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Review

Nanotechnology-Based Strategies in Parasitic Disease Management: From Prevention to Diagnosis and Treatment

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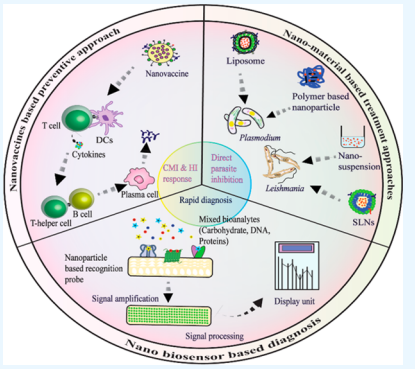
ABSTRACT: Parasitic infections are a major global health issue causing significant mortality and morbidity. Despite substantial advances in the diagnostics and treatment of these diseases, the currently available options fall far short of expectations. From diagnosis and treatment to prevention and control, nanotechnology-based techniques show promise as an alternative approach. Nanoparticles can be designed with specific properties to target parasites and deliver antiparasitic medications and vaccines. Nanoparticles such as liposomes, nanosuspensions, polymer-based nanoparticles, and solid lipid nanoparticles have been shown to overcome limitations such as limited bioavailability, poor cellular permeability, nonspecific distribution, and rapid drug elimination from the body. These nanoparticles also serve as nanobiosensors for the early detection and treatment of these diseases. This review aims to summarize the potential applications of nanoparticles in the prevention, diagnosis, and treatment of parasitic diseases such as leishmaniasis, malaria, and trypanosomiasis. It also discusses the advantages and disadvantages of these applications and their market values and highlights the need for further research in this field.



1. INTRODUCTION

Parasitic diseases have a devastating impact on millions of people, particularly those living in impoverished regions of Africa, Asia, and Latin America. These diseases result in significant suffering and death, with malaria being a leading cause of mortality.[1,2] According to the World Malaria Report 2022, there were 619,000 malaria-related deaths worldwide in 2021, with over half of the world's population at risk of contracting the disease. 95% percent of malaria cases and 96% of malaria-related deaths occurred in African countries. Additionally, 80% of those who died were children under the age of five.[3] Leishmaniasis is a neglected tropical disease (NTD) and stands next to malaria in terms of morbidity and mortality. The specific *Leishmania* species dictates the disease's clinical manifestations, spanning from skin-related issues to potentially fatal visceral conditions. Annually, 700,000 to 1 million new leishmaniasis cases are documented. Cutaneous leishmaniasis comprises 85 to 95% of these cases, while visceral leishmaniasis accounts for the remaining 50,000 to 90,000 instances.[4] Another Neglected Tropical Disease (NTD), Human African Trypanosomiasis (HAT), commonly known as sleeping sickness, jeopardizes the lives of around 70 million people in sub-Saharan Africa. Without medical intervention, this illness almost invariably leads to death.[5] Chagas disease, also known as American trypanosomiasis, is another affliction caused by trypanosomes, affecting an estimated 6−7 million people globally, predominantly in Latin America.[6] Antiparasitic drugs such as pentamidine and nifurtimox address trypanosomiasis, while chloroquine and artemisinin-based therapies combat malaria. These treatments either eliminate or inhibit parasite growth. Repurposed drugs like miltefosine and amphotericin-B, replacing antimonial drugs, significantly enhance leishmaniasis treatment. However, there are several concerns associated with conventional management. One major issue is the potential development of drug resistance by parasites over time, rendering medications less effective. Additionally, these drugs can cause various side effects, including headache, nausea, vomiting, and abdominal pain, which can reduce patient adherence to treatment.[7,8] Moreover, some antiparasitic drugs may not be effective against all parasite species, making it challenging to select the appropriate treatment, especially in regions with multiple parasite species.[9,7,10] Cost is another significant barrier, particularly in resource-limited settings where access to healthcare is limited.[11]

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Nanotechnology offers potential solutions to overcome these limitations. Nanoparticles, engineered on a nanoscale, can be designed to target and penetrate parasite-infected cells, enabling more effective drug delivery and improved therapeutic efficacy.[12,13] By using biodegradable or biocompatible materials, nanoparticles can reduce toxicity compared to traditional drug delivery methods.[14] Moreover, nanoparticles are under investigation for their potential in various fields including diagnostics, vector control, theranostics, bioimaging, and resistance management. They enhance drug effectiveness by improving the solubility, bioavailability, and sustained release. Additionally, they can be customized with specific ligands to detect biomarkers, enabling early diagnosis. Nanoparticles are also being explored for vector control, combining therapeutic and diagnostic capabilities, and utilized in bioimaging and tracking techniques. Another promising application of nanotechnology is the development of nanovaccines. Currently, vaccination appears to be the most effective means of preventing infectious diseases. Vaccine efficacy hinges on factors such as the stimulation of specific adaptive immune responses and the target population. However, many traditional vaccination approaches for parasitic infections, involving live-attenuated pathogens, inactivated pathogens, or subunit vaccines, have faced significant challenges and safety concerns, falling short of delivering the desired level of protection.[15−18] To address these challenges, nanoparticle-based formulations offer a promising solution. They can optimize antigen and adjuvant delivery, enhance stability, enable targeted delivery, and boost immunogenicity, potentially paving the way for safe and effective vaccines against parasitic diseases.[19−22]

Nanotechnology-based biosensors can also play a role in the fight against parasites. Most parasitic disease detection methods currently rely on microscopy, culture, and molecular techniques, requiring specialized expertise, being time-intensive, and incurring high costs, which hinder swift diagnosis. This position places us on the brink of developing more affordable technologies suitable for deployment in resource-constrained settings. Nanomaterials possess unique physical, chemical, and fluorescence properties that can be combined with conventional biosensors to increase the sensitivity and enable early disease diagnosis. This noninvasive approach provides an alternative to invasive techniques and holds promise for improved detection. While the application of nanotechnology in the treatment of parasitic diseases is still in its early stages, it shows great potential. Further research is needed to fully understand its capabilities and to develop it into a common clinical tool.[23−26] This review aims to assess the current state of various nanotechnology-based therapeutic and diagnostic interventions and prospects they bring in the fight against parasitic diseases such as leishmaniasis, malaria, trypanosomiasis, and Chagas disease (Figure 1).

