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Review Article

Revolutionizing Tropical Disease Treatment: The Future of Conjugating Nanomaterials with Drugs

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Abstract

Neglected tropical diseases (NTDs) encompass a range of infectious diseases prevalent in tropical and subtropical regions, often overlooked despite their substantial health impacts and high mortality rates. Current treatments for NTDs frequently cause severe side effects due to the pharmacokinetic properties of drugs, which can be harmful even at therapeutic doses. There is a pressing need for innovative diagnostic and therapeutic strategies to mitigate these side effects and improve diagnostic capabilities, as many NTDs lack adequate diagnostic tools. Nanotechnology presents a promising avenue to address these challenges. Nanomaterials possess unique characteristics that enable dual functionality in disease diagnosis and treatment. When conjugated with drugs, nanomaterials can enhance the efficacy of treatments for parasitic diseases while reducing the toxicity associated with conventional medications. Nanomaterial-drug conjugates also serve as efficient carriers, improving drug delivery systems for existing NTD treatments and minimizing adverse effects. This study explores recent advancements in conjugating nanomaterials with drugs for the treatment and diagnosis of NTDs. A comprehensive review of primary database sources reveals significant gaps in current research, underscoring the vast potential for developing novel therapeutic and diagnostic tools. These innovations could revolutionize the management of NTDs, ushering in more effective and safer treatment modalities in the future.

Introduction

Technological advancements have spurred the rapid development of nanotechnology, expanding its applications across diverse scientific fields.[1,2] Biomedical sciences, in particular, have benefited from nanotechnology, leveraging its potential for pathogen detection and disease diagnosis.[3] Neglected Tropical Diseases (NTDs) have garnered global attention due to their severe symptoms and health implications, necessitating innovative treatment approaches. Nanomaterial-based theranostic tools have emerged as promising solutions for diagnosing and treating NTDs.[4,5]

Nanomaterials offer significant advantages in diagnosing and treating tropical diseases due to their unique physical and chemical properties.[6,7] Their small size, typically ranging from one to 100 nanometers, allows them to interact effectively at the molecular and cellular levels, which is crucial for targeting pathogens and delivering therapeutic agents precisely where needed.[8–10] This precision is particularly advantageous for NTDs, which often require targeted and efficient treatment strategies.[11–15]

One key feature that makes nanomaterials suitable for biomedical applications is their large surface area-to-volume ratio.[15,16] This property enhances their capacity to carry and deliver therapeutic substances such as drugs, peptides, or genetic materials.[17–20] Nanomaterials can encapsulate these substances, protecting them from degradation in the body and enabling controlled release over time, which can improve treatment efficacy and reduce side effects.[13,14]

Moreover, nanomaterials can be engineered to possess specific chemical compositions and surface functionalities, allowing for targeted delivery to diseased tissues or cells while minimizing impact on healthy tissues.[21–23] This targeted delivery reduces systemic toxicity and enhances the overall safety profile of treatments, addressing a significant challenge posed by traditional therapies

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for NTDs.[24,25]

In diagnostics, nanomaterials can be designed to detect specific biomarkers or pathogens with high sensitivity and specificity. Functionalized nanoparticles can selectively bind to disease-specific molecules, facilitating early detection and accurate diagnosis even at low concentrations.[26–28] This capability is crucial for improving the timeliness of treatment initiation and monitoring disease progression.[29,30]

Nanoparticles (NPs) constructed from biodegradable materials such as natural and synthetic polymers and lipids are particularly valuable in biomedicine.[31,32] Their high biocompatibility allows them to carry hydrophilic and lipophilic drugs, enhancing the therapeutic delivery systems used for NTD treatments.[33–35]

According to the World Health Organization (WHO), NTDs encompass a group of 20 diverse conditions caused by various pathogens, including viruses, bacteria, parasites, fungi, and toxins. This group includes diseases such as Buruli ulcer, Chagas disease, dengue, chikungunya, human African trypanosomiasis, leishmaniasis, lymphatic filariasis, and many others.[18,30]

Studies report that NTDs have a significant prevalence, especially in tropical regions, affecting almost two billion people. Approximately one-sixth of the world's population is impacted by one or more NTDs.[30–32] The pathogens involved in NCDs can be multidrug-resistant, and their rapid adaptation to new antibiotics poses a significant challenge for scientists and medical professionals.[36–39] Furthermore, the medications available for treating Non-Cholera Diarrhea (NCDs) generally cause several side effects, leading to severe discomfort in patients. Various therapeutic approaches have been developed for treating Trypanosoma brucei (T. brucei), Trypanosoma cruzi (T. cruzi), and Leishmania dovani.[40–42] In addition to sleeping sickness treatment,[43] there are notable gaps that can be explored through the development of new therapeutic techniques.

