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Current challenges and nanotechnology-based pharmaceutical strategies for the treatment and control of malaria

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ABSTRACT

Malaria is one of the prevalent tropical diseases caused by the parasitic protozoan of the genus *Plasmodium* spp. With an estimated 228 million cases, it is a major public health concern with high incidence of morbidity and mortality worldwide. The emergence of drug-resistant parasites, inadequate vector control measures, and the non-availability of effective vaccine(s) against malaria pose a serious challenge to malaria eradication especially in underdeveloped and developing countries. Malaria treatment and control comprehensively relies on chemical compounds, which encompass various complications, including severe toxic effects, emergence of drug resistance, and high cost of therapy. To overcome the clinical failures of anti-malarial chemotherapy, a new drug development is of an immediate need. However, the drug discovery and development process is expensive and time consuming. In such a scenario, nanotechnological strategies may offer promising alternative approach for the treatment and control of malaria, with improved efficacy and safety. Nanotechnology based formulations of existing anti-malarial chemotherapeutic agents prove to exceed the limitations of existing therapies in relation to optimum therapeutic benefits, safety, and cost effectiveness, which indeed advances the patient's compliance in treatment. In this review, the shortcomings of malaria therapeutics and necessity of nanotechnological strategies for treating malaria were discussed.

1. Introduction

Malaria is one of the common life threatening vector borne infectious diseases caused by single celled apicomplexan parasitic

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protozoa of the genus *Plasmodium* that is transmitted by the bite of infected female Anopheles mosquitos to humans, predominantly affecting children and pregnant women in tropical, subtropical, and temperate regions of the world (Phillips et al., 2017). There are five human-pathogenic *Plasmodium* species identified: *Plasmodium falciparum* (*P. falciparum*) (the most lethal strain with the highest incidence of mortality), *P. vivax* (developing hypnozoites), *P. malariae* (producing long-lasting infection which can persist for a life time), *P. ovale* (developing hypnozoites) and finally, the zoonotic species *Plasmodium knowlesi* found more prevalent in Southeast Asia and infects macaques and humans (White, 2008). According to the World Health Organization (WHO), 228 million cases and 405,000 deaths were reported in 2018 globally, of which 93% cases were from African region, 3.4% cases from South-East Asia Region, and 2.1% cases from Eastern Mediterranean Region (World Malaria Report, 2019).

Clinical characteristic features include fever, chills, headache, muscle aches, vomiting, severe anemia, enlargement of spleen, unarousable coma, and death if left untreated (Patel et al., 2003). Non availability of proper vaccine(s), inadequate vector control measures, and emergence of drug-resistant parasites causes difficulty in treatment and control of malaria (Brian et al., 2008). Further, co-infections of malaria and human immunodeficiency virus (HIV) causes complexity in diagnosis and treatment (Skinner-Adams et al., 2008). Proper diagnosis and identification of malaria species and preventing from the proliferation of the parasite by exploiting different metabolic activities between the host and parasite are important (Winstanley and Ward, 2006). Currently, chemotherapy is the only accessible strategy to treat and control malaria infection. Current chemotherapeutic agents for the treatment of malaria comprrises several problems pertaining to safety, efficacy, and emergence of drug-resistant parasites due to the complex life cycle and biological pattern of the malaria parasite (Brian et al., 2008). The rate of mutation in *Plasmodium* gene is one of the important factors in the emergence of resistant species (Petersen et al., 2011). Under the influence of drugs, this rate of mutation in the parasite increases and consequently resistant species can appear more quickly (Bopp et al., 2013). Due to the widespread emergence of resistant parasites to several highly effective anti-malarials, WHO has recommended the practice of artemisinin-based combination therapies (Nosten and White, 2007). Nonetheless, these artemisinin-based combination therapies got resistance in some malaria endemic areas (Nsanzabana, 2019). Extensive research is necessary, especially for treatment of malaria-infected pregnant women and children (<5 years age). Despite, the fact that chemotherapy is the mainstay of therapy for malaria treatment and control the use of current anti-malarial agents is limited by serious toxic adverse effects and development of drug resistance (Kain, 1996). Therefore, the search for a novel, cost-effective, nontoxic, low propensity to develop drug resistance, and efficacious therapy is of immediate requirement for treating malaria. During the last decade, nanotechnology-based drug delivery systems have been extensively used to improve the performance of drugs in treating several diseases. Some of the nano-based formulations have been approved by the U.S. Food and Drug Administration

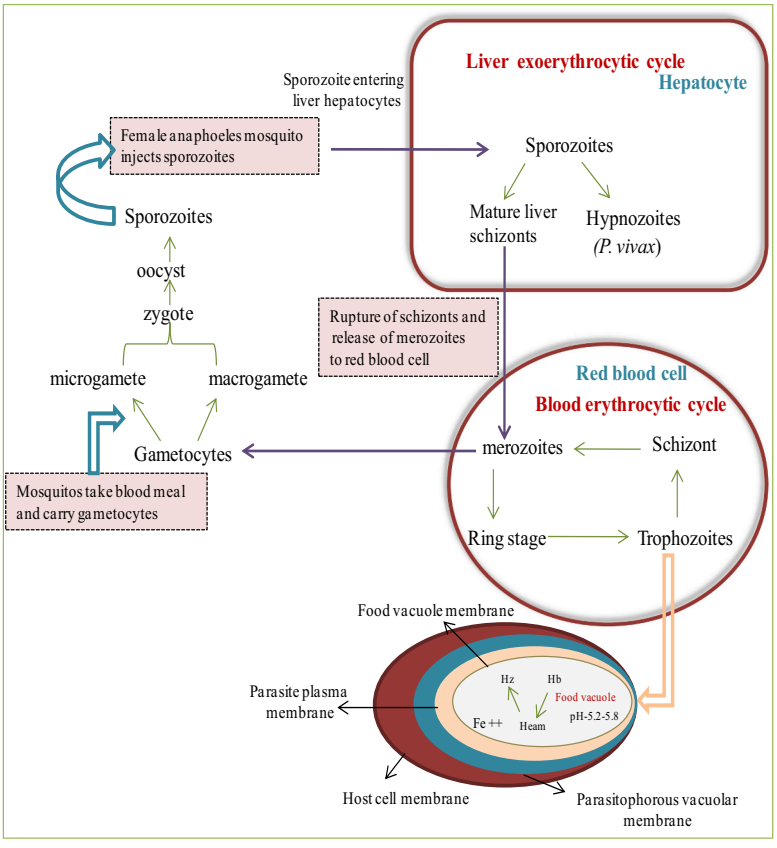

Fig. 1. Life cycle of malaria parasite (Reproduced, adapted and modified from Baruah et al., 2017).

