trends.

To tackle these obstacles, the future of malaria treatment must concentrate on several critical domains. Creating novel antimalarial pharmaceuticals with distinct mechanisms of action is essential to address medication resistance. Research is currently underway to identify lead compounds capable of circumventing resistance and targeting various stages in the life cycle of parasites [96,97]. Combination therapy using novel pharmaceuticals may be crucial in preventing the emergence of resistance. Next-generation vaccinations that enhance efficacy, durability, and coverage are essential. Investigated strategies encompass multi-antigen vaccines aimed at different stages of the parasite life cycle and vaccinations designed to provoke enhanced cellular and humoral immune responses [98]. Promising candidates such as R21/Matrix-M are currently undergoing clinical studies and may demonstrate superior efficacy relative to existing vaccinations.

Ultimately, sustained worldwide collaboration and funding are essential for the advancement of malaria treatment. Collaborations among governments, international organizations, academic institutions, and the commercial sector are crucial. Enhanced financial support for research and development, along with the implementation of novel interventions, would be essential to attain the objective of malaria eradication. By tackling these problems and pursuing these future paths, substantial advancements can be achieved in the battle against malaria, ultimately alleviating the burden of this dreadful illness.

## CONCLUSIONS

While the existing literature provides a comprehensive overview of this subject, additional discussions are necessary to investigate the importance of green-synthesized nanoparticles in malaria prevention and their impact on the vector. A multitude of studies has undoubtedly explored its potential in treatment; however, additional investigation into its role in vector prevention is essential. This paper primarily focused on conducting a comprehensive evaluation of nanoparticles that have been synthesized in the past, which may be effective in decreasing the transmission of malaria. By tackling this research gap, we aim to offer valuable insights into malaria prevention. Nanotechnology stands as a leading area of exploration in the domains of drug delivery and the development of groundbreaking tools. The process of nanoformulating molecules enables the utilization of smaller amounts relative to bulk chemicals, leading to reduced toxicity levels. The properties and substances associated with nanotechnology are an essential topic of discussion because of their potential impact on the biological effects and behavior of nanoparticles. The limitations associated with inorganic nanoparticles (NPs) have led to a significant body of scientific literature focusing on the biogenic synthesis of NPs. There has been considerable investigation into the application of plant extracts for the synthesis of inorganic nanoparticles that exhibit potent effects against the malaria vector and parasite. The synthesis of nanoparticles through the use of plant polyphenols amplifies the effects of metallic nanoparticles, leading to a detrimental impact on every stage of the mosquito vector's development. This is clearly demonstrated by the mortality rates in larvae, a reduction in egg-laying, alterations in feeding behavior, and modifications in both morphology and behavior. Moreover, nanoparticles synthesized from plant extracts exhibit antiplasmodial properties by hindering the growth of parasites. Furthermore, when choosing strategies to address malaria, it is crucial to take into account aspects like fair accessibility, sustainability over time, and the effects on human health.

## CONFLICT OF INTEREST

The authors claim no conflicts of interest because none financial support was received from any government, non-government agency or organization to conduct this research work.

## REFERENCES

1. Al-Awadhi M, Ahmad S, Iqbal J (2021). Current status and the epidemiology of malaria in the Middle East region and beyond. Microorganisms 9: 338.
2. Aliyo A, Golicha W, Fikrie A (2024). Malaria and associated factors among under-five children in Borena pastoral communities, southern Ethiopia. Front Parasitol. 3: 1438218.
3. Anwar M (2024). Introduction: An overview of malaria and *Plasmodium*. *In: Drug Targets for Plasmodium falciparum: Historic to Future Perspectives* (Tarique M, ed). Springer Nature, Singapore. pp. 1–17.
4. Zekar L, Sharman T (2024). *Plasmodium falciparum* malaria. StatPearls Publishing,Treasure Island, FL, USA. http://www.ncbi.nlm.nih.gov/books/NBK555962/ (accessed on 10 August 2024).
5. Varo R, Chaccour C, Bassat Q (2020). Update on malaria. Med Clin Engl Ed. 155: 395–402.

6. Kotepui M, Kotepui KU, Milanez GDJ (2020). Prevalence and risk factors related to poor outcome of patients with severe *Plasmodium vivax* infection: A systematic review, meta-analysis, and analysis of case reports. BMC Infect Dis. 20: 363.