Another important NCD is Zika, and studies have been conducted to discover new substances for its treatment. Research has identified dehydroandrographolide derivatives with hindered C19 ether as potent anti-ZIKV agents with inhibitory activity against ZIKV NS5 MTase; however, this substance has not yet been conjugated to nanomaterials.[44–46]

Thus, nanomaterials conjugated with drugs represent alternative tools for developing new therapeutic strategies. Given that the process of developing new medicines is time-consuming and expensive, theranostic tools based on conjugates of nanomaterials and peptides become attractive options for addressing NTDs.[17,47]

Nanomaterials conjugated with drugs hold immense promise in tackling the unique challenges posed by NTDs.[48,49] These diseases, prevalent in impoverished regions with limited healthcare infrastructure, often lack effective treatments and diagnostic tools. Nanotechnology offers a transformative approach, enabling targeted drug delivery and enhanced therapeutic efficacy. By encapsulating drugs within nanomaterials, these complexes can navigate biological barriers, such as the blood-brain barrier in diseases like sleeping sickness, ensuring precise delivery to affected tissues while minimizing systemic toxicity. This targeted approach improves treatment outcomes and reduces the overall burden on healthcare systems by optimizing drug efficacy and minimizing the need for repeated dosing.[50]

Furthermore, integrating nanomaterials with drugs facilitates the development of multifunctional theranostic platforms. These platforms combine diagnostic capabilities with therapeutic interventions, enabling early disease detection and tailored treatment strategies. Nanoparticles functionalized with targeting ligands can specifically recognize disease biomarkers, allowing for early-stage diagnosis before clinical symptoms manifest. Simultaneously, these nanocarriers deliver therapeutic agents directly to disease sites, enhancing treatment precision and efficacy. This dual functionality accelerates disease management and supports personalized medicine approaches, paving the way for more efficient and patient-centric healthcare solutions in resource-limited settings affected by NTDs.[51,52]

This study explores cutting-edge advancements in nanoparticle-peptide conjugates for diagnosing and treating NTDs. It reviews primary databases to identify gaps in current knowledge and highlight opportunities for developing novel therapeutic strategies. Nanomaterial-conjugated peptides represent a promising avenue for overcoming the limitations of traditional treatments, offering hope for improved outcomes in managing NTDs.

Nanomaterials to neglected tropical diseases

According to the WHO, NTDs comprise a group of 20 diverse conditions caused by various pathogens, including viruses, bacteria, parasites, fungi, and toxins (WHO, 6.15). These diseases are recognized as indicators of poor socioeconomic conditions and manifestations of poverty within vulnerable and marginalized communities. They can lead to devastating socioeconomic consequences, adversely affecting health and quality of life, particularly for women and children.[53,54]

The epidemiology of NTDs is complex and often linked to environmental factors. Many of these diseases are vector-borne, involve animal reservoirs, and have intricate life cycles, posing significant challenges for public health control efforts.[54]

NTDs cause a wide range of health effects, some reversible and others irreversible, often leading to permanent disabilities, disfigurement, and malnutrition.[55] In 2013, these diseases were responsible for an estimated 152,000 deaths and contributed to 48 million disability-adjusted life years globally. The socioeconomic impacts include reduced work capacity, impaired child development, decreased school attendance and learning, and substantial treatment costs.[56]

To combat NTDs, the WHO estimates that over 1.7 billion people worldwide require annual prevention and treatment interventions for at least one of these diseases. A new strategic plan for NTDs, covering 2021–2030, aims to scale up essential interventions through public health approaches, including preventive chemotherapy, case management, vector control, veterinary public health, and improvements in water, sanitation, and hygiene (6). The global targets for 2030 include a 90% reduction in the number of people needing NTD treatment, a 75% decrease in NTD-related disability-adjusted life years, the elimination of at least one NTD in 100 countries, and the eradication of dracunculiasis and yaws.[53,57]

Early diagnosis and treatment are crucial to achieving these ambitious goals and effectively controlling and preventing the spread of NTDs. The following sections will address these efforts in more detail.

Traditional treatments often need replacement due to toxicity, and ongoing studies are exploring ways to optimize these therapies, as shown in Figure 1. (I) For *T. cruzi*, traditional treatments include Benznidazole and Nifurtimox. Researchers are investigating optimized treatments, including Lychnopholide (LYC) nanocapsules, sulfonamide TcCA inhibitor nanoemulsions, and a nanoformulation of a nanoconjugate with gold nanoparticles (AuNPs) and 3-n-propyl(2-amino-4-methyl)pyridinium chloride (SiAMPy+ Cl^-), an organic-inorganic hybrid silsesquioxane (AuNPs-$SiAMPy^+$)). For