(FDA) for clinical application (Patra et al., 2018). Therefore, this review is an effort to comprehensively compile the current anti-malarial chemotherapeutic measures and role of nanotechnology in the development of newer therapeutic options against malaria.

2. Life cycle of malaria parasite

Malaria parasite has a digenetic life cycle, which requires two hosts to complete its developmental stages. Life cycle of malaria parasite starts with the inoculation of sporozoites, present in the salivary glands of an infected female anopheles mosquito, into the bloodstream of the human host (Fig. 1). These sporozoites further invade hepatocytes by migrating into liver within 40–48 h (Shortt and Garnham, 1948). After 72 h, sporozoites grow and mature to form schizont, later it bursts and releases haploid merozoites, which invade the erythrocyte surface proteins through a specific receptors and re-enters into the blood stream. In some species like *P. vivax*, sporozoites develop into hypnozoites in hepatocytes of the host, which can stay in body for several months and these asymptomatic hypnozoites provoke relapse of an infection for upto two years after initiation of infection (Krettli and Miller, 2001). Symptoms of the disease were actually predicted within 14 days after sporozoite inoculation, i.e. at the late trophozoite and schizont asexual stages of the parasite (Brian et al., 2008). Merozoites remain in metabolically inactive form called ring form, similar to signet ring for 10–15 h. Majority of the hemoglobin in RBC is digested by the parasite (trophozoite) that results in the formation of heme, which associates with Fe^{3+} of an adjacent heme through peripheral carboxyl groups to generate insoluble hemozoin. The trophozoite stage ends to form schizont and releases merozoites in the host cells, finally repeats to continue the cycle (Kozicki et al., 2015). After one or more cycles, the sexual stage of the parasite starts. Some of the merozoites-containing RBC develop into macrogametocytes (female, diploid nucleus) or microgametocytes (male, octoploid nucleus) in the systemic circulation. When mosquito bites the malaria-infected host, these gametocytes undergo series of developmental stages in the body of mosquito like gametes, ookinetes, oocysts, and sporoblasts. Elevated protrusions of sporoblast surface are responsible for the passage of nucleus and other organelles to form sporozoites. These free sporozoites emerge into the haemocoelomic fluid; probably concentrate in the salivary glands annexing acinal cells of the mosquito. Then they develop into the mature infective form and restart the infection through the bite of an infected mosquito into the blood stream of the new host (Bray and Garnham, 1982).

3. Current chemotherapeutic options for malaria

3.1. Quinine

Quinine is obtained from the bark of Cinchona, also referred as Jesuits' bark, Cardinal's bark, or sacred bark. The use of quinine was started in 17th century. It is the first successful drug to treat malaria which belongs to the aryl amino alcohol group of compounds. It acts against intra-erythrocytic malaria parasites by interfering the ability of parasites to digest hemoglobin, resulting in build up toxic levels of partially degraded hemoglobin in itself (Baruah et al., 2017). Quinine is absorbed rapidly when administered orally and parenteral routes, and reaches peak concentrations in systemic circulation within 1–3 h. It is a protein bound compound, mainly binds to alpha-1 acid glycoprotein and its half-life ranges between 11 and 18 h. It has also showed gametocytocidal action against *P. vivax* and *P. malariae*. Treatment with the combination of quinine and clindamycin has shown improved anti-malarial effect and reduces the duration of hospital stays when compared to quinine treatment alone (Kremsner et al., 1995). Quinine causes cinchonism, producing tinnitus, impairment of hearing, headache, and nausea. It may also cause loss of vision and vertigo. Most serious adverse effects which are less frequent include asthma, thrombocytopaenia, hepatic injury, and psychosis (Achan et al., 2011).

3.2. Chloroquine

Chloroquine was discovered by Hans Andersag in 1934. It has been used as an anti-malarial agent for treating severe malaria for nearly eight decades and replaced quinine in many areas where there is no systematic malaria eradication campaigns to be conducted. It is stable, extremely tolerated in high doses and easily affordable by common people (Ursos and Roepe, 2002). Chloroquine inactivates parasite proliferation in the erythrocytic stage by hampering the ability of parasite to digest hemoglobin. Chloroquine accumulates in the *Plasmodium* parasite and prevents incorporation of hemozoin crystal. The formed chloroquine heme complexes damage lipid bilayer of *Plasmodium* membrane by peroxidation process. Emergence of chloroquine-resistant strains of *Plasmodium* species made the drug ineffective to treat malaria (Trape, 2001). *Pfcrt* genes expressed in the resistant parasite lessen the accumulation of the chloroquine in the digestive vacuole (Slater, 1993). Higher and longer duration of chloroquine treatment may cause bilateral loss of vision, retinopathy, neuromyopathy, long subtle symptoms of decreased visual acuity and diplopia (Al-Bari, 2014); (Melles and Marmor, 2015).

3.3. Mefloquine

Mefloquine was first developed by the United States Army in the 1970s as an anti-malarial drug. It acts by forming toxic complexes with free form of heme against the parasite. It is a blood schizonticidal agent and had no effect on the hepatic stage of the parasite (Chou and Fitch, 1993). It is extensively used in the treatment of multidrug-resistant *P. falciparum* malaria and prophylaxis in travelers. It is found to be safe in pregnant and breast feeding mothers. It is contraindicated in patients with psychiatric illness due to its neuropsychiatric adverse events (Van Riemsdijk et al., 2004). Increased expression of the gene encoding a parasite transport protein, *Pfmdr1*, is the general predictor of failure in mefloquine treatment. This treatment failure was observed even after effective

combination of mefloquine along with 3 days artesunate chemotherapy (Price et al., 2004).

3.4. Primaquine

Primaquine, an 8-aminoquinoline analogue was firstly introduced in 1950s. It is synthesized from descendent anti-antimalarial drug, plasmoquine (plasmochin, pamaquine). It acts by interfering with the electron transport chain in parasite and also known to generate reactive oxygen species (ROS) that helps in killing of developing parasites in liver, mature gametocytes, schizontsand dormant hypnozoites, responsible for relapses in malaria caused by *P. vivax* and *P. ovale* (Hiebsch et al., 1991). Probability of relapse, however, differs from geographical origin (Recht et al., 2014). Apart from that, they also have the partial asexual stage activity; therefore it is always used in combination with a blood schizonticidal agent. However primaquine is more toxic compound that may cause severe haemolysis in people deficient in glucose-6-phosphate dehydrogenase (G6PD) enzyme. The level of haemolysis depends on the dose and severity of deficiency (White et al., 2012).

