Recent advances in the development of novel drug delivery systems for the prophylaxis of malaria

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Abstract

The present review highlights the advancement in nanoparticles formulations for the prophylaxis of malaria. An attempt has been made to describe various novel drug delivery systems based on approaches such as polymeric, metallic, natural, chitosan/antisense (AS) and chitosan/sense (S) oligodeoxynucleotide based nanoparticles etc. for the treatment of malaria. The polymer such as chitosan, hydroxyl propyl methyl cellulose and polyvinyl pyrrolidone; the metal like gold and silver and other carriers such as glyceryl-dilauroate, albumin etc. have been explored for the development of novel nanoparticles formulations. These developed nanoparticles formulation have improved the targeted drug delivery of various clinically used antimalarial therapeutic agents such as hydroxychloroquine, curcumin, artemisinin, artemether and lumefantrine etc.

Keywords: nanoparticles, polymers, malaria.

Introduction

Malaria is a global health problem. According to the latest estimates, in 2013 there were about 198 million cases of malaria and estimated 584,000 deaths. Malaria death rates have fallen by 47 % world widely since 2000, and by 54 % in the African region. Most deaths arise among children living in Africa, where a child dies every minute from malaria. Malaria death rates among children in Africa have been decreased by an estimated 58% since 2000. Plasmodium parasites cause malaria. Infected Anopheles mosquitoes vectored to people through the bites, which bite mainly between dawn and dusk. [1].

Quinine, artemether (ARM), and artesunate (ARS) are currently available drugs used parenterally for the treatment of severe malaria. Quinine cannot be given fast through intravenous injection because it can cause cardiac arrest, hypotension and quinine also causes hypoglycemia and the patients have to be monitored for glucose levels; it can be given by rate controlled intramuscular injection or intravenous infusion. Intramuscular injection of ARM is painful and shows slow and unpredictable absorption. The half-life of Artesunate is less than 15 minutes. However, for the treatment of malaria currently there is no intravenous formulation available for combination therapy. ARM has drawback that it quickly eliminated from the plasma and also has quick onset of action. On the other hand LFN has drawback that its elimination half-life is longer and slower onset of action. Both the drugs have independent modes of action (4). Innovative useful tools have been provided by nanotechnology. The objective of fast-developing nanomedicine field is to deliver drugs exclusively to a selected target site with minimal exposure for adjacent healthy cells or tissues for the future fight against malaria. The pharmaceutical nanotechnology has been identified as a potentially essential tool [2].
Figure 1 Nanoparticles formulations for the prophylaxis of malaria

Figure 2 Images showing different stages of larvae of vector causing malaria
Novel drug delivery system based advancement in nanoparticles formulation for the treatment of malaria

Hydroxychloroquine-conjugated gold nanoparticles

Recent technology of siRNA delivery relies on pharmaceutical dosage forms to route higher doses of siRNA to tumor. The impact of hydroxychloroquine conjugation on the intracellularly and silencing activity of siRNA conjugated PEGylated gold nanoparticles has been evaluated. Adding up of hydroxychloroquine improved endosomal run off and enhanced siRNA guide strand sharing to the RNA induced silencing complex (RISC), both potency of siRNA to the crucial obstacles. This modification significantly enhanced gene down regulation [3].

Nanostructured lipid carriers of Artemether–Lumefantrine

Patients with cerebral malaria (CM) are not capable to take oral medication due to impaired consciousness and vomiting thus necessitating parenteral therapy. Quinine, ARM, and artesunate which are presently used for parenteral malaria therapy consist of their own drawbacks. World Health Organization (WHO) have now forbidden monotherapy and recommends artemisinin-based combination therapy for malaria treatment. Artemether–Lumefantrine (ARM–LFN) is a WHO permitted combination for oral malaria therapy. However, the low aqueous solubility of artesmether and lumefantrine hinders their intravenous delivery. The purpose of this study was to formulate artesmether–lumefantrine nanostructured lipid carriers (NLC) for intravenous (IV) therapy of CM and was prepared by microemulsion technique [4]. The biocompatible ARM–LFN NLC made-up by an industrially possible technique offer a promising solution for intravenous therapy of CM.

