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REVIEW ARTICLE

Plant-Derived Nanoparticles as Effective and Economical Preventive Strategies against Malaria Parasites

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ABSTRACT

Malaria stands as a significant global health challenge, especially in low-income regions of Sub Saharan Africa. The rising prevalence of malaria morbidity can primarily be attributed to deficiencies in preventative strategies, including the absence of effective vaccines and inadequate management of the parasite vector. Moreover, elevated mortality rates stem from treatment failures linked to inadequate patient adherence and the emergence of drug resistance. Despite the fact that the causative agent (Plasmodium spp.) is an intracellular parasite, the suggested antimalarial medications exhibit extensive volumes of distribution and exhibit low to no specificity towards the host cell. This results in significant adverse effects that hinder patient adherence and encourage the development of drug-resistant strains. Recent investigations are showing promise in the discovery of new antimalarial agents; however, the absence of effective methods for targeted delivery continues to be a concern, considering the potential for further resistance development. Innovative approaches utilizing green nanotechnologies present a promising pathway for malaria management, highlighting their capability to eradicate malaria vectors (Anopheles sp.) and to encapsulate both current and novel antimalarial agents for targeted delivery to various sites. This review focuses on various studies on plant-derived nanoparticles as effective and economical preventive strategies against malaria parasites. The plant-based nanoengineering approaches aimed to target malaria parasites by the site-specific delivery of natural products via ligand-decorated nanoparticles that interact with receptors on either the host cells or the malaria parasites. Such established plant medicines, surface-engineered nanoparticles, and the molecular targets of parasite and host cells provide valuable insights for the future development of antimalarial drugs, facilitating scientific advancements focused on eradicating malaria.

Keywords: *Antimalarial drugs, Insecticides, Green synthesis, Nanoparticles, Plasmodium spp*

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INTRODUCTION

Malaria is among the most fatal and pervasive infectious illnesses globally. The World Health Organization's (WHO) 2022 report indicated that malaria resulted in 619,000 fatalities and 247 million infections worldwide in 2021 [1]. Middle- and low-income nations continue to be the most impacted by the malaria epidemic, mostly because to their less robust and comprehensive strategic methodologies. The prevalence of malaria is increasing annually, particularly among susceptible populations, including children under five years and pregnant women. Malaria infection in pregnancy significantly increases the risk of morbidity and mortality for both the mother and the newborn [2]. Research demonstrates that malaria considerably undermines the economies of impacted nations, particularly those categorized as "medium and low income," primarily due to the high costs associated with eradication efforts [3]. In

prevention, financial and logistical assistance organizations are offering significant support to these nations to aid in their fight against malaria. Significant attempts have been undertaken over the last century to eliminate malaria worldwide. Eradication techniques predominantly emphasize vector control, specifically targeting *Anopheles* mosquitoes in both larval and adult phases, particularly in stagnant water bodies and wetlands. Commonly used compounds include dichlorodiphenyltrichloroethane (DDT), synthetic pyrethroids, and organophosphates, which are utilized in both indoor and outdoor residual spraying aimed at Anopheles mosquitoes [4]. Given the harmful effects of traditional chemical agents and their lasting consequences on human health and the environment, there is a growing focus on natural products, especially essential oils (EOs), which are monoterpenoid compounds obtained from plant extracts [5, 6]. These natural alternatives are attracting interest because of their reduced toxicity, global availability, and cost-effectiveness. They are being investigated for their effectiveness in deterring and eradicating female *Anopheles* [7]. Despite being environmentally safe and demonstrating potential as insecticides and repellents, many essential oils are less effective than synthetic pyrethroids, particularly those with low concentrations of monoterpenoids [8]. Earlier investigations indicated that incorporating 5% vanillin (as a fixative compound) into essential oils can enhance their effectiveness in repelling mosquito bites over an extended period [9]. Furthermore, strategies for controlling vectors are advancing to incorporate the application of mosquito repellents within households and the provision of insecticide-treated mosquito nets to vulnerable populations [10]. The ongoing presence of malaria can be linked to various policy factors, particularly the insufficient or ineffective implementation of environmental sanitation policies. The existence of these policy gaps leads to the accumulation of stagnant water in urban environments, creating ideal conditions for mosquito breeding [11,12]. This results in the ongoing survival and expansion of the mosquito populations that transmit malaria. A variety of pesticides with larvicidal characteristics are utilised to eradicate mosquito larvae in marshy areas. Nonetheless, these chemicals present considerable toxicity hazards to aquatic ecosystems and their overall biomass.

