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Zinc Oxide Nanoparticles Fabricated With Phytoextracts For The Control Of Mosquito Vectors- A Systemic Review

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Abstract

Transmission of pathogens by mosquito vectors pose serious challenges to public health. Controlling the vectors is a promising option in preventing the spread of infectious agents. Several chemical approaches though effectively control mosquitoes, proved to cause side effects including resistant mosquito species and environmental contamination. Green chemistry mediated nanoparticles synthesis is simple, quick, economically modest and environmentally safe and hence could be a safe alternative. The purpose of this review is to categorise, analyse, and organise the main findings from research papers on plant extract mediated zinc oxide nanoparticles (ZnO-NPs) with potential larvicidal properties. The investigation involved analysing the published literature from different scientific databases. The main focus was on identifying scientific reports on the green synthesized ZnO-NPs that showed the larvicidal potency (LC_{50}) less than 25 µg/mL. Further, the review discusses the various methods of synthesis of ZnO-NPs and their mechanism of toxicity against mosquito larvae. The consolidated and organized information presented in this review can be effectively utilized for the design, development, and optimization of phyto-mediate nanoparticles synthesis with potential larvicidal activity. The summarized data provides a foundation for further research and application in the field of herbal insecticides, particularly focusing on their larvicidal properties.

CC License CC-BY-NC-SA 4.0	**Keywords:** Plant extract, Zinc oxide nanoparticles, Larvicidal activity, Sol-gel, Solution combustion, Co-precipitation

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1. Introduction

Mosquitoes, belonging to the Order Diptera and family Culicidae, are significant vectors of deadly pathogens. With approximately 35,000 species found worldwide [1,2], they are responsible for transmitting pathogens that cause diseases such as dengue, chikungunya, filariasis, zika fever, yellow fever, Japanese encephalitis, malaria, West Nile fever, and Rift Valley fever. The *Anopheles* genus comprises more than 53 species, with nine of these species known to transmit the malarial pathogen. Notably, *An. stephensi* is the dominant species responsible for spreading the malarial pathogen to humans [3,4]. Among the *Culex* species, *Culex quinquefasciatus* is responsible for transmitting filariasis [5,6]. Additionally, dengue is transmitted by *Aedes* species, namely *Aedes aegypti* and *Aedes albopictus*, which have persisted for centuries among human populations. The outbreak of dengue is particularly prevalent in tropical and subtropical countries (World statistics and Indian Statistics for the year 2023, sourced from NVCB). In Tamil Nadu, India an estimated 1121 cases of dengue infections were reported [7].

Traditional methods of mosquito control, while effective to a certain extent, face inherent limitations such as environmental concerns, resistance development, and the difficulty of isolating potent bioactive compounds from natural sources. An innovative approach gaining attraction in recent years involves the use of nanoparticles for mosquito control. Nanoparticles, due to their distinct physical and chemical properties, offer a versatile platform for targeted and sustainable mosquito control. Additionally, the synthesis of phyto-mediated nanoparticles, has gained attention for its sustainable and environmentally friendly nature. Metal oxide nanoparticles, particularly ZnO NPs, have emerged as promising candidates for mosquito larvae control. Studies have employed a variety of plant sources, each imparting distinct phytochemicals to the nanoparticles. This review consolidates recent research findings on the application of phyto-mediated ZnO NPs as larvicidal agents and explores the nuanced relationship between synthesis methods, particle characteristics, and larvicidal efficacy.

2. Traditional mosquito control

The traditional approach to mosquito control involves using a combination of chemical insecticides and a microbial toxin (Endotoxin from *Bacillus thuringiensis*). However, these chemical insecticides pose risks to humans and non-target organisms, as well as negative effects on the environment. Besides these limitations, the development of resistance to chemical insecticides by mosquitoes is a significant concern in controlling vector transmissions. Therefore, alternative strategies to address these challenges in controlling mosquito populations and infectious agents is essential [8,9]. The use of phytochemicals for controlling mosquito populations has proven to be highly effective for several reasons:

1. It is simple and environmentally friendly.
2. It achieves high efficiency at low dosages compared to some commercial insecticides.
3. It does not require synthetic surfactants.
4. It exhibits multiple modes of action, thereby avoiding the development of resistance in mosquito populations [10].

The effects of phytochemicals on mosquito larvae are summarized in Fig.1. This review provides an in-depth analysis of various green route techniques for the biogenic fabrication of ZnO- NPs and their larvicidal efficacy against mosquito species.

2.1 Drawbacks of conventional mosquito control

Mosquito control efforts achieved remarkable success with the adoption of various synthetic insecticides, after the discovery of DDT [11]. Since then, insecticides have been widely employed to control mosquitoes. However, overuse of these insecticides led to the emergence of resistance in vector species and raised concerns about their harmful impact on human health and the environment [12]. Hence, insecticide substitutes that is affordable, effective, and safe to humans and to the environment should be the prioritized in the search for an alternative. The alternative insecticides should possess the property of not being resisted by mosquito population as development of resistance has become frequent among mosquito species which hinders the control of mosquito species and in preventing the transmission of vector-borne infections [13]. The mosquito species are even capable of developing resistance to diverse combination of chemicals [14]. The residual insecticides left on the surface due to spraying of chemical insecticides are toxic to humans when they are inhaled [15]. The bad odour of organic insecticides, the difficultly in sight after space spraying led to unacceptability of the chemical agents. Further, they are highly expensive and demands technical skills. The biological insecticides from plant and microbial source were also challenged with the development of resistance by mosquito vectors [13]. The non-target organisms might be in danger due to the biocontrol agents as they affect the food chain and cause loss in biodiversity [16,17]. Development of transgenic mosquitoes as part of mosquito control programme, face difficulties such as ethical issues [18], maintenance of mutant stains and interaction with non-target organisms [19].

3. Nanotechnology

Nanoscience is a fascinating field that involves the creation of materials with interatomic structural properties, typically with particles measuring 1 to 100 nm in size [18,20]. The nano size of these particles results in a high surface area, achieving their applicability in various fields such as chemistry [21], medicine [22,23], agriculture [24], pharmaceuticals, electronics [25], and catalysis [26]. Nanoparticles play a significant biological role, with characteristics features such as anticancer, antimicrobial, antioxidant, anti-inflammatory, and anti-angiogenic effects, making them a crucial component in biomedical research [20]. The extensive utilization of nanoparticles across various fields is attributed to their high stability, biocompatibility, solubility, adhesive properties, and therapeutic potential [21]. Additionally, nanotechnology provides the opportunity to finely tune the intrinsic traits and functions of materials to achieve desired outcomes compared to their bulk form [27].

Nanomaterials interact with cells at a molecular level with a high degree of specificity, effectively integrating technology with biological systems. Nanotechnology is an interdisciplinary scientific discipline that bridges traditional sciences including chemistry, physics, biology, and material science. Consequently, this novel method for producing nanoparticles draws on the collective expertise of all these fields. It's also worth noting that the production of nanoparticles by different microbes in response to the toxicity of heavy metals indicates that the production of nanoparticles cannot be characterized as a recent technological breakthrough [28].