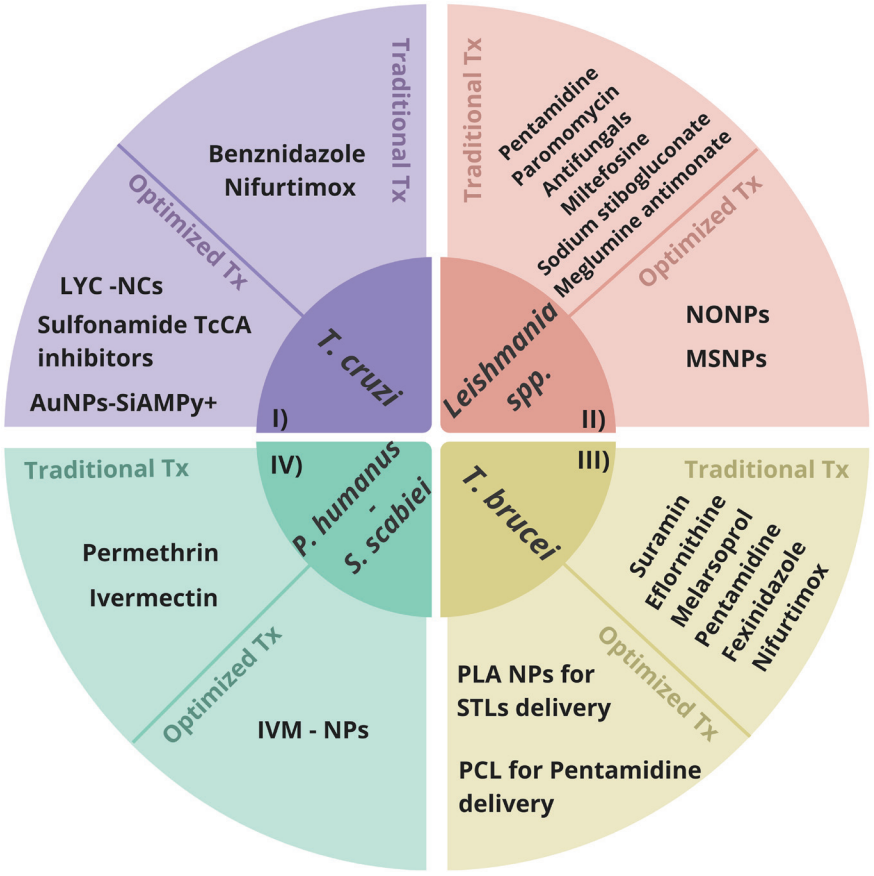

Fig. 1. Traditional and optimized treatments for diseases caused by *Trypanosoma cruzi*, *Leishmania* spp., *Trypanosoma brucei*, *Pediculus humanus*, and *Sarcoptes scabiei*. MSNP, Multi-Subunit Nuclease Proteins; NONP, Non-Nucleoside Organic Compounds; PLA NP, Poly(lactic acid) Nanoparticles.

leishmaniasis, traditional treatments include pentavalent antimonial salts, such as sodium stibogluconate and meglumine antimonate. However, the emergence of drug-resistant parasites has prompted the exploration of alternatives, such as pentamidine, paromomycin (antimicrobials), amphotericin B, fluconazole, ketoconazole (antifungals), and miltefosine (antitumor).

However, these alternatives also exhibit toxicity. As a result, researchers are developing chitosan nanoparticles conjugated with a nitric oxide (NO) donor, S-nitrosothiol (CSNPs), and myrrh silver nanoparticles (MSNPs) to optimize treatment. (II) Human African Trypanosomiasis (HAT), caused by T. brucei, is subdivided into T. brucei gambiense and T. brucei rhodesiense. Six medications, including Pentamidine, Eflornithine, Nifurtimox, and Fexinidazole, are used for gambiense-HAT, while Suramin and Melarsoprol are used for rhodesiense-HAT. New research is exploring the use of polymeric nanoparticle systems, such as polylactic acid nanoparticles (PLA-NPs), to act as delivery vehicles for sesquiterpene lactones (STLs). Another study involving Pentamidine aimed to assess whether polycaprolactone (PCL) NPs and phosphatidylcholine liposomes are effective *in vitro*. (III) Ectoparasites, such as Pediculus humanus and Sarcoptes scabiei, are traditionally treated with topical applications of permethrin or oral administration of ivermectin. However, due to the development of drug resistance in these ectoparasites, new treatments are being explored, such as ivermectin-loaded nanoparticles (IVM-NPs) for topical use.

Parasitics

Protozoa

Chagas disease

Chagas disease is caused by the flagellated protozoan Trypanosoma cruzi. After infection, immunocompetent patients enter the acute phase, characterized by high parasitemia and mild febrile symptoms. After two to three months, the disease transitions to the chronic phase, where serology is positive, but parasitemia becomes microscopically undetectable. The chronic phase persists throughout life in the absence of effective treatment. Although many individuals remain asymptomatic, 20% develop cardiomyopathy or mega syndromes of the digestive tract.[58,59]

Accurate diagnosis of acute and congenital Chagas disease requires the direct visualization of trypomastigotes in the blood, primarily by microscopy, and occasionally in other body fluids, with sensitivity ranging from 34% to 85%.

In congenital infection, a diagnosis can be made after eight months using serology. Concentration methods, such as microhematocrit and the Strout method, significantly increase diagnostic efficacy, achieving rates greater than 95%.[59,60] The chronic phase of the disease is characterized by low and intermittent parasitemia. Therefore, diagnosis in this phase relies on serological tests that detect IgG antibodies against *T. cruzi*. Indirect fluorescence, indirect hemagglutination, and ELISA are the most widely used se-

rological methods for accurately diagnosing Chagas disease.[59,60]

Point-of-care tests (POCs) are invaluable for monitoring Chagas disease serodiagnosis in resource-limited areas, where marginalized populations often have restricted access to healthcare. A study from New York described the development of a lateral flow assay (LFA) using 150 nm gold nanoparticles (AuNPs) conjugated to synthetic recombinant *T. cruzi antigens*, which encompass antigens present in different morphological stages of the parasite. This assay eliminates the need for multiple serological tests. The LFA demonstrated a sensitivity of 83% and a specificity of 95%, providing analytical performance comparable to conventional serological assays, with minimal sample processing and a response time of just 15 m. Furthermore, the AuNPs-LFA platform represents a significant reduction in both cost and time.[61]

The new Chagas urine nanoparticle test, known as Chunap, was developed for diagnosis via urine and tested in cases of congenital infection and HIV co-infection.[58,62] A novel nanotechnology utilizes nanoporous particles containing trypan blue in their inner core to concentrate and preserve antigens in urine. Chunap has shown excellent agreement with standard diagnostic tests in the direct diagnosis of congenital Chagas disease. The nanoporous structure of the particles enables dimensional sieving, allowing proteins to penetrate the interior based on their molecular weight and shape.

