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Review Article

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A Review on Recent Advances Using Green Nanotechnological Approaches in the Treatment of Malaria

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ABSTRACT

Malaria is a tropical disease that affects more than 2.7 million people annually. There are various species of plasmodium associated with malaria. They include *Plasmodium falciparium, P. vivax, P. malariae* and *P. Ovale*. Major challenges associated with malaria infection are resistance to antimalarial drugs and the lack of an effective vaccine against malaria. There are new prospects that have evolved in the treatment of malaria which include recent developments in nanotechnology. This is due to the fact that these nanoparticles possess unique characteristics such as less toxicity, high biocompatibility, environmentally friendly and cost effective. The use of plants and micro-organisms in the development of green nanoparticles have been documented. This review was carried out to ascertain the recent advances in the use of nanotechnological approach in the treatment of malaria. Prevalence of malaria is due to widespread drug resistance to antimalarial drugs and insecticides used to control vectors. These limitations have led to the development of new approaches to combat this tropical disease.

Keywords: Malaria, Antimalarial drugs, Nanotechnology, Nanoparticles.

INTRODUCTION

According to World Health Organization (WHO), malaria is a tropical disease due to its high mortality rate [1]. There are various species of plasmodium associated with malaria. They include *Plasmodium falciparium, P. vivax, P. malariae* and *P. Ovale*. The well-known malaria infection, is caused by adult female anopheles' mosquitoes [2]. According to statistics in 2020, 245 million people were infected with malaria parasites, and the highest death rate of over 90 % was recorded in Africa [3]. Among the different

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species associated with malaria, the *P. falciparium* is the most common that causes tropical malaria. Prevalence of malaria is due to widespread drug resistance to antimalarial drugs and insecticides used to control vectors. These limitations have led to the development of new approaches to combat this tropical disease.

There is hope in the fight against malaria with the use of nanotechnology-based approaches. The use of nanotechnology in the treatment of malaria has three major objectives; which include the ability to deliver the drugs directly to the parasitic vacuoles, maintaining drug levels in the bloodstream for extended period of time and the lower toxicity associated with drugs [4]. In drug delivery systems, nanoparticles have shown unique characteristics such as the ability to protect the drug from degradation and reduction on the frequency of drug administration.

Green synthesis has been used over the years to synthesize metallic NPs [5]. This study aims to analyze the different studies on metallic nanoparticles (NPs), in relation to their advantages, toxicities and antimalarial effects.

Mechanism of action of nanoparticles

Some of the limitations associated with the use of conventional strategies in the treatment of malaria include low pharmacokinetics, toxicity, drug resistance and low biocompatibility [6]. The advent development of NPs is to overcome these challenges. Active and passive targeting is used to achieve the delivery of these antimalarial drugs [7]. Passive targeting involves the use of liposomes and hydrophobic polymeric NPs. The use of hydrophilic polymers to modify the surfaces of NPs delays phagocytosis and prolongs the half-life of the drug in the blood [8]. In malaria treatment, the use of intravenous administration is preferred due to their inability to have longer contact with red blood cells (RBCs) [9]. Active targeting involves the use of liposomes and solid lipid NPs (SLN). Although one major limitation associated with active targeting, is that some ligands exhibit unwanted immune response [10].

Gold nanoparticles

There are diverse biomedical fields that have utilized the need for the use of gold nanoparticles (Au-NPs) especially in the areas of biosensors, clinical chemistry, immunoassays, genomics, targeted drug delivery and *in vivo* photo-acoustic techniques [11-20]. The role of Au-NPs in acting as a carrier for drugs and vaccines to the targeted cells has also been documented [21]. This was achieved by conjugating drugs and biomolecules with slight modification of the Au-NPs. A modification on the Au-NPs physical, chemical and photo-thermal properties also affects the control release of the drug into the cells [22,23]. Au-NPs are characterized based on physical properties, size and shape. Nanospheres were the first achievement in Au-NPs field [23]. Subsequently other forms were later developed which include nanorods, nano shells and nanocages. Gold nanospheres also known as 'Au nanospheres' has diameters in the range of 2-100 nm. They are produced by reducing aqueous HAuCl4 solution with addition of various reducing agent with standardized parameters and conditions. Limitations associated with this technique include the low yield and non-use of water as a solvent. To produce the desired shape and size of Au-NPs, there are parameters that need to be controlled; which include the concentration of the reactants, HAuCl4 and blocked co-polymers [24]. There are several strategies that have been deployed in the production of nanorods [25]. The most common was the use of template method which involved the deposition of Au within the pores of nano porous polycarbonate membranes [25,26]. The diameter and length of Au nanorods could be pre-determined by the amount of deposited Au within the membrane pores respectively. Its own limitation is associated with the production of low yield of Au nanorods. The seed-mediated synthesis produces higher aspect ratios, thus making it the most commonly used technique in production [27,28].