7. Naik DG (2020). *Plasmodium knowlesi*-mediated zoonotic malaria: A challenge for elimination. Trop Parasit. 10: 3.
8. Oriero EC, Amenga-Etego L, Ishengoma DS, Amambua-Ngwa A (2021). *Plasmodium malariae*, current knowledge and future research opportunities on a neglected malaria parasite species. Crit Rev Microbiol. 47: 44–56.
9. Dagen M (2020). History of malaria and its treatment. *In: Antimalarial Agents* (Patrick GL, ed). Elsevier, Amsterdam, Netherlands. 2020: 1–48.
10. Dhorda M, Amaratunga C, Dondorp AM (2021). Artemisinin and multidrug-resistant *Plasmodium falciparum*- A threat for malaria control and elimination. Curr Opin Infect Dis. 34: 432–439.
11. Siqueira-Neto JL, Wicht KJ, Chibale K, Burrows JN, Fidock DA, Winzeler EA (2023). Antimalarial drug discovery: Progress and approaches. Nat Rev Drug Discover. 22: 807–826.
12. Pandey SK, Anand U, Siddiqui WA, Tripathi R (2023). Drug development strategies for malaria: with the hope for new antimalarial drug discovery- An update. Adv Med. 5060665.
13. Shibeshi MA, Kifle ZD, Atnafie SA (2020). Antimalarial drug resistance and novel targets for antimalarial drug discovery. Infect Drug Resist. 13: 4047–4060.
14. Kapishnikov S, Hempelmann E, Elbaum M, Als-Nielsen J, Leiserowitz L (2021). Malaria pigment crystals: The achilles heel of the malaria parasite. Chem Med Chem. 16: 1515–1532.
15. Biswas P, Roy R, Ghosh K, Nath D, Samadder A, Nandi S (2024). To quest new targets of *Plasmodium* parasite and their potential inhibitors to combat antimalarial drug resistance. J Parasit Dis. 48(4): 671-722
16. Wilkins CA, du Plessis LH, Viljoen JM (2021). Investigating in vitro and ex vivo properties of artemether double-fixed dose combination lipid matrix tablets prepared by hot fusion. Pharmaceutics 13: 922.
17. Popovici J, Tebben K, Witkowski B, Serre D (2021). Primaquine for *Plasmodium vivax* radical cure: What we do not know and why it matters. Int J Parasitol Drugs Drug Resist. 15: 36–42.
18. Capela R, Moreira R, Lopes F (2019). An overview of drug resistance in protozoal diseases. Int J Mol Sci. 20: 5748.
19. Yadessa AM, Zeleke D (2021). A Review on synthesis of quinoline analogs as antimalarial, antibacterial and anticancer agents. Ethiop J Sci Sustain Dev. 8: 73–95.
20. Chamma-Siqueira NN, Negreiros SC, Ballard SB, Farias S, Silva SP, Chenet SM, Santos EJM, de Sena LWP, da Costa FP, Cardoso-Mello AGN (2022). Higher-dose primaquine to prevent relapse of *Plasmodium vivax* malaria. N Engl J Med. 386: 1244–1253.
21. Hanboonkunupakarn B, White NJ (2022). Advances and roadblocks in the treatment of malaria. Br J Clin Pharmacol. 88: 374–382.
22. Lacerda MVG, Llanos-Cuentas A, Krudsood S, Lon C, Saunders DL, Mohammed R, Yilma D, Batista Pereira D, Espino FEJ, Mia RZ (2019). Single-dose tafenoquine to prevent relapse of *Plasmodium vivax* malaria. N Engl J Med. 380: 215–228.
23. Wangdahl A, Sondén K, Wyss K, Stenstrom C, Bjorklund D, Zhang J, Hervius Askling H, Carlander C, Hellgren U, Farnert A (2022). Relapse of *Plasmodium vivax* and *Plasmodium ovale* malaria with and without primaquine treatment in a nonendemic area. Clin Infect Dis. 74: 1199–1207.
24. Zottig VE, Carr KA, Clarke JG, Shmuklarsky MJ, Kreishman-Deitrick M (2020). Army antimalarial drug development: An advanced development case study for *Tafenoquine*. Mil Med. 185: 617–623.
