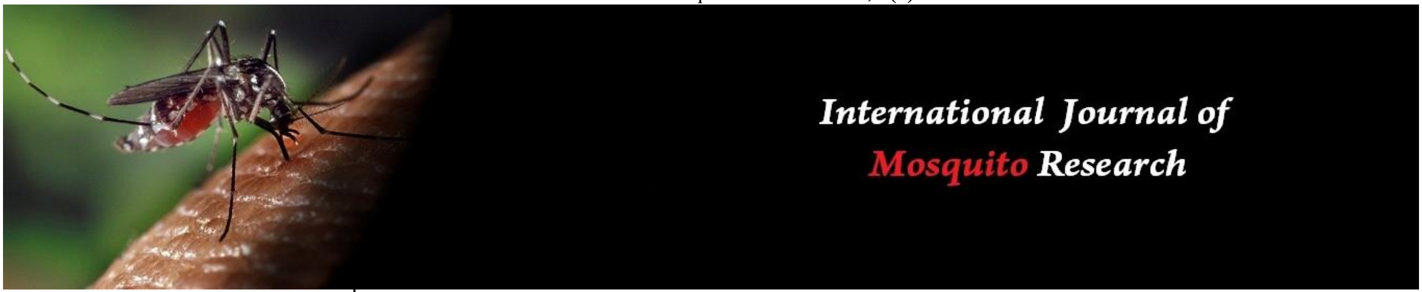

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Reforming roadmap for vector control strategies for malaria elimination and eradication from transmission in context to the current evidence

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Abstract
Recent outbreaks of new arbovirus, the development of resistance in some Culicidae species, and the fast expansion of highly invasive mosquitoes globally are all posing significant and timely challenges to mosquito control initiatives. Plant-mediated nanoparticle production has several advantages over chemical and physical approaches, including cost, simplicity, and the absence of high pressure, energy, temperature, or the use of highly toxic compounds. A rising variety of plant-borne chemicals have been proposed in recent years for the efficient and quick extracellular synthesis of metal nanoparticles that are effective against mosquitoes at very low levels. Furthermore, we reviewed current evidence on the non-target effects of these nanocomposites used for mosquito control, highlighting their moderate acute toxicity for non-target aquatic organisms, lack of genotoxicity at the doses tested against mosquitoes, and the potential to increase the predation rates of biological control agents against mosquitoes by treating the aquatic environment with ultra-low doses (e.g. 1–3 ppm) of green-synthesized nanoparticles, which reduces mosquito population of larvae. Using genetically engineered mosquitoes, there are two primary techniques to control mosquito. These are referred to as population suppression and replacement and both systems are capable of modifying genetically engineered mosquitoes into the wild. The current study focused on the possible usefulness of nanoparticles in mosquito control.

Keywords: Mosquito, green nanosynthesis, nanotechnology, *Aedes aegypti*, larvicides

Introduction

Malaria is usually seen in poor tropical and subtropical areas. Malaria is a primary cause of illness and death in many of the malaria-affected countries. Young children, who have not yet gained immunity to malaria, and pregnant women, whose immunity has been weakened by pregnancy, are the most vulnerable groups in places where transmission is strong. In 2021, an estimated 627,000 people died of malaria—most were young children in sub-Saharan Africa [1]. Female mosquitoes of the genus *Anopheles* transmit malaria to humans. Female mosquitoes need blood to produce eggs, and these blood meals represent the parasite life cycle's link between human and mosquito hosts. Several factors influence the malaria parasite's development in the mosquito (from the "gametocyte" stage to the "sporozoites" stage) [2]. Humans and female *Anopheles* mosquitoes are infected cyclically in the natural history of malaria. The parasites in people grow and reproduce first in the liver cells, then in the red blood cells. In the blood, successive broods of parasites invade and destroy red cells, releasing daughter parasites (merozoites) that continue the cycle by infecting additional red cells [3]. There is considerable attention which has been received by various plant products which acted as potential bioactive compounds against different mosquitoes species. This problem can be eliminated by developing more biocompatible nanoparticles using plants and microorganisms. There have been previous reports on mixture of pure metallic silver and gold nanoparticles with the help of neem leaf broth as extracellular material. There has been successful synthesis of silver nanoparticles at room temperature using crude neem leaf extract at room temperature.