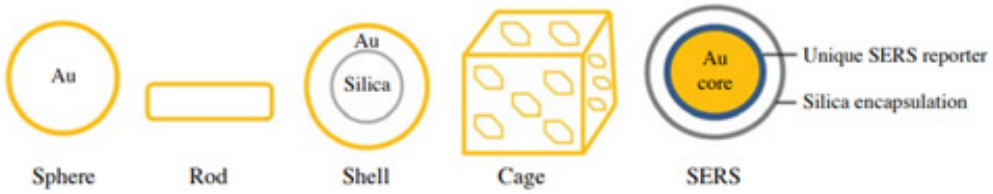

Figure 1. Types of gold nanomaterials [28].

Gold nano shells are spherical nanoparticles that have a dielectric core and a thin metallic shell. There are two major techniques used in the production of gold nano shells. They include the quantum plasma oscillation technique which involves the use of electrons that simultaneously oscillate with ions, and change in the composition and dimensions of layers using the surface plasmon resonance (SPR) [29].

Applications of gold nanoparticles for drug delivery

There are several biomolecules that have been deployed in drug delivery such as proteins, antibodies, peptides, genes and vaccines. Some of the limitations associated with them include enzymatic degradation by organisms and molecular size. These limitations led to the development of novel drug delivery systems in order to increase the reproducibility, reliability and sensitivity in the targeted areas. They include the self-micro emulsifying drug delivery system, neural drug delivery system and acoustic targeted drug delivery system which involves the use of ultrasound to transfer molecules into the tissue. The main motive of using Au-NPs in malaria treatment was to enhance the targeted drug delivery.

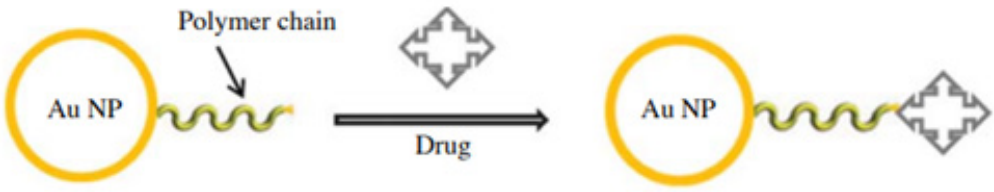

Figure 2. Schematic representation of surface modified Au-NPs [21].

Nanocarriers are employed for drug delivery in malaria treatment in order to overcome most of the limitations associated with current therapies. Increased drug resistance has been the major problem associated with the conventional malaria treatment. Other factors are low bioavailability, fast metabolism and poor absorption [30,31]. These limitations led to the development of nanoparticles which have unique characteristics such as small particle size, high bioavailability, reduced toxicity and prevention of drug resistance [32]. The major role associated with the use of nanocarriers in malaria treatment is their ability to stay in the bloodstream for an extended period of time in order to interact with the parasites and infected red blood cells [33].

Silver nanoparticles

Although silver has been in use in the early 20th century, especially for the treatment of microbial infections, their limitations such as high toxicity and the advent of antibiotics limited their use [34]. Of recent, they regained credibility mostly as in colloidal suspension. They are currently the ideal candidates in the search of new therapeutic agents both in metallic and ionic forms [34].

According to Media et al (2015), a lot of metal nanoparticles and their complexes have been used in medicine. The use of silver nanoparticles against malaria have very few examples cited on it [35]. Wysor et al (1977), reported that an oral or subcutaneous administration of silver sulfadiazine in doses of 1.050 mg/kg/day once a day for five days cured a CF-1 mice affected by *P. berghei* with a minimal toxicity, while within 24 hours, death occurred on administration of high dose [36]. According to Hemmert et al, (2013), they prepared a series on mono and dinulcear silver and gold complexes containing mono and bis (N-heterocycliccarbene) NHC-based ligands and