Furthermore, there have been observations of resistance to these larvicides in various regions worldwide [13]. A significant concern is the emerging resistance of female Anopheles mosquitoes to the insecticides utilised in insecticide-impregnated mosquito nets. In countries with middle and low income, restricted access to healthcare services and skilled medical professionals frequently leads to postponements in malaria diagnosis and the initiation of suitable treatment. This delay not only worsens the infection but can also, unfortunately, result in patient deaths [14]. The interplay of increasing insecticide resistance and difficulties in accessing healthcare highlights the necessity for a comprehensive strategy in the control and treatment of malaria. In 2012, the WHO established a global plan for managing insecticide resistance in malaria (GPIRM), consisting of five strategies to be executed in nations impacted by insecticide-resistant mosquitoes. These strategies serve as the foundational elements in the battle against insecticide resistance: i) devise and execute strategies for managing insecticide resistance in regions affected by malaria; ii) guarantee accurate and prompt monitoring of entomological data and resistance, along with efficient data management; iii) create novel and innovative tools for vector control; iv) address knowledge gaps regarding the mechanisms of insecticide resistance and assess the effectiveness of existing management strategies; and v) secure the necessary advocacy, human resources, and financial support [16,17]. Innovative tools are being developed using nanotechnologies to control the vectors of parasitic diseases, especially malaria (Fig. 1). Studies indicate that metallic nanoparticles derived from plants and plant extracts demonstrate efficacy against mosquito eggs, larvae, pupae, and adults, specifically targeting *Anopheles* mosquitoes [18].

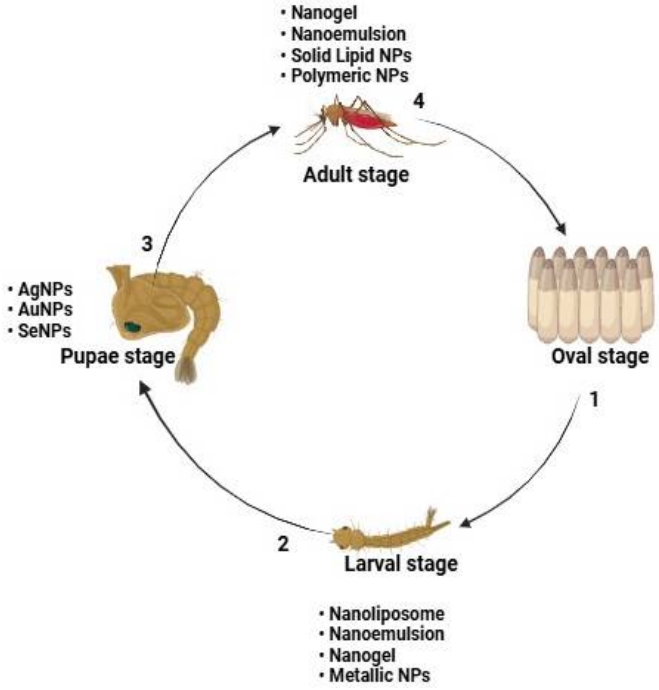

Figure 1: Life cycle of *Plasmodium* and nanoparticles used to control the different stages.