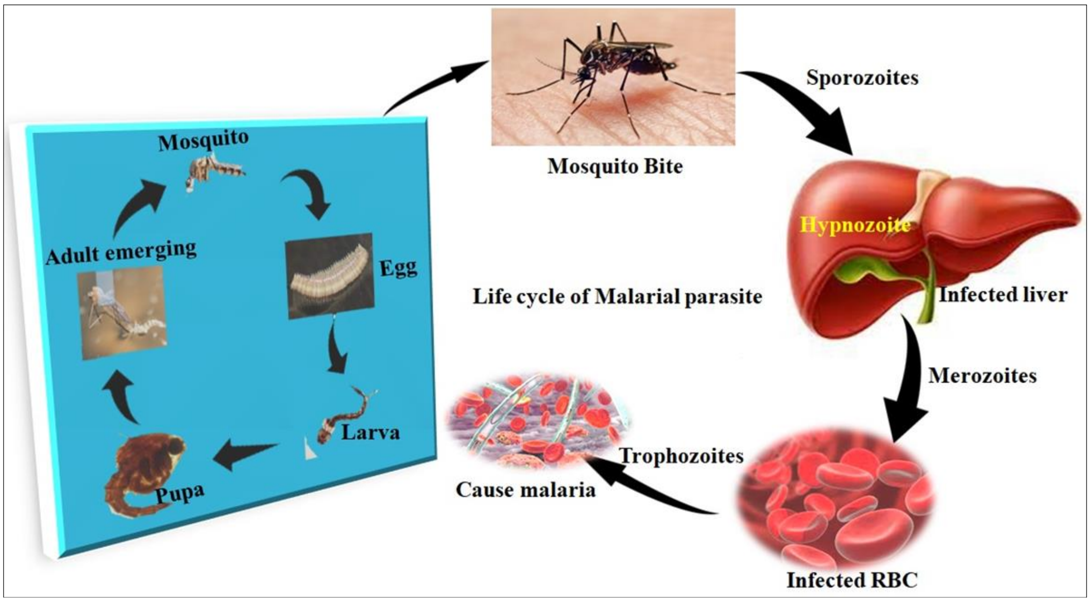

Fig 1: The life cycle and replication process of malaria parasite.

The evaluation based on larvicidal activity of biosynthesized nanoparticles has been undertaken against filariasis and malaria diseases which are caused by genus *Anopheles* and *Culex* mosquito vectors [4] Fig.1. Chemotherapy is the current strategic cure for malaria, but depicts dangerous effects and finally may lead to treatment failure. There is an urgent requirement of latest drug development in order to eradicate the clinical failures of anti-malarial chemotherapy, although the discovery of new drug and its development process is time consumption and high expense process [5]. An impressive approach required against malaria based on biogenic nature of mosquito body Fig. 2. The biologically synthesized nanoparticles are now considered as more sustainable with knowledge of specific dosage towards host [6]. Nanomedicine is the field of biological sciences which have varied applications and high impact on biotechnological and pharmaceutical industries in terms of initial structure and development of nanostructures (mostly up to 10000 nm) having antimicrobial and therapeutic properties [7].