25. Pethrak C, Posayapisit N, Pengon J, Suwanakitti N, Saeung A, Shorum M, Aupalee K, Taai K, Yuthavong Y, Kamchonwongpaisan S (2022). New insights into antimalarial chemopreventive activity of antifolates. Antimicrob Agents Chemother. 66: e01538-21.
26. Abugri J, Ansah F, Asante KP, Opoku CN, Amenga-Etego LA, Awandare GA (2018). Prevalence of chloroquine and antifolate drug resistance alleles in *Plasmodium falciparum* clinical isolates from three areas in Ghana. AAS Open Res. 1: 1.
27. Shamshad H, Bakri R, Mirza AZ (2022). Dihydrofolate reductase, thymidylate synthase, and serine hydroxy methyltransferase: Successful targets against some infectious diseases. Mol Biol Rep. 49: 6659–6691.
28. Sehrawat R, Rathee P, Khatkar S, Akkol E, Khayatkashani M, Nabavi SM, Khatkar A (2024). Dihydrofolate Reductase (DHFR) inhibitors: A comprehensive review. Curr Med Chem. 31: 799–824.
29. Nzila A (2006). The past, present and future of antifolates in the treatment of *Plasmodium falciparum* infection. J Antimicrob Chemother. 57: 1043–1054.
30. Laminou IM, Issa I, Adehossi E, Maman K, Jackou H, Coulibaly E, Tohon ZB, Ahmed J, Sanoussi E, Koko D (2020). Therapeutic efficacy and tolerability of artemether-lumefantrine for uncomplicated *Plasmodium falciparum* malaria in Niger, 2020. Malar J. 23: 144.
31. Huillier AG, Lau R, Bitnun A, Boggild AK (2020). Atovaquone-proguanil treatment failure in a case of pediatric *Plasmodium falciparum* infection: Malabsorption and resistance. Travel Med Infect. Dis. 37: 101829.
32. Kurup N, Rajnani N (2022). Chronology of drug development for malaria. *In: Drug Development for Malaria* (Hoboken NJ, ed). John Wiley and Sons, Ltd., USA. pp. 1–23.
33. Fernandes VdS, da Rosa R, Zimmermann LA, Rogério KR, Kummerle AE, Bernardes LSC, Graebin CS (2022). Antiprotozoal agents: How have they changed over a decade? Arch Pharm. 355: 2100338.

34. Mbeye N, ter Kuile FO, Davies MA, Phiri K, Egger M, Wandeler G (2014). Cotrimoxazole prophylactic treatment prevents malaria in children in sub-Saharan Africa: Systematic review and meta-analysis. Trop Med Int Hlth. 19: 1057–1067.
35. Egwu CO, Augereau JM, Reybier K, Benoit-Vical F (2021). Reactive oxygen species as the brainbox in malaria treatment. Antioxidants 10: 1872.
36. Egwu CO, Tsamesidis I, Pério P, Augereau JM, Benoit-Vical F, Reybier K (2021). Superoxide: A major role in the mechanism of action of essential antimalarial drugs. Free Radic Biol Med. 167: 271–275.
37. Gupta Y, Goicoechea S, Pearce CM, Mathur R, Romero JG, Kwofie SK, Weyenberg MC, Daravath B, Sharma N, Poonam (2022). The emerging paradigm of calcium homeostasis as a new therapeutic target for protozoan parasites. Med Res Rev. 42: 56–82.
38. Erhunse N, Sahal D (2021). Protecting future antimalarials from the trap of resistance: Lessons from artemisinin-based combination therapy (ACT) failures. J Pharm Anal. 11: 541–554.
39. Wicht KJ, Mok S, Fidock DA (2020). Molecular mechanisms of drug resistance in *Plasmodium falciparum* malaria. Annu Rev Microbiol. 74: 431–454.
40. Derbie A, Mekonnen D, Adugna M, Yeshitela B, Woldeamanuel Y, Abebe T (2020). Therapeutic efficacy of artemether- lumefantrine (CoartemR) for the treatment of uncomplicated *Falciparum* malaria in Africa: A systematic review. J Parasitol Res. 2020: 7371681.
41. Mumtaz R, Okell LC, Challenger JD (2020). Asymptomatic recrudescence after artemether–lumefantrine treatment for uncomplicated falciparum malaria: A systematic review and meta-analysis. Malar J. 19: 453.
