Nanoparticles: New agents toward treatment of leishmaniasis

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Leishmaniasis is a widespread disease that causes 20,000 to 30,000 deaths annually, making it a major health problem in endemic areas. Because of low-performance medications, drug delivery poses a great challenge for better treatment of leishmaniasis. The present study's purpose was to review the application of nanoparticles as a new method in leishmaniasis treatment. To identify all relevant literature, we searched Web of Sciences, Scopus, PubMed, NCBI, Scielo, and Google Scholar, and profiled studies published between 1986 and 2019. In the present study, we tried to identify different research efforts in different conditions that examined the influence of various nanoparticles on different forms of leishmaniasis. In this way, we could compare their results and obtain a reliable conclusion from the most recent studies on this subject. Our review's results indicate that incorporating nanoparticles with chemical drugs improves the quality, efficiency, and sustainability of drugs and reduces their costs. Finally, considering the use of nanoparticles in the destruction of parasites, their inhibitory effect (making drugs more effective and less harmful), and their utility in making effective vaccines to prevent and fight against parasites, further research on this issue is highly recommended.

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1. Introduction

Leishmaniasis is a parasitic disease epidemic in humans, carnivores, and rodents that spreads by sandflies bites. The disease can occur in three main types: visceral leishmaniasis (Kala-azar) (VL), which is the most serious type of the disease; cutaneous leishmaniasis (CL), which is the most common type; and ultimately, mucosal leishmaniasis (ML) (Alvar et al., 2012). Epidemiology of leishmaniasis as an endemic disease plays a major role in 88 countries, with 700,000 to 1 million new cases per year. These cases are mostly concentrated in several countries, with an estimated 50,000 to 90,000 new cases of VL and 600,000 to 1 million new cases of CL occurring worldwide annually (https://www.who.int/news-room/fact-sheets/detail/leishmaniasis, n.d.).

Leishmaniasis is one of the diseases that still need new countermeasures and controls. Unfortunately, there has not yet been a vaccine or a safe drug for inhibition of parasites and various forms of the disease, as well as a suitable chemical method to combat it (Mahmoudvand et al., 2017). Therefore, several efforts have been continuously made in this regard. New access control tools should help improve control activities in epidemic areas (Sharifi et al., 2015). Anthropology centers have an important impact on mortality, disease, and transmission. Although recognizing the disease as a public health problem, leishmaniasis remains one of the most endemic infections in the tropics. Its control also has barriers, such as the lack of safe and effective drugs, easy diagnosis, effective vaccines, and control devices, especially in sub-Saharan Africa (Rijal et al., 2019).

Nanoparticles (NPs) are made up of tens or hundreds of atoms or molecules of varying sizes and morphologies (e.g., amorphous, crystalline, spherical, and needle-shaped). NPs are a broad class of substances carrying particles that have at least one dimension less than a hundred nanometers (Mahmoudvand et al., 2014a). In current studies, small NPs are specifically considered in medicine. Nanoparticles not only have the ability to circulate widely all over the body, but they can also enter the cells, control the distribution of the drug in the body, and carry the drug specifically to the place of action. Therefore, these particles are considered as an effective and targeted solution to treatment (Ebrahimi et al., 2017). NPs used to transfer drugs include various types of structures with different sizes, shapes, and materials, each having certain drug loading capacity, liberation, cellular targeting, and stability. Treatment and diagnostic methods based on the use of NPs are expected to have important health benefits in the future; nevertheless, using NPs also poses important challenges, especially in terms of human health effects (Wolfram et al., 2015).

Traditional treatment of leishmaniasis is associated with the injection of low-tolerance and toxic drugs. Antimonial pentavalent antimoniate and sodium stibogluconate are a group of compounds used in the first-line systemic treatment of leishmaniasis (Mahmoudvand et al., 2014b). Pentamidine and amphotericin B are among the other drugs used in this category. The lack of potential use of drug resistance to these agents has been improved in patients in the last few years. In addition, no effective vaccine has been discovered for the prevention of leishmaniasis (Carvalho et al., 2019). Skin lesions in cutaneous leishmaniasis usually recover on their own and are sometimes left untreated. However, this can take months or even years, and wounds can leave ugly scars. Another potential concern is that some types of parasites in Latin America may spread lesions from the skin and create ulcerations in the mucous membranes of the mouth, nose, or throat (Sunyoto et al., 2019).