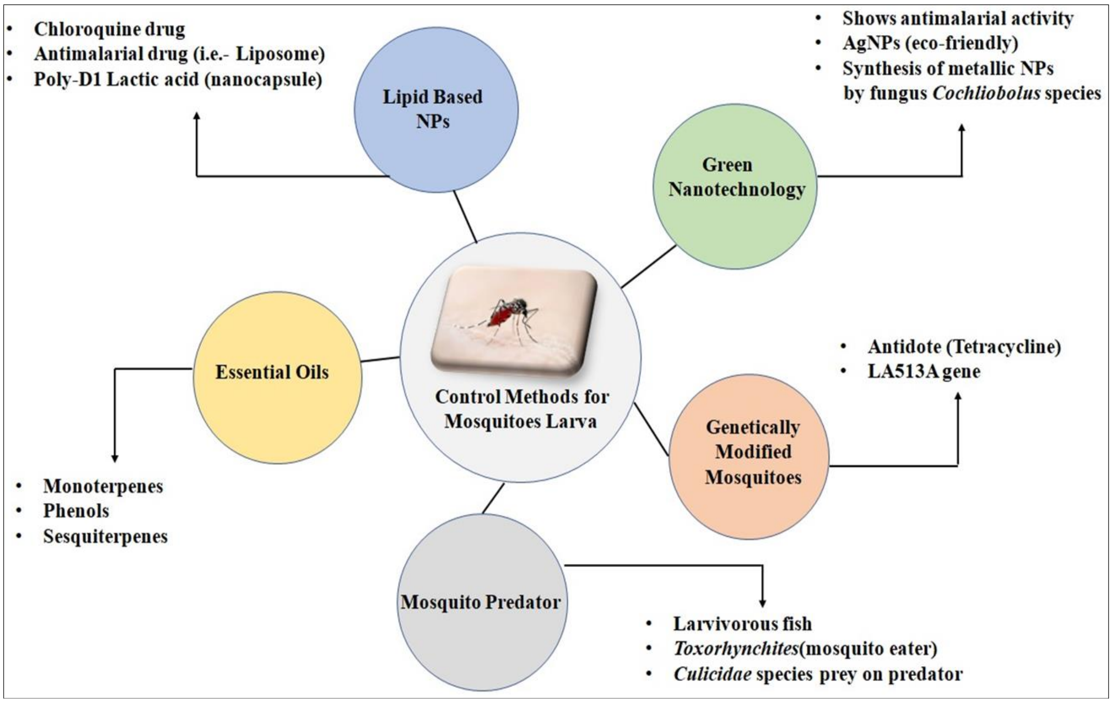

Fig 2: The development of core strategies and system for control of malaria vector.

Control method of mosquito larva with help of Nanotechnology

In order to reduce the extensive application of insecticides, various biocontrol methods for mosquito borne diseases are needed that are currently used as the primary method for mosquito control. The methods to target wide range of mosquito species should be environment friendly, sustainable and safe [8]. The significant study of nanotechnology is the mixture of different types of nanoparticles in various sizes, shapes and chemical compositions. With the requirement of eco-friendly sociable technologies in the material, various productions of noble metal nanoparticles like silver, gold, platinum, palladium has been obtained [9]. In order to biosynthesize nanoparticles, there are different parts of plant like leaf; seed, latex and root have been utilized. *Bacillus thuringiensis* is often used to control malaria in various parts of the world that can be used for the control of malaria vectors in many parts of the world by using biosynthesized gold, silver and zinc nanoparticles from the particular bacterial species [10, 11]. Currently, malaria specific antigen is carried to the target receptor with the help of nano-protein adjuvant. These adjutants in conjugation with specific antigens ranging in size from 16 to 73 nm diameter upon injection into the mice showed a better immune response against malaria as compared with antigens alone [12].

Lipid based nanoparticles

During the last decade, there was revolving interest in the lipids carrying nanoparticles such as solid lipid NPs (SLNs) in progression delivery of different drugs, this is because these are extracted from natural lipids (triglycerides, fatty acids and waxes) due to their less toxicity in comparison to polymeric nanoparticles [13].The anti-malarial drug with liposome's tagged antibody against infected erythrocytes presented a cure of 75%–90% in infected mice [14].A molecular study based on Polyethylene glycol (PEG)-coated halofantrine loaded poly-d, l-lactic acid (PLA) nano-capsules was conducted in mice that showed reduction in cardiotoxicity which was infected with *P. berghei*. In the experiment, a higher lifespan index was observed in case of mice infection with *P. berghei* for primaquine-loaded nanoparticles [15]. Chloroquine phosphate (an antimicrobial drug) encapsulated with gelatin nanoparticles was studied in a physiological medium (pH 7.4), and its release kinetics was demonstrated in the acidic pH range [16]. Various solid lipid nanoparticles such as transferrin-conjugates were examined for cerebral malaria treatment. The liposomes were seen showing more efficiency as compared to its free form through suppression of mice parasitemia, which help in preventing ECM-associated mortality [17].