Chitosan nanoparticles of Curcumin

Curcumin bound to chitosan nanoparticles to increase its bioavailability and chemical stability. It was observed that curcumin bound to chitosan nanoparticles did not degrade much faster in comparison to free curcumin. The uptake of bound curcumin from chitosan nanoparticles nearby mouse RBC was much better than from free curcumin. Curcumin loaded chitosan nanoparticles when taken orally increase the bioavailability of curcumin in the plasma and RBCs [5].

Doublestranded RNA nanoparticles

A promising opportunity in the expansion of antimalarials therapy is based on RNA intervention targeting expression of malaria parasite vital genes, viz. DNA topoisomerase II gene (PITOP2). Biodegradable chitosan nanoparticle system have established to be useful in delivering DNA and small double-stranded intrusive RNA to target cells. A long double-stranded (dsRNA) targeting the coding region of (Pf TOP2) to complexes with chitosan nanoparticles has been developed in order to hinder with the cognate mRNA expression and examine its activity on P. falciparum growth in culture. This inhibitions were shown to arise during maturation of trophozoite to schizont stages. These results propose that chitosan-based nanoparticles may be a useful tool for delivering dsRNA into malaria parasites [6].

Hydrogel nanoparticle of Curcumin

The recent investigation involved preparation of hydrogel nanoparticles with a combination of hydroxyl propyl methyl cellulose and polyvinyl pyrrolidone. The objective was to develop nanocarriers to increase absorption and extend the fast clearance of curcumin due to possible evasion of the reticulo-endothelial system. In vivo anti-malarial studies have shown significant action of nanoparticles over curcumin control suggesting the possibility of the formulation being employed as an adjunct anti-malarial therapy beside with the standard therapy. Acute and subacute toxicity studies established the oral safety of the formulation. To evaluate the non genotoxic potential of the developed formulation a sequence of genotoxicity studies were conducted which indicating the possibility of the formulation being employed for prolonged duration [7].

Antisense nanoparticles

New effective antimalarial agents are immediately needed due to enhancing drug resistance of Plasmodium falciparum. Phosphorothioate antisense oligodeoxynucleotides (ODNs) silencing of malarial topoisomerase II gene has exposed to acquire promising features as anti malarial agents. ODNs wascomplexes with the biodegradable polymer chitosan to form solid nanoparticles with an initial diameter of 55 nm in order to increase stability and to increase the intracellular penetration. However, nanoparticles was much more sequence specific in their antisense effect than free ODNs. Nanoparticles with negative surface charge exhibited a significantly stronger inhibitory effect on the parasite growth in comparison to the positive ones or free ODNs [8].

Silver nanoparticles of Anisomeles indica

Green synthesis of silver nanoparticles (AgNP) using an inexpensive, aqueous leaf extract of Anisomeles indica by decreasing Ag ions from silver nitrate solution have been investigated. The acute toxicity of A. indica leaf extract and biosynthesized AgNP were examine against larvae of the malaria
vector Anopheles subpictus, the Japanese encephalitis vector, the
dengue vector Aedes albopictus and the Japanese encephalitis
vector, Culex tritaeniorhynchus. Both the Anisomeles indica leaf
extract and AgNP showed dose dependent larvicidal effect against
all tested mosquito species. Compared to the leaf aqueous extract,
biosynthesized AgNP showed superior toxicity against An
subpictus, Ae. albopictus, and Cx. tritaeniorhynchus. Overall, this
study firstly shed light on the mosquitocidal potential of A. indica, a
potential bioresource for fast, inexpensive and useful AgNP
synthesis [9].

Silver nanoparticles of Zornia diphylla leaves

In this scenario, environmental control tools of mosquito vectors are
a priority. Silver nanoparticles (AgNP) by taking an inexpensive
aqueous leaf extract of Zornia diphylla as decreasing and capping
agent of Ag+ ions has been synthesized by single step fabrication.
The acute toxicity of Z. diphylla leaf extract and biosynthesized
AgNP were tested against larvae of the dengue vector Aedes
albopictus and malaria vector Anopheles subpictus. Both the Ag
NP and Z. diphylla leaf extract showed dose dependent larvicidal
activity against all tested mosquito species. Overall Z.
diphylla-fabricated Ag NP are a promising and eco-friendly tool
against larval populations of mosquito vectors of medical and
veterinary importance, with negligible toxicity against other non-
target organisms [10].