tested them on a chloroquine-resistant strain of P. falciparum [37]. Metal nanoparticles have demonstrated a wide range of applicability in all spheres. The special interest assigned to silver nanoparticles is due to their broad-spectrum antimicrobial activities [38]. Report by Rawani et al (2013), demonstrated the antilarval activity of AgNPs synthesized by aqueous extracts of dry leaves, fresh leaves and berries of *Solanum nigrum* against *A. stephensi* [39]. The result obtained showed that the synthesized AgNPs showed significant antilarval activity with LC50 values of 1.33, 1.59 and 1.56 ppm and LC90 values of 3.97, 7.31 and 4.76 ppm for dry leaves, fresh leaves and berries respectively. According to Veerakumar and Govindarajan (2014), they synthesized AgNPs by using leaf extract of *Feronia elephantum*. The obtained result showed a great significant activity against *Anopheles stephensi, A. aegypti* and *Culex quinquefasciatus*. The LD_{50} and LD90 values for *A. stephensi, A. aegypti* and *C. quinquefasciatus* were 18.041 and 32.575 ug/mL, 20.399 and 37.534 ug/mL and 21.798 and 39.596 ug/mL respectively [40]. Mishra and coworkers (2013), evaluated the antiplasmodial activity of AgNPs synthesized from purified alpha amylase, aqueous leaf extract of *Saraka indica* and *Azadirachta indica* against *P. falciparum*. The result obtained indicated that the antiplasmodial activity of AgNPs confirmed by the IC50 values were 3.75, 8.0 and 30 ug/mL respectively for AgNPs from amylase, Saraka indica and *Azadiraclita indica*. Veerakumar (2014), studied the adulticidal activity of AgNPs synthesized using Heliotropium indicum leaf extracts against adults of *A. stephensi, A. aegypti* and *C.quinque fasciatus*. The result obtained on the LD_{50} of *A.Stephensi* was LD_{50} = 26.712 ug/mL, LD90 = 49.061 ug/mL. *A aegypti* was LD_{50} = 29.626 ug/ml, LD90 = 54.269 ug/ml and *C. quinquefasciatus* LD_{50} = 32.077 ug/mL and LD90 =58.426 ug/mL [41].

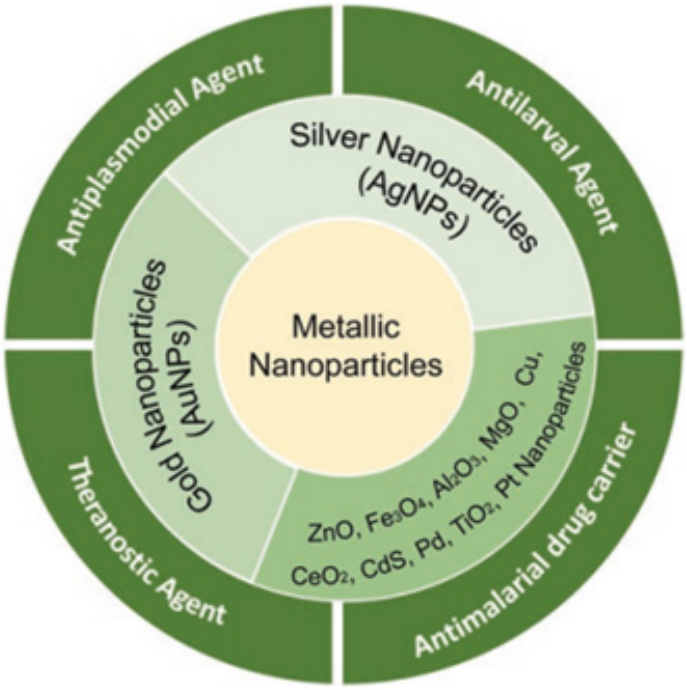

Figure 3. Metallic nanoparticles and their application in malaria [42].