These bio-derived nanoparticles are termed "Green nanoparticles" because they are synthesized using low-toxicity reagents. They offer several advantages compared to traditional insecticides, such as ease of formulation, low toxicity, and the absence of known resistance to date. The battle against malaria encompasses various downstream initiatives, including intermittent preventive treatments aimed at safeguarding vulnerable populations from infection by the plasmodium parasite. A multitude of studies indicates that nanotechnologies improve the pharmacokinetic profiles of current antimalarials and enhance the larvicidal potential of plant-derived metallic nanoparticles [19-22]. The main objectives of studies in nanotechnology focus on enhancing the water solubility and oral bioavailability of active pharmaceutical ingredients (API), minimizing their toxicity via encapsulation in nanocarriers, leveraging them for the reduction of metal ions to produce metallic nanoparticles with intrinsic antivectorial or antiplasmodial properties, and using them as foundational components in the development of drug delivery systems (DDSs) [23]. Furthermore, initiatives are underway to modify nanocarriers for the targeted delivery to malaria-related sites, thereby improving the accuracy and effectiveness of treatments. This paper presents a thorough examination of plant materials utilised in two significant ways: as economical sources for the production of intrinsically active nanoparticles and as foundations for encapsulating both established and novel antimalarial agents, encompassing plant extracts, fractions, and pure compounds. This approach addresses both the vector and human phases of *Plasmodium falciparum*, with the goal of achieving complete eradication of malaria [24]. The analysis emphasizes the tactical application of plant-derived nanotechnologies in the fight against malaria, targeting various stages of the parasite's lifecycle. This document outlines the molecular targets associated with malaria, emphasizing the importance of surface functionalization of nanoparticles [25]. This technique is essential for improving the targeted delivery and effectiveness of plant-derived antimalarial medications in both prevention and treatment strategies.

PLANTS AND NANOFORMULATIONS

Plants in their natural habitats have developed intrinsic defense mechanisms to fend off pests, predators, and competing species [26]. Consequently, utilizing the natural capabilities of these plants to address the issue of naturally occurring mosquitoes represents a thoughtful approach to maximize their biological effectiveness for human health, all while reducing potential adverse impacts on the ecosystem. Plants expanding in tropical and subtropical regions are especially valuable for the development of green insecticides, particularly regarding malaria control. This can be attributed to their accessibility, low risk to humans, and effectiveness even at minimal dosages [27]. Extracts from seaweed, especially those derived from the *Caulerpa acemose* species, have demonstrated toxicity to mosquito larvae, such as *Anopheles stephensi,* at a concentration of 0.06 µg/mL, which is regarded as half the lethal dose (LC_{50})

[28]. The essential oil obtained from *Zingiber cernuum* demonstrates significant efficacy in eliminating larvae and inhibiting the ovipositor of malaria-carrying mosquito's *A. stephensi* and *A. subpictus*. Significantly, it does not adversely affect other mosquito predators that are outside the scope of control initiatives [29]. The essential oil derived from *Heracleum sprengelianum* demonstrates effectiveness against *A. subpictus* larvae, exhibiting a lethal concentration (LC_{50}) of 33.4 µg/mL [30]. A diverse array of plant species is often utilised in traditional medicine for the treatment of malaria and the alleviation of symptoms related to Campo's disease. This is because these plants have antiparasitic properties, supported by various studies [31,32]. Historically, the active compounds utilised in malaria treatments have been derived from botanical sources. Quinolines, utilised in medications such as chloroquine, are derived from Cinchona trees [33]. Artemisinin, extracted from the plant *Artemisia annua* L., stands as the leading therapeutic option for malaria treatment. The discovery's origins date back to the 1960s, when it was employed as herbal remedy in China [34].

One challenge in employing raw plant extracts is the degradation and loss of chemical constituents in outdoor environments. Moreover, most compounds derived from plants that are isolated exhibit a short half-life, highlighting the need for the development of a more effective administration method. Phytochemicals nanoformulation, referring to non-nutrients derived from plants, holds promise for improving bioavailability, increasing water solubility, and providing protection against enzymatic degradation [35]. Nanoparticles derived from botanical sources present a sustainable alternative to conventional chemical pesticides, which can cause considerable damage to the ecosystem [36].

Alongside plants, a variety of other biological sources have been employed for the synthesis of nanoparticles (NPs). The nano-pesticide developed from *Metarhizium robertsii* showed effective larvicidal properties against fourth instar larvae of *A. stephnsi* at low concentrations, while proving to be non-toxic to non-target organisms such as earthworms and crustaceans [37]. Sardine-fish-scale silver nanoparticles demonstrated significant larvicidal, pupicidal, and ovicidal activity against *A. stephensi*. The study notably uncovered an increase in predatory behavior targeting the larvae of the mosquito fish *Gambusia affinis* [38]. The silver nanoparticles (AgNPs) generated by *Bacillus marisflavi* demonstrated notable ovicidal, larvicidal, and pupicidal activities against *A. stephensi*. The mortality rates of both eggs and pupae were found to be the highest in comparison to other mosquito species [39]. Chitosan AgNPs demonstrated toxicity to *A. stephensi* larvae, with a fourth instar LC_{50} of 5.51 ppm, and to pupae, with an LC_{50} of 6.54 ppm [40]. Silver nanoparticles synthesized from *Cochliobolus lunatus* exhibited toxicity to second to fourth instar larvae of *A. stephensi* at concentrations of 5-10 ppm, while showing no harmful effects on the non-target species *Poecilia reticulata* [41].