Nanoparticles of Artemisinin

Artemisinin have become the most promising antimalarial agent
from more than 40 years after its discovery. Due to its poor
aqueous solubility no intravenous formulation is available. The
nanoparticles were formulated by a combination of a bottom-up and
a top-down processes and characterized by different spectroscopic
techniques. The preparation process was optimized to develop a
nano formulation for intravenous injection enabling direct contact of
artemisinin with infected erythrocytes with the smallest possible
diameter and good homogeneity. Physically and chemically stable
artemisinin nanoparticles were obtained with excellent entrapment
efficiency. This nanoparticulate albumin-bound system allows the
intravenous administration of artemisinin for the first time without
harsh organic solvents or co-solvents with 100 % bioavailability

Albumin-bound nanoparticles

The indolone-N-oxides have been examined as promising
candidates for the treatment of chloroquine-resistant malaria.
However, in vivo assays have been hampered by the very poor
aqueous solubility of these compounds resulting in poor and
variable activity. Nanoparticles were prepared by precipitation
followed by high-pressure homogenization. The process was
optimized to yield nanoparticles of controllable diameter with
narrow size distribution suitable for intravenous administration,
which definitely showed direct drug contact with parasitized
erthrocytes. Stable nanoparticles showed highly increased
dissolution rate (complete drug release within 30 min compared to
1.5% of pure drug) preserving the rapid antimalarial activity. The
formation achieved complete cure of Plasmodium berghei-infected
mice at 25 mg/kg with parasitemia inhibition (99.1%) similarly to
that of artesunate and chloroquine proving to be extremely highly
effective in increasing survival time and inhibiting recrudescence. In
“humanized” mice infected with Plasmodium falciparum, the same
dose proved to be highly effective: with parasitemia reduced by
97.5% and prolongation of the mean survival time. This formulation
can help advance the preclinical trials of indolone-N-oxides.
Albumin-bound nanoparticles represent a new strategic approach
to use this most abundant plasma protein to target malaria-infected
erthrocytes [12].

Earthworm-mediated synthesis of silver nanoparticles

Currently, metal nanoparticles have been developed as highly
effective tools towards cancer cells and Plasmodium parasites.
Silver nanoparticles (EW–AgNP) using Eudrilus eugeniae
earthworms as decreasing and stabilizing agents have been
synthesized. MTT assays was used to measure the effect of EW–
AgNP on in vitro HepG2 cell proliferation. EW–AgNP was toxic to
Anopheles stephensi larvae and pupae. EW–AgNP having
antiplasmodial activity which was evaluated against CQ-resistant
and CQ-sensitive strains of Plasmodium falciparum. Overall, this
research highlighted the EW–AgNP potential against hepatocellular
carcinoma, Plasmodium parasites and mosquito vectors, with little
effects on mosquito natural enemies [13].

Nanostructured lipid carrier (NLC) of glyceryl-dilaurate
(GDL)

Antimalarial therapy is a key provider to declining malaria morbidity
and mortality. The low bioavailability and the high toxicity of recent
antimalarials and emerging drug resistance necessitates drug-
delivery research. GDL-NLCs directly act on red blood cells which
is infected by the plasmodium parasite and cause the severe
impairment. The glyceryldilaurate lipid-moety was used for the
targeting. GDL-NLCs present on the parasite mitochondrion and
uptake led to mitochondrial-membrane polarization and Ca2+ ion
accumulation, stage-specific iRBC lysis and ROS release. Thus,
this nanostructured lipid formulation can solubilize lipophilic drugs,
selectively target and impair the parasite-infected red cell, and
therefore constitutes a potent delivery vehicle for antimalarials [14].

Gold nanoparticles of marine Actinobacterial and
antimalarial
Streptomyces sp LK-3 mediated Gold nanoparticles (Au-N-LK3) were formulated within the size range of 5-50nm. Au-N-LK3 have been found to be useful for treatment of Plasmodium berghei ANKA (PbA) infected mice which delayed the parasitemia increases as compared to PbA infection on 8 days post infection. Survivability of mice rises in Au-N-LK3 treated mice in disparity to in PbA infected mice in 8 days post infection with respect to control. During Au-N-LK3 treatment in PbA infection, histomorphological analysis exposed as such no change in spleen and liver tissue during 8 days post infection. The results obtained proposed that the Au-N-LK3 have anti-malarial activity and could be considered as a potential source for anti-malarial drug development [15].