Mucosal leishmaniasis may be improved a few years after primary ulcers. Ensuring proper treatment of skin infections can help prevent mucosal leishmaniasis. Headaches, gastrointestinal disorders, and musculoskeletal pain are majority of the clinical effects of pentamidine and antimonials (Sundar et al., 2019). The duration of QTc with electrocardiogram as well as elevated liver enzymes and pancreas are the extra side effects of antimonial pentavalent. Patients receiving amphotericin B liposomes had moderate obstruction and erythema. Other side effects connected with these drugs include nausea, vomiting, diarrhea, increased blood sugar, and moderate levels in aminotransferases and creatinine. However, careful monitoring of the therapies for cutaneous leishmaniasis is required. It is noteworthy that anticoagulant medications are generally secured, and severe complications resulting from the discontinuation of medication are comparatively rare (Sousa-Batista et al., 2019; Kirchberger et al., 2019).

Due to the uncertainty regarding the therapeutic and adverse effects of anti-parasitic drugs, the application of nanoparticles in the medication, including parasitic diseases, has earned a special recognition in the last few years. Medical uses of nanoparticles have a deep history in the prescription of various diseases (Samuel Singh and Phillips Singh, 2019). Different nanoparticles are currently used to treat cancers and rheumatoid arthritis. In recent years, the use of gold and silver derivatives has been considered inappropriate for parasitic diseases (Kirchberger et al., 2019). Nonetheless, limited research has been done in this regard. The findings indicate that nanoparticles of silver, gold, chitosan, and a metal oxide on parasites such as Leishmania, malaria, and insect...
larvae have an inhibitory effect on growth. Numerous studies have evaluated the therapeutic impacts of nanoparticles, such as gold and silver, on the protozoan factors, especially leishmaniasis and malaria (Akhlagh et al., 2019).

Nanoparticles can be used singly or in combination with others to eliminate parasites. Thus, as they have a destructive and inhibitory effect, it is recommended to use nanoparticles for destroying parasites, making drugs more effective and less harmful, and producing useful vaccines for preventing and fighting parasites (van and Diro, 2019).

These new combinations, regardless of their production costs, can increase the chances of developing effective leishmaniasis treatments by reducing the adverse effects and the number of doses at a reasonable cost (Chavez-Fumagalli et al., 2015).

Newly produced medicines in pharmaceutical factories have had low solubility and many biological difficulties. An alternate and encouraging method to deal with this issue is to produce nanoparticles to solve these problems. Two of the benefits of this technology are its usability in most medications and its ease of use. Nanomedicine has emerged as a broad field that can help resolve the issues related to the unwanted effects of old drugs (Keyhani et al., 2019). This dissatisfaction originates from inadequate biodistribution of a drug, which leads to limited therapeutic response and also to various side effects on healthy organs (M1 et al., 2012; Barratt, 2003). Nanoparticles generally have multiple benefits, such as solubility of hydrophobic activation, improved bioavailability, and pharmacokinetic enhancement of active pharmaceutical ingredients (APIs). API nanoparticles protect against chemical and biological damages (Couvreur and Vauthier, 2006; Maeski, 2002; Huh and Kwon, 2011).

In addition, other observations indicate the importance of nano-dimensionality in improving the performance of processes such as crossing biological barriers and cellular absorption, which can help produce drugs effective for targeting tissues such as tumors (Couvreur and Vauthier, 2006; Maeski, 2002; Huh and Kwon, 2011). In this study, we investigated new approaches in nanotechnology toward better treatment of leishmaniasis while examining nanotechnology’s effectiveness and drawbacks to develop other researchers’ knowledge of nanoparticles, which can lead to better approaches in the future. Table 1 shows the list of nanoparticles tested to treat leishmaniasis.