3.5. Atovaquone

Atovaquone (hydroxy-1,4-naphthoquinone) is a broad-spectrum antiprotozoal agent, that effectively kills both liver and blood stages of *Plasmodium* parasite. It is a structural analogue of protozoan ubiquinone, which was introduced as an anti-malarial drug by Wellcome laboratories in 1980s (Vaidya and Mather, 2000). It acts by inhibiting parasite mitochondrial electron transport chain selectively without affecting host mitochondria, as it is a competitive inhibitor of ubiquinol. In erythrocytic stage of infection, mitochondrion of the parasite in the form of merozoite converts dihydroorotate to orotate through dihydroorotate dehydrogenase (DHODH) enzyme for pyrimidine biosynthesis of parasite (Fry and Pudney, 1992). Malarone, (combination of atovaquine and proguanil) developed by GlaxoSmithKline, is highly effective and approved for the treatment and prophylaxis of *P. falciparum* malaria (Kremsner et al., 1999). It is available in combination of atovaquone (250 mg) and Proguanil (100 mg) formulation for adults and in combination of atovaquone (62.5 mg) and proguanil (25 mg) formulation for pediatrics(Baggish and Hill, 2002). Single amino acid substitutions at position 268, in exchange of tyrosine for serine (Y268S) of the cytochrome *b* gene have found in atovaquone-resistant isolates of *Plasmodium* spp., *Toxoplsma gondi*, and *Pneumocytosis* (Shakir et al., 2011); (Nixon et al., 2013).

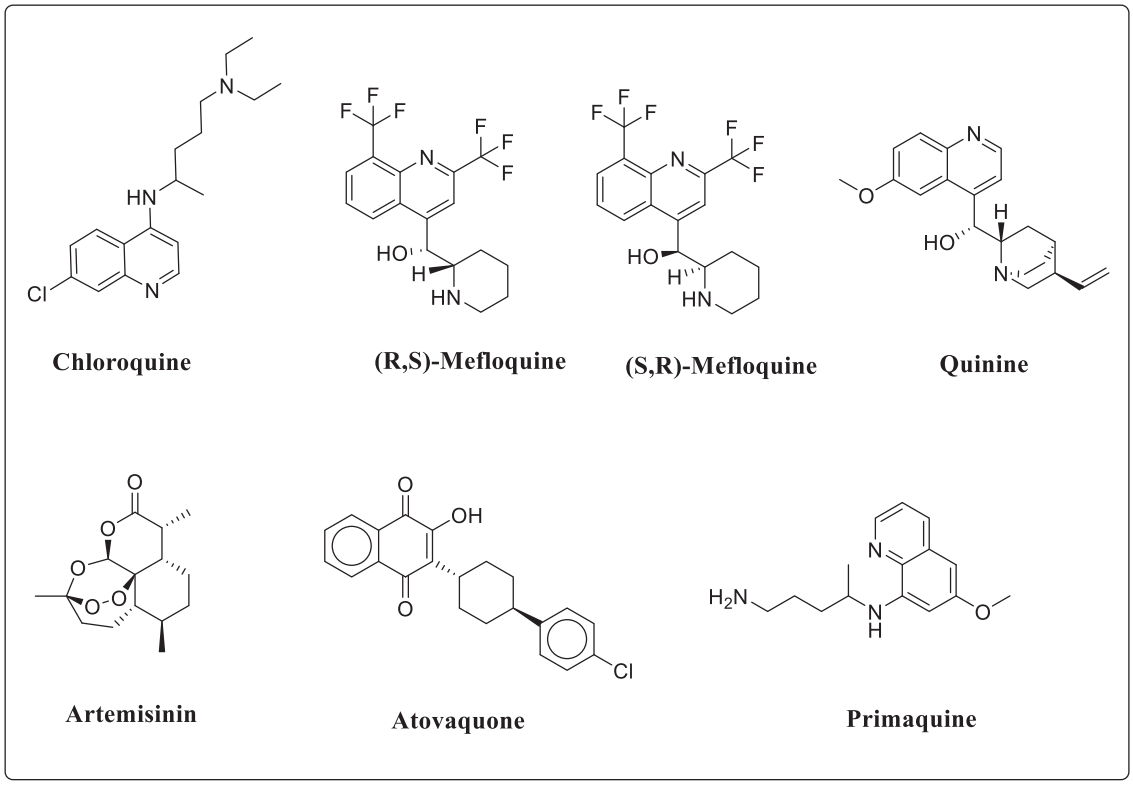

Fig. 2. Chemical structures of anti-malarial agents.

3.6. Artemisinin

Artemisinin also called qinghaosu, is the principle active component derived from the sweet wormwood plant, *Artemisia annua*. It is a sesquiterpene lactone compound, acts by generation of free radicals in food vacuole, inhibiting calcium ATPase and disrupting mitochondrial function in the parasite. In addition to the parent compound, various artemisinin derivatives are available including artesunate, artemether, artemotil, and dihydroartemisinin. It has also shown to inhibit phosphoinositide 3-kinase (PI3K) /protein kinase B (AKT) activity, nuclear translocation of NF-ĸB along with the consequent expression of intercellular adhesion molecule 1 (ICAM-1) and matrix metallopeptidase 9 (MMP-9) expression (Meshnick, 2002); (Eckstein-Ludwig et al., 2003). Artemisinin acts efficiently against erythrocytic stages of the parasite, recrudescence, and gametocyte carriage. Introduction of artemisinin-based combination therapy (oral fixed dose combinations) was significantly reduced the treatment failure and helps to prevent late recrudescence (Woodrow et al., 2005). Common toxic effects of artemisinins were nausea, vomiting, anorexia, and dizziness. Rarely more serious adverse effects were also been noticed including neurotoxicity, neutropenia, anemia, hemolysis, and elevated levels of liver enzymes (Olliaro, 1998); (Brewer et al., 1994). Chemical structures (Fig. 2) and limitations of current anti-malarial chemotherapeutic agents were listed (Table 1).

4. Nanotechnological approaches for malaria therapeutics

Current anti-malarial therapy depends mainly on chemotherapy, comprising serious toxic adverse events and development of drug

Table 1
Advantages and disadvantages of currently available anti-malarial agents.