Nanoemulsion and Porous Polymeric Nanoparticles

CHrPfs25 which is a malaria transmission blocking vaccine antigen was prepared by using nanoemulsions (NE) and poly(D,L-lactide-co-glycolide) nanoparticles (PLGA-NP) and evaluated through IM route in mice. By standard mosquito membrane feeding test using purified IgG from immune sera, transmission blocking efficiency of antibodies was characterized. The prepared formulation were evaluated for stability particle size zeta potential and polydispersity index. The overall study reveals that CHrPfs25 prepared using NE and PLGA-NP shows maximum antibody response and elicited powerful functional immunogenicity [16].

Green synthesized silver nanoparticles

In the recent study silver nanoparticles (silvemp) was synthesized from Alpha Amylase or aqueous leaf extracts of Ashoka and Neem respectively. The use of plant extract for synthesis of nanoparticles(NPs) is an ecological process and cost efficient. The synthesized NPs were established to be anti plasmodium with IC50 (μg/ml) 3.75 (Amylasenp), 8 (Ashokanp) and 2.75 (Neemp) while plant extracts or amylase alone do not show any activity up to 40 μg/ml. Even though AgNO3 were also established to have intrinsic anti plasmodium action, the hemolytic tendencies appeared to be superior for AgNO3 against the nanoparticulate preparations (MHC10: > 40 μg/ml [17].

Silver nanoparticles of Aristolochia indica

Silver nanoparticles (AgNP) were biologically synthesized by using Aristolochia indica. The formulated AgNP were evaluated by using XRD, FTIR, UV–vis spectroscopy, EDX and SEM. A. indica extract and AgNP directs to 100% decrease in larva after 72 hrs. A indicabiosynthesized AgNP can be may be employed as a safer and novel tool against the malaria vector Anopheles stephensi [18].

Lipid nanoparticles of Curcuminoids

In the recent work, curcuminoids loaded lipid nanoparticles for parenteral administration was successfully prepared by a nanoeulsion technique employing high-speed homogenizer and ultrasonic probe. For the development of nanoparticles, trimyristin, tristerin and glyceryl monostearate was selected as solid lipids and medium chain triglyceride (MCT) as liquid lipid. Nanoparticles were further sterilized by filtration process which was established to be higher over autoclaving in preventing thermal degradation of thermo-sensitive curcuminoids. The in vivo pharmacodynamic activity exposed 2-fold enhances in antimalarial activity of curcuminoids entrapped in lipid nanoparticles when compared to free curcuminoids at the tested dosage level [19].

Solid lipid nanoparticles of dihydroartemisinin

Dihydroartemisinin is having poor water solubility and poor pharmacokinetic profile. To enhances the solubility and pharmacokinetic of (DHA), it was reformulated into solid lipid nanoparticles (SLNs) as a nanomedicine drug delivery system. DHA-SLNs was characterized for physical parameters and evaluated for in vitro and in vivomarial efficacy. Increasing in vitro(C50 0.25 ng/ml) and in vivo(97.24% chemo suppression at 2 mg/kg/day) antimalarial activity were found A rise in effectiveness was 24% when compared to free DHA [20].

Silver nanoparticles of Annona muricata leaf extract

The larvicidal activity of green synthesized silver nanoparticles was tested by using Annona muricata plant leaf extract against third instar larvae of three medically important mosquitoes, such as, Culex quinquefasciatus, Anopheles stephensi and Aedes aegypti. The prepared nanoparticles were characterized using UV visible spectroscopy and X-rays diffraction analysis etc. The different conc. of AgNP and aqueous crude leaf extract were examined against the larvae shows high toxicity of AgNP than aqueous crude leaf extract. The overall study exposed that AgNP synthesized from A. muricata has probability to beused as a eco-friendly strategy for the control of mosquitoes [21].