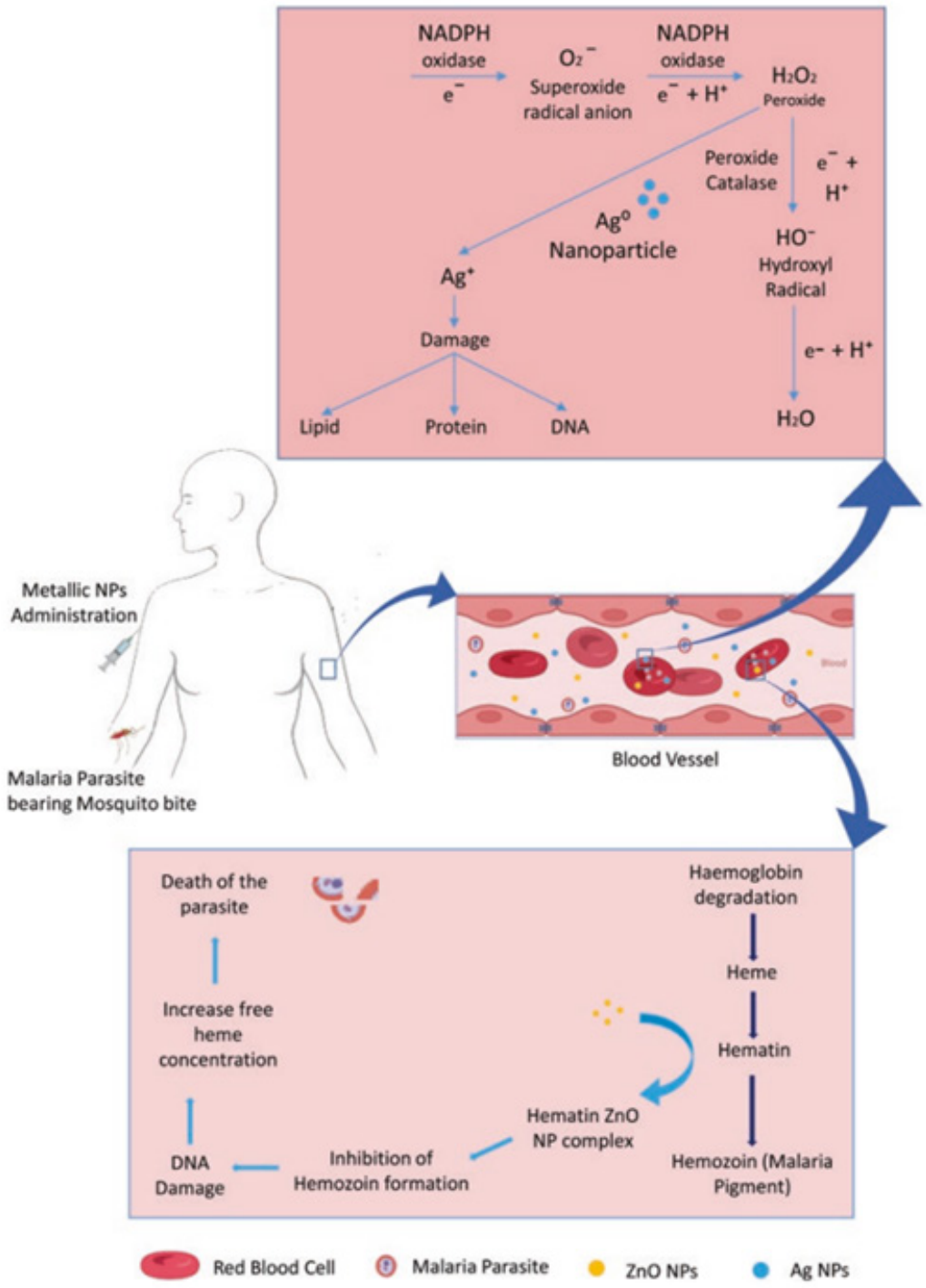

Figure 4. *In vivo* fate of metallic nanoparticles and their antimalarial mechanism [42].

Calcium phosphate nanoparticles

There are many members of the calcium phosphate family that are of great interest in biomedical applications which are classified based on their Ca/P atomic ratio, pH stability ranges in aqueous solution and density [43-48].

Table 1. Calcium-phosphate phases used in biomedical applications [43-48]

Ca-Phosphate Phase name	pH stability range
MCPM (monobasic calcium phosphate monohydrate)	0.0-2.0
DCPA (dicalcium phosphate anhydrous)	2.0-5.5
DCPD (dibasic calcium phosphate dehydrate)	2.0-6.0
OCP (octa calcium phosphate)	5.5-7.0
ACP (amorphous calcium phosphate)	5-12

There are different methods deployed in the synthesis of calcium phosphate, which include the sol-gel, flame spray pyrolysis, solid state reactions and wet-chemical precipitation [49-55].