Drug with mode of action	Advantages	Disadvantages	Clinical indications
Chloroquine (CQ) phosphate ➢ Accumulation of the toxic heme in the parasite by preventing the conversion of toxic heme into nontoxic hemozoin ➢ Lysosomotropic	✓ Fast action in RBC stages ✓ High volume of distribution ✓ Oral dosage forms ✓ Very low in toxicity ✓ High bioavailability	✓ Widespread development of resistance ✓ Macular retinopathy ✓ 1–2 months of half-life (long)	✓ Uncomplicated malaria ✓ *P. falciparum* (CQ-sensitive) ✓ *P.vivax* (CQ-sensitive) ✓ *P. malariae*
Quinine (QN) sulfate ➢ Accumulation of cytotoxic heme within the parasite by acting on heme detoxification pathway	✓ Fast action in RBC stages ✓ Oral route formulation ✓ High oral bioavailability ✓ Resistance is uncommon	✓ Less potent than CQ ✓ Cause cinchonism ✓ Hypoglycemia ✓ Serious hematologic disorders ✓ Small therapeutic index ✓ Drug association is needed ✓ Neurotoxicity dose-dependent ✓ *i.v.* bolus is forbidden	✓ Severe malaria ✓ *P. vivax* and *P. falciparum* ✓ CQ-resistant uncomplicated malaria ✓ Association with doxycycline, tetracycline, or clindamycin
Artemisinin ➢ Inhibits P*f*ATP6 outside the parasite's food vacuole ➢ Acts as a gametocytocidal and schizontocidal	✓ Safe and well-tolerated ✓ Potent and fast action in blood stages ✓ Gametocytocidal effects ✓ No widespread resistance	✓ Poor water solubility ✓ Unavailable *i.v.* dosage form ✓ Low bioavailability by oral route ✓ Very short-elimination half-lives ✓ Expensive drug	✓ Severe complicated malaria management ✓ *P. falciparum* CQ-resistant
Primaquine (PQ) phosphate ➢ It acts by inhibiting the formation of functional transport vesicles in the golgi apparatus ➢ Interference with ubiquinone	✓ The only hypnozoidal and transmission blocking drug for *P. vivax* and *P. ovale* ✓ Prophylactic action	✓ Must not be used during pregnancy ✓ Limited oral availability ✓ Hemolytic anemia ✓ Methemoglobinemia ✓ Hemeolysis in patients with glucose6- phosphate dehydrogenase (G6PD) deficiency	✓ Uncomplicated malaria ✓ *P. vivax* and *P. ovale* (radical cure)
Mefloquine (MQ) ➢ Heme metabolism ➢ Blood schizontocide	✓ Potent action against erythrocytic stages ✓ *P. vivax* (gametocidal)	✓ Causes severe neuropsychiatric reactions ✓ Expensive drug ✓ Long half life	✓ Uncomplicated malaria ✓ *P. falciparum* malaria ✓ *P. vivax* CQ-resistant ✓ *P. Malariae*
Atovaquone (AT) ➢ Inhibits mitochondrial respiration of the parasite	✓ Used as a prophylactic for treating *P. falciparum* malaria	✓ Long elimination half-life (50–70 h) ✓ Poor and variable absorption	✓ Uncomplicated malaria ✓ *P. falciparum* (CQ-resistant ✓ Chemoprophylaxis

resistant parasites and leads treatment failure. To overcome the clinical failures of anti-malarial chemotherapy, new drug development is of an immediate need, nevertheless the drug discovery and development process is expensive and is time consuming (Tse et al., 2019). Globally, several universities, research institutions, pharmaceutical industries and a non-profit organization like Medicines for Malaria Venture (MMV), have designed, synthesized novel anti-malarial compounds and tested against *Plasmodium* parasite in both in vitro and in vivo models; however, these have shown some extent of toxicity in the preclinical studies (Gelb, 2007). The complexity of parasite life cycle, scattered locations (erythrocytic and *exo*-erythrocytic stages) of malaria parasite in the host and incomplete knowledge on biology and pathology of malaria parasite, has created a great challenge for researcher to develop a new drugs against malaria (Nureye and Assefa, 2020);(The malERA Consultative Group on Basic Science, 2011). Recently, nanotechnological approaches have gained importance for target specific drug delivery of drugs with improved safety and efficacy (Rizvi and Saleh, 2018). The application of nanotechnologies to medicine, or nanomedicine, is the field of science having extensive applications and great impact on biotechnological and pharmaceutical industries in design and development of nanostructured (1 nm to 1000 nm) materials encapsulated with antimicrobial agents as a promising approach to encounter the complication as associated with existing antimicrobials (Masri et al., 2019); (Zhu et al., 2014). The primary goal of the nanotechnology based malaria therapy is to deliver anti-malarial chemotherapeutic agent, which is encapsulated in nanomaterial to target parasite infected erythrocytes and intracellular parasitic vacuoles. Additionally, the use of nanomaterials would permit augmented efficacy, safety, selectivity, alters the drug pharmacokinetic properties, improves solubility profile of drug, avert drug degradation, and endorse a constant release of drug directly at the target location. Encapsulation of more than one chemotherapeutic drugs with nano-vectors allows the combinatorial treatment that might have a synergistic effect (Patra et al., 2018). Numerous nanoparticles like liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), metallic nanoparticles, nano-emulsions, and polymeric nanoparticles have been explored and found to be very advantageous for drug delivery applications as nanocarriers (Naseri et al., 2015); (Gedda et al., 2020). These nanotechnological-based products may attest to exceed the limitations of existing therapies with respect to safety, efficacy and cost effectiveness, which certainly improves the patient's compliance to treatment (Chowdhury et al., 2017). Recently U.S. FDA approved Liposomal amphotericin B for the treatment of visceral leishmaniasis, a neglected tropical protozoal parasitic infection and have shown improved efficacy and safety (Singh et al., 2020a). Surface modification of nanoparticles encapsulated anti-malarials increases selectivity and specificity against target resulted in improved safety and efficacy (Baruah et al., 2017). Several research groups have designed nano-based formulations with standard anti-malarial drugs and screened against *Plasmodium* parasite-infected animal models have shown promising results, however, a greater attentiveness of the scientific communities are vital to such a poverty-stricken tropical infectious diseases (Table 2).