2. NANOTECHNOLOGY: A NEW HORIZON FOR THE TREATMENT AND DIAGNOSIS

Nanoparticles offer promising prospects for the treatment and diagnosis of various conditions, including parasitic infections. Liposomes, polymer nanoparticles, solid lipid nanoparticles (SLNs), nanosuspensions, and other types of nanoparticles like carbon, gold, and silver nanoparticles are being extensively researched for delivering antiparasitic drugs.[27−31] These advancements have led to improved therapeutic outcomes. Additionally, an early and accurate diagnosis plays a crucial

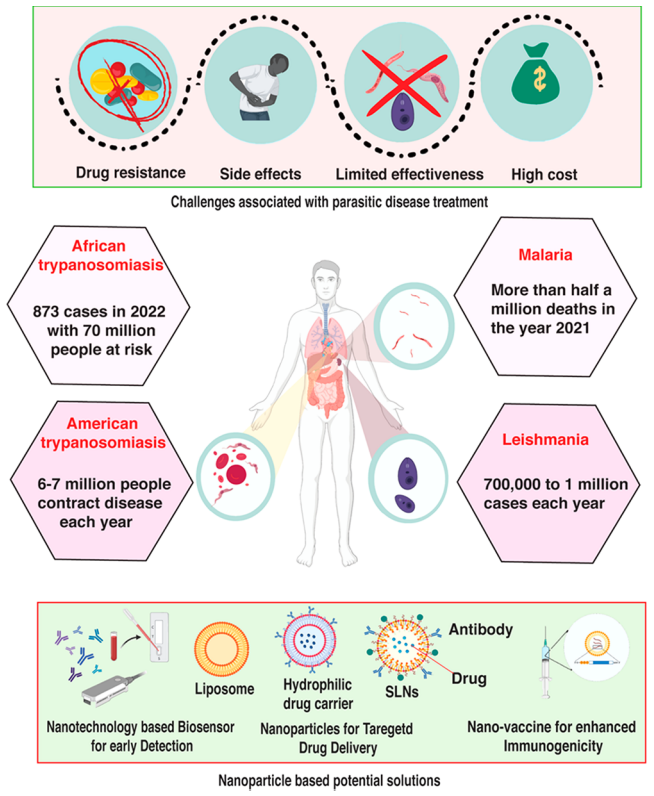

Figure 1. Treating parasitic diseases presents challenges, including drug resistance, side effects, limited efficacy, and high costs. Nanotechnology-based treatments, such as liposomes and SLNs, enhance drug effectiveness and bioavailability. Nanotechnology aids disease diagnosis and prevention through highly sensitive and specific diagnostic tools. Nanovaccines offer a superior alternative to conventional vaccination methods.

role in the effective management and treatment of parasitic infections. While parasitological and immunological tests are commonly used for diagnosis, they often have limitations such as cross-reactivity and reduced accuracy. In recent years, innovative nanotechnology-based techniques have emerged as potential solutions to enhance diagnostic accuracy.[32−34]

2.1. Liposomes. Liposomes are spherical structures with a size range of 0.025−2.5 μm[35] and consist of a lipid bilayer that can serve as a drug delivery vehicle for antiparasitic drugs. The lipid bilayer acts as a protective barrier, encapsulating the drug either in the inner aqueous compartment or within the bilayer, depending on its nature. This encapsulation enhances drug stability, longevity, and efficacy while reducing toxicity. Liposomes have demonstrated effectiveness against a wide range of parasitic diseases, including malaria, leishmaniasis, and Chagas disease.[36,37] They have also been developed as antifungal drugs for systemic fungal infections caused by *Candida albicans* and *Aspergillus fumigatus* and have shown superior effectiveness and reduced toxicity compared to conventional antifungal drugs.[38,37] They are capable of penetrating deep into infected tissues and organs, effectively targeting the fungal pathogens.[39] In addition, liposomes can be modified in various ways to improve their pharmacokinetic and pharmacodynamics properties, such as their circulation time, target specificity, and release rate.[40] To improve their pharmacokinetic and pharmacodynamic properties, liposomes can be modified in various ways. They can be functionalized with targeting molecules such as antibodies (immunolipo-

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somes)[41] or peptides[42] that selectively bind to specific cell types or organs. This enhances the selectivity and effectiveness of the medicine. Another advantage of liposomes is their biocompatibility and biodegradability, which minimizes significant side effects in the body.[43] They can be designed to be long-circulating, remaining in the bloodstream for an extended period and effectively reaching their target sites. Liposomes offer versatility in drug delivery, accommodating various types of drugs including small molecules, proteins, and RNA for the treatment of parasitic diseases.[44] They are capable of solubilizing hydrophobic drugs that have poor water solubility and protecting them from degradation in the body. Liposomes loaded with drugs have demonstrated effective intracellular activity, allowing them to penetrate macrophages during phagocytosis.[45] The distinctive structure of liposomal nanoparticles enables controlled drug encapsulation, release, and functionalization with targeted moieties for drug delivery. This mechanism of action drives their effectiveness as drug delivery vehicles in the treatment of parasitic diseases.