The trypan blue within the particles captures proteins with extremely high affinity within minutes.[58,62] These nanoporous particles were successfully used to sequester, concentrate, and preserve *T. cruzi* antigens in urine.[58,62] Chunap demonstrated a sensitivity of 91.3% and a specificity of 96.5% for congenital samples, with sensitivity levels comparable to qPCR,[47,63] making it a promising tool for improving the Chagas diagnostic algorithm in clinical settings.

Treatment with antitrypanosomal medications is essential for all forms of Chagas disease. Only two drugs, Benznidazole *and Nifurtimox, are licensed for treatment.[59,64,65] However, the use of Nifurtimox is limited due to significant side effects, including renal and hepatic failure, as well as adverse neurological and gastrointestinal effects. Benznidazole's most commonly reported side effect is hypersensitivity. Additionally, the development of drug resistance poses a significant challenge to the successful treatment of Chagas disease.[66,67]

In this context, a research group from Brazil aimed to increase the bioavailability of a new antitrypanosomal agent, LYC, a lipophilic sesquiterpene lactone through nanoencapsulation.[68,69] The antitrypanosomal efficacy of LYC *in vivo* had already been demonstrated by the same group.[69,70] The study involved the development of polymeric nanocapsules containing LYC and used high-performance liquid chromatography with ultraviolet detection to quantify LYC kinetics in mouse plasma samples.

Encapsulation of LYC was achieved with a high payload, and the nanocapsules remained stable after storage, with sizes suitable for intravenous administration. The formulation effectively controlled the release of LYC into plasma and significantly increased body exposure, while protecting LYC from degradation in mouse plasma.[68]

Thinking about inhibitors of sulfonamide carbonic anhydrase (CA, EC 4.2.1.1), which target the α-class enzyme of *T. cruzi,* another study reported that *T. cruzi* encodes an α-CA enzyme called TcCA. Although many sulfonamides inhibited this enzyme *in vitro*, they did not inhibit parasite growth *in vivo*, likely due to the poor permeability of sulfonamides across the protozoan's biological membranes. To address this, the research group formulated sulfonamides, which are highly effective as TcCA inhibitors, in nanoemulsions (NEs) to increase their bioavailability and penetrability through membranes.

Sulfonamide TcCA inhibitors formulated as NEs in clove oil have been reported to inhibit the growth of *T. cruzi ex vivo*, showing potential as a new class of antitrypanosomal drugs. These effects are probably due to the enzyme inhibitor's increased permeation through the NE formulation, which interferes with the pathogen's life cycle by inhibiting pH regulation or carboxylation reactions.[71]

In 2022, the Lima group conducted a study involving AuNPs for both diagnosis and treatment. Considering the promising characteristics of silsesquioxane polyelectrolytes for the synthesis of nanomaterials and the remarkable properties of AuNPs, they formulated a nanoconjugate with AuNPs, 3-n-propyl(2-amino-4-methyl)pyridinium chloride ($SiAMPy^+$ Cl^-), and organic-inorganic hybrid silsesquioxane (AuNPs-$SiAMPy^+$).

There was no toxicity of AuNPs-$SiAMPy^+$ in human white and red blood cells, highlighting the potential of these nanoconjugates for future studies investigating their therapeutic and biomedical properties. These nanoconjugates have also shown promise in constructing electrochemical biosensor devices capable of detecting antibodies related to Chagas disease in serum samples.[72]

Nanomaterials conjugated with drugs represent a critical advancement in addressing the diagnostic and therapeutic challenges posed by Chagas disease. This neglected tropical disease, caused by Trypanosoma cruzi, manifests in varying clinical presentations, from acute to chronic phases, and often leads to severe cardiac or gastrointestinal complications. Current diagnostic methods rely heavily on serological tests, which may lack sensitivity or require complex procedures, particularly in resource-limited settings. Nanotechnology offers innovative solutions, such as the development of LFAs using gold nanoparticles (AuNPs) conjugated with T. cruzi antigens. These LFAs provide rapid and reliable results comparable to traditional serological assays but with minimal sample processing and shorter incubation times, making them suitable for point-of-care testing in endemic regions.

Additionally, nanomaterials facilitate novel therapeutic approaches for Chagas disease treatment. For example, nanocapsules containing LYC, a potent antitrypanosomal agent, have been developed to enhance drug stability and efficacy. These nanocapsules ensure sustained drug release and improved bioavailability, potentially overcoming the limitations associated with conventional treatments like Benznidazole and Nifurtimox, which often induce severe side effects and face challenges of drug resistance. Furthermore, NEs formulated with sulfonamide carbonic anhydrase inhibitors have shown promising results by enhancing drug permeability across T. cruzi membranes, effectively inhibiting parasite growth *in vitro*.