4.1. Liposomes

Liposomes are the most commonly and extensively used nano-vectors for targeted drug delivery. They can improve therapeutic outcomes by stabilizing active therapeutic agents, conquering impediments to cellular and tissue uptake, and enhancing bio distribution of active drugs to target sites in animal models (Sercombe et al., 2015). These are artificially prepared spherical vesicular structures contains one or more concentric lipid bilayers encompassing distinct aqueous space. Cholesterol or any natural non-toxic phospholipids are generally used in liposomal preparations. The unique properties of liposomes like small size, charge, number of lamellae, lipid composition, hydrophilic-hydrophobic balance, biocompatibility, favors to encapsulate both hydrophilic and lipophilic therapeutic agents as cargo and further surface modification with polymers and ligands efficiently delivers the active drug at specific target site causes with improved safety and efficacy. Liposomes have high retention time and prolonged circulation (Momeni et al., 2013); (Lasic, 1998). Liposomes were first time described by Bangham, a British haematologist and called these structures as 'smectic mesophases' and later named as 'liposomes' by Gerald Weismann, an American physician (Bangham et al., 1965). Drugs loaded in liposomal layer exhibited an effective intracellular activity allowing them to penetrate into the macrophages in the course of

Table 2
Advantages and limitations of various nanocarrier systems.

Type of nano- carriers	Advantages	Limitations
Liposomes	Both hydrophilic and hydrophobic drugs can be carried, highly stable, biodegradable, non-toxic, can be administered by parenteral and cutaneous routes, enhanced therapeutic index, possibilities of surface functionalization	Highly expensive, short half-life, encapsulated drugs may leak into the systemic circulation
Polymeric nanoparticles	Biocompatible, affordable, avoid reticular endothelial system, flexible for ligand specific interaction, avoids leakage of the drug	Difficult to scale up
Solid lipid nanoparticles (SLNs)	Biocompatible, easy scale up and sterilize, highly stable, can be administered by oral, parenteral and cutaneous routes, avoidance of organic solvents, encapsulation of both lipophilic and hydrophobic drugs	Drug loading efficacy is low, chances of initial burst and drug explosion due to its crystalline structure, short half-life and surfactant toxicity
Nanostructured lipid carriers (NLCs)	Improved stability and drug loading compared to SLNs, long shelf life, easy scale up and sterilize	toxicity related to surfactant
Nanoemulsions	Easy to prepare, long shelf life, both lipophilic and hydrophobic drugs can be carried, used for oral, parenteral and cutaneous routes of administration, thermodynamically stable, can be sterilized by filtration	Huge amount of surfactants are used, hence causes risk of toxicity.
Metallic nanoparticles	Antifungal, antibacterial, highly stable and uniform in structure	Toxic adverse reactions

phagocytosis (Ahsan et al., 2002). Most important benefit of liposomes is the improvement of pharmacokinetic properties of the drug at specific target site for desired pharmacological effect. Cholesterol and egg phosphatidylcholine were widely used in the preparation of neutral liposomes which were proposed to be the first nanovectors employed drug delivery system for antimalarials. Recently, phosphatidylethanolaminein conjugation with polyethylene glycol and phosphatidylglycerol were used in the preparation of negatively charged liposomes for antimalarial drug delivery (Baruah et al., 2017). Liposomes-encapsulated chloroquine has shown protective effects in murine malaria model. Augmented therapeutic and prophylactic efficacies were observed in liposomal chloroquine in comparison with free chloroquine in *P. berghei*-infected Swiss mice (Eling et al., 1989). Primaquine, 6-methoxy-8-(4′-amino-I′-methylbutyl-amino) quinolone, a prophylactic antimalarial agent encapsulated in liposomes and tested against *P. berghei* ANKA infected-male TB_{EsP} mice shown reduced parasitemia and toxic events compared to free drug (Pirson et al., 1980). Surface modification with distearoylphosphatidylethanolamine-methoxy-polyethylene glycol 2000 (DSPE-mPEG-2000) on liposome-encapsulated chloroquine has shown improved efficacy and reduced parasitemia in choroquine-resistant and susceptible strains of rodent malaria (Rajendran et al., 2016b). Monensin, a polyether antibiotic ionophore encapsulated in stearylamineliposomes alone or combination with free artemisinin effectively clears the blood stage parasites in *P. falciparum*-infected red blood cells (Pf-IRBCs) in vitro and *P. berghei*-infected Swiss mice model without causing any serious toxic effects (Rajendran et al., 2016a). Curcuminoids-loaded phosphatidylcholine liposomes (40 mg/kg body wt) alone or in combination with α/β artemether (30 mg/kg body wt) lowers blood schizonts and increases survival rate. These combination inhibited parasite recrudescence (Aditya et al., 2012). Combination of artemisinin and curcumin-loaded PEGylated liposomes has shown protective effects in erythrocytic stage of parasite in *P. berghei* NK-65-infected mice (Isacchi et al., 2012). Surface modification of chloroquine-encapsulated liposomes with F(ab')2 fragments of a mouse monoclonal antibody (MAb), MAb F10, raised against the host cell membranes taken from the *P. berghei*-infected mouse RBCs, effectively cures the chloroquine-resistant murine malaria at lower doses (Owais et al., 1995). Recombinant human tumor necrosis factor-α (rhTNF-α)-encapsulated liposomes exhibited enhanced therapeutic efficacy and protection against *P. berghei* k173-induced experimental cerebral malaria (ECM) in mice compared to free rhTNF-α (Postma et al., 1999). Fusogenic liposome encapsulated cytosolic proteins (sAg) of *P. yoelii nigeriensis* enhances CD4+ and CD8+ T cell populations and also up-regulated the expression of CD80 and CD86 molecules on the surface of antigen presenting cells, IFN-γ and IL-4 cytokines. Liposome-delivered vaccines can enhance immune boosting properties and helps in the elimination of intracellular parasites (Isacchi et al., 2012).