2.2. Solid Lipid Nanoparticles (SLNs). Solid lipid nanoparticles (SLNs) are small, spherical particles composed of solid lipids at room temperature. SLNs utilize lipids, either natural or synthetic, as a medium to adsorb, encapsulate, or disperse drugs.[46−48] They have a solid lipid core with surfactants, with a size typically not exceeding 1000 nm.[49] The lipid core's matrix plays a critical role in controlling the release pattern and protecting the loaded pharmaceuticals from enzymatic and chemical degradation.

SLNs possess unique qualities such as compact size, high drug loading capacity, vast surface area, and interactions of different phases at interfaces. They are typically nontoxic, biodegradable, and biocompatible, making them suitable for various medicinal applications.[50] The lipids used in SLN formation include waxes, monoglycerides, diglycerides, triglycerides, fatty acids, and steroids. SLNs can be used for both hydrophilic and hydrophobic drugs, depending on the manufacturing process employed.[51] However, there are some common shortcomings of SLNs. These include lipid particle development, susceptibility to gelation, kinetics of polymorphic changes, intrinsically low drug integration rate due to solid lipid crystallization, and initial burst release of the drug.[52] These challenges need to be addressed to optimize the performance of SLNs as drug delivery systems.

Research indicates the potential of employing SLNs for treating parasitic diseases, yielding superior outcomes compared to those of conventional drugs. SLNs enhance intracellular targeting, optimize drug distribution, reduce dosage needs, and mitigate toxicity, all without compromising antiparasitic efficacy.[53,54] Unlike traditional oil-in-water emulsions, polymer nanoparticles, and liposomes, SLNs offer a unique combination of benefits: easy mass production, excellent physiological compatibility, and degradability.[55] Their superiority over conventional counterparts positions SLNs as compelling candidates for exploration and application in resource-limited settings.

2.3. Nanosuspensions. Nanosuspensions are colloidal particles on a submicron scale that contain insoluble compounds, typically in the presence of polymers, surfactants, or a combination of both. The size of the nanoparticles in a nanosuspension can vary widely, typically ranging from a few nanometers to hundreds of nanometers. The choice of nanoparticle shape and size depends on factors such as the intended drug delivery mechanism, target site, desired release profile, and stability considerations.[56,57] Nanosuspensions offer several advantages, including improved drug solubility,[58] enhanced bioavailability, controlled release of drugs,[59] and active ingredients.

One of the major issues with existing antiparasitic medications is their poor solubility and low bioavailability, which can lead to decreased treatment efficacy and the development of drug resistance. Nanosuspensions provide a solution to these problems by improving the solubility and bioavailability of antiparasitic drugs.[60] Nanosuspensions of several antiparasitic drugs have been tested against animal models and shown improved solubility and bioavailability.[61−63] The increased therapeutic efficacy of nanosuspensions is attributed to their prolonged release time, which allows for lower dosages, reduced costs, improved patient compliance, and increased access to treatment. While nanosuspensions offer numerous advantages, there are also certain drawbacks that need to be considered. The assessment of their safety, targeting capabilities, and potential off-target effects is crucial to ensure their effective and safe use in medical applications. Therefore, a multidisciplinary approach is necessary to evaluate the benefits and potential dangers of nanosuspensions in different applications.[64]

2.4. Polymer-Based Nanoparticles. Polymer-based nanoparticles, with their small size and customizable properties, have emerged as a versatile platform for various biomedical applications. These nanoparticles are composed of synthetic or natural polymers and have dimensions smaller than 1000 nm.[65] These particles have a high surface area to volume ratio, which makes them attractive for use in a wide range of biomedical applications, such as drug delivery, gene therapy, and imaging.[66]

They offer several advantages such as high stability, controlled release, and biocompatibility.[67] Commonly used polymers for synthesizing nanoparticles include poly(lactic acid) and glycolic acid (PLGA), polyethylene glycol (PEG), and chitosan. The core of the nanoparticles contains the therapeutic agent, while the polymer shell or coating protects the drug and controls its release. The release rate can be modulated through drug−polymer interactions, breakdown of the polymer coating, or diffusion of the drug through the polymer matrix. Additionally, the surface of polymer-based nanoparticles can be modified by attaching ligands or antibodies to enhance the targeting of specific cells or tissues. They are also nontoxic, which makes them effective for usage in a variety of applications like imaging or therapeutics.[68−70] Overall, polymer-based nanoparticles hold great potential for the treatment and diagnosis of parasitic diseases, offering improved drug delivery, enhanced therapeutic efficacy, and targeted interventions.

2.5. Nanotechnology-Based Vaccines. Nanotechnology-based vaccines have the potential to improve the efficacy of existing vaccines and enable the development of new vaccine formulation strategies for various parasitic diseases.[71] By utilizing nanoparticles, these vaccines enhance antigen delivery, trigger robust immune responses, and provide opportunities for targeted and controlled vaccine delivery. Continued research in this field holds promise for the advancement of antiparasitic vaccine development. Moreover, merging immune stimulatory molecules with nanovaccines has demonstrated favorable outcomes in preclinical investigations. Integration of immune stimulants, like adjuvants, into nanovaccines augments the resulting immunogenicity. By fusing immune boosters,