The synthesis of nanoparticle through various methods have been reported, including physical and chemical approaches. However, the biogenic mode of nanoparticle synthesis has gained prominence due to its avoidance of toxic chemicals. This method utilizes organic sources such as plant products, and microorganisms. The constraints associated with the use of botanical insecticides is isolating bioactive compounds from potentially toxic plants. However, this challenge can be addressed through polyploidization to increase the production of specific bioactive compounds [10,14,29]. Additionally, safety concerns arise with the use of botanical pesticides in aquatic environments due to their weak stability and short durability. To address this, innovative technologies have been developed to enhance the stability, durability, and overall performance of botanical insecticides [30]. One such technology is encapsulation, which improves the stability of botanical insecticides and their effectiveness in aquatic environments through controlled release of bioactive compounds [31,32]. Another important technology for enhancing the potential of phytochemicals as insecticides is nanotechnology, where phytochemicals are surface-coated on nanoparticles [33,34].

3.1 Synthesis Techniques

Two types of conventional techniques in the nanoparticle fabrication includes “Top-Down” and “Bottom-Up” procedures. These methods further branch into sub categories such as physical, chemical, and biological methods. The bottom-up methods produce nanoparticles through nucleation mechanism [35,36], while the top-down process forms nanoparticles from their bigger materials. The various synthetic approaches except the biological synthesis involves in the use of toxic chemicals, high pressure, temperature and energy. The biological synthesis involves plant extract [37], algae [26], enzymes [38], Cyanobacteria [39], fungi [40] and bacteria [41]. In the green mode of synthesis, the phytochemicals or secondary metabolites perform as reductants and stabilizers. Thus, the nanomaterial syntheses are devoid of harmful chemicals and eco-friendly, cheap, pure and possess the tuneable properties in the obtaining the desire size and morphology [42]. Even before the precise mechanism was understood, phytochemicals have been used as reducing and stabilising agents for different metal ions in the creation of nanoparticles since the early 1900s [42]. The nanoparticles are classified into 1D (thin films), 2D (carbon tubes) and 3D (Quantum dots, dendrimers) [43] and the different types of synthetic methods are summarized in Fig. 2

3.1.1 Physical methods

Physical methods for nanoparticle synthesis, such as sputtering, deposition, ball milling, and plasma-based techniques, are widely used in the creation of nanoparticles [44]. However, these methods often have limitations. For instance, ball milling exhibits only 50% efficiency compared to other techniques, while sputtering results in a large particle size distribution, with only 6-8% of materials falling below 100 nm. Laser and plasma techniques require high energy, contributing to high energy consumption and limiting their commercial viability [45,46].

In the physical approach, nanoparticles are stabilized and shaped using physical forces. Methods utilizing physical forces include amorphous crystallization, colloidal dispersion, vapour condensation, and physical fragmentation [44]. Among physical methods, laser ablation has been noted for its unique properties, offering the synthesis of nano-sized, and pure ZnO-NPs [46]. The properties of the synthesized nanoparticles depend on factors such as ablation time and laser wavelength [47]. In the thermal evaporation process, precursor materials in powdered form are heated to high temperatures to vaporize them. The resulting vapor is then condensed under high pressure to produce ZnO-NPs with the desired size and form [48]. This approach has led to the synthesis of various ZnO-NPs structures, including nano rings, nanobelts, nanorods, and nano combs, with effective photocatalytic activity for the breakdown of harmful dyes [49,50]. However, physical methods also come with drawbacks such as the need for expensive equipment, high temperatures, high pressures, and large spaces [51]. While physical methods have their limitations, they continue to offer valuable insights and advancements in the field of nanoparticle fabrication. Ongoing research and development efforts aim to address these drawbacks and enhance the efficiency and commercial viability of physical synthesis techniques.

3.1.2 Chemical Methods

Pyrolysis, chemical reduction, polyol, chemical vapor deposition, hydrothermal, and sol-gel are some of the significant chemical techniques used in nanoparticle synthesis [52]. While chemical synthesis is an efficient way to produce nanoscale materials, it also comes with several drawbacks, including the use of potent chemicals and the generation of harmful by products from chemical breakdown. These by products, which include toxic chemicals used in the synthesis, pose risks to both human health and the environment [48]. Despite these challenges, the chemical technique enables the production of nanoparticles with desired characteristics, such as size and shape, by incorporating stabilizers like citrates or polyvinylpyrrolidone into the ZnO-NPs synthesis process. These stabilizers prevent nanoparticles from agglomerating [53]. Nanoparticles ranging in size from micrometers (µg) to nanometers (nm) can be generated by varying the concentration of precursor molecules and reducing agents. However, a key challenge in the chemical method is the requirement for high energy, toxic chemicals, sophisticated and expensive equipment [54].

3.1.3 Biological Methods

The biological method of nanoparticle synthesis involves the extracellular or intracellular generation of nanoparticles using microorganisms such as bacteria, fungi, algae, yeast, and plant extracts [55] and synthesis methods are summarized in Fig. 3. This innovative approach provides a quick, affordable, and sustainable way to produce nanoparticles, offering an alternative to traditional chemical and physical methods. By utilizing biomolecules and phytochemicals, this method avoids the use of toxic chemicals, high energy, and pressure in reducing precursor molecules and decorating the reduced materials.

Both prokaryotic and eukaryotic microorganisms are employed in the fabrication of metallic and metal oxide nanoparticles, making this method a bottom-up approach that encompasses the production of nanomaterials from simple unicellular to complex multicellular organisms [50,53–57]. While the biological synthesis using microorganisms is highly effective, caution should be exercised in the selection of microorganisms due to potential toxicity and safety concerns during their culture. Additionally, the high cost involved in maintaining cultures presents a challenge that needs to be addressed [58].

3.1.4 Bacterial Synthesis

The synthesis of nanoparticles using microbes can occur through either extracellular or intracellular methods. In intracellular production, nanoparticles are formed within the microbial cells in the presence of enzymes, leading to smaller particle sizes due to nucleation [59]. The specific mechanism of intracellular nanoparticle synthesis is still not fully understood. Previous research suggests that metal ions trapped inside or on the surface of bacterial cells can lead to nanoparticle formation. Additionally, when the ion is catalysed by a bacterial enzyme, it undergoes a reduction reaction [60].

Extracellular synthesis is preferred over intracellular synthesis due to the ease of harvesting and purifying nanoparticles [61,62]. In intracellular production, sugar molecules and membrane protein are utilized as reducing agents. Co-factors such as nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) have been identified as electron carriers. The extracellular mode of nanoparticle synthesis by microbes avoids unnecessary cellular components.