1.1. Liposome nanoparticles

New discoveries in the field of liposomes have led to a tremendous leap in the drug delivery system. Liposomes are the most extensively investigated structures among various colloidal carriers, microscopic liposomes being the most commonly used colloidal carriers (AA1 et al., 2007). LFAB, as a liposome nanoparticle, can provide a safe, practical, and less toxic therapeutic alternative to pentavalent antimonials. LFABs are also called second-line drugs, Pentamidine, and amphotericin B deoxycholate (Amato et al., 2004). A study’s results showed that liposomal HePC is less toxic than the free drug, despite the absence of significant antitrypanosomal activity (Papagiannaros et al., 2005).

In a study by Berman, the antileishmanial activity of liposome-encapsulated amphotericin B (L-AmB) was examined in hams ters and monkeys (Berman et al., 1986). L-AmB’s effectiveness in humans for the treatment of visceral and cutaneous leishmaniasis was examined in several works (Couvell and Brodgen, 1998). Many other studies’ results suggest that liposomes loaded in Leishmania drugs are more effective than the free drug against this parasitic disease (V1 and Croft, 2000; Cauchetier et al., 2000). Plasmid DNA (pDNA) vaccines are prophylactic agents for commonly used disease treatments. However, naked plasmids have been shown to be very responsive to degeneration and not effectively enter the cells.

In a study conducted to develop a process to prepare lipidic nanoparticles (NPs) loaded with plasmid pVAX1-NH36 for application as leishmaniasis nanovaccine, all the samples presented sufficient stability in the experimental period study (Ureña-Búrquez et al., 2019a). Chaubey et al. (2014) investigated the effectiveness of rifampicin packed with mannose-conjugated chitosan nanoparticles as nanodrugs for the delivery of drugs specifically to macrophages infected with Leishmania. The results were promising for increasing the efficacy and reducing the toxicity of these drugs (Chaubey and Mishra, 2014). In another study, curcumin (CUR) nanoparticles were used to improve visceral leishmaniasis. As expected, Cur-MCNPs can serve as a promising delivery strategy toward the active targeting of CUR to macrophages for the adequate treatment of VL (Chaubey et al., 2014). Also, in another study conducted on the antileishmanial activity of bovine serum albumin (BSA) containing AmB against L. amazonensis, BSA containing AmB was found to be an appropriate candidate for treating cutaneous leishmaniasis because of lower toxicity (Casa et al., 2018).

1.2. Polymeric nanoparticles

One of the main biomedical applications concerning biodegradable polymer nanomaterials is drug delivery. Polymer nanomaterials have several advantages, including the following: The controlled release model provides a controlled matrix structure to a particular section, in particular, the tissue of the body; covering unstable molecules (such as DNA, RNA, and proteins); it prevents their destruction; and it is suitable for surface engineering with a ligand under in vitro and in vivo conditions (Nanotherapeutics CV-PN, 2019; Banik et al., 2016). PACA nanoparticles were examined against macrophages infected with L. donovani for the first time (Gaspar et al., 1992a).

Gaspar (1992) did another research in the same year and revealed that the same particles can be used as carriers for the delivery of drugs to a specific cell and showed antileishmanial activities (Gaspar et al., 1992b). In another study in 2002, nanoparticles failed to show any development in the AmB activity against parasites (Espuelas et al., 2002). Ammar (2019) found that AmB-carrying nanoparticles have effective and positive results in reducing this drug’s toxicity and can act as AmB carriers (Abu Ammar et al., 2019). In a 2019 study, Pluronics P-123 and F-127 were considered a safe solution for future treatment