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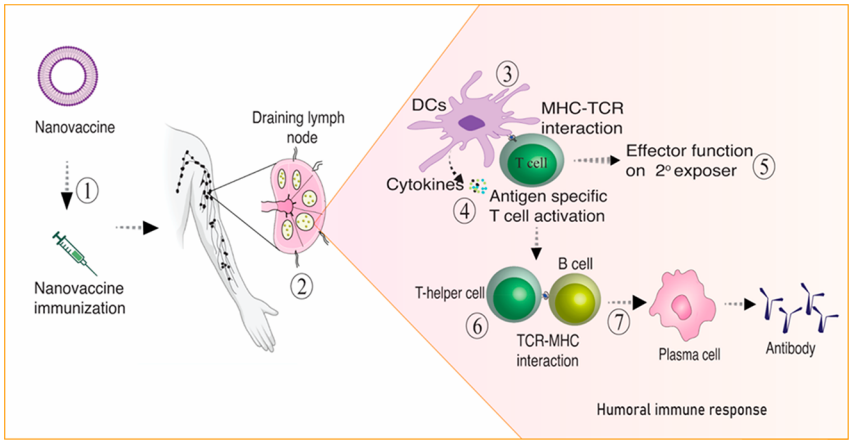

Figure 2. Nanovaccines impregnated with antigens and/or adjuvants show enhanced uptake upon immunization (1,2). Processing and presentation of antigenic molecules to T cells by MHC-TCR interaction takes place in draining lymph nodes (3), resulting in cytokine secretion that modulates the immune microenvironment (4). All the primary exposers prime the immune system for quick and robust effector response on a secondary exposer (5). After activation, antigen-primed T helper cells interact with B cells (6), assisting their differentiation into antibody-producing plasma cells (7).

such as adjuvants, into nanovaccines, the resulting immunogenicity is magnified, amplifying immune responses and elevating vaccine effectiveness.[72−74]

Nanotechnology-based vaccines have emerged as a promising approach for the treatment of antiparasitic diseases.[75] These vaccines utilize nanoparticles to enhance the effectiveness of existing vaccines and enable the development of novel vaccines against various parasitic diseases.[76] Nanoparticle-based vaccines offer several advantages. Adjuvants and targeting motifs can be incorporated into the nanoparticles to enhance the delivery of antigens to antigen-presenting cells, thereby triggering a robust immune response against the parasite. These nanoparticles can also be designed to facilitate improved immunogenicity by promoting the trafficking of antigens to local lymph nodes. Studies in leishmaniasis have shown promising results with nanoparticle-based delivery of DNA vaccines against murine disease.[77,78]

Virus-like particles (VLPs) are another type of nanoparticle used in the development of vaccines against parasitic diseases. VLPs are self-assembling nanoparticles that mimic the structure of viruses but are noninfectious and have been investigated for a range of parasitic diseases including malaria and schistosomiasis,[79] and VLP-based vaccines have been used to deliver malaria antigens, stimulating an immune response against the parasite.[80,81] Compared to whole cell or inactivated vaccines, VLPs do not require inactivation and maintain the native conformation of B cell epitopes. They also have a well-defined composition and can be easily scaled up for production.[82]

3. EMPLOYMENT OF NANOTECHNOLOGY IN PARASITIC DISEASES

3.1. Leishmaniasis. Leishmaniasis is a parasitic infection caused by the *Leishmania* parasite, and it encompasses different forms of the disease, including cutaneous leishmaniasis, mucocutaneous leishmaniasis, and most fatal visceral leishmaniasis. The currently available treatment options for leishmaniasis are limited and can be associated with various side effects.[83] Antimonial drugs have been the mainstay of treatment for many years; however, their efficacy has declined due to increasing resistance, and they can cause severe side effects.[84] Other drugs like amphotericin B and miltefosine have their limitations and associated toxicities as well.[85,86] Paromomycin, an aminoglycoside antibiotic, is another drug used for the treatment of visceral leishmaniasis. However, its efficacy can vary depending on the region and the specific species of *Leishmania* involved in the infection. One of the limitations of paromomycin is that it requires intravenous infusion for several days, which can be challenging in areas with poor healthcare infrastructure or where patients cannot afford hospitalization.[87]

One of the major challenges in treating leishmaniasis is delivering drugs to the site of infection, as the parasites reside within macrophages, which are difficult to target with conventional drugs.[88] Nanoparticles offer a potential solution to this challenge by enabling targeted drug delivery to infected cells or macrophages.[89] Nanoparticles are increasingly being investigated as a potential treatment for leishmaniasis. They have unique physical and chemical properties that make them suitable for drug delivery applications in leishmaniasis.[90]

Liposomal amphotericin B (L-AmB) is a nanoparticle-based drug that has shown high effectiveness against leishmaniasis. Encapsulating amphotericin B within liposomes, small gel-like membranes composed of high transition temperature phospholipids like phosphatidylcholine, distearoylphosphatidylglycerol, and cholesterol, reduces its toxicity through slow release and enhances its specificity for infected cells.[91−93] These lipids interact with amphotericin B, facilitating its temperature-dependent release primarily at the intended target membrane containing ergosterol, maintaining a consistent rate,[94,93] facilitating extended half-life within the body, minimal renal and faecal clearance, and superior drug distribution at the tissue level, thereby necessitating less frequent drug administrations.[95] Global human trials unequivocally highlight the superiority of L-AmB over standard AmB, demonstrating virtually no adverse effects, heightened efficacy, elevated cure rates, and the flexibility to administer it at varying dosage concentrations across extended time frames.[96−98] Owing to its efficacy and tolerability, L-AmB is now recommended by the World Health Organization as a first-line treatment for leishmaniasis.[98] Similarly, amphotericin B-loaded nanoparticles, such as those based on PLGA, have demonstrated