3.1.5 Fungal synthesis

Fungi are particularly effective in the extracellular synthesis of nanoparticles, as they can produce large quantities of diverse bioactive compounds that are involved in reducing precursor metal ions [59]. In the extracellular mode, the metabolites and enzymes present in the cell filtrate of fungi act as reducing and stabilizing agents [63]. Fungi are capable of producing redox enzymes such as NADH, NADPH, and peroxidase, which play a key role in reducing the metal ion precursor and facilitating the formation of nanomaterials. This extracellular approach offers advantages in terms of the ease of nanoparticle isolation and purification.

Conversely, when nanomaterials are synthesized within fungal cells, the precursor metal is introduced into the culture media for internalization. However, the purification of the generated nanoparticles represents a challenging step in fungi-based nanoparticle manufacturing. Processes such as filtration, centrifugation, and washing are typically employed to remove unwanted fungal by products and isolate the nanoparticles [64]. Understanding the distinct mechanisms and challenges associated with intracellular and extracellular fungal synthesis of nanomaterials is crucial for optimizing these processes and harnessing the potential of fungi in sustainable nanotechnology applications.

3.1.6 Green synthesis

The utilization of plant extracts (Green synthesis) in nanoparticle production has proven to be one of the most successful methods among various biological approaches. The presence of phytochemicals or secondary metabolites enables the efficient synthesis of ZnO-NPs from plant extracts, allowing for the creation of nanoparticles with diverse morphologies by varying the quantities and qualities of these secondary metabolites [65]. It has been established that secondary metabolite, including biomolecules such as proteins and carbohydrates, alkaloids, flavonoids, tannins, saponins, terpenoids, and phenolic chemicals, function as efficient reducing agents [66]. This approach is risk-free, economical, environmentally friendly, and biocompatible, and it can be easily applied in large-scale production due to the reducing and stabilizing properties of phytochemicals [67,68]. Selecting the appropriate plant species for nanoparticle synthesis is a critical consideration. Utilizing plant varieties with a history of medicinal use ensures the safety and non-toxicity of the resulting nanoparticles to humans [33]. Plants offer exceptional optical and catalytic properties, along with an increased surface area to volume ratio, making them ideal carriers of phytochemicals [10].

In the synthesis of nanoparticles from metal precursors, the initial step involves the formation of hydroxyl complexes. This occurs through the dissociation of metallic salts into anions and cations, leading to the saturation of cations. Subsequently, crystalline growth of metal with oxygen species occurs, resulting in the formation of crystalline planes with different energy levels. Phytocomponents act as capping agents, inhibiting the growth of high-energy atomic planes. The surface of the nanomaterials is adorned with a variety of molecules, including proteins, alkaloids, flavonoids, polyphenols, terpenoids, and alcohol-based chemicals, which serve to reduce the precursor molecules and maintain the stability of the nanomaterials [69]. The advantages of green nanoparticle synthesis, utilizing plants as a sustainable and eco-friendly approach, are summarized in Figure 4. This approach holds great promise for the development of environmentally friendly nanomaterials with diverse applications.

4. Metal oxide nanoparticles

Zinc oxide is exceptional due to its physical and chemical characteristics, including its high stability, radiation absorption, electrochemical coupling coefficient, strong photostability and paramagnetic nature [70]. The wurtzite structure and electromechanical coupling of ZnO-NPs is utilized in vast variety of applications such as mechanical actuators and in piezoelectric sensors. Because wurtzite lacks a symmetry center and electromechanical coupling, zinc oxide (ZnO) is used in mechanical actuators and piezoelectric sensors. Additionally, ZnO is a semiconductor with a broad band gap (3.37 eV) that can be used in a variety of applications. Metal oxide nanoparticles exhibit exclusive properties, including dense edges, surface atom purity, relatively smaller size, and diverse structural morphology, making them of great interest in the domains of mechanical, physical, and electronics [66,71,72]. In biomedical applications, the importance of biodegradable and biocompatible materials cannot be overstated [73,74]. The bioaccumulation effect of ZnO-NPs has been leveraged in mosquito control programs, making them a valuable alternative for controlling mosquito vectors, especially the dengue vector, *Ae. aegypti*. Furthermore, metal oxide nanoparticles exhibit high stability in body fluids and are less toxic compared to metallic nanoparticles [75].

The methodology generally adopted for synthesizing nanoparticles from plant extracts involves adding the extract to a metal salt solution at room temperature. This approach using plant extracts as catalysts allows for rapid nanoparticle synthesis. Silver, gold, and a number of other metals have been utilized for the synthesis of nanoparticles using this technique [76]. The characteristics of the nanoparticles, such as their rate of synthesis, amount, and other properties, depend on factors such as the concentration of plant extract, precursor material, pH, temperature, and reaction time [77].

The present study involved an in-depth review of published literature from multiple scientific databases, focusing on the biogenic synthesis of ZnO-NPs for mosquito control and their use as larvicides. The search for research articles published between 2014 and 2023 was carried out, specifically targeting cases where herbal extracts formulated ZnO-NPs demonstrated an LC_{50} value of less than 25 µg/mL. The essential data from this research, including the plant's name, the specific section of the plant employed, the method of synthesis of nanoparticles, the particle size and shape, the secondary metabolites present on the surface of the synthesized nanoparticles, the larval species, and the larvicidal potency, were examined. A total of twenty-nine published research articles were collected and analysed to investigate the green-mediated synthesis of ZnO-NPs as a larvicidal agent.

The synthesis of phyto-mediated zinc oxide nanoparticles (ZnO-NPs) as larvicidal agents has been achieved through diverse methods, including sol-gel, solution combustion, coprecipitation, and hydrothermal processes. This section delves into the various plant extracts employed for the synthesis of ZnO-NPs, elucidating their characteristic features and examining their impact on the larvicidal efficacy of the synthesized *Aedes*, *Culex*, *Anopheles* mosquito species.

4.1.1 Sol gel method

The synthesis of nanoparticles using aqueous leaf extracts through the sol-gel method has unveiled a diverse array of characteristics and larvicidal efficacies against various mosquito species. Nanoparticles derived from *Pterolobium hexapetalum* exhibited a spherical morphology within the size range of 10 – 93 nm, demonstrating notable larvicidal efficacy against *Ae. aegypti* larvae with an LC_{50} value of 8.982 µg/mL [2]. *Myristica fragrans* mediated ZnO-NPs, characterized by rod shaped morphology and an average size of 100 nm, displayed effectiveness against *Ae. aegypti* larvae with LC_{50} values of 3.44 µg/mL [78]. *Cipadessa baccifera* mediated ZnO-NPs, spherical in shape and measuring 41.48 nm, exhibited remarkable potency against *Ae. aegypti* larvae with LC_{50} values of 0.55214 µg/mL [79].