The therapeutic properties of coelomic fluids from earthworms, including their cytotoxic, proteolytic, and antibacterial effects, have been thoroughly utilised. Scientists utilised *Eudrilus eugeniae* earthworms as reducing and stabilizing agents in the synthesis of Ag NPs, which were evaluated against *A. stephensi*. The *E. eugeniae* AgNPs demonstrated a significant ability to target larvae and pupae, resulting in an increase in the predation efficiency of the mosquito fish *G. affinis* from 68.50% to 89.25% in second instar larvae [42]. *G. affinis* and *Poecilia reticulata*, among other species, are larvivorous fish commonly utilised in malaria prevention initiatives for the biological management of *Anopheles* mosquitoes [43]. These fish have demonstrated remarkable efficiency in a nation that is devoid of malaria. Furthermore, nanoformulated natural compounds have shown effectiveness against various disease-transmitting mosquitoes, such as *Aedes sp.* [44] and *Culex sp.* [45]. Furthermore, it exhibits antibacterial properties and shows acaricidal activities. Furthermore, nanotechnology can be applied in various strategies to address malaria, such as improving the delivery of medications in malaria instances, as explored by our research team [46], and creating nanoformulations of repellents to control disease transmission.

PLANT-BASED NANOPARTICLES AND MOLECULAR TARGETS OF MALARIA CHEMOTHERAPY

Recent investigations indicate that plant-based nanoparticles represent a significant advancement in combating malaria, demonstrating their efficacy as ovicides, larvicides, pupicides, adulticides, and oviposition deterrents targeting mosquito vectors [47]. The nanoparticles synthesized with phytochemicals exhibit significant toxicity towards the *A. Stephensi* mosquito, which is a crucial vector for Malaria. Lipid nanocarriers have been investigated for their potential in Malaria chemotherapy, providing a platform to formulate antimalarial drugs and alter their pharmacokinetic profile [48]. Investigations have been conducted on the application of nanotechnology-based carriers, such as liposomes and polymeric nanovesicles, for the efficient delivery of antimalarial agents. These carriers demonstrate potential in reducing the side effects associated with drug therapy while improving the targeting of antimalarial to infected cells. Moreover, discovering new molecular targets in the malaria parasite, including histone deacetylase and aminopeptidases, has created opportunities for developing novel

antimalarial agents [49,50]. Gold nanoparticles have been investigated as nano vaccines for Malaria, especially in relation to the *P. falciparum* antigen. The exploration of green synthesized nanoparticles, especially those exhibiting antiplasmodial activity, has been undertaken in the battle against Malaria [51]. Surface-engineered nanoparticles demonstrate potential in effectively targeting and inhibiting *P. falciparum*. Created glucose-based ultra-small gold nanoparticles or gold nanoclusters (Glc-NCs) that attach to cysteine-rich domains *of P. falciparum* surface proteins, improving the delivery of antimalarial drugs. The surface proteins of *P. falciparum* are characterized by cysteine-rich domains that are crucial during the invasion process. Notable examples include reticulocyte binding homolog 5 (PfRh5), cysteine-rich protective antigen (CyRPA), erythrocyte-binding antigen-175 (EBA-175), cysteine repeat molecular proteins (PfPCRMP1-2), and Duffybinding like erythrocyte-binding protein (DBL-EBP). These cysteine-rich domains are present on the surface of schizonts, gametocytes, and sporozoites of *P. falciparum* [52-55].

