

## Silver nanoparticles: A promising approach for controlling vector-borne diseases by *Aedes Spp* and *Culex Spp* – A comprehensive review

Sadhana kumari Sah

Department of Life Science and General Microbiology, Garden City University, Bengaluru, Karnataka, India

### Abstract

Mosquito-vector diseases are prevalent globally, particularly in tropical and subtropical regions with ideal meteorological conditions. Mosquitoes are often controlled with the use of larvicide and repellent. However, employing these chemically derived Insecticides have rendered larvae resistant to them. Green nanotechnology, namely silver nanoparticles, is gaining popularity. These mosquito control products are made from plant extracts, reducing the danger of hazardous chemical exposure. This review study examines the synthesis of silver nanoparticles using phytoextracts and their impact on mosquito larvae and pupae. Silver nanoparticles outperformed the basic plant extract in terms of larvicidal efficacy. Furthermore, green silver nanoparticles require a substantially lower dosage to induce a 50% reduction in larvae/pupae population than plant extracts.

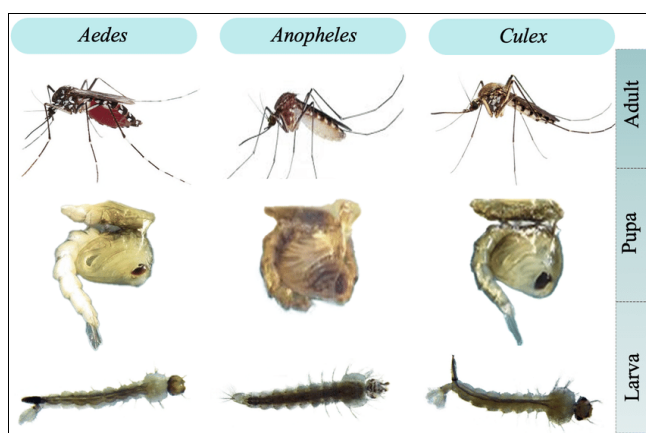
**Keywords:** Mosquito-vector diseases, silver nanoparticles, larvicidal activity, reactive oxygen species (ROS)

### Introduction

Out of all diseases that are infectious, 17% are vector-borne and caused by parasites, bacteria, or viruses. According to the World Health Organization (WHO), they kill about 700,000 people each year. Mosquitoes, particularly the *Anopheles* and *Aedes* species, are strong public health foes, serving as vectors for a wide range of life-threatening infections. The World Health Organisation (WHO) has designated mosquitos as 'public enemy no. 1' due to their role in the transmission of illnesses such as chikungunya, malaria, dengue fever, yellow fever, filariasis, encephalitis, and West Nile virus infection (Wilson *et al.*, 2020) [24]. With roughly three-quarters of the approximately 3500 mosquito species indigenous to the humid tropics and subtropical regions, the effect of these illnesses is especially severe in these locations (Wang *et al.*, 2023) [22]. Temperature, rainfall, and humidity all have a substantial impact on mosquito growth, behaviour, and endurance, impacting disease spread (Wilson *et al.*, 2020) [24].

by the evolution of mosquito-resistant strains, as well as negative environmental and health effects caused by their composition, which includes organophosphates, carbamates, and pyrethroids (Wang *et al.*, 2023) [22]. Mosquito repellents such as N-diethyl-meta-toluamide (DEET), dimethyl phthalate (DMP), N-diethyl mandelic acid amide (DEM), and mosquito pesticide are used to suppress mosquito populations. These repellents are widely known to be synthetically synthesised, resulting in the production of mosquito-resistant strains and harming both the environment and people since they contain organophosphates, carbamates, and pyrethroids (Thorsell *et al.*, 1998) [20].