Lantana camara mediated nanoparticles, spherical and ranging in size from 12.2 to 25.3 nm, demonstrated efficacy against *Ae. aegypti* larvae with an LC_{50} value of 14.85 ppm [80]. *Plectranthus amboinicus* mediated nanoparticles, ranging from 20 to 50 nm and displaying both spherical and hexagonal shapes, exhibited effectiveness against *Cx. quinquefasciatus* larvae with an LC_{50} value of 3.1 mg/mL [81]. ZnO-NPs mediated with *Momordica charantia* were spherical in shape and measuring 21.32 nm, proved effective against *Cx. quinquefasciatus* larvae with an LC_{50} value of 4.87 µg/mL [82]. *Ficus religiosa* mediated nanoparticles were irregular in shape with an average size of 12.82 ± 2.50 nm, demonstrated effectiveness against *An. stephensi* larvae with an LC_{50} value of 2.74 ppm [83]. *Lumnitzera racemose* nanoparticles, characterized by a rod-shaped structure within the size range of 250 – 300 nm, were effective against *Ae. aegypti* larvae with an LC_{50} value of 24.74 µg/mL [17]. *Lagenaria siceraria* nanoparticles exhibited hexagonal shape and measuring 81.8 nm, exhibited effectiveness against *An. stephensi* larvae with an LC_{50} value of 3.873 µg/mL [84].

4.1.2 Coprecipitation method

The coprecipitation technique for synthesizing ZnO-NPs has emerged as an effective method for mosquito larvae control, as evidenced by findings from recently published articles. In a study, ZnO-NPs mediated by the aqueous seed extract of *Elettaria cardamomum* were characterized by an average size of 18.72 nm and with a spherical morphology. These nanoparticles exhibited noteworthy efficacy against *Ae. aegypti* larvae, with an LC_{50} value of 13.27 µg/mL [85]. Similarly, *Pleurotus djamor* aqueous fruit extract mediated nanoparticles, with sizes ranging from 70 to 80 nm and a spherical shape, demonstrated effectiveness against *Ae. aegypti* larvae, exhibited an LC_{50} value of 10.1 µg/mL [86].

The utilization of *Azadirachta indica* gum extract in nanoparticle synthesis resulted in particles ranging from 60 to 80 nm with a circular shape, exhibiting significant effectiveness against *Cx. quinquefasciatus* larvae with an LC_{50} value of 10.25 µg/mL [87]. *Murraya koenigii* aqueous leaves extract mediated nanoparticles, with a size range of 10 to 15 nm and hexagonal structures, proved effective against *Cx. quinquefasciatus* larvae, exhibiting an LC_{50} value of 2.1 µg/mL [88]. Furthermore, *Cuscuta reflexa* aqueous stem extract mediated nanoparticles, measuring 40.86 nm and displaying a spherical shape, demonstrated efficacy against *An. stephensi* larvae, with an LC_{50} value of 24.32 µg/mL. These findings highlight the potential of coprecipitation synthesized ZnO-NPs as a versatile and promising approach for mosquito larvae control across various species.

4.1.3 Solution combustion method

Research on ZnO-NPs synthesized through the solution combustion method has revealed promising outcomes in mosquito larvae control. The aqueous leaves extract of *Solanum lycopersicum* was employed to mediate the ZnO-NPs synthesis, resulting in particles with the average size of 100 nm, characterized by a rod-like and pellet-like structure. These nanoparticles exhibited effectiveness against *Ae. aegypti* larvae, with an LC_{50} value of 9.311 µg/mL [89]. Similarly, *Knoxia sumatrensis* aqueous leaves extract-mediated nanoparticles, with sizes ranging from 50 to 80 nm and a rod-shaped morphology, demonstrated significant efficacy against *Cx. quinquefasciatus* larvae, exhibiting an impressively low LC_{50} value of 0.08 µg/mL [2]. *Ulva lactuca* aqueous seaweed extract-mediated ZnO-NPs, with an average size of 15 nm and an agglomerated sponge-like structure, displayed effectiveness against *An. stephensi* larvae, exhibiting an LC_{50} value of 22.38 µg/mL [90].

4.1.4 Hydrothermal method

The hydrothermal method for the synthesis of ZnO-NPs has proven effective against *Cx. quinquefasciatus* larvae. In a recent study, Cucurbita seed aqueous seed extract was utilized as a mediator for nanoparticle synthesis, resulting in particles within the size range of 45 – 65 nm. The synthesized nanoparticles exhibited a hexagonal shape and demonstrated larvicidal efficacy, with an LC_{50} value of 24.822 ppm [91]. The utilization of *Tarenna asiatica* aqueous leaves extract for nanoparticle synthesis through hydrothermal method yielded nanoparticles within the size range of 22.35 - 31.27 nm, characterized by a spherical shape. These nanoparticles demonstrated efficacy against *Ae. aegypti*, with an LC_{50} value of 220 ppm [92]. Despite the nanoparticles mediated through Cucurbita seed aqueous seed extract and *Tarenna asiatica* aqueous leaves extract using the hydrothermal method are within the nano size range, the significant variance in LC_{50} values underscores substantial differences in larvicidal efficacy against various mosquito species. *Cx. quinquefasciatus* and *Ae. aegypti* are distinct mosquito species with varying sensitivities to environmental factors, including nanoparticles. The difference in LC_{50} values may reflect the intrinsic susceptibility of each species to the nanoparticles. Similarly, the surface chemistry, composition, and shape of nanoparticles can influence their interaction with biological systems. The hexagonal-shaped nanoparticles synthesized through the hydrothermal method may interact differently with *Cx. quinquefasciatus* larvae compared to the spherical nanoparticles synthesized from *Tarenna asiatica* extract.

The selection of the nanoparticle synthesis method plays a pivotal role in determining the size, shape, and efficacy of nanoparticles targeted against specific mosquito species. The differences observed in LC_{50} values, can be attributed to various factors, encompassing the synthesis method, plant extract employed, and the specific mosquito species targeted. Notably, the sol-gel and coprecipitation methods exhibited low LC_{50} values, suggesting their potential for efficient control of mosquito larvae. These methods, along with the solution combustion method, particularly when incorporating plant extracts, demonstrate environmental friendliness compared to hydrothermal synthesis, which involves high temperatures and pressures. The sol-gel method, utilizing aqueous leaf extracts, has demonstrated effective larvicidal activity. Likewise, the coprecipitation method, employing leaf extracts, and the solution combustion method, incorporating seaweed extract, have proven to be successful in inhibiting the growth of mosquito larvae and synthesis methods are summarized in Table. 1.

4.2 Functional group

The biogenic "green route" of nanoparticle synthesis utilizes plant extract for the reduction of bulk materials into the nanostructures. This reduction was achieved because of the phytochemicals present in the plant extract. The secondary metabolites such as proteins, carbohydrates, terpenoids, alkaloids, flavonoids, phenolic, compounds, glycosides, etc. play an important role in reducing metal ions and stabilizing the synthesized nanoparticles by surface coating. Also, the surface-coated phyto-chemical exerts surface charge to the nanoparticles leading to their stability [93]. From the reported literature on the larvicidal efficacy of phyto-mediated ZnO-NPs, analysis was carried out to find the role of functional groups present in phytochemicals in the synthesis of ZnO-NPs. Alcohol, phenol, aromatic, amine, amide, alkenes, alkyl halides, carboxylic acid, carbonyl group, vinyl ether, and ß-lactone were generally reported in the reduction of ZnO-NPs that exhibited LC_{50} value below 4 µg/mL. For instance, ZnO-NPs mediated with *K. sumatrensis* observed with OH, phenol, alcohol, carboxylic acid, sulfonamines, oxamines, phosphine, alkenes, and chlorides exhibited high efficiency against *Cx. quinquefasciatus* LC_{50} and LC_{90} value of 0.08 µg/mL and 19.46 µg/mL [2].