In summary, the integration of nanomaterials with drugs is revolutionizing Chagas disease diagnosis through innovative diagnostic tools and improving therapeutic outcomes by enhancing drug delivery and efficacy. These advancements underscore the transformative potential of nanotechnology in combating neglected tropical diseases, offering new avenues for more effective and targeted management strategies in clinical practice.

Leishmaniasis

Leishmaniasis is a group of infectious parasitic diseases caused by protozoa from various species of Leishmania. It is primarily found in three clinical forms: visceral, cutaneous, and mucocutaneous, which differ in their immunopathologies and mortality rates.[73,74]

In diagnosing leishmaniasis, methods must effectively analyze the clinical form of the disease, identify asymptomatic or co-infected cases, and differentiate between individuals infected by

other parasitic diseases.[35,75,76] Conventional diagnostic methods for leishmaniasis include parasitological, molecular, and immunological approaches. Parasitological methods involve detecting Leishmania through direct microscopy, histopathology, and parasite culture. Several molecular techniques, such as polymerase chain reaction (PCR), offer high sensitivity and specificity. Immunological tests such as direct agglutination, ELISA, and immunochromatographic assays are also widely used for the diagnosis of leishmaniasis.[77,78]

Similar to diagnostic methods for *T. cruzi*, new tests for detecting leishmaniasis can be based on the characteristics of POCs. Two distinct research groups have explored the use of AuNPs.[79,80] The first group utilized AuNPs as nanocarriers, conjugated with casein for amperometric detection of *L. infantum* on screen-printed carbon electrodes. The conjugation interacts with *Leishmania parasites* by leveraging the specificity of the interaction between casein and GP63 proteins.[81] The second group conjugated AuNPs with polyethylene glycol, immobilizing a thiolated sequence of the *Leishmania genome* on gold electrodes for hybridization with cDNA. This approach led to the development of an ultrasensitive DNA-based biosensor for detecting *Leishmania* spp.[80]

Continuing the development of genosensors, a research group conducted two experiments. In the first, they developed a one-step Loop-Mediated Isothermal Amplification Assay (LAMP) using dual indicators to detect Leishmania DNA in the buffy coat of asymptomatic HIV patients. The technique employed fluorescence and colorimetric precipitation, with the AuNP probe serving as a second indicator in a closed-tube SYBR Safe-LAMP assay. This simplified and cost-effective approach allowed rapid visual interpretation in minutes, achieving high sensitivity (94.1%) and specificity (97.1%).[82] In the second experiment, a similar one-step LAMP reaction combined SYBR Safe with a gold nanoparticle probe to detect and semi-quantify Leishmania in buffy coats. Notably, this technique was implemented on paper, with sensitivity and specificity of 95.5% and 100%, respectively.[83]

Historically, treatment for leishmaniasis has relied on the pentavalent antimonial salts sodium stibogluconate and meglumine antimonate for visceral, cutaneous, and mucocutaneous forms. These are the primary antileishmanial compounds used. However, the emergence of drug-resistant parasites has led to the exploration of alternatives, such as pentamidine, paromomycin (antimicrobials), amphotericin B, fluconazole, ketoconazole (antifungals), and miltefosine (an antitumor agent). These alternatives are currently the only available medications but are associated with limitations, including side effects, toxicity, drug resistance, and prolonged administration requirements.[73,78] Given these challenges, exploring new therapeutic strategies and alternatives is essential to address treatment gaps globally.

Brazilian researchers have identified chitosan nanoparticles that release NO, which could be used to treat cutaneous leishmaniasis. These chitosan NPs were conjugated with an NO donor, CSNPs. Encapsulation of the NO donor in CSNPs prevents degradation of the molecule and allows for controlled NO release. The study demonstrated the potential of NO nanoparticles for effective *dose-dependent inactivation* of *L. amazonenses in vitro*.[84]

Ongoing research into the antileishmanial effects of silver nanoparticles includes a study from Saudi Arabia where researchers synthesized MSNPs and evaluated their efficacy in inhibiting the proliferation of promastigotes *in vitro* and in treating lesions in BALB/c mice *in vivo*. MSNPs significantly reduced the viability of Leishmania promastigotes and, when applied topically for 21 days, contributed to the healing of skin lesions.[85]

Nanomaterials conjugated with drugs are crucial in advancing the diagnosis and treatment of leishmaniasis. Current diagnostic methods, including parasitological, molecular, and immunological approaches, have limitations in sensitivity and specificity. Nanotechnology offers innovative solutions, such as developing biosensors with AuNPs for sensitive detection of Leishmania. Researchers have utilized AuNPs conjugated with casein and polyethylene glycol for amperometric and DNA-based biosensors, demonstrating enhanced specificity and rapid detection capabilities suitable for point-of-care settings. These advancements improve diagnostic accuracy and facilitate early detection in asymptomatic cases, which is critical for effective disease management and control.

In addition to diagnostics, nanomaterials hold promise for overcoming therapeutic challenges in leishmaniasis treatment. Conventional treatments heavily rely on antimonial salts and other compounds that are prone to drug resistance and adverse effects. Novel approaches include chitosan nanoparticles loaded with nitric oxide donors, which exhibit potent *in vitro* activity against Leishmania while offering controlled, sustained drug release profiles. Similarly, silver nanoparticles synthesized from myrrh have shown efficacy in inhibiting parasite proliferation and promoting wound healing in animal models. These nanotechnological innovations not only enhance the effectiveness of current treatments but also pave the way for developing alternative therapies with improved safety profiles and shorter treatment durations, addressing critical gaps in global leishmaniasis management.