42. Maude RJ, Plewes K, Faiz MA, Hanson J, Charunwatthana P, Lee SJ, Tarning J, Yunus EB, Hoque MG, Hasan MU (2009). Does artesunate prolong the electrocardiograph QT interval in patients with severe malaria? Am J Trop Med Hyg. 80: 126–132.
43. Marwa K, Kapesa A, Baraka V, Konje E, Kidenya B, Mukonzo J, Kamugisha E, Swedberg G (2022). Therapeutic efficacy of artemether-lumefantrine, artesunate-amodiaquine and dihydroartemisinin-piperaquine in the treatment of uncomplicated *Plasmodium falciparum* malaria in Sub-Saharan Africa: A systematic review and meta-analysis. PLoS ONE 17: e0264339.
44. Zwang J, Dorsey G, Martensson A, Alessandro U, Ndiaye JL, Karema C, Djimde A, Brasseur P, Sirima SB, Olliaro P (2014). *Plasmodium falciparum* clearance in clinical studies of artesunate-amodiaquine and comparator treatments in sub-Saharan Africa, 1999–2009. Malar J. 13: 114.
45. Mohammed H, Sime H, Hailgiorgis H, Gubae K, Haile M, Solomon H, Etana K, Girma S, Bekele W, Chernet M (2022). Therapeutic efficacy of dihydroartemisinin–piperaquine for the treatment of uncomplicated *Plasmodium vivax* malaria in Seacha area, Arbaminch Zuria District, South West Ethiopia. Malar J. 21:351.
46. Popovici J, Vantaux A, Primault L, Samreth R, Piv EP, Bin S, Kim S, Lek D, Serre D, Menard D (2018). Therapeutic and transmission-blocking efficacy of dihydroartemisinin/piperaquine and chloroquine against *Plasmodium vivax* malaria, Cambodia. Emerg Infect Dis. 24: 1516–1519.
47. Carrara VI, Sirilak S, Thonglairuam J, Rojanawatsirivet C, Proux S, Gilbos V, Brockman A, Ashley EA, McGready R, Krudsood S (2006). Deployment of early diagnosis and mefloquine-artesunate treatment of falciparum malaria in Thailand: The Tak Malaria Initiative. PLoS Med. 3: e183.
48. Nosten F, van Vugt M, Price R, Luxemburger C, Thway KL, Brockman A, McGready R, ter Kuile F, Looareesuwan S, White NJ (2000). Effects of artesunate-mefloquine combination on incidence of *Plasmodium falciparum* malaria and mefloquine resistance in western Thailand: A prospective study. Lancet Lond Engl. 356: 297–302.
49. Dondorp AM, Nosten F, Yi P, Das D, Phyo AP, Tarning J, Lwin KM, Ariey F, Hanpithakpong W, Lee SJ (2009). Artemisinin resistance in *Plasmodium falciparum* malaria. N Engl J Med. 361: 455–467.
50. Price RN, Nosten F, Luxemburger C, Kham A, Brockman A, Chongsuphajaisiddhi T, White NJ (1995). Artesunate versus artemether in combination with mefloquine for the treatment of multidrug-resistant falciparum malaria. Trans R Soc Trop Med Hyg. 89: 523–527.
51. Sirima SB, Ogutu B, Lusingu JPA, Mtoro A, Mrango Z, Ouedraogo A, Yaro JB, Onyango KO, Gesase S, Mnkande E (2016). Comparison of artesunate–mefloquine and artemether–lumefantrine fixed-dose combinations for treatment of uncomplicated *Plasmodium falciparum* malaria in children younger than 5 years in sub-Saharan Africa: A randomised, multicentre, phase 4 trial. Lancet Infect Dis. 16: 1123–1133.
52. Lee SJ, ter Kuile FO, Price RN, Luxemburger C, Nosten F (2017). Adverse effects of mefloquine for the treatment of uncomplicated malaria in Thailand: A pooled analysis of 19,850 individual patients. PLoS ONE 12: e0168780.
53. Belete TM (2020). Recent progress in the development of new antimalarial drugs with novel targets. Drug Des Devel Ther 14: 3875–3889.