Quinine-based antimalarial medications such as chloroquine and artesunate are quite effective, but mosquitos ultimately develop resistance to them. Even though several medications have been produced and proven effective against various illnesses, the fundamental issue is that mosquitos have acquired resistance to them (Hyde, 2007) [7]. Mosquitocidal sprays and mosquito coils are two more strategies for controlling mosquito populations. Mosquitocide has been successfully synthesised from eighty different plant species. Fogging for pest management is also used to destroy larvae and adult mosquitos. Removing the source of mosquito breeding places where water is collected can lower the risk of illness transmission. Other approaches that are still being researched include oviposition deterrents (Panneerselvam *et al.*, 2013) [17]. It is well acknowledged that oviposition is critical since it incorporates visual, olfactory, and tactile information. One method is to utilise predators that eat larvae and pupae. *Gambusia* and *Poecilia* are often used to control mosquitos. Copepods such as *Cyclops vernalis*, *Megacyclops formosanus*, *Mesocyclops (M.) aspericornis*, *M. edax*, *M. guangxiensis*, *M. longisetus*, and *M. thermocyclopoides* are known to feast on mosquito instars (Udayanga *et al.*, 2019) [21].



**Fig 1:** Morphological difference between *Aedes*, *Anopheles*, and *Culex Spp* (Hossain *et al.*, 2022) [5]

Traditional mosquito control approaches, such as the use of synthetic repellents and insecticides, have been hampered



**Fig 2:** Images of Adult guppies, *Poecilia reticulata* - females (1-2) and males (3-4) (Krinski *et al.*, 2017) <sup>[10]</sup>

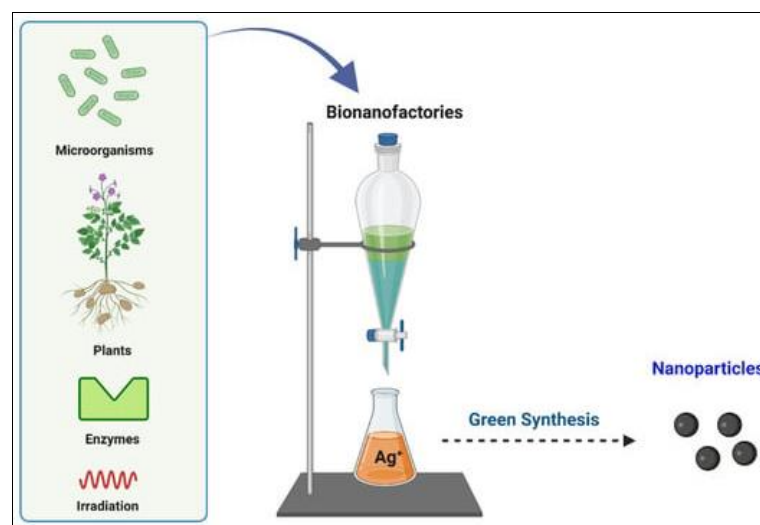
### Epidemiology

Malaria is transmitted by anopheline mosquitos, and 219 million cases are reported worldwide each year, with over 400,000 deaths, the majority of which are children under the age of five. Every year, the *Aedes* mosquito transmits dengue, which affects 96 million people and kills 40,000. Among South-East Asian nations, India has witnessed a significant decline in malaria infections, from 20 million in 2000 to around 5.6 million in 2020. Malaria incidence and fatalities fell by 28% and 41%, respectively, in 2019, thanks to consistent management measures. However, the figures remain troubling (Sharifi *et al.*, 2022) <sup>[19]</sup>. In 2019, 338,000 persons were afflicted by malaria, and 175,000 by dengue. India is one of the top 11 countries with the highest malaria incidence. In 2020, India in South-East Asia accounted for 86% of malaria-related fatalities. In 2015, there were 27,533 suspected cases of Chikungunya, with only 3342 verified. It dramatically climbed in 2016, with 64057 suspected and

26364 confirmed cases, before falling in 2017, 2018, and 2019, with 67769, 57813, and 65217 suspected cases and 12548, 9756, and 9477 confirmed cases of Chikungunya, respectively (Kumar *et al.*, 2018) <sup>[13]</sup>. As a result, new medicines including a range of active ingredients are badly needed to handle insecticide-resistant vectors that transmit outdoors. In this context, nanotechnology has emerged as a possible vector control solution. According to the literature, several nanoparticles, including TiO<sub>2</sub>, Ag, CuO, and Pd, exhibit insecticidal properties against vectors. However, the processes causing the higher toxicity of nanoparticles at low doses are not adequately understood (Nie *et al.*, 2023) <sup>[16]</sup>.