HAT/sleeping sickness

HAT, also known as Sleeping Sickness, is caused by the protozoan parasite *Trypanosoma brucei*, which is subdivided into *T. brucei gambiense* and *T. brucei rhodesiense.* Both subspecies are transmitted by infected tsetse flies, found in sub-Saharan Africa, with only a few species responsible for transmitting the disease.[86,87] After injection, trypanosomes initially multiply in subcutaneous, blood, and lymphatic tissues, constituting the hemolymphatic or first stage, which presents non-specific symptoms. Subsequently, the parasites overcome the blood-brain barrier, reaching the central nervous system and causing the meningoencephalic or second stage of the disease.[86,88] Given the biphasic nature of HAT pathogenesis, treatment depends on the clinical evaluation of patients and whether the parasites have crossed the blood-brain barrier, which is determined through diagnosis.

The diagnosis of HAT involves the observation of parasites in peripheral blood smears; however, this often requires challenging serological methods. The Card Agglutination Test for Trypanosomiasis (CATT), widely used in high-prevalence regions, is problematic in low-prevalence areas due to a high rate of false positive results. Advanced molecular techniques, such as PCR, have been tested but face significant technical challenges and are not practical under field conditions, similar to CATT.[86,88] Despite our efforts, we could not identify literature on diagnostics using nanomaterials.

Current pharmacological therapy for HAT is based on drugs developed many years ago, known for their aggravated toxicity in advanced stages of the disease. Early treatment improves the prospects for a cure, requiring continuous evaluation for up to 24 months due to the possibility of viable parasites persisting after treatment. In the second stage, medications that can cross the blood-brain barrier are necessary.[88,89]

Antitrypanosomal drugs are donated to the WHO by manufacturers and distributed free of charge to endemic countries, following the new WHO guidelines for gambiense HAT issued in 2019.

For gambiense HAT, six medications can be used, including Pentamidine (intramuscular, generally well tolerated), Eflornithine (intravenous), Nifurtimox (oral), and Fexinidazole (oral). In contrast, for rhodesiense HAT, Suramin (intravenous) is used in the first stage but can cause adverse effects such as nephrotoxicity and allergic reactions. In the second stage, Melarsoprol (intravenous), an arsenic derivative, presents many adverse effects, the most severe being reactive encephalopathy, with a fatality rate of 3–10%.[89,90]

New research involving nanomaterials is being conducted to address the problems of existing antitrypanosomal drugs. Drug-loaded NPs often exhibit superior properties compared to unencapsulated drugs, such as improved pharmacokinetics and prolonged, controlled drug release. In this context, a polymeric nanoparticle system composed of PLA-NPs is being developed to serve as vehicles for STLs, demonstrating the antitrypanosomal efficacy of the resulting formulation.[91]

Another slightly more advanced study using Pentamidine aimed to analyze *in vitro* whether PCL NPs and phosphatidylcholine liposomes improved drug transport across the blood-brain barrier and explored the feasibility of reducing pentamidine toxicity. Researchers observed that liposomal nanocarriers performed better, transporting a higher percentage of the pentamidine dose than PCL nanoparticles and unencapsulated drug delivery.[92]

Nanomaterials conjugated with drugs are increasingly recognized for their potential to address the diagnostic and therapeutic challenges associated with HAT, commonly known as Sleeping Sickness. Diagnosis of HAT traditionally relies on parasitological methods like peripheral blood smears, which can be insensitive and impractical in low-prevalence settings. Nanotechnology offers a promising avenue to enhance diagnostic accuracy through innovative approaches such as biosensors and nanoparticle-based assays, yet specific applications in HAT diagnostics remain underexplored.

In therapeutics, existing treatments for HAT suffer from severe toxicity and limited efficacy, particularly in the advanced stages of the disease, where parasites breach the blood-brain barrier. Nanoparticle formulations, such as PLA-NPs loaded with STLs, demonstrate the potential to overcome these challenges. These nanoformulations improve drug pharmacokinetics, enable controlled release, and enhance drug delivery efficiency to target sites, including the central nervous system. Furthermore, nanocarriers like phosphatidylcholine liposomes show promise in enhancing the transport of medications across the blood-brain barrier, thereby reducing toxicity and improving therapeutic outcomes. These advancements underscore the critical role of nanomaterials in advancing treatment options for HAT, offering hope for improved patient outcomes and disease management strategies in endemic regions.