4.3 Shape

ZnO-NPs have garnered significant attention due to their diverse applications, including their potential as larvicidal agents. The ZnO-NPs obtained using the biogenic method of synthesis showed varying shapes including hexagonal, spherical, rod, triangular, cubic, circular, and irregularly shaped nanoparticles.

4.3.1 Hexagonal shaped ZnO-NPs

The synthesis of hexagonal ZnO-NPs was primarily achieved through sol-gel and co-precipitation methods, with a limited number of studies reporting the use of the hydrothermal method. The resulting nanoparticles exhibited hexagonal structures, with a particle size distribution ranging from 10 nm to 81.8 nm. The variation in size may be attributed to the specific synthesis method and conditions employed. The larvicidal activity of the synthesized hexagonal ZnO-NPs recorded LC_{50} values ranging from 2.1 µg/mL to 130 µg/mL. Notably, ZnO-NPs synthesized using rhizome extract of *D. quercifolia* exhibited a high LC_{50} value, indicating a lower larvicidal (130.725 µg/ml) potency [94]. This observation may be, potentially attributed to the presence of limited functional groups such as carbonyl, amines, and sulfonamines in the plant extract, potentially influencing the larvicidal activity of the nanoparticles.

4.3.2 Rod-shaped ZnO-NPs

The synthesis of rod-shaped ZnO-NPs was specifically conducted using the sol-gel and solution combustion methods, with no documentation on co-precipitation and hydrothermal methods. Notably, the ZnO-NPs produced through the sol-gel and solution combustion methods were > 50 nm in size. Published literature revealed that the rod-shaped ZnO-NPs achieved very low LC_{50} values < 25 µg/mL. For example, the rod-shaped ZnO-NPs synthesized using *K. sumatrensis* exhibited an exceptionally low LC_{50} value of 0.08 µg/mL [2]. This high larvicidal potential observed in rod-shaped ZnO-NPs might be attributed to the presence of various functional groups in the plant extract used for synthesis. Despite their larger size, these nanostructures were found to be effective in inhibiting the growth of mosquito larvae, demonstrating high larvicidal activity compared to hexagonal and spherical-shaped ZnO-NPs.

4.3.3 Irregular shaped ZnO-NPs

The irregular-shaped ZnO-NPs have been reported to be synthesized exclusively through the sol-gel method. These irregular-shaped nanoparticles have shown high effectiveness in controlling mosquito larvae. For instance, *F. religiosa* leaf extract-mediated ZnO-NPs had an average particle size of 12.82 nm and exhibited significant larvicidal activity, with an LC_{50} value of 2.74 ppm [95]. Similarly, *S. officinalis*-mediated ZnO-NPs had a particle size ranging from 3.22 to 11.5 nm and demonstrated larvicidal activity with an LC_{50} value of 31.823 ppm [96]. The findings suggest that irregular-shaped ZnO-NPs synthesized using the sol-gel method, particularly those mediated by plant extracts, possess potent larvicidal activity against mosquito juveniles.

4.3.4Spherical shaped ZnO-NPs

Spherical ZnO-NPs were synthesized using various methods including sol-gel, solution combustion, co-precipitation, and hydrothermal techniques. Among these, the sol-gel method was the most commonly employed synthesis method that was documented in seven studies followed by co-precipitation (4), solution combustion (2), and one study utilizing the hydrothermal method for ZnO-NPs synthesis using plant extracts. The size of the synthesized nanoparticles ranged from 3 to 81.8 nm, demonstrating larvicidal efficacy with LC_{50} values ranging from 0.55214 µg/mL to 185.78 ppm. Notably, ZnO-NPs mediated through *L. siceraria* using the sol-gel method exhibited high larvicidal potential against *Ae. aegypti*, *Cx. quinquefasciatus*, and *An. stephensi*, while *C. baccifera*-mediated ZnO-NPs showed no larvicidal potential against *An. stephensi* [79,97]. The sol-gel method and solution combustion method derived spherical ZnO-NPs showed high LC_{50} values of 51.94 ppm against *Ae. aegypti* and 49.22 µg/mL against *Ae. aegypti.* Notably, spherical-shaped ZnO-NPs synthesized using the hydrothermal method demonstrated the highest LC_{50} value of 220 ppm against *Ae. aegypti* among the different methods of synthesis and functional groups, shapes and size are summarized in Table. 1.

5. ZnO-NPs action against mosquito species

The toxicity exerted by ZnO-NPs depends on multiple factors. The cytotoxicity of ZnO-NPs is dependent on its shape. Also, the toxicity of nanoparticles against insects and mosquito larvae is significantly influenced by their size. Compared to its macrostructure, ZnO-NPs have a higher level of toxicity at the nanoscale [98]. The mechanism underlying ZnO-NPs toxicity against mosquito larvae is

1. Cell membrane disruption and accumulation within the cytoplasm.
2. Induce apoptosis by releasing Zn^{2+} ions which exerts toxicity.
3. Stimulate intracellular ROS cytotoxicity cell damage.

Damage to the head, thorax, abdomen, and siphon regions in mosquito larvae was observed with the treatment of ZnO-NPs. Because of their nano size, ZnO-NPs were able to successfully bind to the surface of larvae, causing detrimental effects and also easily penetrating the cuticle. They attack specific cells after breaking through the cuticle barrier and obstruct the physiological functions of mosquito larvae. ZnO-NPs mediated by *P. hexapetalum* aqueous leaf extract effectively killed *Cx. quinquefasciatus*, *Ae. aegypti*, and *An. stephensi* IV instar larvae [2]. ZnO-NPs produced by the *E. cordamomum* extract were successful in disrupting larval epithelial cells and were also shown to accumulate in the mid-gut area [85]. ZnO-NPs cause aberrant cell shape, cell cycle disruptions, and loss of mitochondrial activity when the larval cells are exposed for an extended period [99].