### Synthesis of silver nanoparticles

The nanoparticles are created by the so-called green synthesis technique, in which extracts from fungus, bacteria, plants, their purified metabolites, and even dead insects are utilized to reduce and stabilize nanoparticles in aqueous suspensions. When opposed to traditional physical and chemical synthesis processes, the green manufacturing process offers major advantages since it does not involve the use of very toxic chemicals or high energy inputs. The whole process is affordable and easy, producing a wide variety of nanoparticles including gold, zinc oxide, iron, silver, titania, palladium, and carbon. These nanoparticles have been effectively tested against a wide range of harmful arthropods, including agricultural pests, public health vectors, and livestock science (Kulkarni *et al.*, 2023) <sup>[11]</sup>.



**Fig 3:** Strategies for Green Synthesis of Silver nanoparticles (Jain *et al.*, 2021)

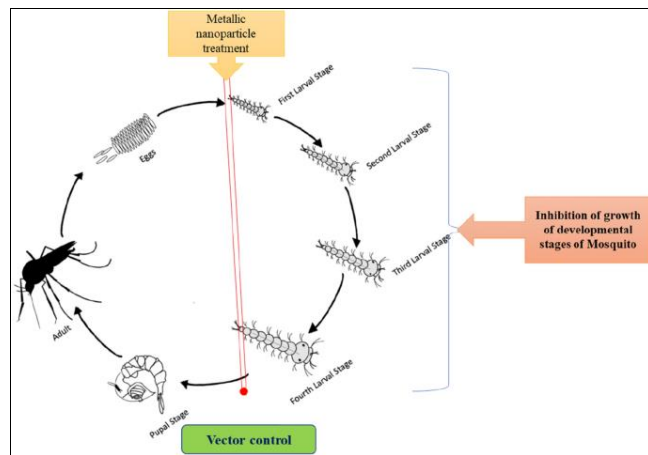
Recent research on nanoparticles as novel insecticides has revealed a growing body of evidence suggesting limited impact of green-capped nanoparticles in aquatic environments. At concentrations effective against mosquito young instars, minimal acute and chronic toxicity has been observed in most cases, along with negligible genotoxicity and absence of detrimental behavioral changes in non-target species such as fishes, dragonfly nymphs, and tadpoles (Shamseldean *et al.*, 2022) <sup>[18]</sup>. Exposure to silver nanoparticles, however, has been linked to morphological deformities and DNA damage in both invertebrate and vertebrate creatures, as well as adverse effects on the enzymatic activities of various non-target species (Kulkarni

*et al.*, 2023) <sup>[11]</sup>. Insights from recent studies shed light on the consequences of subjecting mosquito early instars to green-synthesized nanoparticles. Kalimuthu *et al.* (2017) <sup>[9]</sup> observed that exposing fourth instar larvae of *Aedes aegypti* (L.) to silver nanoparticles synthesized from *Hedyotis coronarium* J. Koenig rhizome (with an LC<sub>50</sub> of 72 ppm) led to partial lysis of midgut epithelial cells. Additionally, they noted the presence of vesicles and damaged membranes on the apical side of epithelial cells. The question of whether the toxicity of nanoparticles, particularly metallic ones, arises from the nanomaterial itself or from the ions it generates remains debated. Huang *et al.* (2017) <sup>[6]</sup> have discussed how various types of nanoparticles may act as toxic agents by traversing

cellular barriers and producing toxic ions that harm cellular machinery.