54. Ibraheem ZO, Abd Majid R, Noor SM, Sedik HM, Basir R (2014). Role of different Pfcrt and Pfmdr-1 mutations in conferring resistance to antimalaria drugs in *Plasmodium falciparum.* Malar Res Treat. 2014: 950424.
55. Habtamu K, Petros B, Yan G (2022). *Plasmodium vivax*: The potential obstacles it presents to malaria elimination and eradication. Trop Dis Travel Med Vaccines 8: 27.
56. Nureye D, Salahaddin M, Zewudie A (2020). Current medicines for malaria including resistance issues. J Pharmacol Pharmacother. 11: 90–99.
57. Rumaseb A, Moraes Barros RR, Sá JM, Juliano JJ, William T, Braima KA, Barber BE, Anstey NM, Price RN, Grigg MJ (2023). No association between the *Plasmodium vivax* crt-o MS334 or In9pvcrt polymorphisms and chloroquine failure in a pre-elimination clinical cohort from Malaysia with a large clonal expansion. Antimicrob Agents Chemother. 67: e01610-22.

58. Orjuela-Sánchez P, de Santana Filho FS, Machado-Lima A, Chehuan YF, Costa MRF, Alecrim MdGC, del Portillo HA (2009). Analysis of single-nucleotide polymorphisms in the crt-o and mdr1 genes of *Plasmodium vivax* among chloroquine-resistant isolates from the Brazilian Amazon region. Antimicrob Agents Chemother. 53: 3561–3564.
59. Mayxay M, Barends M, Brockman A, Jaidee A, Nair S, Sudimack D, Pongvongsa, T, Phompida S, Phetsouvanh R, Anderson T (2007). In vitro antimalarial drug susceptibility and Pfcrt mutation among fresh *Plasmodium falciparum* isolates from the Lao PDR (Laos). Am J Trop Med Hyg. 76: 245–250.
60. Legrand E, Volney B, Meynard JB, Mercereau-Puijalon O, Esterre P (2008). In vitro monitoring of *Plasmodium falciparum* drug resistance in French Guiana: A synopsis of continuous assessment from 1994 to 2005. Antimicrob Agents Chemother. 52: 288–298.
61. sOgetii GN, Akech S, Jemutai J, Boga M, Kivaya E, Fegan G, Maitland K (2010). Hypoglycaemia in severe malaria, clinical associations and relationship to quinine dosage. BMC Infect Dis. 10: 334.
62. Wroblewski HA, Kovacs RJ, Kingery R, Overholser BR, Tisdale JE (2012). High risk of QT interval prolongation and torsades de pointes associated with intravenous quinidine used for treatment of resistant malaria or babesiosis. Antimicrob Agents Chemother. 56: 4495–4499.
63. Henry M, Briolant S, Fontaine A, Mosnier J, Baret E, Amalvict R, Fusai T, Fraisse L, Rogier C, Pradines B (2008). In vitro activity of ferroquine is independent of polymorphisms in transport protein genes implicated in quinoline resistance in *Plasmodium falciparum*. Antimicrob Agents Chemother. 52: 2755–2759.
64. White N, Looareesuwan S, Edwards G, Phillips R, Karbwang J, Nicholl D, Bunch C, Warrell D (1987). Pharmacokinetics of intravenous amodiaquine. Br J Clin Pharmacol. 23: 127–135.
65. Nasveld PE, Edstein MD, Reid M, Brennan L, Harris IE, Kitchener SJ, Leggat PA, Pickford P, Kerr C, Ohrt C (2010). Randomized, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. Antimicrob Agents Chemother. 54: 792–798.
66. Price RN, Simpson JA, McCarthy JS, Halofantrine (2017). Kucers' the Use of Antibiotics, 7th ed. CRC Press: Boca Raton, FL, USA.
67. Wattanakul T, Ogutu B, Kabanywanyi AM, Asante KP, Oduro A, Adjei A, Sie A, Sevene E, Macete E, Compaore G (2020). Pooled multicenter analysis of cardiovascular safety and population pharmacokinetic properties of piperaquine in African patients with uncomplicated falciparum malaria. Antimicrob Agents Chemother. 64: e01848-19.