Gold nanoparticles of Couroupita guianensis

Gold nanoparticles (AuNPs) were biologically synthesized using an economical flower extract of Couroupita guianensis as a stabilizing agent. Fourier transform infrared (FTIR) spectroscopy, transmission electron microscopy (TEM), UV–vis spectrophotometry, energy-dispersive X-ray (EDX) spectroscopy etc. was used to confirm the bio fabrication of AuNP, particle size and zeta potential. C. guianensis flower extract and AuNP was evaluated for antiplasmodial activity against CQ-sensitive (CQ-s) and CQ-
resistant (CQ-r) strains of *Plasmodium falciparum* concurrently. The result of study exhibited versatile efficacy of guianensis synthesized AuNPs, hence can be used as a safer and novel tool against CQ-r strains of *P. falciparum* [22].

### Polyphosphazene based nanoparticles of Primaquine and Dihydroartemisinin

Recently, our research group has synthesized polyphosphazene based nanoparticles of primaquine and dihydroartemisinin and tested in *P. berghei* infected mice model. The combination therapy exhibited promising antimalarial efficacy at lower doses in comparison to the standard drug combination. Further, this combination therapy provided protection over 35 days without any recrudescence, thus proving to be effective against resistant malaria. The study provides an alternative combination regimen found to be effective in the treatment of resistant malaria [23].

### Nanostructured lipid carrier of artemether: Nanoject

Artemether is poorly water soluble antimalarial agent. The objective of the recent investigation was to explore the potential of nanostructured lipid carrier for the I.V delivery of artemether. Microemulsion template technique were employing to formulated the artemether nanostructured lipid carrier. The antimalarial activity of artemether I.V formulation was evaluated in *Plasmodium berghei* infected mice. ARM released in sustained manner from the nanoject. Nanoject showed significantly higher antimalarial activity, nanoject lasted for the longer duration more than 20 days and are long circulating in vivo and also showed higher survival rate even 31 days as compared to marketed formulation. Nanoject having several advantages over the recently marketed oily intramuscular formulation [24].

### Silver nanoparticles of Nerium oleander

The present study was carried out to establish that the synthesized silver nanoparticles (AgNPs) using leaf extract of *Nerium oleander* (Apocynaceae) shown larvicidal activity Against the first to fourth instar larvae and pupae of malaria vector, *Anopheles stephensi*. Penetration of nanoparticles through a membrane shows the possible larvicidal activity. The results could suggest that the synthesize silver nanoparticles by using of plant *N. oleander*, is rapid, greener and environmentally safer approach for mosquito control [25].

### Silver nanoparticles of Aloe vera

Silver nanoparticles were synthesized by using *A. vera* leaf extract which shows the mosquitocidal property. The mosquitocidal properties of *A. vera* were tested in laboratory against pupae and larvae (I-IV instar) of the malaria vector *Anopheles stephensi*. The synthesized silver nanoparticles were characterized by, Fourier transform infrared spectroscopy (FTIR), UV–vis spectrum, X-ray diffraction (XRD) and scanning electron microscopy (SEM). Synthesized silver nanoparticles of *A. vera* leads to *A. stephensi* larval reduction and the study show that the synthesized silver nanoparticle of *A. vera* propose to use as effective candidates to develop newer and safer mosquitocidal control tools [26].

### Monensin Loaded PLGA Nanoparticles

By using emulsion solvent evaporation method the PLGA nanoparticles loaded with monensin (carboxylic ionophore) were prepared using PLGA of molecular weight (Mw.) 19 000 and 110 000 Da. The nanoparticles were characterized by applying atomic force microscopy (AFM), Fourier transformed infrared spectroscopy (FTIR), differential scanning calorimetry (DSC) and dynamic light scattering (DLS). Monensin-PLGA nanoparticles was examined for the antimalarial efficacy. As compared to free monensin, the monensin loaded in nanoparticles was 10-fold more effective in inhibiting the growth of *P. falciparum* [27].