### Mode of action

Although nanoparticles have shown great promise as insecticides and acaricides, there are still questions regarding their practical application in terrestrial and aquatic environments. The lack of understanding of their ecotoxicological effects makes it difficult to forecast their environmental fate and possible implications on human health (Zaheer *et al.*, 2022) [25]. Surprisingly, despite extensive data on their toxicity against certain pests and vectors, full understanding of the precise mechanisms of nanoparticle activity against insects and mites is missing.



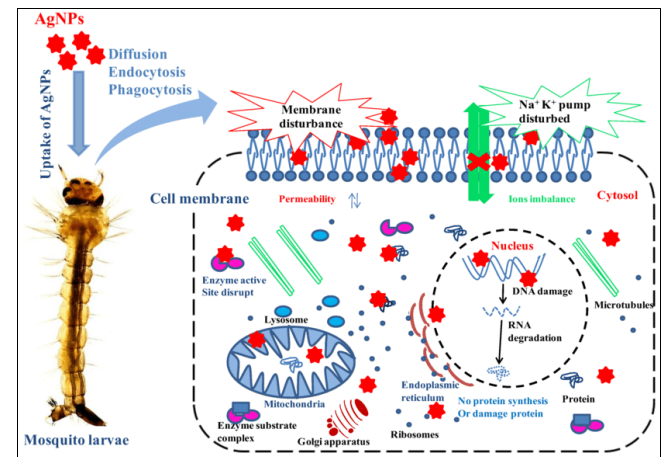
**Fig 4:** Action of nanoparticles on stages of *A. aegypti* (Hossain *et al.*, 2022) [5]

This knowledge is critical to foreseeing the toxicological effects of nanoparticle pesticide applications in the actual world. Mechanisms underlying cytotoxicity and genotoxicity have been studied particularly for silver nanoparticles, as their toxicity in model organisms is substantially impacted by parameters such as dimensions, form, and charge (Benelli, 2018) [2].

One strategy uses the nanoparticle scale effect, which improves pesticide adhesion in the environment and increases the possibility of insect exposure to nanoparticles. Nanoparticles can cause cell dehydration by adsorbing onto the stratum corneum, resulting in morphological and histological defects in insects (Chaud *et al.*, 2021) [3]. Sultana's experiments indicated that carbon-dotted silver nanoparticles were very poisonous to *A. stutzeri* and *C. quinquefasciatus*. SEM study indicated abnormalities in larvae induced by carbon-dotted silver nanoparticles, and X-ray analysis verified the presence of nanohybrids in the treated specimens. The presence of silver in mosquito tissues shows that nano-silver's cellular toxicity may lead to their demise. Furthermore, high-resolution transmission electron microscopy (HR-TEM) revealed damage to both the stratum corneum and cellular tissue. Third-instar *A. aegypti* larvae were subjected to zinc oxide nanoparticles (1.57 mg/mL, 24 h) generated from *Lobelia*, which caused abdominal contractions, changed thorax shape, midgut lesions, and loss of lateral hairs, anal gills, and brushes. Zinc oxide nanoparticles accumulated in the chest and belly (Nie *et al.*, 2023) [16].

Another mechanism involves nanoparticles entering the insect body and producing oxidative stress, protein damage,

and disruption of the insect's normal physiological function. *In-vivo* studies show that when cells take up nanoparticles, DNA damage and oxidative stress are found. Previous research has shown that nanoparticles have insecticidal properties because they may destroy cells (Mir *et al.*, 2020) [15]. Certain nanoparticles, such as TiO<sub>2</sub>, may absorb UV radiation from their surroundings. When electrons absorb energy, they become very active, forming holes in the valence band. When oxygen in the air combines with these electrons, it produces oxygen radicals.