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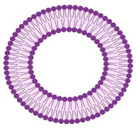
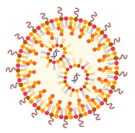
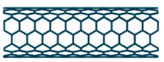
Table 1. Information about the Common Nanocarriers of Drugs, Their Characteristics, and Their Applications in Parasitic Diseases

Nanocarriers and its Design	Advantages	Limitations	Potential applications	References
Liposomes: Small spherical vesicles composed of lipid bilayer membrane. 	Biocompatible, can encapsulate both hydrophilic and hydrophobic drugs, and can target specific cells or tissues.	Limited stability, potential for opsonization by the immune system.	Liposomal encapsulation of amphotericin B (L-AmB) for leishmaniasis. Liposomal and PEGylated liposome formulations for antimalarial drug delivery.	159 115 98 116 117 118
Polymeric nanoparticles: Solid nanoparticles made of biodegradable polymers. 	Can encapsulate a variety of drugs, provide sustained release of drugs, and can be modified with targeting ligands.	May exhibit burst release of drug, potential toxicity of polymer degradation products	AmB loaded PLGA and Chitosan-based nanoparticles against leishmaniasis. Chitosan nanofibers for detection of antibody against *leishmania* parasite. Polymeric microparticles for antimalarial primaquine delivery. Mesoporous ferrite to deliver artemisinin directly to *Plasmodium* infected RBCs. PEI based nano-vaccine for delivery of DNA. Chitosan for delivery of dsRNA against *plasmodium*. Pentamidine PEGylated-chitosan nanoparticles coated with antibodies to target *T. brucei* surface. chitosan-coated benznidazole against *T. cruzi* infection.	100 99 160 106 120 115 122 123
Solid lipid nanoparticles (SLNs): Solid nanoparticles composed of a lipid core surrounded by a solid shell of lipids. 	Biocompatible, can encapsulate hydrophobic drugs, and provide sustained release of drugs.	Limited drug-loading capacity, potential for particle aggregation.	Benznidazole delivery using SLNs against Chagas disease. S-benzyl dithiocarbazate encapsulated SLNs with trypanocidal effect. AmB and Paromomycin encapsulated in SLNs against experimental leishmaniasis. Tanespimycin formulation for leishmaniasis. Chloroquine and Dihydroartemisinin formulation against malaria.	161 54 162 112 49 163 140 141 138

Nanocarriers and its Design	Advantages	Limitations	Potential applications	References
Dendrimers: Highly branched, nanoscale polymers with a core-shell structure. 	Can be precisely engineered for size, shape, and surface chemistry, and can encapsulate a variety of drugs.	Potential toxicity due to non-biodegradable nature and high charge density.	Amphiphilic dendrimer encapsulating chloroquine and primaquine for efficient delivery. AmB loaded dendrimer against leishmaniasis.	164 165 77 166
Carbon nanotubes: Cylindrical structures made of carbon atoms with high aspect ratios. 	High surface area and unique electronic properties, can be functionalized with targeting ligands.	Potential toxicity due to bio-persistence and size, limited solubility in aqueous environments.	Ambisome delivery using nanotubes. Carbon nanotube–zinc oxide nanofiber for detection of malaria biomarker. Detection of antibodies against *Plasmodium* using carbon nanotube based microfluidic system.	167 168 169 170 171
Metallic nanoparticles: Solid particles made of metals such as gold, silver, or iron. 	Unique optical and magnetic properties, can be functionalized with targeting ligands.	Potential toxicity due to size and composition, potential for accumulation in organs.	AuNP for *Leishmania* specific IgG antibodies detection. AuNP for targeted antimalarial delivery. AuNP as antigen delivery system and biomarker detection against malaria. Pentamidine-loaded NMOFs coated with polyethylene glycol against African trypanosomiasis.	172 107 108 126 31 132 125
Nano-emulsions: Liquid droplets consisting of an oil phase, a water phase, and an emulsifier. 	Stable, can encapsulate both hydrophilic and hydrophobic drugs, and can be formulated to have specific properties such as long-term stability or rapid drug release.	Potential for droplet aggregation or coalescence, can be difficult to scale up.	Arteether nano-emulsion against *Plasmodium yoelii* malaria. Quercetin nano-emulsion for leishmaniasis. Resveratrol nano-emulsion against *Leishmania major*. Nano-emulsion of *Copaifera pauper* against leishmaniasis. Formulation of Carbonic anhydrase inhibitors against *T. cruzi*. Essential oils nano-emulsion with trypanocidal activity.	173 174 175 176 51 177 178

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efficacy in treating cutaneous leishmaniasis in animal models reducing lesions on intralesional administration.[99] In a different study, amphotericin B was encapsulated in chitosan-based particles, improving the stability of the formulation and mannose-mediated targeting of sugar moieties on macrophages enhancing uptake and *in vitro* antileishmanial activity.[100] The chitosan nanoparticles acted as carriers for the drug, facilitating its delivery to parasites and increasing its effectiveness. The different variants of carbon-based nanoparticles like graphene sheets, carbon nanotubes (CNTs), and a hybrid of graphene and CNTs have shown excellent efficacy against visceral leishmaniasis with minimum toxicity.[29]

Nanoparticles have also been explored for the development of vaccines against leishmaniasis. Nanovaccine formulations have shown promising results by inducing both humoral and cell-mediated immune responses (Figure 2).[101] For instance, polyprotein complexes of parasites with PLGA nanoparticles have been used to generate peptide-specific $CD8^+$ T-cell responses and induce dendritic cell maturation, offering protection against experimental leishmaniasis in animal models. After C57BL/6 mice were infected with *L. infantum*, the introduction of a peptide-based PLGA nanoformulation containing MPLA as an adjuvant wielded remarkable results. At one month postinfection, a substantial decrease in parasitic load was observed, notably in the liver (72.81% reduction) and spleen (61.98% reduction). This promising trend persisted into the second month, with parasitic loads in the liver and spleen showing impressive declines of 64.4% and 73.64%, respectively.[102] In another study using BALB/c mice, a polyprotein complex of *L. infantum* with PLGA (poly(lactic-*co*-glycolic acid)) nanoparticles promoted the protective immune response.[103] When the vaccinated mice were challenged with *L. infantum*, they exhibited splenic lymphoproliferation and elevated levels of interferon-gamma (IFN-γ), interleukin-2 (IL-2), and tumor necrosis factor-alpha (TNF-α).