Ectoparasites

Ectoparasites are pathogens that typically infect only the superficial layers of the skin. Within this group, epidermal parasitic skin diseases stand out as a family of diseases of significant public health importance. These parasitic diseases are characterized by their restriction to the superficial layers of the skin during parasite-host interactions. They are prevalent in resource-limited settings and are associated with significant morbidity.[93]

Lice and scabies are caused by *Pediculus humanus and Sarcoptes scabiei*, respectively, and have a global distribution. In contrast, cutaneous larva migrans and tungiasis, caused by *Larva migrans* and *Tunga penetrans*, are more common in hot climates. Reliable data on the epidemiology, immunology, therapy, and biology of epidermal parasitic skin diseases are still limited. Although the general prevalence of ectoparasitosis in the population is low, it can be significantly higher in vulnerable population groups.[93,94]

Each ectoparasitosis has its own specific treatment considerations. However, as the typical symptoms of these diseases—primarily related to scabies and lice—are directly associated with ectoparasite infestations, the main objective of treatment is to eliminate the organisms. The first-choice treatment is the topical application of permethrin or the oral administration of ivermectin. Other second-line alternatives include malathion and topical ivermectin.[95–97]

IVM has been associated with severe side effects at high doses, especially when accidentally ingested. To minimize systemic side effects, topical treatment of dermatoses has proven to be a favorable option. The topical application of IVM is practical and has comparable costs in treating infections such as scabies or lice.[98,99]

To address this issue, attempts have been made to develop and optimize IVM-NPs. IVM-NP formulations have been successfully prepared, and release studies indicate slow and sustained release patterns, providing an advantage for topical application. The drug's *in vitro* skin penetration tests revealed that IVM-NPs penetrated the skin more quickly than the ivermectin suspension, opening possibilities for the topical application of IVM-loaded NPs.[98,99]

Nanomaterials loaded with drugs play a crucial role in addressing the treatment challenges posed by epidermal parasitic skin diseases, such as scabies and lice. These diseases are prevalent in resource-limited regions and can cause significant morbidity. Traditional treatments, often involving permethrin or oral ivermectin, aim to eradicate ectoparasites but may be associated with systemic side effects, particularly with high doses of oral medications like ivermectin. The development of IVM-NPs represents a promising advancement. These nanoparticles exhibit controlled and sustained release properties, enhancing drug delivery efficiency and minimizing systemic exposure, thus potentially reducing the adverse effects of conventional treatments. Moreover, IVM-NPs have enhanced skin penetration capabilities compared to traditional formulations, suggesting their suitability for topical application, which is advantageous in effectively managing skin infections like scabies and lice.

In addition to improving drug delivery and reducing systemic side effects, nanotechnology offers novel opportunities for enhancing the efficacy of treatments against epidermal parasitic skin diseases. Researchers are exploring new avenues to optimize therapeutic outcomes by encapsulating drugs like ivermectin within nanoparticles. These advancements are particularly significant for vulnerable populations where ectoparasitosis is prevalent, offering safer and more effective treatment options that could improve public health outcomes. As research continues to refine nanoparticle formulations and evaluate their clinical efficacy, integrating nanotechnology into dermatological treatments holds promise for transforming the management of epidermal parasitic skin diseases, ultimately benefiting affected individuals worldwide.

Neglected tropical diseases require diagnostic tests that can operate under various local conditions and detect infections at different stages. Figure 2 shows the methodology used with nanomaterials conjugated with drugs.

The development of new devices is always necessary. (a) *T. cruzi* is primarily diagnosed through the visualization of the parasite using techniques such as blood smear, microhematocrit, the Strout method, and indirect immunofluorescence, as well as serological

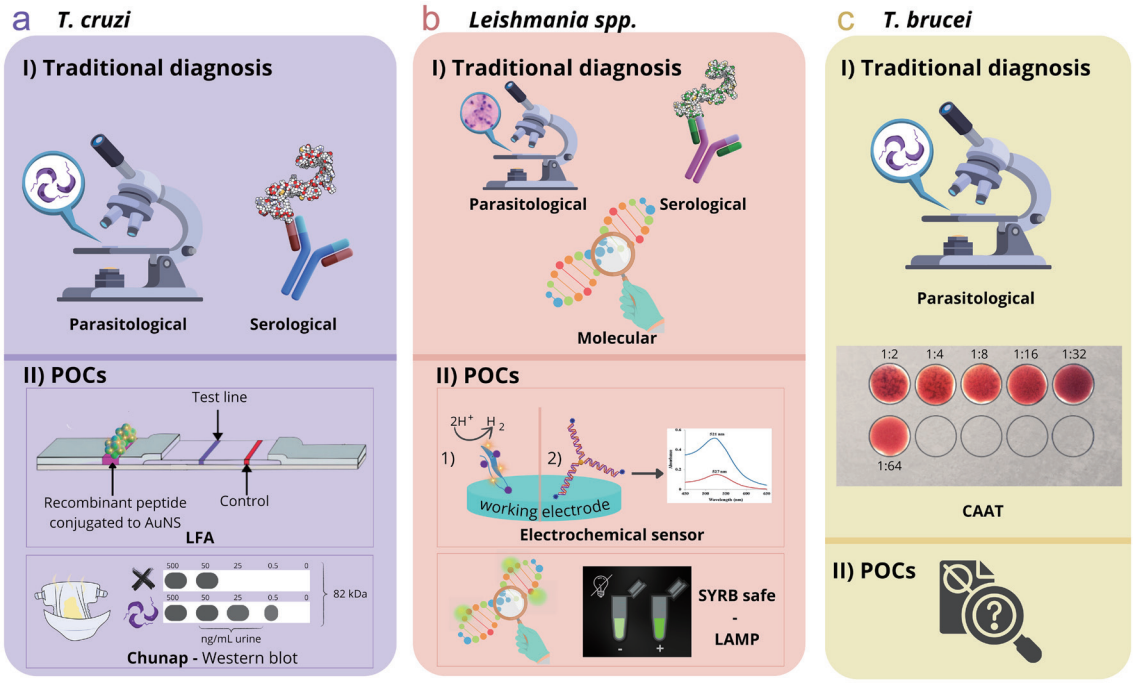

Fig. 2. Traditional Diagnosis and New POCs for Diseases Caused by *Trypanosoma cruzi, Leishmania* spp., and *Trypanosoma brucei*. CAAT, Cellular Automated Analysis Technique; LAMP, Loop-mediated Isothermal Amplification; LFA, Lymphocyte Function-Associated Antigen; POC, Point-of-care tests.

methods like ELISA. A new immunochromatographic test that incorporates antigens from the different morphological stages of T. cruzi, conjugated with AuNPs, is capable of detecting antibodies.