**Fig 5:** Mechanism of silver nanoparticles on mosquito (Kumar *et al.*, 2020) [13]

Water oxidises with created holes, producing reactive oxygen species (ROS) such as H<sub>2</sub>O<sub>2</sub> and O<sup>2-</sup>. These ROS trigger cell death when they react with glycosides, unsaturated fatty acids, proteins, and other biological components (Li *et al.*, 2020) [14]. Furthermore, metal ions in the material may enter cells during the outward release phase and bind to amino acids in proteins like sulphur and phosphorus, reducing cell membrane permeability. Nanoparticles can cause DNA damage and impair the activity of intracellular enzymes once within cells (Wang *et al.*, 2017) [23].

To obtain insight into toxicity processes, researchers examined gene expression alterations in midges exposed to nanosilver. They discovered that exposure reduced the expression of the ribosomal protein gene (CrL15), which controls ribosomal assembly and hence protein synthesis. Furthermore, upregulation of the gonadotrophin-releasing hormone gene (CrGnRH1) and the Balbiani ring protein gene (CrBR2.2) indicated the activation of gonadotrophin-releasing hormone-mediated signal transduction pathways, reproductive failure, and organism defence mechanisms (Flanagan and Manilall, 2017) [4]. The study also found that Cu and Mn superoxide dismutase were increased in response to Ag<sup>+</sup> ions and silver nanoparticles, respectively. Furthermore, treatment to silver nanoparticles elevated transcript levels of catalase, phospholipid hydroperoxide glutathione peroxidase 1, and thioredoxin reductase 1, but no changes were seen when exposed to free ionic silver. Furthermore, exposure to Ag nanoparticles resulted in increased expression of glutathione S-transferase classes delta-3, sigma-4, and epsilon-1 compared to free ionic silver. Overall, the study found that exposure to silver nanoparticles had a greater influence on the activation of oxidative stress and detoxification genes than free silver ions (Wang *et al.*, 2017) [23].

### Future Perspectives and Research Challenges

The current study identifies a large void in the literature on nanoparticle toxicity to agricultural, medicinal, and veterinary arthropods. The promise of environmentally friendly nanoparticle manufacturing methods has sparked considerable attention among research organizations worldwide, possibly paving the door for novel approaches to arthropod pest and vector management. Despite some researchers' careful attempts to unravel the methods by which silica, alumina, silver, gold, and graphene nanoparticles cause toxicity in mosquitoes, our understanding of this topic remains restricted. Furthermore, more study is needed into the processes behind the reported toxicity of copper, iron, and chitosan nanoparticles, which are important classes of nanomaterials employed in entomological and parasitological studies (Amarasinghe *et al.*, 2020) [1].

Furthermore, the effect of nanoparticle size, shape, and charge on the numerous mechanisms of action remains unknown. To avoid insecticidal effects, green production methods employing chemicals like  $\beta$ -caryophyllene, stearic acid, and zein are preferred over using botanicals and microbial compounds as reducing and capping agents. This technique reduces differences in findings caused by the wide range of green reducing agents investigated. Finally, more study is needed to evaluate the suggested nanopesticides in real-world field situations, as well as to monitor their stability, environmental destiny, and sublethal effects on non-target species. This involves a strong emphasis on genotoxicity, as well as minor physiological and behavioral effects. A thorough knowledge of the many processes that contribute to chronic nanoparticle toxicity in vertebrates, with a particular emphasis on human health, is critical and urgently needed (Mir *et al.*, 2020) [15].

### Conclusion

In conclusion, the escalation of mosquito-borne diseases prompted the development of chemical insecticides, which initially seemed effective but ultimately caused harm to the environment and led to the emergence of resistant strains. While the traditional approach resulted in a never-ending cycle of developing new insecticides, a promising alternative has emerged in the form of silver nanoparticles synthesized from plants. This innovative solution offers cost-effectiveness, environmental friendliness, and minimal energy requirements for synthesis. By addressing the shortcomings of chemically synthesized insecticides, silver nanoparticles hold significant potential for effective mosquito population control without adverse environmental impacts. However, further research in this area is imperative to realize a sustainable and green future.

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