The structural parameters that affect ZnO-NPs toxicity differ. For instance, rod-shaped ZnO-NPs are significantly more hazardous than spherical-shaped structures [100]. Star-shaped ZnO-NPs exerted high toxicity against *Ae. albopictus* and *An. vagus* larvae. Several characteristics of star-shaped ZnO-NPs were implicated for this high toxicity. When star-shaped particles come into direct contact with cells, their spatial arrangement and randomly oriented spikes abrade and damage membranes in the larvae [101]. Additionally, the high surface to volume ratio and availability of polar surfaces allows it to grab many oxygen molecules [102,103]. Because there are so many oxygen molecules present, which help to produce intracellular ROS, ZnO-NPs have a greater larvicidal capacity. Many mosquito species can be killed by ZnO-NPs through their ovicidal, larvicidal, and adulticidal effects, and their toxicity was linked to the presence of zinc and oxygen ions. The generation of reactive species from singlet oxygen ions prevents all stages of the mosquito life cycle from developing [104]. Zinc ion accumulation stops mosquito larvae from growing and produces metal ion poisoning in them. Moreover, the zinc ions inhibit the function of the enzyme carboxypeptidase, which prevents mosquito growth and development. The Malpighian tubules and alimentary canal are both affected by ZnO-NPs. The cytoplasm can vacuolate and cluster, and the peritrophic membrane can become damaged. ZnO-NPs cause a shrinking effect on the gastric caeca and the formation of basement membrane before the epithelial cells, some of which still had their nuclei. The posterior midgut's tall cuboidal and regenerating cells get degraded and disconnected. Malpighian tubules displayed adoration in the form of cell shapes. Haemocytes' structural deformation brought on by ZnO-NPs exposure eventually reduces their viability [105].

Ae. aegypti showed morphological and histological changes in response to ZnO-NPs that were mediated by *S. lycopersicum* aqueous extract. The ZnO-NPs caused syphon tube suffocation, which resulted in mortality [89]. Zn ions reduced by *S. cumini* were efficient against IV-instar *Ae. aegypti*, with an LC_{50} value of 49.22 ppm [106]. ZnO-NPs produced by *L. racemosa* aqueous were found to build up in the alimentary canal and disrupt physiological functions, such as moulting. The development of the mosquito larvae was hampered by this interference. The toxicity of ZnO-NPs resulted in larval body shrinkage and a burnt appearance. Moreover, the syphon was severely impacted by the nanoparticles, which led to larval death [17]. The effect of ZnO-NPs is summarized in Fig. 5.

6. Conclusion

The Green Chemistry approach for the synthesis of ZnO-NPs for the control of mosquito vectors is an effective alternative to synthetic insecticides. The various techniques employed for the synthesis of ZnO-NPs resulted in the formation of spherical, rod, triangle, hexagonal, and irregular shaped nanoparticles that showed effective larvicidal activity. Among the different shapes spherical-shaped ZnO-NPs were found to be excellent larvicidal agents. However, the efficacy of these spherical shaped ZnO-NPs is correlated with the particle size. On the contrary, rod-shaped ZnO-NPs with large particle sizes compared to spherical shaped ZnO-NPs showed better larvicidal activity. Further, the larvicidal efficacy of the green route mediated ZnO-NPs is highly influenced by the phytochemicals. The functional groups such as ethers vinyl ethers, beta lactone, and aromatic amines coating the surface of ZnO-NPs exhibited high larvicidal efficacy. Thus, the larvicidal efficacy of the ZnO-NPs depends on the nanoparticle characteristics such as the method of synthesis, the size and shape of the synthesized nanoparticles, and the functional groups present on the surface of the synthesized nanoparticles.

Statement

During the preparation of this work the author(s) used poe.ai in order to compare the characteristic features of the zinc oxide nanoparticles and its influence on the larvicidal efficacy. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Figure Legends

Figure 1. Mechanism of action of phytochemicals in mosquito larvae
Figure 2. Modes of nanoparticle synthesis
Figure 3. Green chemistry of nano synthesis
Figure 4. Advantages of green nano synthesis
Figure 5. Effect of ZnO-NPs

I. Induce ROS generation
II. Disturbs membrane protein, nucleic acid and lipids
III. Induce apoptosis
IV. Cytotoxicity cell damage
V. Block respiratory system and damage digestive track
VI. Larval hemocyte toxicity