PLANT-BASED NANOPARTICLE STRATEGIES TO PREVENT MALARIA

Disrupting the mosquito life cycle is an essential approach in controlling mosquito-borne diseases. A range of approaches has been utilised for vector control, such as synthetic insecticides, plant extracts, essential oils, nereistoxin derived from marine annelids has been utilized to synthesized nanoparticles [56]. Safeguarding individuals from diseases transmitted by mosquitoes can be accomplished through two main approaches: preventing mosquito bites and focusing on the control of mosquito larvae. The combination of these two strategies highlights the efficacy of personal protection measures alongside larval stage control in mitigating the spread of mosquito-borne diseases. The advancement and execution of vaccine platforms signify a hopeful and evolving avenue in the thorough management of malaria [57]. This discussion highlights advancements in nanotechnology aimed at enhancing three key preventative strategies: mosquito repelling, larval elimination, and vaccination, all crucial for the future eradication of malaria. The rise of chloroquine-resistant malaria strains has increased focus on alternative methods to address the disease, including the application of mosquito repellents [58,59]. This change in emphasis is emphasized by the findings of, which illustrate the increasing significance of repellents in combating malaria, particularly in light of the diminished efficacy of conventional antimalarial medications such as chloroquine.

Mosquito repellents are formulated substances intended for application on various surfaces, modifying the characteristics of the treated area and its environment to render them unappealing and unsuitable for mosquitoes [60-62]. Repellents can be categorised into two distinct groups based on the source of their raw materials: synthetic and biological repellents. Synthetic repellents originate from chemical compounds, whereas biological repellents are sourced from natural, biogenic materials. Insect repellents generally create a vapour barrier that keeps mosquitoes from coming into contact with human skin [63]. Textiles can be infused with both chemical and natural repelling agents, resulting in the creation of mosquito repellent textiles. These textiles are gaining recognition as a valuable method in the discipline, providing crucial attributes for repelling mosquitoes. These repellent methods play a vital role in safeguarding humans against mosquito bites, which are linked to the spread of numerous mosquito-borne diseases such as malaria, dengue, yellow fever, and filariasis, in addition to the irritation caused by bites [64]. Common commercial mosquito repellents like N, N-diethylmeta-toluamide (DEET), dimethyl phthalate (DMP), and allethrin are widely utilised, yet they present environmental and health risks when exposure levels are elevated. The association of these substances with a range of adverse effects is noteworthy. They include bioaccumulation, resistance to degradation, allergic reactions, asthmatic symptoms, skin irritations, cardiovascular and neurological disorders, dermatitis, and damage to synthetic fabrics and plastics. Considering these potential hazards, there is an increasing focus on the creation and application of eco-friendly repellents as a more secure option for safeguarding against mosquito bites [65-67].

ESSENTIAL OILS-BASED NANOFORMULATIONS AS REPELLENTS

The movement towards creating environmentally friendly repellents has attracted growing attention as a practical substitute for conventional synthetic options. Essential oils derived from a range of plants, including *Ficus glomerata*, *Eucalyptus globulus*, and *Mentha piperita*, have demonstrated significant repellent properties against *A. stephensi* mosquitoes [68]. The shift towards natural, plant-based repellents highlights an increasing focus on environmentally friendly and health-oriented approaches in the prevention of mosquito-borne diseases. Regrettably, the practical use of essential oils as repellents faces challenges due to their instability, vulnerability to degradation when exposed to light, oxygen, and temperature, as well as their typically reduced effectiveness in comparison to synthetic insecticides.

Nonetheless, the integration of essential oils into nanoformulations, including nanoemulsions, solid lipid nanoparticles, polymeric nanoparticles, and nanogels, offers a promising solution in the realm of phyto-insect repellents [69]. The nanoformulations are capable of stabilizing essential oils, improving their dispersion, and potentially augmenting their effectiveness as repellents, utilizing nanogels derived from essential oils of *Elettaria cardamomum Malton* and *Zataria multiflora* Boiss. The authors assessed the complete protection times (CPT) of these nanogels against mosquitoes, juxtaposing the findings with DEET, a conventional repellent. The nanogels infused with 2.5% *Z. multiflora* Boiss essential oil exhibited remarkable efficacy, achieving a CPT of 600 min, in contrast to DEET's CPT of 242 min. Conversely, the essential oil of *E. cardamomum* Malton demonstrated reduced efficacy, showing a CPT of 63 min. The remarkable efficiency of *Z. multiflora* Boiss essential oil is recognized for its primary components, carvacrol and thymol, which have been documented to exhibit effectiveness against specific mosquito species [70].