In addition to treatment and vaccines, nanotechnology has also been applied to improve the diagnostics for leishmaniasis. The accurate diagnosis of leishmaniasis can be challenging due to the limitations of current diagnostic techniques, especially in cases where the infection is asymptomatic or the symptoms are not specific. However, in recent years, nanotechnology-based methods and devices have been explored to improve the detection of *Leishmania* parasites, related toxins, antigens, and other biomarkers for the diagnosis of the disease.[104] For example, Maki et al. developed biosensors that measured the agglutination response as an electric signal and amplified it for easier detection of antileishmanial antibodies.[105] Other advancements include the use of immobilized *Leishmania* antigens on platforms such as chitosan nanofibers for antibody detection.[106] The plasmonic ELISA approach, employing gold nanoparticles (AuNPs) as a reporter, has been used to detect *Leishmania*-specific IgG antibodies with high sensitivity and specificity.[107] Furthermore, researchers have utilized AuNP-based techniques and antibodies for the detection of *Leishmania* parasites. A novel approach, the triple line lateral-flow assay, harnesses the extraordinary attributes of gold nanoparticles and precise antibody interactions to amplify the sensitivity of *Leishmania infantum* DNA detection in canine VL blood samples. Employing this pioneering approach, the assay not only showcased its remarkable ability to identify a mere 0.038 spiked *Leishmania* parasite per DNA amplification reaction but also translated to detecting a single parasite within a 100 μL DNA sample. This leap in diagnostic capability holds immense promise for enhancing the precision of canine VL diagnosis, facilitating earlier interventions, and vastly improving disease management.[108]

These nanotechnology-based diagnostic methods hold promise for improving the identification and tracking of leishmaniasis. They offer enhanced sensitivity, specificity, and potential for detecting various biomarkers associated with the disease. However, it is important to address challenges related to the accessibility, usability, and cost-effectiveness of these technologies to ensure their practical implementation in resource-limited settings.

3.2. Malaria. Malaria is a severe illness caused by the *Plasmodium* parasite and can lead to severe complications, including potential cerebral involvement. Although several drugs exist for malaria treatment, their effectiveness is hampered by various challenges. One significant issue is the development of drug resistance by the *Plasmodium* parasite, rendering certain medications less effective.[109] Additionally, some antimalarial drugs can be toxic, and ensuring patient compliance with the treatment regimen can be difficult.

To address these challenges, nanoparticles have emerged as a promising approach. Nanoparticles offer targeted drug delivery, allowing medications to be delivered specifically to infected red blood cells, where the parasites reside. This targeted delivery reduces exposure to healthy cells, increases drug concentration at the infection site, and enhances efficacy while minimizing toxicity.[110] Various nanoparticle platforms, including liposomes, immunoliposomes, chitosan-based nanoparticles, peptide-associated liposomes, and solid lipid nanoparticles, have been explored for their ability to deliver drugs to infected red blood cells, enhancing drug efficacy and combating drug resistance. These nanoparticles not only were able to deliver drug at a specific site which reduces the required doses but also can help fight efflux-associated drug resistance.[111,112,111,113,114] An ingenious chloroquine formulation, rooted in chitosan and infused with dehydroascorbic acid (DHA), exhibited a remarkable surge in the level of drug uptake by infected red blood cells (iRBCs). DHA's strategic competition for glucose uptake facilitated drug delivery to the cells, leading to a profound inhibition of parasite growth at an astonishingly low 1 nM concentration, dwarfing the effects of free chloroquine, which required a far higher 100 nM concentration to produce similar results.[111] Liposomal formulations, including PEGylated liposomes, have been investigated for delivering antimalarial drugs such as maduramicin, chloroquine, artemisinin, and dihydroartemisinin.[115−118] In an *in vivo* study, a comparison between PEGylated and liposome-encapsulated artemisinin, administered both alone and in combination with curcumin, yielded remarkable results. A 100% cure rate was achieved, coupled with a sustained release of the drug, as evidenced by plasma concentration levels compared with conventional artemisinin treatment.[119] Similarly, polymeric microparticles, such as primaquine polymeric microparticles, have demonstrated efficacy and protection against parasite development in mice, showing potential as a delivery strategy for malaria treatment (Table 1).[120] While the study conducted by de Brossa et al. demonstrated enhanced drug delivery efficacy at lower dosages and sustained drug retention in the liver, they fell short of achieving results on par with the administration of free, pure primaquine.

Metal nanoparticles have also been investigated as therapeutic tools for malaria. Mesoporous ferrite nanoparticles

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provide a novel approach and utilize the magnetic property of the nanocarrier to be adsorbed at hemozoin-rich iRBCs, releasing artemisinin in close proximity and enhancing antiplasmodial activity.[121] Gold nanoparticles have also been employed in target therapy, binding to cysteine-rich proteins in membranes and parasites to improve drug delivery.[28] To combat both the blood and erythrocytic phases of the parasite effectively, this study underscores the significance of targeting parasite membrane proteins.