| Structural nanocomponent | DRUG | Leishmania species | Stage employed | Ref. |
|--------------------------|------|-------------------|----------------|-----|
| **Liposome**             |      |                   |                |     |
| Lipid formulations of amphotericin B [LFAB] | L. chagasi | CL | Human | Amastigote | (Amato et al., 2004) |
| Liposomes composed of hexadecylphosphocholine [HePC] | L. donovani | VL | Culture CD 1 | Amastigote | (Papagiannaros et al., 2005) |
| Liposomal amphotericin B [LAB] | L. infantum | VL | BALB/c mice | Amastigote | (Coukell and Brogden, 1998) |
| L. donovani | L. infantum | VL | BALB/c mice | Amastigote | (V1 and Croft, 2000) |
| L. infantum | L. major | CL | Murine | Amastigote | (Cauchetier et al., 2000) |
| Nanovaccine of pVAX1-NH36 | L. spp | – | – | – | (Ureña-Búrquez et al., 2019a) |
| Curcumin-loaded mannosylated chitosan nanoparticles [Cur-MCNPs] | L. donovani | VL | Male albino rats | Amastigote | (Chaubey et al., 2014) |
| Mannose-conjugated chitosan nanoparticles [mCNPs] | Leishmania spp | VL | Albino rats | – | (Chaubey and Mishra, 2014) |
| Rovine serum albumin nanoparticles containing amphotericin B [AMB-loaded RSA nanoparticles] | L. amazonensis | CL | BALB/c mice | Amastigote | (Gaspar et al., 1992a) |
| Primaqueine-loaded polyisohexylcyanoacrylate nanoparticles [PIHCA] | L. donovani | VL | Culture | Amastigote | (Ali Ammar et al., 2019) |
| Amphotericin B-loaded nanoparticles [AMB NPs] | L. amazonensis | CL | BALB/c mice | Amastigote | (Oyama et al., 2019) |
| Pluronic® P-123 and F-127 | L. amazonensis | CL | BALB/c mice | Amastigote | (Afzal et al., n.d.) |
| Nanoparticles loaded with meglumine antimoniate | L. infantum | VL | BALB/c mice | Amastigote | (AJ et al., n.d.) |
| Mannose-anchored thiolated amphotericin B nanocarriers | L. donovani | VL | Culture | Amastigote | (Shahnaz et al., 2017) |
| (MTC AmB) | L. amazonensis | CL | BALB/c mice | Amastigote | (Rodrigues et al., 1994) |
| Pluronic®-loaded poly (d,L-lactide) nanoparticles [PLA nanoparticles] | L. donovani | VL | Murine | Promastigote | (Corpas-López et al., 2019) |
| MDG | L. donovani | VL | Culture | Amastigote | (Aftal et al., 2019a) |
| Mannosylated thiolated paromomycin-loaded PLGA nanoparticles [nanovaccine of pVAX1-NH36] | L. donovani | VL | Culture | Amastigote | (Siefert et al., 2016) |
| NP-CpG | L. (V.) panamensis | CL | Murine | – | (Das et al., 2013) |
| Gold nanoparticles | L. donovani | VL | Culture | Amastigote | (Mahmoudvand et al., 2014c) |
| Biogenic selenium nanoparticles [Se NPs] | L. major | VL | Culture | Amastigote | (Afzal et al., n.d.) |
| Lipid nanoparticles | L. infantum | VL | Culture | BALB/c mice | Promastigote | (Lopes et al., 2012) |
| Lipid nanoparticles containing oryzalin | L. donovani | VL | Culture | BALB/c mice | Amastigote | (Want et al., 2015) |
| Artemisinin-loaded poly lactic co-glycolic acid nanoparticles [ALPLGA] | L. donovani | VL | Culture | BALB/c mice | Amastigote | (Tomiooto-Pellissier et al., 2020) |
| Biogenic silver nanoparticle | L. amazonensis | VL | Culture | BALB/c mice | Amastigote | (Roy et al., 2010) |
| Andrographolide nanoparticles [AGnp] | L. donovani | VL | Culture | BALB/c mice | Amastigote | (Sousa-Batista et al., 2017) |
| Qcqueretin in nano-capsules containing LNC [LNC-Qc] | L. amazonensis | CL | BALB/c mice | Amastigote | (Heidari-Kharaji et al., 2016) |
| Amphotericin B –loaded Solid lipid nanoparticles [Amb-SLN] | L. donovani | VL | Culture | BALB/c mice | Amastigote | (Amor et al., 2017) |
| Paromomycin loaded in solid lipid nanoparticles [PM-SLN] | L. tropica | CL | Culture | Promastigote | (Allahverdiyev et al., 2011b) |
| TiO2 and Ag2O nanoparticles | L. tropica | CL | Culture | Promastigote | (Baker et al., 2019) |
| Silver nanoparticles [Ag-NPs] | L. tropica | CL | Culture | Promastigote | (Delavari et al., 2014) |
| ZnO nanoparticles | L. mexicana | CL | Culture | Promastigote | (Nadhiman et al., 2014) |
| Iron oxide magnetic nanoparticles | L. tropica | CL | Culture | Promastigote | (Nadhiman et al., 2016) |
| ZnO Nanoparticles | L. tropica | CL | Culture | Promastigote | (Nadhiman et al., 2016) |
| ZnO nanoparticle | L. tropica | CL | Culture | Promastigote | (Nadhiman et al., 2016) |
because of their anti-leishmanial effects on amastigotes and promastigotes through impacts on the mitochondrial membrane (Oyama et al., 2019).