Figure 1

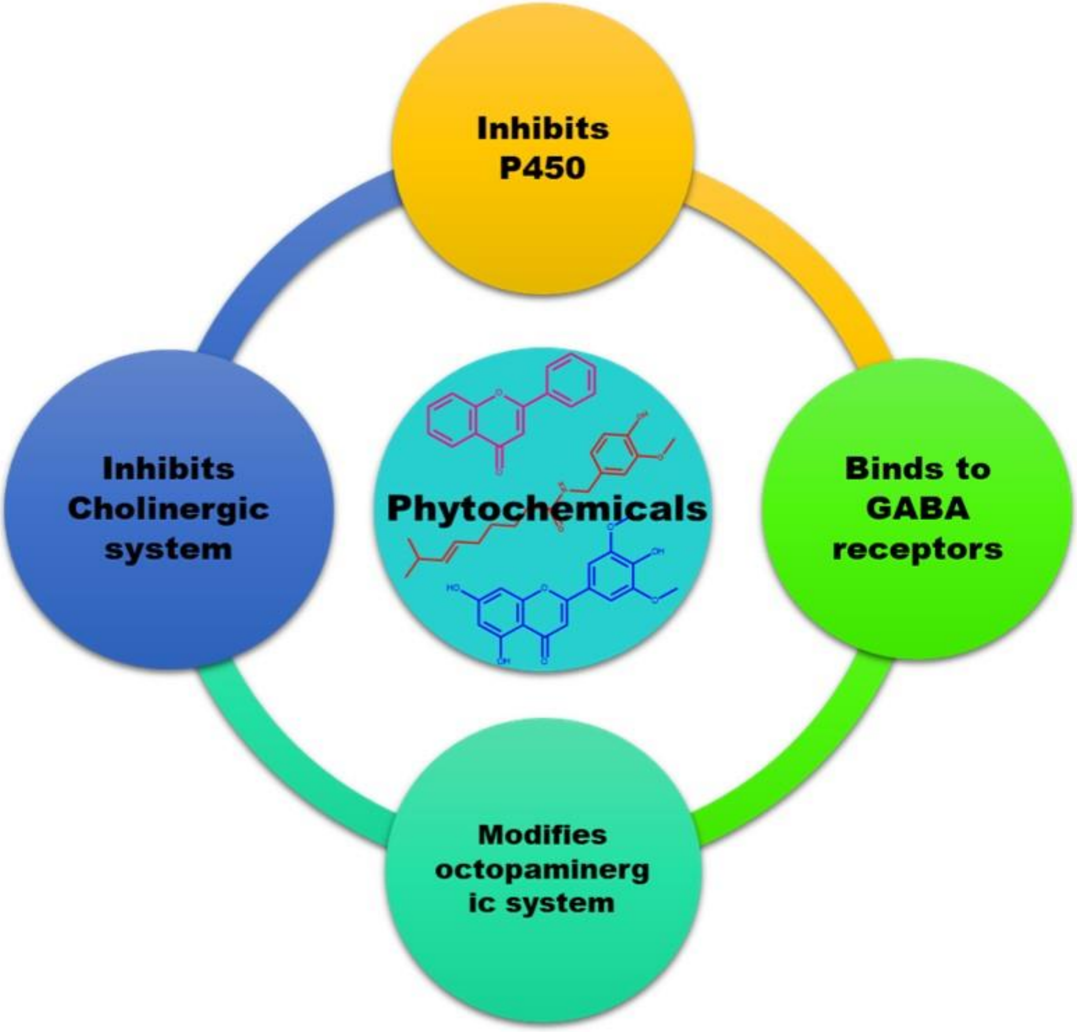

Figure 2

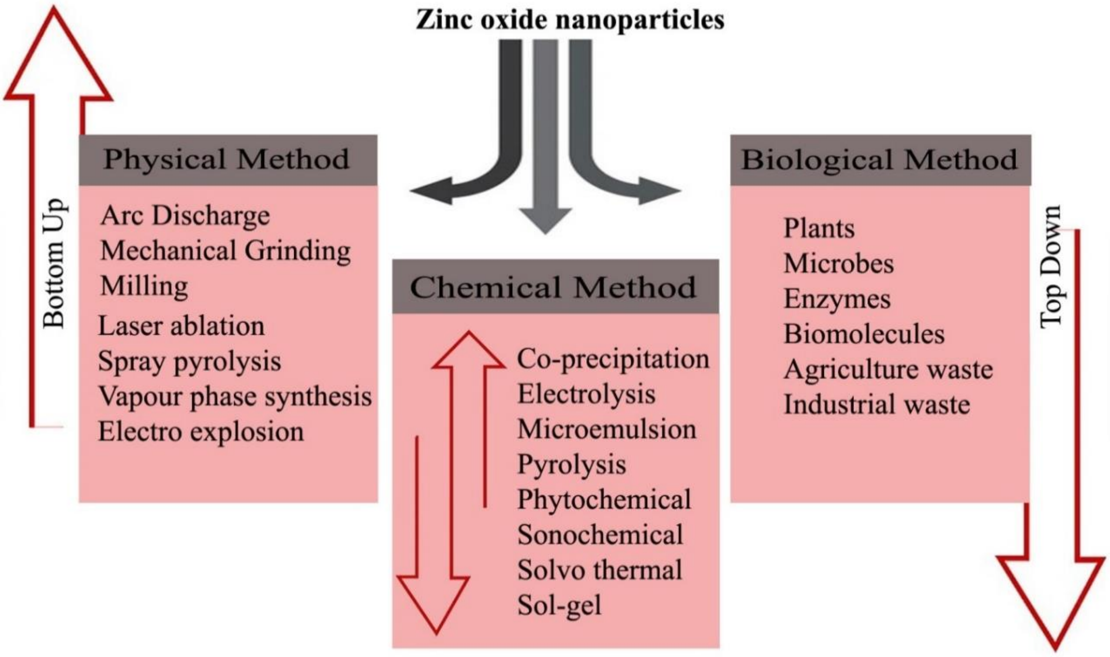

Figure 3

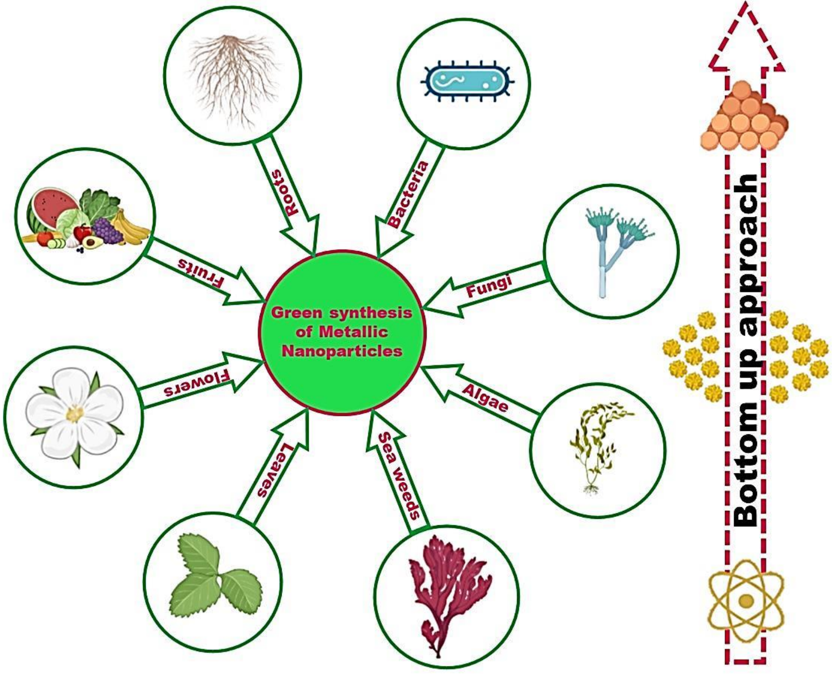

Figure 4

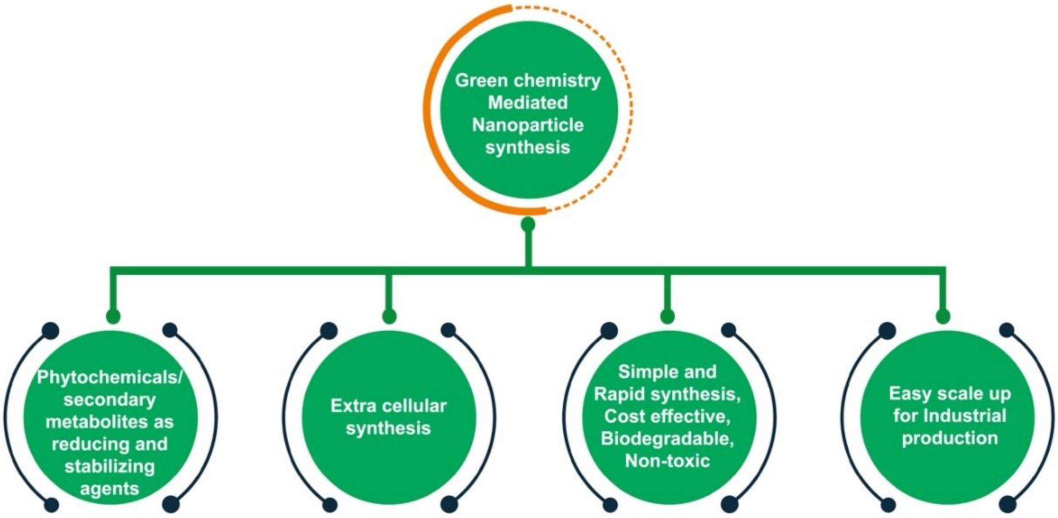

Figure 5

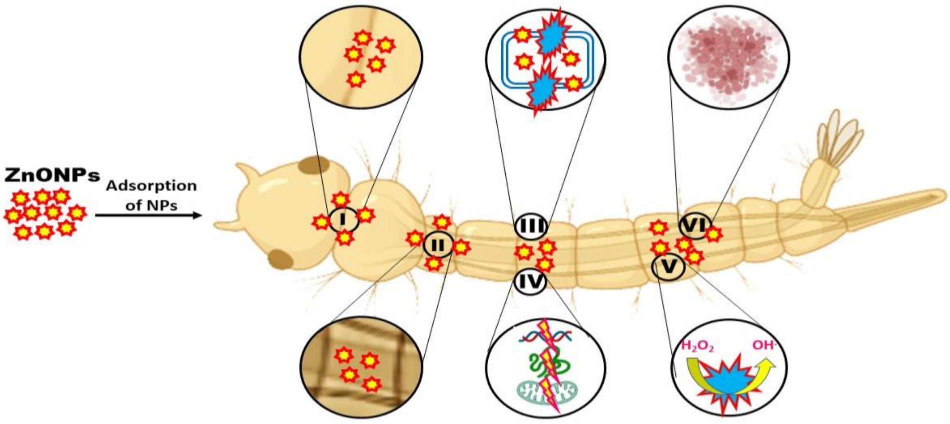

Table Legends

Table 1. Plant mediated ZnO-NPs with their characteristic features and larvicidal efficacy against mosquito species