A nanoemulsion was developed in another study utilizing essential oils from *E. globulus* and *Syzygium aromaticum*. The application of this nanoemulsion to cotton polyester fabrics was conducted through a spray drying procedure. The effectiveness of the formulated nanoemulsion in repelling mosquitoes was evaluated using a cage test designed for this purpose. The textiles treated with nanoemulsion demonstrated a notable increase in protection, achieving a CPT of 285 min, in contrast to the less than 5 min protection times provided by bulk essential oils. This significant enhancement in effectiveness illustrates the promise of nanoemulsion-based repellents for use in textiles [71]. The summary of the repellent effects and formulation descriptions of various essential oil-based nanoformulations are presented in Table 1.

Table 1: Description of essential oil loaded in nanoformulation-repellent properties.

Source of Essential oils	Nanomaterial type	Nanomaterial composition	size (nm)	Target larvae species	Ref.
Zataria multiflora Boiss	Nanogel	EO/Tween® 20: 7.5/2.5% w/v and Carboxymethyl cellulose (3.5%)	8	*An. Stephensi*	69
Zataria multiflora	Solid lipid nanoparticles	EO/Stearic acid/Span® 60/Tween® 80: 1%/4%/ 2%/4%	134	*An. Stephensi*	70
Elettaria cardamomum	Polymeric nanoparticles	EO/Tween® 20: 7.5/ 2.5% w/v and Carboxymethyl cellulose (3.5%)	86	*An. Stephensi*	71
Eucalyptus Globulus	Nanoemulsion	EO/Tween® 80/Tween® 20/propylene glycol/ DW: 3%/2%/7%/7%/ 16%/65%	131	*An. Stephensi*	72

Note: EO: essential oil; DW: distilled water.

NANOFORMULATIONS WITH LARVICIDAL ACTIVITY

Synthetic insecticides like permethrin and dieldrin have seen extensive application, largely because of their swift effectiveness in pest control [73]. Nonetheless, the implementation of these raises considerable apprehensions. These chemicals present significant risks to human health, non-target organisms, and the overall ecological equilibrium. The widespread application of chemical insecticides has resulted in the emergence of resistant species, which adds complexity to pest control strategies [74]. The dual challenges highlight the necessity for enhanced sustainable and ecologically responsible pest management approaches. Plants are acknowledged for their significant contributions as sources of bioactive compounds, exhibiting a range of properties, such as mosquitocidal effects [75]. The adoption of plant-derived insecticides has gained traction owing to their economic viability and eco-conscious characteristics. As a result, a plant-based nanoparticle is becoming a noteworthy alternative to synthetic insecticides, providing a more sustainable method for pest management [76]. In the field of nanotechnology, a leading area in contemporary material science, the distinctive properties of nanoparticles, including their nanometric dimensions and elevated surface-to-volume ratios, render them a promising substitute for traditional materials, particularly in situations where effectiveness or safety is lacking [77]. Different varieties of plant-derived nanoparticles have demonstrated potent mosquitocidal effects, either through their inherent larvicidal capabilities, as observed in metallic green nanoparticles, or by encapsulating larvicidal agents, like lipid-based nanoparticles enriched with essential oils. This text explores innovative methods that highlight the adaptability and promise of plant-based nanoparticles in managing mosquito populations, especially in focusing on their larval stages [78].

ESSENTIAL OIL-LOADED NANOFORMULATION WITH LARVICIDAL PROPERTIES

In addition to the naturally larvicides MeNPs, various nanoformulation have been created to encapsulate and regulate the delivery of plant-derived larvicidal agents. The nanoformulation act as carriers, improving the dispersion, bioavailability, efficacy, and specificity of larvicidal compounds [79]. For instance, the study detailed the larvicidal effects of liposomes composed of a blend of egg yolk lecithin (2.5% *w/v*), cholesterol (0.5% *w/v*), Tween 20 (1.0% *w/v*), and essential oils (2.0% *w/v*) derived from *Citrus aurantium*, *C. limon, C. sinensis*, and crude limonene extracts. The liposomes, especially those infused with limonene and limonene-rich essential oils, exhibited markedly increased toxicity (nearly 10 times for *C. aurantium*) in comparison to free essential oils when tested against *A. stephensi*. This highlights the vital function of liposomes in improving the delivery of essential oils [80]. The findings indicated that *C. aurantium* liposomes demonstrated the highest larvicidal efficacy against *A. stephensi*, with an LC50 value of 6.63 µg/mL, highlighting their potential as a viable alternative to synthetic insecticides. Encapsulating these oils enhances their stability, efficacy, and potential for targeted application in larvicidal treatments [81]. Besides liposomes, various other nanoformulations like nanoemulsions and nanogels have demonstrated considerable promise in improving the larvicidal effects of essential oils. Table 2 provides further examples of nanoformulations that incorporate essential oils from different plants, recognized for their larvicidal properties. The nanoformulations demonstrate the variety and effectiveness of plant-derived essential oils in controlling mosquitoes, particularly when improved by nanotechnology.