### Silver nanoparticles of Gmelina asiatica

The recent study was carried out to set up the larvicidal potential of leaf extract of *Gmelina asiatica* and synthesized silver nanoparticles using aqueous leaf extract against late 3rd instar larvae of *Culex quinquefasciatus*, *Anopheles stephensi*, and *Aedes aegypti*. The synthesized AgNPs and larvae were exposed to altering the concentration of plant extract for 24 h. The results were recorded from Fourier transform infrared spectroscopy, scanning electron microscopy, UV–visible spectroscopy, transmission electron microscopy, X-ray spectroscopy and energy-dispersive analysis support the characterization and biosynthesis of AgNPs. The increasing efficacy was observed in synthesized AgNPs against the larvae of *C. quinquefasciatus* and *A. stephensi* respectively. This the first report on mosquito that show larvicidal activity of plant synthesized nanoparticles. Therefore, the use of *G. asiatica* to synthesize silver nanoparticles is a eco-friendly, rapid and a single-step approach and the AgNPs formed can be potential mosquito larvicidal agents [28].

### Silver nanoparticles using leaves of Catharanthus roseus Linn. G. Don

For the synthesis of silver nanoparticles using aqueous leaves extracts of Catharanthus roseus (C. roseus) Linn. G. Don which was shows the activity against the malaria parasite *Plasmodium falciparum* (*P. falciparum*). The synthesized silver nanoparticles
were characterized by using energy dispersive X-ray, X-ray diffraction, ultraviolet-visible (UV-Vis) spectrophotometer and scanning electron microscopy (SEM). The study was concluded that the synthesized silver nanoparticles of the leaves of C. roseus shows antiplasmodial activity against P. falciparum. The outcome of study will be the development of value added products from medicinal plants C. roseus for biomedical and nanotechnology based industries [29].

**Transferrin-conjugated solid lipid nanoparticles**

For the delivery of quinine dihydrochloride to the brain, the Transferrin (Tf)-conjugated solid lipid nanoparticles (SLNs) were investigated for the management of cerebral malaria. SLNs were prepared by an ethanol injection method using distearoylphosphatidylethanolamine (DSPE), triolein, cholesterol and hydrogenated soya phosphatidyl choline (HSPC). Incubator is used for the coupling of SLNs with Tf, with quinine-loaded SLNs in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) hydrochloride in phosphate buffered saline (pH 7.4) as a cross-linker. Fluorescence studies revealed that increased the uptake of Tf-SLNs in brain tissue compared with un conjugated SLNs. Coujugation of SLNs with Tf significantly increased the brain uptake of quinine which was shown by the improvement of a higher %age of the dose from the brain following administration of Tf-coupled SLNs compared with un conjugated SLNs or drug solution [30].

**Silver nanoparticles of Metarhizium anisopliae**

700 million people were infected by mosquito borne disease which may lead to one million death. The silver nanoparticles of Metarhizium anisopliae-based method were discovered by the scientists to prevent the rural malaria vector Anopheles culicifacies. The characterization of silver nanoparticles were often done by different methods such as – X-ray, Fourier transform infrared spectroscopy, energy-dispersive X-ray analysis, X-ray diffraction and Fourier transform infrared spectroscopy. The LC50 value were found to be 32.8 ppm (I), 39.8 ppm (II), 45.9 ppm (III), 51.9 (IV), and 60.0 ppm (pupa) against larvae (I–IV instar) and pupae of A. culicifacies. Lower concentration has not shown a major effect to treat malaria. Thus, this research has been the new myco-synthesized silver nanoparticles for the environment in the prevention of rural malaria vector A. culicifacies [31].

**Seaweed-synthesized silver nanoparticles**

This research using a cheap seaweed extract of Ulva lactuca which is a novel method of plant-mediated synthesis of silver nanoparticles, acting as a capping and decreasing agent. AgNP were characterized by scanning electron microscopy (SEM), and X-ray diffraction (XRD), energy-dispersive X-ray spectroscopy (EDX), Fourier transform infrared (FTIR) spectroscopy and UV–Vis spectrophotometer. Green-synthesized AgNP of Ulva lactuca were tested against pupae of the malaria vector and larvae Anophelod stephensi. The antiplasmodial activity of U. lactuca-synthesized AgNP and U. Lactuca extract was evaluated against CQ-sensitive (CQ-s) strains and CQ-resistant (CQ-r) of Plasmodium falciparum. Fifty percent inhibitory concentration (IC50) values of ; U. lactuca-synthesized AgNP IC50 values were 76.33 μg/ml (CQ-s) and 79.13 μg/ml (CQ-r); of U. lactuca were 57.26 μg/ml (CQ-s) and 66.36 μg/ml (CQ-r). Overall, our result suggested that U. lactuca-synthesized AgNP may be employed to develop a new and safer agents for malaria control [32].