Polyethylenimine (PEI) nanoparticles, known for their ability to bind DNA and enhance cellular absorption, have been studied for gene delivery applications in malaria.[122] Chitosan nanoparticles have been used to deliver long dsRNA molecules, targeting essential genes of *Plasmodium* parasites, resulting in a significant reduction in parasite burden in culture medium.[123]

Nanoparticles have also been explored as carriers for malaria vaccine antigens as a versatile self-assembly polypeptide.[124] Gold nanoparticles have also been used as a carrier to deliver nanoparticles loaded with a malaria antigen, *P. falciparum* Circumsporozoite protein (CSP), which have shown stability and the ability to induce a strong immune response in CSP antigens to test the transmission blocking vaccine (TBV) in animal models. The results of the study demonstrated that the TBV formulation induced a strong immune response, leading to the production of antibodies that effectively blocked the transmission of the malaria parasite from infected individuals to mosquitoes.[125] This approach shows promise in reducing the spread of malaria by targeting the sexual stages of the parasite and interrupting its life cycle.

In addition to targeted drug delivery, nanoparticles have also been investigated for their potential as diagnostic tools for malaria. Gold nanoparticles functionalized with antibodies specific to malaria biomarkers, such as histidine-rich protein 2 (HRP2), have been used for the early detection and diagnosis of malaria.[126] Overall, nanoparticles offer potential benefits in targeted drug delivery, gene therapy, vaccine delivery, and diagnostic applications for malaria. Further research and development in this field hold promise for improving the treatment, prevention, and diagnosis of malaria.

3.3. Human African Trypanosomiasis. Human African Trypanosomiasis (HAT), also known a African sleeping sickness, is a parasitic neglected tropical disease caused by the protozoan *Trypanosoma brucei* and transmitted by the tsetse fly, mostly in sub-Saharan Africa.[127] In the early stage of disease, also known as the hemolymphatic stage, individuals may experience nonspecific symptoms that include fever, headache, joint pain, and general malaise. These symptoms can be mistaken for other common illnesses, leading to a delayed diagnosis. If left untreated, the infection progresses to the late or neurological stage of HAT, which is characterized by the invasion of the central nervous system. At this stage, the parasites can be found in the cerebrospinal fluid. The symptoms become more severe and can include neurological manifestations such as behavioral changes, disorientation, confusion, sleep disturbances, and seizures and also can be fatal if left untreated. The current treatments for HAT, such as pentamidine, melarsoprol, and nifurtimox-eflornithine combination therapy (NECT) have limitations and adverse effects, making the development of novel approaches necessary.[128−131]

Nanoengineered particles have emerged as a potential strategy for improving the treatment of African trypanosomiasis. One approach involves the use of nanoscale metal−organic frameworks (NMOFs) loaded with antitrypanosomal medications. NMOFs are porous structures composed of metal ions or clusters connected by organic ligands, allowing for the controlled release of medications. Studies have shown that pentamidine-loaded NMOFs can inhibit the reproduction of *T. brucei* both *in vitro* and *in vivo*. Coating the NMOFs with polyethylene glycol (PEG) enhances their stability and biocompatibility, leading to reduced parasitaemia and increased survival in a mouse model of African trypanosomiasis.[132] Another approach involves the use of nanoparticles coated with antibodies to specifically target trypanosomes. By recognizing the variable surface glycoprotein (VSG) present on the trypanosomes, these nanoparticles can enter the parasites through endocytosis, releasing the drug (e.g., pentamidine) and improving its delivery while minimizing harm to host cells.[133] The studies focus on surface glycoproteins and the nanocarrier's ability to be readily internalized through endocytosis, effectively bypassing resistance caused by surface glycoprotein mutations common in *Trypanosoma*, which adds an even greater level of importance to its findings. Lipid-based nanoparticles, such as liposomes and SLNs, have also shown promise in the treatment of *Trypanosoma* infections. Studies have demonstrated that liposomes and SLNs loaded with drugs such as pentamidine can effectively reduce parasitaemia in animal models of African trypanosomiasis with improved drug delivery efficacy.[31] For example, when using liposomes to assess drug delivery across the blood−brain barrier, it was observed that 87% of the encapsulated pentamidine reached its target, surpassing the delivery rate of the free drug.[31] This work illustrates how liposomal drug formulations represent a more efficient approach for delivering hydrophilic drugs, such as pentamidine, across biological membranes.

3.4. Chagas Disease. Chagas disease is caused by the parasitic protozoan *Trypanosoma cruzi* and is characterized by acute and chronic phases, with symptoms ranging from fever and fatigue to heart failure and neurological damage.[134] There is currently no effective vaccine for Chagas disease, and the available drugs have limited efficacy and can cause severe side effects.[135] It can exist in two forms: the extracellular bloodstream form and the intracellular amastigote form that reside within the host cells. The intracellular amastigote form is responsible for the chronic phase of the disease and is the target of treatment with trypanocidal agents, such as nifurtimox and benznidazole. However, the plasma membrane of host cells can create a barrier that hinders the entry of drugs into the cell and prevents the drugs from reaching the site of the amastigote nests. In addition, the microenvironment within host cells can be quite rigid, making it difficult for drugs to penetrate the cells and reach the parasites.[136] Nifurtimox and benznidazole are both hydrophilic drugs that have a low lipid solubility, which can limit their ability to penetrate the plasma membrane of host cells. This can lead to poor bioavailability of the drugs and reduced efficacy against the intracellular amastigote form of the parasite.