S. No	Name of the plants	Parts used	Method of synthesis	Particle size	Particle shape	Species	LC50	LC90	References
1	*Plectranthus amboinicus*	Leaves	Sol gel	20 – 50 nm	Spherical, hexagonal	*Cx. quinquefasciatus*	3.1 mg/mL	4.5 mg/mL	[81]
						An. stephensi	3.1 mg/mL	4.6 mg/mL	
						Cx.tritaeniorhynchus	4.2 mg/mL	5.7 mg/mL	
2	*Syzgium cumini*	Fruit	Sol gel	50-60 nm	Spherical	*Ae. aegypti*	51.94 ppm	119.99 ppm	[106]
3	*Sargassum wightii*	Seaweed	Solution combustion	40 – 50 nm	Spherical	*Ae. aegypti*	49.22 µg/mL	86.96 µg/mL	[31]
4	*Ulva lactuca*	Seaweed	Solution combustion	15 nm	Agglomerated sponge	*An. stephensi*	22.38 µg/mL	41.94 µg/mL	[90]
5	*Momordica charantia*	Leaves	Sol gel	21.32 nm	Spherical	*Cx. quinquefasciatus*	4.87 µg/mL	8.29 µg/mL	[82]
						An. stephensi	75.14 µg/mL	111.36 µg/mL	
6	*Scadoxus multiflorus*	Leaves	Solution combustion	31 nm	Spherical	*Ae. aegypti*	34.04 mg/mL	78.06 mg/mL	[43]
7	*Lagenaria siceraria*	Fruit	Sol gel	81.8 nm	Hexagonal	*An. stephensi*	3.873 µg/mL	8.83 µg/mL	[107]
8	*Myristica fragrans*	Leaves	Sol gel	100 nm	Rod	*Ae. aegypti*	3.44 µg/mL	14.63 µg/mL	[78]
9	*Azadirachta indica*	Gum	Co-precipitation	60 -80 nm	Circular	*Cx. quinquefasciatus*	10.25 µg/mL	_	[87]
10	*Murraya koenigii*	Leaves	Co-precipitation	10 - 15 nm	Hexagonal	*Cx. quinquefasciatus*	2.1 µg/mL	12.1 µg/mL	[88]
11	Cucurbita seed	Seed	Hydrothermal	45 – 65 nm	Hexagonal	*Cx. quinquefasciatus*	24.822 ppm	_	[91]
12	*Lumnitzera racemose*	Flower	Sol gel	250–300 nm	Rod	*Ae. aegypti*	24.74 µg/mL	42.09 µg/mL	[108]
13	*Elettaria cardamomum*	Seeds	Co-precipitation	18.72 nm	Spherical	*Ae. aegypti*	13.27 µg/mL	25.36 µg/mL	[85]
14	*Ficus religiosa*	Leaves	Sol gel	12.82 nm	Irregular	*An. stephensi*	2.74 ppm	_	[109]
15	*Cuscuta reflexa*	Stem	Co-precipitation	40.86 nm	Spherical	*An. stephensi*	24.32 µg/mL	_	[110]
16	*Pterolobium hexapetalum*	Leaves	Sol gel	10 – 93 nm	Spherical	*Ae. aegypti*	8.982 µg/mL	43.563 µg/mL	[2]
						Cx. quinquefasciatus	4.178 µg/mL	16.157 µg/ml	
						An. stephensi	6.247 µg/mL	16.157 µg/mL	
17	*Solanum lycopersicum*	Leaves	Solution combustion	100 nm	Rod and pellet	*Ae. aegypti*	9.311 µg/mL	25.26 µg/mL	[89]
18	*Knoxia sumatrensis*	Leaves	Solution combustion	50–80 nm	Rod shape	*Cx. quinquefasciatus*	0.08 µg/mL	19.46 µg/mL	[111]
19	*Lawsonia inermis*	Leaves		5 - 35 nm	Cubic,rod, triangular, spherical	*Cx. quinquefasciatus*	10.736 µg/mL	14.335 µg/mL	[112]
20	*Lagenaria siceraria*	Peel	Co-precipitation	81.8 nm	Spherical	*An. stephensi*	185.78 ppm	389.05 ppm	[84]
21	*Pleurotus djamor*	Fruit	Co-precipitation	70 - 80 nm	Spherical	*Ae. aegypti*	10.1 µg/mL	14.4 µg/mL	[86]
						Cx. quinquefasciatus	14.4 µg/mL	31.7 µg/mL	
22	*Cipadessa baccifera*	Leaves	Sol gel	41.48 nm	Spherical	*Ae. aegypti*	0.55µg/mL	0.75 µg/mL	[79]
						Cx. quinquefasciatus	0.05 µg/mL	0.03µg/mL	
						An. stephensi	0.05 µg/mL	0.98 µg/mL	

23	*Lavandula angustifolia*	Leaves	Sol gel	74.58 nm	Hexagonal	*Ae. aegypti*	118 µg/mL	135 µg/mL	[113]	
24	*Spongia officinalis*	Sponges	Sol gel	3.22-11.5 nm	Irregular, spherical shape	*Cx.pipiens*	31.823 ppm	80.09 ppm	[43]	
						An.pharoensis	12.634 ppm	66.118 ppm		
25	*Vitis vinifera*	Fruit	Co-precipitation	30 - 73.5 nm	Conical shape	*Ae. aegypti*	80.27 µg/mL	136.39 µg/mL	[86]	
26	*Lantana camara*	Leaves	Sol gel	12.2 - 25.3	Spherical	*Ae. aegypti*	14.85 ppm	30.41 ppm	[80]	
27	*Drynaria quercifolia*	Rhizome	Sol gel	10 nm	Hexagonal	*Cx. quinquefasciatus*	130.72 µg/ml	-	[94]	
28	*Tarenna asiatica*	Leaves	Hydrothermal	22.35 - 31.27 nm	Spherical	*Ae. aegypti*	220 ppm	260 ppm	[92]	
29	*Ficus racemosa*	Leaves	Co-precipitation	14.8 nm	Hexagonal	*An. stephensi*	65.94 µg/mL	-	[83]	