4.2. Solid lipid nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) are enticing formulation scientists globally owing to its benefits such as cost and safety compared to other colloidal nanoparticles (liposomes, emulsionsand polymeric nanoparticles). SLNs were introduced in 1991 and it contains a core of solid lipid with surfactants having a size not more than 1000 nm. (Parvez et al., 2020a), The matrix of the lipid core has a significant role in regulating the release pattern and protects the loaded drugs from chemical and enzymatic degradation (Parvez et al., 2020c). In SLNs, the matrix is a composition of high melting solid lipids, different from the liposome and emulsion, where the vesicles and droplets are made up of low melting phospholipids and liquid oil, respectively (Parvez et al., 2020b); (Ali and Singh, 2016). SLNs offer unique characteristics such as small size, large surface area, high drug loading and the interaction of phases at the interfaces, and are attractive for their potential to enhance the activity of neutraceuticals, pharmaceuticals, and other materials (Mukherjee et al., 2009). Lipid-based formulations can decrease drug toxicity and improve bioavailability due to its unique physiological and biodegradable properties (Severino et al., 2012). SLNs are widely used as drug delivery systems in cancer and several parasitic diseases like leishmaniasis, malaria, human African trypanosomiasis, and tuberculosis (Sun et al., 2019); (Singh et al., 2020b). Dihydroartemisinin-loaded SLNs have been synthesized by single emulsion solvent evaporation technique, characterized and tested for antimalarial activity for overcoming the problems (poor water solubility, poor pharmacokinetic and pharmacodynamics properties) associated with dihydroartemisinin. Dihydroartemisinin SLNs have shown enhanced anti-plasmodial activity in vitro (IC_{50} 0.25 ng/mL) and in vivo (97.24% chemo suppression at 2 mg/kg/day) (Omwoyo et al., 2016). Primaquine-loaded SLNs were prepared by a modified solvent emulsification evaporation method based on a water-in-oil-in-water (w/o/w) double emulsion with the aim to limit the severe toxic events (hematological and gastrointestinal) induced by primaquine. Primaquine-loaded SLNs has 20% more efficacythan conventional oral dose and at the dose of 2 mg/kg/ day, has effectively treated (chemo suppression of 93.5%) *P. berghei*-infected Swiss albino mice without showing any toxic effects (Ogutu et al., 2014). Surface modification of SLNs with heparin encapsulated chloroquine prepared by modified double-emulsion solvent evaporation technique and has shown improved anti-malarial effect against chloroquine sensitive (D6) strains of *P. falciparum* compared to the free chloroquine and specific targeting of Pf-IRBCs as afforded by surface modification of SLNs with heparin (Muga et al., 2018). SLNs-encapsulated lumefantrine and artemether has shown enhanced efficacy and safety with high clearance of parasitemia and no report of recrudescence (Attama et al., 2016). Transferrin-conjugated SLNs encapsulated quinine dihydrochloride has been formulated for effective delivery to brain to treat cerebral malaria (Gupta et al., 2007).

4.3. Nanostructured lipid carriers (NLCs)

Lipid nanocarriers are introduced as an alternative to emulsions, liposomes, and polymeric nanoparticles. Additionally, nanostructured lipid carriers (NLCs) are the second generation lipid carriers established to correct the complications accompanying with SLNs and are utilized in numerous therapeutic applications. Muller in 1999/2000 has coined the name nanostructured lipid carriers (Salvi and Pawar, 2019). NLCs are drug-delivery systems, attracted growing attention in recent years and having the benefits for drug therapy than conventional carriers, pertaining to improved solubility, permeability and bioavailability, storage stability, diminished toxicity, extended half-life, and target specific delivery (Fang et al., 2012). NLCs were principally deliberated for the delivery of

lipophilic drugs but their appropriateness for hydrophilic drugs is now well documented. NLCs are extensively explored and gaining importance due to its unique characteristics like biological compatibility, non-toxic, and non-immunogenic nature (Salvi and Pawar, 2019). NLCs encapsulated artemether synthesized, characterized and tested against *P. berghei*-infeced rodent malaria model. Artemether-loaded NLCs has shown protection in malaria induced mice model with enhanced oral bioavailability in comparison with free artemether (Ali et al., 2016). Artemether-loaded NLCs were prepared, characterized, and tested against cerebral malaria induced mice model. It has shown better anti-malarial activity in *P. berghei* ANKA-infected C57BL/6 mice without showing any toxic adverse effects in comparison with free artemether (Vanka et al., 2018). WHO has approved the fixed-dose combination of artemether-lumefantrine for treating malaria. These fixed dose combinations have the problems of low solubility and poor oral bioavailability. NLCs-encapsulated artemether-lumefantrine was synthesized to improve the oral efficacy and bioavailability by using the micro-emulsion template technique. NLCs-encapsulated artemether-lumefantrine treatment (16 mg artemether and 96 mg lumefantrine, given once a day at 1/5 of therapeutic dose) have shown complete clearance of parasitemia and 100% survival rate in *P. berghei*-infected mice (Prabhu et al., 2016). NLCs-loaded curcumin has formulated and characterized for overcoming the problems (poor bioavailability, enhanced metabolism, and chemical instability) associated with free curcumin. NLCs-loaded curcumin has shown better anti-plasmodial effect against *P. berghei*-infected mice compared to free curcumin (Rashidzadeh et al., 2019).

4.4. Metallic nanoparticles

Metal oxide nanoparticles such as zinc oxide, silver nitrate, chloroauric acid, iron oxide, copper oxide, and aluminium oxide are being extensively used by researchers for various medical applications. Metal oxide nanoparticles prepared by chemical and microwave methods can degrade the β–hematin (biomarker for malaria) (Obisesan et al., 2020). Silver and silver based formulations have been used for the treatment of several microbial infections since antiquity. Silver based nanoparticles have synthesized and shown effectiveness against *P. falciparum* (Rai et al., 2017). Commercially available nanoparticles such as MgO, Fe_3O_4, ZrO_2, CeO_2, and Al_2O_3 were tested against *P. falciparum* for their anti-malarial activity. The nanoparticles showed minimum level of IC_{50} value Al_2O_3(71.42 $\pm$ 0.49 μg mL^{-1}), MgO (72.33 $\pm$ 0.37 μg mL^{-1}), and Fe_3O_4 (77.23 $\pm$ 0.42 μg mL^{-1}). Further surface coating of metal nanoparticle with poly 4,4′-diaminodiphenyl sulphone (PDSS) enhances its anti plasmodial activity. IC_{50} value was 48.66 $\pm$ 0.45 μg mL^{-1} for PDDS-coated Fe_3O_4, 60.28 $\pm$ 0.42 μg mL^{-1} for PDDS-coated MgO, and 67.06 $\pm$ 0.61 μg mL^{-1} for PDDS-coated CeO_2 (Jacob Inbaneson and Ravikumar, 2013). Titanium oxide (TiO_2) nanoparticles were prepared by using *Momordica charantia* leaf aqueous extract as a stabilizing and reducing agent and screened against *P. falciparum*. These TiO_2-loaded nanoparticles showed protective effects against chloroquine-resistant and susceptible strains of *P. falciparum* (Gandhi et al., 2018). Surface modified iron-oxide nanoparticle fortified artesunate was formulated and tested against experimental malaria models. These nanoparticles effectively killed the *P. falciparum* with IC_{50} value of 8 times lesser than the free artesunate in vitro and clears the parasitemia in *P. berghei*-infected Swiss mice with 8- to 10-fold lessened dose of artesunate. Iron-oxide nanoparticle fortified artusunate showed its anti-plasmodial effects through enhanced release of reactive oxygen species (ROS) in parasitic food vacuole (Kannan et al., 2019).