68. Dhingra SK, Redhi D, Combrinck JM, Yeo T, Okombo J, Henrich PP, Cowell AN, Gupta P, Stegman ML, Hoke JM 2017. A variant PfCRT isoform can contribute to *Plasmodium falciparum* resistance to the first-line partner drug piperaquine. mBio 8: e00303-17.
69. White NJ, van Vugt M, Ezzet FD (1999). Clinical pharmacokinetics and pharmacodynamics of artemether-lumefantrine. Clin Pharmacokinet. 37: 105–125.
70. Stover KR, King ST, Robinson J (2012). Artemether-Lumefantrine: An option for malaria. Ann Pharmacother. 46: 567–577.
71. Ashley EA, Recht J, White NJ (2014). Primaquine: The risks and the benefits. Malar J. 13: 41\18.
72. Ganesan S, Chaurasiya ND, Sahu R, Walker LA, Tekwani BL (2012). Understanding the mechanisms for metabolism-linked hemolytic toxicity of primaquine against glucose 6-phosphate dehydrogenase deficient human erythrocytes: Evaluation of eryptotic pathway. Toxicology 294: 54–60.
73. Frampton JE (2018). Tafenoquine: First global approval. Drugs 78: 1517–1523.
74. de Kock M, Tarning J, Workman L, Allen EN, Tekete MM, Djimde AA, Bell DJ, Ward SA, Barnes KI, Denti P (2018). Population pharmacokinetic properties of sulfadoxine and pyrimethamine: A pooled analysis to inform optimal dosing in African children with uncomplicated malaria. Antimicrob Agents Chemother. 62: e01370-17.
75. Helsby N, Edwards G, Breckenridge A, Ward S (1993). The multiple dose pharmacokinetics of proguanil. Br J Clin Pharmacol. 35: 653–656.
76. Veenendaal R, Edstein MD, Rieckmann KH (2009). Pharmacokinetics of chlorproguanil in man after a single oral dose of LapudrineR. Chemotherapy 34: 277–283.
77. Ashton M, Gordi T, Hai TN, Van Huong N, Sy ND, Nieu NT, Huong DX, Johansson M, Công LD (1998). Artemisinin pharmacokinetics in healthy adults after 250, 500 and 1000 mg single oral doses. Biopharm. Drug Dispos. 19: 245–250.
78. Gobbi F, Buonfrate D, Menegon M, Lunardi G, Angheben A, Severini C, Gori S, Bisoffi Z (2016). Failure of dihydro artemisin in piperaquine treatment of uncomplicated *Plasmodium falciparum* malaria in a traveller coming from Ethiopia. Malar J. 15: 525.
79. Naing C, Racloz V, Whittaker MA, Aung K, Reid SA, Mak JW, Tanner M (2013). Efficacy and safety of Dihydroartemisinin- Piperaquine for treatment of *Plasmodium vivax* malaria in endemic countries: Meta-analysis of randomized controlled studies. PLoS ONE 8: e78819.
80. Li J, Zhang J, Li Q, Hu Y, Ruan Y, Tao Z, Xia H, Qiao J, Meng L, Zeng W (2020). Ex vivo susceptibilities of *Plasmodium vivax* isolates from the China-Myanmar border to antimalarial drugs and association with polymorphisms in Pvmdr1 and Pvcrt-o genes. PLoS Negl Trop Dis. 14: e0008255.
81. Sridapan T, Rattanakoch P, Kijprasong K, Srisutham S (2024). Drug resistance markers in *Plasmodium vivax* isolates from a Kanchanaburi province, Thailand between January to May 2023. PLoS ONE 19: e0304337.
82. Shekalaghe SA, ter Braak R, Daou M, Kavishe R, van den Bijllaardt W, van den Bosch S, Koenderink JB, Luty AJF, Whitty CJM, Drakeley C (2010). In Tanzania, hemolysis after a single dose of primaquine coadministered with an

artemisinin is not restricted to Glucose-6-Phosphate Dehydrogenase-Deficient (G6PD A−) individuals. Antimicrob Agents Chemother. 54: 1762–1768.
83. Plowe CV, Kublin JG, Doumbo OK (1998). *P. falciparum* dihydrofolate reductase and dihydropteroate synthase mutations: Epidemiology and role in clinical resistance to antifolates. Drug Resist Updat. 1: 389–396.