Green Nanotechnology

The metallic synthesis of nanoparticles like gold, silver, copper and zinc through biological method have the shown enhanced antimicrobial properties against different *Plasmodium* species. In this type of synthesis, the crucial biomolecules like lipids and proteins takes the place of reducing agents. Such biological synthesis of AgNPs through plants is environment friendly [18]. Both gram positive and gram negative bacteria are regarded as important for synthesis of Ag nanoparticles, similar to plants. Some bacteria have the capability to produce both extracellular as well as intracellular Ag nanoparticles simultaneously. The dark brown colouration of the solutions shows the formation of Ag nanoparticles [19]. Recent findings have suggested that, fungi are basic source for producing the nanoparticles. Such kind of synthesis using fungi can be used as better effective agent for producing metallic nanoparticles with the help of *Cochliobolus lunatic* (a filamentous fungus) which have the extreme activities against *Anopheles stephensi* [20]. A gold nanoparticle which is formed by extracellular synthesis using *Aspergillus niger*, are highly toxic for malarial vectors. To stabilize metallic nanoparticles, bacteria and plants are used to inspire of fungal mediated nanoparticles .In order to control malarial vectors in various parts of the world ,bacterial nanoparticles are used (silver, copper, gold and zinc) by using *Bacillus thurigiensis* [21, 22].

Genetically modified mosquito

The deadly gene which is repressed using tetracycline in order to proper rearing of mosquito to adulthood under favourable condition hence produce off springs which generally die at larval stage due to lack of supply of tetracycline. It is observed that majority of larval population die except those carrying the LA513A insertion gene which shows normal development. This may lead to environmental consequences as it is stated that this strategy is dependent on self limiting gene of mosquitos which is termed as incomplete penetrance of lethal type of population. There is favourable lysis of the X chromosomes during the meiosis of the male which is induced by the gene modification. In the absence of tetracycline, larvae carrying one or more copies of the LA513A insertion develop normally but the vast majority (95%–97%) die at pupation [23]. Genetic modification can provide a bias towards male gamete production by inducing preferential breakdown of the X chromosome during male meiosis. With the lysis of X chromosome from the *Anopheles gambiae* further stop it from transmitted to the future generations which may lead to fertile strain which produces more than 95% male offspring's [24].

Mosquito predator

The natural feeders play a crucial role in the reduction of *Culicidae* population in the aquatic environment which feed on the mosquito pupa and larva [25,26].There has been great focus on the larvivorous fish which generally feed on the larval stage of the mosquitos which is the index of biological control of mosquitoes using vertebrate [27].There are plenty of environmental system which is recorded for fish predation of mosquitos, which can be wide ranging from small containers [28] to a typical natural ecosystems, which may include the coastal wet land environments [29].There have been various effective methods in the reduction of the mosquito larva in many parts of the world such as introduction of the larvivorous fish in a variety of habitats [30].The adults feed on the glucose rich materials like fruits, honey dew and nectar whereas the larvae feed on the larvae of other mosquito and nektonic organisms [31, 32].

Essential oils as larvicidal

A complex mixture of constituents such as monoterpenes, phenols and sesquiterpenes could readily act in synergetic way as well as more active than individual compounds. There is wide acceptance of essential oils which are plant based and obtained from a renewable resource, despite of its economical feasibility. Henceforth, the toxic nature of essential oils against larva is subsequently dependent on the age of plant, its vegetative parts chemotype and other conditions for the growth [33].

Polymer-based RBC membrane

A brilliant methodology needs to be created to overcome life cycle of the parasite that create intrusion of host RBCs. For that reason, nanostructures emulating RBC films, for example nanomimics, based on square copolymers with heparin as a host cell receptor were assembled. The antimalarial movement of various nanomimics developed by changing the number and length of heparin particles on their surface was assessed [34].

Conclusions

Mosquito control programs are facing important and timely challenges due to extensive use of synthetic mosquito repellent has resulted in resistance in mosquitoes. Novel ecofriendly strategies to manage mosquito vectors are urgently needed. Therefore, the current findings suggest that the green, biological synthesis of metal nanoparticles along with lipid based nanomaterial, essential oils, mosquito predators and genetically modified mosquito has the potential to be a good, quick, and environmentally acceptable method for mosquito population control. Although all the methods have completely novel mechanism, it can be used to successfully kill mosquitoes. Research papers on nanoparticles synthesis using biological organisms such as plant extracts, fungi, and bacteria are being analyzed and discussed in terms of type of nanoparticles, test species, exposure medium, and appropriate concentration to understand the trends in mosquito control. With very little uncovered mechanism of nanotechnology, there is a wide scope for detailed investigation in the future for the application of nanoparticles in the area of control management.

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