4.5. Emulsomes

Emulsomes (nanoemulsions) are novel colloidal nanocarriers, with an internal solid fat core surrounded by a phospholipid bilayerand, is stabilized by high concentration of lecithins in the form of oil/water emulsion. The formulation of emulsomes is easy and advantageous in encapsulation of both aqueous and fat soluble drugs. Nanoemulsions exemplify as a lipid-based drug delivery vehicles with extensive range of therapeutic applications predominantly for poor water soluble drugs. Emulsomes comprise both internal hydrophobic core as in emulsions and stabilized by adjacent concealment by means of one or more phospholipid bilayers as in liposomes. These systems are commonly prepared by emulsion solvent diffusive extraction or melt expression method (Kumar et al., 2013); (Gupta and Vyas, 2007). Clotrimazole nanoemulsions effectively cleared the blood stage parasites in *P. berghei*-infected Swiss mice with enhanced efficacy and safety (Borhade et al., 2012). Primaquine acts precisely on the liver stage parasites (pre-erythrocyticschizonts) and causes relapse after proliferation nonetheless the main disadvantage of this compound is lower dissolution in blood to achieve therapeutic effect. To overcome these drawbacks, primaquine oral lipid nanoemulsion (10–200 nm particle size) was successfully prepared for targeting relapsing malaria. Primaquine is freely absorbed by the liver >45% than previously (Khan et al., 2019). Artemether nanoemulsions were formulated by ultrasonication method using internal oil phase (artemether dissolved in coconut oil and span 80) and external aqueous phase (tween 80 and ethanol in H_2O) and tested for in vivo oral bioavailability. Artemether nanoemulsions showed 2.6 times higher oral bioavailability than free artemether as noticed from pharmacokinetic experiments (Laxmi et al., 2015). Nanoemulsions consisting of combination of artemether-curcumin were formulated by aqueous titration technique to target cerebral malaria via olfactory delivery system to reach brain. These nanoemulsions showed promising results in *P. berghei* ANKA-infected murine model of cerebral malaria (Jain et al., 2012). Artesunate and quercetinen capsulated self-nanoemulsifying drug delivery system were successfully prepared and tested in preclinical models for its bioavailability, safety and efficacy. These formulations showed higher oral bioavailability in Wistar rats as observed from pharmacokinetic experiments and enhanced parasite clearance was observed in *P. berghei*- infected Swiss mice without showing any toxic side effects (Puttappa, 2020).

4.6. Polymeric nanoparticles

Polymeric nanoparticles have gained importance in biomedical field as drug delivery systems. Polymeric nanoparticles have the capacity to cross the intracellular membranes and increase the cellular uptake of therapeutic agents and ultimately augment the

efficiency of antimicrobial agents. Polymeric nanomaterials are composed of both natural and synthetic polymers and are highly biocompatible and biodegradable with size ranging from 10 to 1000 nm (Hirenkumar and Steven, 2012). They offer numerous advantageous as drug delivery systems such as high biocompatibility, enhanced drug solubility, bioavailability, and improved efficacy and safety of therapeutic agents. Polymeric drug conjugates are prepared for the incorporation of therapeutic agents into polymers (linear or branched) through specific functional groups (amino groups, alcohols, and carboxylic acids) (Mhlwatika and Aderibigbe, 2018). Aqueous soluble polymer-conjugated amino chloroquine was found to be more effective agains tchloroquine sensitive strains of *P. falciparum* (Aderibigbe et al., 2014). Curcumin-artesunate-*co*-encapsulated poly D,L-lactic-*co*-glycolic acid (PLGA) polymeric nanoparticles were prepared by solvent evaporation from oil-in-water single emulsion method and evaluated preclinically for its safety and anti-plasmodial activity. These PLGA-encapsulated nanoparticles showed augmented anti-parasitic effects in *P. berghei*-infected Swiss mice with limited toxic side effects (Oyeyemi et al., 2018). Recently, in vivo effect of pyrimethamine-loaded poloxamer 407 nanoparticle was evaluated on *P. berghei* strain NICD. A considerable decrease in the parasitemia and histopathological damages and an increase in the survival time of *P. berghei*-infected mice was observed as compared to the group received pyrimethamine alone (Pestehchian et al., 2020).