In the search for a less invasive test capable of detecting the disease in its congenital form, the Chunap was developed (Fig. 2). This technology uses nanoporous particles containing trypan blue in the inner core to concentrate and preserve antigens in urine. (b) For leishmaniasis, conventional diagnostic methods include parasitological, molecular, and immunological approaches.

Regarding new POC methods, electrochemical biosensors are increasingly being used, as seen in Figure 2: (1) an immunosensor with screen-printed carbon electrodes, which uses AuNPs as nanocarriers for casein to identify the parasite in the sample through the GP63 protein; and (2) a genosensor conjugated with AuNPs and polyethylene glycol, where the thiolated sequence of the Leishmania genome was immobilized on the surface. Another development in genosensors is a one-step LAMP assay. This technique used fluorescence and colorimetric precipitation, with the AuNP probe acting as a second indicator in a closed-tube SYBR Safe-LAMP assay. (c) Diagnostic methods for *T. brucei* require more attention. (I) The diagnosis of HAT involves observing parasites and the CATT. (II) Despite our efforts, we could not identify any literature on the diagnosis of HAT using nanomaterials.

Future directions

The integration of nanomaterials with drugs for theranostic applications targeting neglected tropical diseases (NTDs) represents an exciting and transformative direction in global health innovation. Given the significant challenges posed by NTDs, including limited treatment options, inadequate diagnostic tools, and the adverse effects of conventional drugs, there is an urgent need for novel strategies to address these gaps.

Nanotechnology offers a unique platform for advancing both diagnostic and therapeutic capabilities. The conjugation of nanomaterials with drugs has demonstrated the potential to enhance drug efficacy, minimize toxicity, and enable dual functionality for disease diagnosis and treatment. Future research should prioritize the design and optimization of nanomaterial-drug complexes tailored to specific NTDs, focusing on improving the pharmacokinetics and bioavailability of therapeutic agents. This approach could significantly enhance treatment outcomes, reduce side effects, and improve patient compliance.

Another critical area for future exploration is the development of targeted delivery systems using nanotechnology. By engineering nanomaterials with high specificity for NTD-causing pathogens or infected tissues, researchers can reduce off-target effects and maximize therapeutic efficiency. Furthermore, integrating nanotechnology with advanced diagnostic techniques could enable early and accurate detection of NTDs, addressing one of the most pressing challenges in managing these diseases.

Collaboration across disciplines will be essential to accelerate these advancements. Partnerships between researchers, clinicians, and industry stakeholders can facilitate the translation of nanotechnology-based innovations from the laboratory to real-world applications. Moreover, efforts to address the ethical, regulatory, and cost-related challenges associated with nanotechnology adoption in low-resource settings are crucial to ensure equitable access to these groundbreaking solutions.

As the field of nanotechnology continues to evolve, it holds immense promise for revolutionizing the management of NTDs. The development of multifunctional nanomaterials for theranostic applications could significantly impact global health by providing more effective, safer, and sustainable solutions for these historically neglected diseases.

Conclusions

Integrating nanomaterials with drugs for theranostic applications targeting NTDs represents a pivotal and innovative approach. NTDs present significant global health challenges, often exacerbated by limited treatment options and adverse drug effects. This study highlights the diverse applications of nanoparticles and their conjugation with drugs, showcasing their potential to revolutionize therapeutic strategies. These advancements address the shortcomings of current medications by leveraging nanotechnology, offering enhanced therapeutic efficacy and reduced treatment-related complications. The development of nanomaterial-drug complexes not only improves treatment outcomes but also mitigates the toxicity associated with conventional drugs. This transformative approach marks a promising frontier in managing neglected tropical diseases and holds substantial potential for advancements in global public health. These findings underscore the critical role of nanomaterials in advancing therapeutic methodologies, paving the way for the development of novel theranostic compounds poised to significantly improve patient outcomes and quality of life. As research in this field continues to evolve, nanotechnology stands at the forefront of innovation, offering hope for more effective and sustainable solutions in combating neglected tropical diseases worldwide.

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Conflict of interest

There are no conflicts to declare.

Author contributions

Conceptualization (EAA, AVB, HFP, MVdS, ACAS), experimental design (EAA, AVB, HFP, MVdS, ACAS), visualization (EAA, AVB, HFP, MVdS, ACAS), analyses of results (EAA, AVB, HFP), writing – original draft (EAA, AVB, HFP, MVdS, ACAS), review & editing (EAA, AVB, HFP, MVdS, ACAS), funding acquisition (MVdS, ACAS), supervision (MVdS, ACAS).

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