Table 2: Essential oils-containing nanoformulation with larvicidal effect against malaria vector larvae.

Plant name	Nanomaterial type	Formulation composition	size (nm)	Target larvae species	Reference
Artemisia annua	Liposome	Egg lecithin/Chol/Tween® 20/E.O: 3.0/0.5/2.0/2.0%w/v	137 nm	*A. stephensi*	82
Artemisia dracunculus	Liposome	Egg lecithin/Chol/Tween® 20/E.O: 3.0/0.5/2.0/2.0%w/v	151 nm	*A. stephensi*	83
Artemisia sieberi	Liposome	Egg lecithin/Chol/Tween® 20/E.O: 3.0/0.5/2.0/2.0%w/v	92 nm	*A. stephensi*	84
Artemisia dracunculus	Nanoemulsion	E.O/Tween® 20/Water	152 nm	*A. stephensi*	85
Artemisia dracunculus	Nanogel	E.O/Tween® 20/Water/ Carboxycellulose	NA	*A. stephensi*	86
Citrus aurantium	Liposome	Egg lecithin/Chol/Tween® 20/E.O: 2.5/0.5/1.0/2.0%w/v	52 nm	*A. stephensi*	87
Citrus limon	Liposome	Lecithin/Chol/Tween® 20/ E.O: 2.5/0.5/1.0/2.0%w/v	67 nm	*A. stephensi*	88
Citrus sinensis	Liposome	Lecithin/Chol/Tween® 20/ E.O: 2.5/0.5/1.0/2.0%w/v	53 nm	*A. stephensi*	89

Note: NA: not available; EO: essential oil; Chol: Cholesterol.

CHALLENGES ASSOCIATED WITH PLANT BASED NANOTECHNOLOGIES

Plant-derived nanoparticles encounter considerable obstacles and constraints in their development process for malaria treatment. This encompasses attaining consistency and stability in nanoparticle preparations, while assuring therapy efficacy, safety, accessibility, and regulatory approval. Confronting these obstacles is essential for advancing plant-based NPs from experimental research to realistic clinical applications, especially in the treatment of malaria in low-income areas. The subsequent lines succinctly underscore the issues related to plant-based nanoparticles across many situations [90].

Protocol standardization

The tabular data summarized in the preceding sections reveals significant variations in the experimental conditions employed to study plant-based nanoparticles. These arise from the variability in nanoparticle characteristics (e.g., particle size) to general experimental conditions such as nanoparticle concentrations, which have been quantified in ppm or weight by volume, without accounting for the actual number of nanoparticles present in the biological medium. Additional variable characteristics, including cell types, culture medium, animal models, and methodologies, may potentially impede the comparability of

nanomedicine efficacy studies. Standardising these methods is crucial for the progression of clinical research [91].

Targeting and delivery

Improving the targeted delivery of antimalarials via nanoparticle surface modification is essential for tackling the challenges associated with the variability in pharmacokinetic profiles, efficacy, and safety of different drugs, particularly concerning infections caused by *Plasmodium vivax* and *P. ovale,* which produce dormant hypnozoites in the liver and contribute to drug resistance [86]. Recent studies have formulated diverse ways for the surface decorating of nanoparticles to enhance the precision of medication targeting. Nevertheless, maintaining constant control over ligand density and structure on nanoparticle surfaces presents considerable problems, affecting both preclinical efficacy and safety. This variability will ultimately hamper product scalability and regulatory approval, as production processes must be modified for industrial scale-up. Standardizing surface decoration techniques is essential for advancing nanoparticles from experimental applications to broadly accessible therapeutics, especially in malaria-endemic areas [92].