The sol-gel synthesis involves the reaction between a calcium source and a phosphate source which is used in the fabrication of a wide range of structured nanomaterials. Tetrabutylammonium phosphate is injected into oleic acid at temperature of 200-330 oC and controlled by nucleation-growth kinetics. Advantages associated with this technique include high versatility, simplicity and low synthesis temperature [56-58].

The flame-spray pyrolysis is used in synthesis of calcium phosphate NPs on a large scale [59-61]. It involves the injection of the precursor into a flame at high temperature. This technique requires a specialized equipment and is useful in the preparation of large quantities of calcium phosphate nanoparticles [62].

Application of calcium phosphate nanoparticles

For surface functionalization of the CaNPs, various methods have been deployed using both covalent and non-covalent conjugation of macromolecules. The use of polymers, lipososomes and inorganic materials have been devised in producing various shapes of CaNPs [63]. The four categories involved in the production of Ca-NPs include:

a. The mix-cap creation using phosphate water solutions and chemotherapeutics

b. Preparation of the calcium phosphate core, addition of chemotherapy and nuclei acid drugs to form a phosphate core

c. Combination of a multi-layer with calcium phosphate and pharmaceuticals

d. Creation of a cap-shell by combining medication molecules and cap shell

Titanium oxide nanoparticles (TiO2)

The two main groups of nanoparticles are: the inorganic and organic nanoparticles. Liposomes, chitosan, dendrimers and ferritin constitute the organic nanoparticles, while the inorganic types include the metals, semiconductors and magnetic nanoparticles [64].

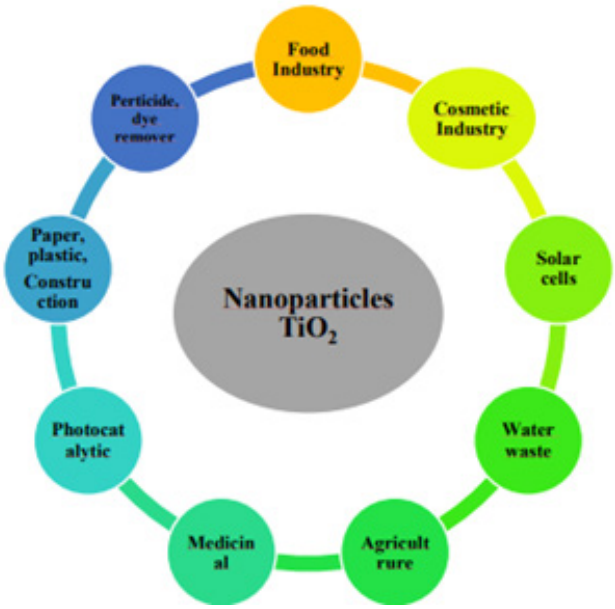

Figure 5. Applications of titanium oxide nanoparticles [64].

According to Machala et al, [65], the activities of larvicides on some mosquito pathogens such as Aedes, has caused rapid development associated from its negative impact. They discovered the role green synthesis of TiO_2 nanoparticles have to play on larvicidal activity. Plant extracts used in the green synthesis of TiO_2 NPs contain secondary metabolites [65].

There are unique qualities associated with TiO_2 NPs such as photocatalytic activity, larvicidal activity, optical properties and strong chemical stability. According to Balaraman et al, *Sargassum myriocystum* was utilized with a precursor, titanium tetrabutoxide on larvicidal action. The result obtained indicated the extract of *S. wightii* outperformed those of *A. subpictus* and *C. quinquefasciatus* in mortality rate with recorded values of LC_{50} = 26.12 and 27.28, LC90 =80.89 and 82.65 respectively, while the NP-TiO_2 recorded an excellent activity against *A. subpictus* and *C. quinquefasciatus* with values at LC=4.37 and 4.68, LC90 = 8.33 and 8.97 [66]. The synthesis of TiO_2 nanoparticles has demonstrated unique advantages such as safety, simple process, it doesn't cause pollution nor require the use of high energy and temperature.

CONCLUSION

In the fight against malaria, the major challenge lies in the development of antimalarial drug resistance in malaria parasites, coupled with insecticide resistance in vectors. Over the years, nanotechnology advancements have given rise to novel prospects. Green nanotechnology-based acceleration of using metal NPs against many diseases and in vaccine development holds promise for new approaches against malaria parasites and vectors. Using non-hazardous or non-chemical reagents in the green synthesis of NPs makes them more effective, biocompatible, and technologically environmentally friendly.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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