**Silver nanoparticles of Pergularia daemia**

Now a days, the study has been proposed for the synthesis of silver nanoparticles and latex obtained from the plant Pergularia daemia which is used against larval instars of Aedes aegypti and Anopheles stephensi mosquito larvae. The plant latex and AgNPs having the concentrations of 1,000, 500, 250, 125, 62.25, 31.25 ppm and 10, 5, 2.5, 1.25, 0.625, 0.3125 ppm has been synthesized respectively. The LC50 and LC90 were found in accordance with different concentrations to observe the instars of A. aegypti and A. Stephensi. The LC50 and LC90 study of AgNPs for fourth-instar larvae of A. aegypti and A. Stephensi does not showed any promising effect on Poecillia reticulata even after lasting for 24 or 48h. The prepared AgNPs showed spherical shape in TEM, absorbs UV-visible rays at 520nm, particle size in the range of 44 to 255nm and having zeta potential of -27.4 Mv. These results were showed mosquito larvicidal activity [33].

**Gold nanoparticles of Couroupita guianensis**

Many people were died because of mosquito-borne diseases. About 3.2 billion people in world’s population got affected by the malaria. Numerous chloroquine-resistant plasmodium and pesticide-resistant Anophelos has been growing day by day which in turn lead to increase in malaria in surrounding. Now, flower extract of Couroupita guianensis with gold nanoparticles (AuNPs) has been used as reducing and stabilizing agent. The research of AuNPs was satisfied after several analysis like UV–Vis spectrophotometer, Fourier transform infrared (FTIR) spectroscopy, TEM, energy-dispersive X-ray (EDX) spectroscopy, zeta potential, X-ray diffraction (XRD), and particle size analysis. LC50 were also performed for AuNPs and found to be toxic for Anophelos stephensi larvae, pupae, and adults. In the study, larval mortality was about for 72 h while treated with C. guianensis flower extract and AuNPs. The antiplasmodial activity of the extract and AuNP were studied for CQ-resistant (CQ-r) and CQ-sensitive (CQ-s) strains of Plasmodium falciparum. C. Guianensis synthesized
Silver nanoparticles of *Murraya koenigii* leaf extract

Now a days, physiological resistance and side effects became a major huddle in the use of synthetic insecticides. Natural products are now in use for the synthesis of insecticides which prevent the mosquitoes transmit serious human diseases. Plant leaf extract of *Murraya koenigii* has been synthesized using silver nanoparticles (AgNPs). This nanoparticles were tested against first to fourth instars larvae and pupae of Anopheles stephensi and Aedes aegypti with varying concentration. The synthesized AgNPs from *M. koenigii* has been found to be toxic in comparison to alcoholic extract of crude leaf in different species of mosquito. Several spectrscopical studies were done with the help of energy-dispersive X-ray spectroscopy analysis, UV–Vis spectrum, Fourier transform infrared spectroscopy and scanning electron microscopy. From the above studies, *M. koenigii* synthesized silver nanoparticles may be eco-friendly, safe which shows promising effect against vector mosquitoes [35].

**Conclusion**

In conclusion, we have demonstrated some novel nanoparticles formulation for the control of larvae of the vector causing malaria. The nanoparticles formulation such as Silver nanoparticles of *Anisomeles indica*, Silver nanoparticles of *Zornia diphylla* leaves, Lipid nanoparticles of Curcuminoids, Silver nanoparticles of *Nerium oleander*, Silver nanoparticles of *Aloe vera*, Silver nanoparticles of *Gmelina asiatica* have shown promising results. The novel drug delivery system by employing polymers like hydroxyl propyl methyl cellulose and polyvinyl pyrrolidone; the metal like gold and silver and other carriers such as glyceryl-dilaurate, albumin, lipids have improved the targeted drug delivery to control of the larvae and hence augmenting prophylaxis of malaria.

**References**