Safety and Toxicity

Environmental effects and toxicity profiles are crucial issues. Plant-derived metallic and metal oxide nanoparticles may build in ecosystems due to insufficient environmental management in low-income nations. This accumulation may result in the contamination of water bodies, impacting aquatic ecosystems and communities dependent on untreated river water [88]. Furthermore, the skin permeability of essential oil-based nanoformulations, especially in children under two years of age, requires additional research regarding their safety and biocompatibility. Certain NPs demonstrate inherent antimalarial efficacy without requiring activation; however, their long-term safety has yet to be established [89]. The advancement of antimalarial vaccines utilising plant viruses is a challenging domain that necessitates careful innovations to produce safer delivery systems and suitable adjuvants. The haemolytic potential of saponin-based adjuvants has constrained vaccine development, requiring meticulous molecular engineering to avoid worsening malaria-induced anaemia [93].

Manufacturing and scalability

Reproducibility and standardization pose considerable challenges in the large-scale implementation of plant-based nanoparticles for malaria treatment. The inconsistency in the quantity and quality of phytochemicals necessitates the standardization of harvesting conditions for plant materials to guarantee uniformity in production worldwide. Although these nanoformulations are economically viable at the laboratory level, their transition to industrial production faces financial obstacles, which may restrict accessibility in low-income nations [94]. It is essential to consider factors like long-term stability, zeta potential, size homogeneity, and optimal storage conditions to avoid degradation of NPs and maintain consistent performance. Furthermore, aspects such as surface characteristics, dosage, encapsulation efficiency, loading capacity, release profiles, effective dose, and biodistribution require optimisation for successful scale-up [94]. It is essential to tackle these challenges to move plant-based NPs from laboratory studies to industrial applications while adhering to good manufacturing practices (GMP) guidelines, thereby facilitating their clinical use in the management of malaria in resource-limited environments.

CONCLUSION

Malaria continues to be a significant contributor to illness and death in low-income nations worldwide, with the infection dynamics centered on the *Plasmodium spp*. parasites, especially *P. falciparum*, recognized as the most virulent species. The female *Anopheles* mosquitoes, particularly *Anopheles stephensi* and *A. gambiae*, play a crucial role in transmission, with humans acting as the intermediate host for the maturation and infectious development of the parasite. Efforts to combat malaria have been focused on two main fronts: upstream strategies that target vector control to disrupt the mosquito life cycle of the parasites, and downstream approaches that involve administering antimalarial drugs to impede the parasite's development within the host. Nonetheless, the effectiveness of conventional antimalarial agents, including DDT, pyrethroids, chloroquine, and even the more recent artemisinin derivatives, has diminished over time as a result of resistance development in both vectors and parasites. Moreover, the toxicity these agents present to both the environment and human health introduces additional complexities. This review emphasized the changing dynamics of antimalarial approaches, pointing out the promise of plant-derived nanotechnologies in addressing the previously discussed challenges in malaria treatment and prevention. The investigation into plant-based nanotechnologies offers an innovative strategy for addressing malaria, especially in developing nations where the disease continues to pose a significant health threat. Utilizing the distinctive characteristics of nanoparticles, such as improved solubility, stability, and targeted delivery capabilities, these technologies present a

promising approach to address the challenges faced by conventional antimalarial treatments and vector control strategies. Formulations of nanoparticles sourced from plant materials demonstrate lower toxicity levels and effectively address the increasing resistance to traditional antimalarial medications and pesticides. Modifying these nanoparticles to precisely target malaria presents exciting opportunities for enhancing drug pharmacokinetics, minimizing toxicity, and improving patient compliance with treatment. The precise administration of antimalarial medications via nanoparticles enables direct interaction with the parasites residing in infected red blood cells and Anopheles mosquitoes, thus promoting a more effective and efficient treatment strategy. Moreover, nanoparticles that are inherently effective against *Anopheles* mosquitoes present an innovative approach to vector control, potentially leading to a substantial decrease in transmission rates. Plant-based nanotechnologies represent a comprehensive approach to tackling the complex issues surrounding malaria eradication in developing nations, focusing on improving drug effectiveness and patient compliance, as well as advancing vector control and preventive strategies.

CONFLICT OF INTEREST

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