Nanoengineered particles, such as liposomes, nanoparticles, polyalkyl cyanoacrylate (PACA) nanoparticles, and chitosan-coated nanoparticles, have been investigated for their ability to encapsulate drugs like nifurtimox and benznidazole, the standard medications used for Chagas disease treatment. These particles can improve the drugs' pharmacokinetics, biodistribution, and cellular penetration, enhancing their effectiveness against the intracellular form of the parasite.[137] Nanoformulations of traditional trypanocidal drugs, such as

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benznidazole, have showcased heightened trypanocidal potency in *in vitro* assays, outperforming free drugs. This underscores the potential of nanocarrier-based drug delivery as an avenue for combating drug resistance, warranting further exploration.[138] Studies have also shown that nifurtimox-loaded PACA nanoparticles can provide sustained drug release and significantly reduce parasitaemia in infected cells compared to the free drug alone.[139] In another study, nifurtimox-loaded PACA nanoparticles have shown sustained release over 24 h and significant reduction of parasitaemia in *T. cruzi*-infected cells compared to the free drug alone.[140−142] Similarly, chitosan-coated nanoparticles loaded with benznidazole have demonstrated increased stability and improved drug delivery.[143] *S*-Benzyl dithiocarbazate, a potential alternative therapeutic option for Chagas disease, has exhibited exceptional trypanocidal efficacy in both *in vivo* and *in vitro* settings when encapsulated in SLNs, surpassing conventional benznidazole.[54]

Gold nanoparticles have also been utilized due to their unique physical and chemical properties. They can be easily synthesized and functionalized with various ligands to improve their targeting and therapeutic properties.[144] The gold nanoparticles were able to penetrate the parasite's membrane and deliver the drug directly.[145]

The development of an effective vaccine against Chagas disease remains a challenging task, but various strategies have been explored and have contributed to our understanding of how to induce a protective immune response against the disease.[146] In recent years, nanocarriers have been investigated as antigen delivery systems in the development of Chagas disease vaccines. Studies in animal models have demonstrated that nanocarriers can enhance antigen delivery and improve the effectiveness of the immune response against Chagas disease.[147−149] Nanotechnology-based approaches have also shown promise in the diagnosis of Chagas disease, addressing the limitations of conventional diagnostic methods in terms of sensitivity and time consumption. For example, nanoparticles have been employed in a well-known diagnostic method that detects antigens in urine.[150] Additionally, innovative nanotechnology-based devices like the electrochemical immune sensing device Nanopoc[151] and others that detect serum antibodies[152,153] have demonstrated effectiveness in the diagnosis of Chagas disease. These advancements in nanotechnology offer promising avenues for both vaccine development and diagnostics in the fight against Chagas disease. Continued research and development in these areas hold the potential to improve prevention, treatment, and detection of the disease.

4. FUTURE PERSPECTIVES AND CONCLUDING REMARKS

The use of nanoparticles in the treatment and diagnosis of parasitic diseases, such as Leishmaniasis, Malaria, and Chagas disease, holds great promise. Nanoparticles have shown the ability to improve drug delivery, increase efficacy, reduce toxicity, and enhance the bioavailability of drugs. They can be engineered to specifically target parasites and deliver drugs directly to the intracellular amastigote form, which is often challenging to reach with conventional drug treatments. Nanoparticle-based vaccines and nanosensors also offer potential advancements in the field of parasitic disease control. While numerous established methodologies exist for nanoparticle synthesis, their applicability in biomedical contexts remains constrained by prevalent issues of cellular and environmental toxicity.[154] The utilization of plant-derived products or ethnobotanical remedies holds potential for parasite disease treatment. Nevertheless, a significant limitation of ethnobotanical treatments lies in their inefficacy, attributed to unequal drug distribution at the target site. To address this challenge, nanoparticles offer a promising solution, as evidenced by several studies employing diverse techniques and yielding encouraging results.[155−158] Nanoparticle-based therapeutics are now widely used by patients and have successfully entered the market. These products, offered by various global companies, demonstrate the current and future potential of nanoparticles in medicine. Notable nanoformulations include liposomes, pegylated biologics, gels, emulsions, nanocrystals, and metallic nanoparticles. The global distribution of nanopharmaceuticals is expected to expand in the future. Compared to conventional medications, nanopharmaceuticals have a higher added value. The market for nanoparticle-based tools in parasitic disease treatment is substantial, driven by the increasing number of parasitic infections, the demand for more effective therapies, and the benefits of nanotechnology. In 2022, the parasitic disease treatment market was valued at USD 1.7 billion. Factors such as rising disposable incomes, population growth, and parasite prevalence are fueling the market growth. According to reports by Grand View Research, Inc., the market is projected to grow at a 5% CAGR and reach USD 2.6 billion by 2031 (source: https://www.expertmarketresearch.com/reports/parasitic-diseases-therapeutics-market). With ongoing research advancements, the market for nanoparticle-based tools in parasitic disease treatment is expected to expand significantly in the coming years. Before nanoparticles can be considered to be a commercially viable alternative to current treatment methods, several challenges must be effectively addressed. Further research is needed to optimize nanoparticle design, improve targeting strategies, and evaluate long-term safety and efficacy. Clinical trials and animal studies will play crucial roles in assessing the effectiveness of nanoparticle-based therapies.

Despite these challenges, the future of nanoparticle-based therapies for parasitic diseases looks promising. Continued advancements in nanotechnology, along with collaborative efforts among researchers, clinicians, and policymakers, will contribute to the development of safer and more effective treatments and diagnostic methods for parasitic infections. These innovations have the potential to make a significant impact on global health by improving patient outcomes and reducing the burden of parasitic diseases.

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Notes

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