4.7. Nanotechnology based vaccines

Current therapeutic options for malaria are finite and accompanying with severe toxic adverse effects, emergence of drug-resistant parasites and high cost. Vaccine based alternative therapies to the existing chemotherapy could conquer the limitations of antimalarials and could be effective in eliminating malaria. Many research groups have been identified several vaccine candidates to target malaria. Presently, WHO malaria vaccine list contains 38 *P. falciparum* and 2 *P. vivax* candidate malaria vaccines or vaccine components, which are in progressive preclinical or clinical phase (Karunamoorthi, 2014). Recombinant vaccines with one or more specific antigens have been developed to persuade immunological response against malaria parasite. RTS,S vaccine (trade name Mosquirix), the first licensed vaccine approved for use by European regulators in July 2015 to target malaria showed reliable efficacy and safe results in clinical trials (Molina-Franky et al., 2020);(Morrison, 2015). This vaccine is composed of C-terminal T-cell multiepitope of *P. falciparum* circumsporozoite protein, fused with the S-antigen of hepatitis B virus and the *N*-acetylneuraminic acid phosphatase central repeat combined with an AS adjuvant system (AS01). However, it revealed better immune responses in encapsulated liposomal form (Campo et al., 2011). Nano vector-mediated delivery systems of vaccines offer an opportunity to augment the antibody and cell mediated immune responses. Nanoparticles facilitate the enhanced cellular uptake by immune cells such as macrophages; dendritic cells and gut-associated lymphoid tissue (GALT), causing an effective antigen processing and presentation. This also makes a vaccine more efficient toselectively target cell surface receptors in order toinduce protective immunity (Kim et al., 2014). Polystyrene nanoparticles-encapsulated merozoite surface protein (MSP4/5) conjugates showed moderate protection against blood stage parasites and induced T_H1 cellular cytokines, IgG1, IgG2a, and IgG2b, and IFN-γ levels in BALB/c mice model (Wilson et al., 2019). Liposomes encompassing cobalt porphyrin–phospholipid mixed with transmission blocking antigen candidate (polyhistidine-tagged (his-tagged) Pfs25) induced antibody mediated immune responses against malaria (Huang et al., 2018). A vaccine delivered in liposomal nanocarrier-loaded antigen form is found more effective than conventional form. These liposome based vaccines can potentially induce high antibody and T-cell responses by triggering major histocompatibility complex (MHC) I and MHC II pathways (Alving and Richards, 1990). Intramuscular administration of CpG oligodinucleotide (CpGODN) along with *Pfs*25, the transmission blocking antigen in a liposomal carrier adjuvant gel core form, enhanced the immune responses compared to monotherapeutic vaccine (Tiwari et al., 2009). Cationic liposomal vaccine carrier loaded with recombinant plasmid DNAs comprising of the C terminus of merozoite surface protein 1 (MSP119) of *P. vivax* and *P. falciparum* Rhoptry protein 5 (PfRH5) antigens showed strong immune responses against circumsporozoite protein of *P. vivax* (PvCS). This approach was found hopeful in targeting blood stage infection of *P. falciparum* (Fotoran et al., 2017). Nanovaccine carriers developed from CHr*Pfs*25 with gold nanoparticles as adjuvants produced transmission-blocking antibodies that prevent (human to mosquito) transmission by targeting the sexual, sporogonic, or mosquito stages of the parasite (Kumar et al., 2015). Currently, malaria vaccine development strategies need regular boosting because of the problem of resistance to recombinant antigens. High doses of *Plasmodium* are required to prepare live attenuated parasites, thus the production of such vaccines are still limited (Mettens et al., 2008).

4.8. Green nanotechnology prospect to control malaria

Green nanotechnology integrates the principles of green chemistry and green engineering to formulate safe and eco-friendly nanocomplexes to fight against the impediments affecting the human health or environment. Consequently, combination of green nanotechnology with drug delivery area has essentially initiated a unique realm of green nanomedicine (Kanwar et al., 2019). Silver nanoparticles (35–55 nm) synthesized by green nanotechnology using *Andrographis paniculata* Nees showed anti-plasmodial effect against *P. falciparum*. Ecofriendly and biosynthetic silver nanoparticles prepared from Ashoka and Neem leaf extracts have the ability to inhibit *Plasmodium* parasites effectively (Mishra et al., 2013). Green nanotechnology based zinc oxide nanoparticles synthesized by using aqueous peel extract of *Lagenaria siceraria* and tested against *P. falciparum*. These zinc oxide nanoformulations inhibit the formation of hemozoin, which is required for *Plasmodium* parasite survival (Kalpana et al., 2020). Palladium green nanoparticles from *Eclipta prostrata* extract showed anti-plasmodial effects in *P. berghei*-infected Swiss mice (Rajakumar et al., 2015). Silver nanoparticles synthesized from *Catharanthus roseus* have potential anti-plasmodial effects, in vitro (Ponarulselvam et al., 2012).

4.9. Role of nanotechnological approaches to control malaria transmission by targeting vectors

Malaria is a vector borne parasitic infectious disease transmitted by the bite of infected female *Anopheles* mosquitoes to the humans. Vector control is an extremely efficient way to decrease malaria transmission and is a key factor for malaria control and elimination strategies. Insecticide-treated bed nets (ITNs) and indoor residual spraying (IRS) are currently available methods to control *Anopheles* mosquitoes (Tizifa et al., 2018). Unfortunately, resistance has developed to conventional insecticides due to their indiscriminate use. Thus, development of safe and effective insecticides is an immediate need. In such a scenario, nanotechnology plays an important role in vector control due to its biodegradable, biocompatible, non-toxic properties that can be effectively used for encapsulation of potent insecticides. The small size of the particles allows them to be delivered directly to biological targets and protects the encapsulated compounds from degradation and volatilization by increasing their half-lives with a controlled release rate (Rahman et al., 2019). *Cinnamomum zeylanicum* oil nanoemulsion showed potential larvicidal effect against *Anopheles* vector (Firooziyan et al., 2021). Bio-fabricated sardine fish scale silver nanoparticles effectively killed the *Anopheles* larvae (Murugan et al., 2021). Chitosan polymeric nanoparticles encapsulated *Trachyspermum ammi* essential oil (particle size 158 $\pm$ 7 nm) showed enhanced larvicidal effects with a lethal concentration of 50 (LC_{50}) 13.67 µg/mL against *Anopheles* larvae. This biosynthesized chitosan formulation could be presented as a potent candidate against other mosquitoes and prospective field application opportunity (Zarenezhad et al., 2021). Silver nanoparticles synthesized by leaf extracts of *Nelumbo nucifera* has shown potent larvicidal against *Anopheles* mosquitoes (Santhoshkumar et al., 2011). Ecofriendly and cost effective green nanotechnology based silver nanoparticles synthesized by *Belosynapsis kewensis* leaf extract showed efficient larvicidal activity against *Anopheles* mosquitoes and can become a potential candidate for malaria vector control (Bhuvaneswari et al., 2016).

5. Conclusion

Malaria is one of the most prevalent and serious public health issues of tropical diseases worldwide. Emergence of drug-resistant parasites, severe toxic adverse events of existing anti-malarial chemotherapeutics, and non-availability of proper vector control measures and vaccine(s) against malaria leads to difficulty in malaria control and treatment. Many research organizations were trying to develop therapeutic strategies to combat malaria but no satisfactory results were obtained. The expansion of nanotechnological based therapeutic agents against malaria has engendered excessive interest in formulation and drug development scientists. Nano based drug delivery systems have shown exciting data in preclinical studies, demonstrating their potential as therapeutics carriers. Various nanoparticles like liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), metallic nanoparticles, nanoemulsions, and polymeric nanoparticles have been explored as drug carrier systems for anti-malarial chemotherapeutic agents to target malarial with improved efficacy and safety. Various research organizations have designed and developed nanotechnology based formulations with standard anti-malarial drugs. Some of these nano-based drugs have been pre-clinically studied and shown positive outcomes. Nonetheless a superior attention of the scientific communities is crucial for such a potentially life-threatening infectious diseases.

Declaration of Competing Interest

The authors declare no financial or commercial conflict of interest.

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