84. Nair S, Miller B, Barends M, Jaidee A, Patel J, Mayxay M, Newton P, Nosten F, Ferdig MT, Anderson TJC (2008). Adaptive copy number evolution in malaria parasites. PLOS Genet. 4: e1000243.
85. Kidgell C, Volkman SK, Daily J, Borevitz JO, Plouffe D, Zhou Y, Johnson JR, Roch KGL, Sarr O, Ndir O (2006). A systematic map of genetic variation in *Plasmodium falciparum*. PLoS Pathog. 2: e57.
86. Cowell AN, Winzeler EA (2019). The genomic architecture of antimalarial drug resistance. Brief Funct Genom. 18: 314–328.
87. Velu K, Elumalai D, Hemalatha P, Janaki A, Babu M, Hemavathi M, Kaleena PK (2015). Evaluation of silver nanoparticles toxicity of *Arachis hypogaea* peel extracts and its larvicidal activity against malaria and dengue vectors. Environ Sci Pollut Res. 22: 17769–17779.
88. Kamaraj C, Gandhi PR, Ragavendran C, Sugumar V, Kumar RCS, Ranjith R, Priyadharsan A, Cherian T (2022). Sustainable development through the bio-fabrication of ecofriendly ZnO nanoparticles and its approaches to toxicology and environmental protection. Biomass Convers Biorefin. 1–17.
89. Sabzalizade S, Amani A, Vatandoost H, Hosseini F, Najafi-Taher R, Basseri HR (2021). Evaluation of nanoemulsion of *Eucalyptus globulus* oil as potent botanical larvicide against malaria vector, *Anopheles stephensi* and West Nile vector, *Culex pipiens* under laboratory and semi-field conditions. J Arthropod Borne Dis. 15: 380–388.
90. Govindarajan M, Benelli G (2016). Facile biosynthesis of silver nanoparticles using *Barleria cristata*: Mosquitocidal potential and biotoxicity on three non-target aquatic organisms. Parasitol Res. 115: 925–935.
91. Suman TY, Elumalai D, Kaleena PK, Rajasree SRR (2013). GC–MS analysis of bioactive components and synthesis of silver nanoparticle using *Ammannia baccifera* aerial extract and its larvicidal activity against malaria and filariasis vectors. Ind Crops Prod. 47: 239–245.
92. Nalini M, Lena M, Sumathi P, Sundaravadivelan C (2019). Effect of phyto-synthesized silver nanoparticles on developmental stages of malaria vector, *Anopheles stephensi* and dengue vector, *Aedes aegypti*. Egypt J Basic Appl Sci. 4: 212–218.
93. Arjunan NK, Murugan K, Rejeeth C, Madhiyazhagan P, Barnard DR (2012). Green synthesis of silver nanoparticles for the control of mosquito vectors of malaria, filariasis, and dengue. Vector Borne Zoonotic Dis. 12: 262–268.
94. Gandhi PR, Jayaseelan C, Mary RR, Mathivanan D, Suseem SR (2017). Acaricidal, pediculicidal and larvicidal activity of synthesized ZnO nanoparticles using *Momordica charantia* leaf extract against blood feeding parasites. Exp Parasitol. 181: 47–56.
95. Priyadarshini KA, Murugan K, Panneerselvam C, Ponarulselvam S, Hwang JS, Nicoletti M (2012). Biolarvicidal and pupicidal potential of silver nanoparticles synthesized using *Euphorbia hirta* against *Anopheles stephensi* Liston (Diptera: Culicidae). Parasitol Res. 111: 997–1006.
96. Roni M, Murugan K, Panneerselvam C, Subramaniam J, Hwang JS (2013). Evaluation of leaf aqueous extract and synthesized silver nanoparticles using *Nerium oleander* against *Anopheles stephensi* (Diptera: Culicidae). Parasitol Res. 112: 981–990.
97. Govindarajan M, Khater HF, Panneerselvam C, Benelli G (2016). One-pot fabrication of silver nanocrystals using *Nicandra physalodes*: A novel route for mosquito vector control with moderate toxicity on non-target water bugs. Res Vet Sci. 107: 95–101.
98. Kumar D, Kumar P, Singh H, Agrawal V (2020). Biocontrol of mosquito vectors through herbal-derived silver nanoparticles: Prospects and challenges. Environ Sci Pollut Res Int. 27: 25987–26024.