In another study in 2019, the use of polycaprolactone antimony nanoparticles was reviewed to advance the effectiveness of meglumine antimoniate. The work showed promising results for the future of leishmaniasis drugs (AJ1 et al., n.d.). Elsewhere, AmB was connected with a mannose-anchored thiolated chitosan nanocarrier in order to improve efficacy and reduce toxicity. The results showed a positive perspective through MTC as a safe nanoparticle for future nano drugs (Shahnaz et al., 2017). The association between primaquine and PLA nanoparticles was investigated in 1994, and the study found that there is a great difference in anti-leishmanial effects that reduce the toxicity of these drugs (Rodrigues et al., 1994).

Histone deacetylases (HDACs) are among the most encouraging therapeutic targets for leishmaniasis treatment. For example, in a 2017 study, the combination of meglumine antimoniate and MDG was found as an effective solution for leishmaniasis treatment (Corpas-López et al., 2019). Another study evaluated the efficacy of paromomycin (PM)-loaded mannosylated thiomeric nanoparticles for the targeted delivery of oral therapy to pathological organs in visceral leishmaniasis. The results produced the concept of MTC-PLGA-PM nanoparticles as a promising strategy for visceral leishmaniasis (Afzal et al., 2019a). In another study in 2016, biodegradable NPs were examined for the productive therapeutic effects of CpG oligonucleotide on leishmaniasis. The results showed great effectiveness on a Leishmania parasite, which presents a potential approach for the future of leishmaniasis drugs (Siefert et al., 2016). In a 2013 study, quercetin conjugated gold NPs (Aunp) were examined against macrophages contaminated with Leishmania. The result showed a promising future for better research on this subject (Das et al., 2013). Biogenic Se NPs were also studied and analyzed as a possible agent in better treatment of Leishmania, and promising results were obtained (Das et al., 2013). In a study conducted by Mahmoudvand et al. (2014a, 2014b, 2014c), it has been proven that the different doses of Se NPs considerably inhibited the growth of promastigotes and amastigote forms of sensitive and glucantime resistance Leishmania tropica in vitro (Mahmoudvand et al., 2014c).

1.3. Lipid nanoparticles treatment of leishmaniasis

Lopes et al. (2012) studied the effects of using NPs in Oryzalin, a selective drug in the treatment of leishmaniasis. Oryzalin is used as an antiparasitic therapeutic agent that is limited by low water solubility. As a result, it leads to the administration of larger and probably toxic doses, which may cause unwanted side effects. Cell viability studies confirmed that the incorporation of Oryzalin in nanoparticles decreases cytotoxicity, which leads to a step further in the treatment of leishmaniasis using low-risk and safe drugs (Lopes et al., 2012).

Heidari-Kharaji et al. showed that the PM-SLN formulation is a safe compound, and SLN in the PM-SLN compound is effective for the treatment of leishmaniasis. It develops the efficiency of Paromomycin sulfate in killing the parasite and switching toward Th1 response (Heidari-Kharaji et al., 2016). Hence, it represents another successful compound of nanoparticles with a leishmanial drug. SLNs have many advantages, making them a subject of intense research. For example, one of the benefits is the quick and easy production of these materials. Another reason for using this substance in drugs is to increase the life expectancy of the drugs, as well as their compatibility with the biocompatible environment (Alavi, 2019).

Solid lipid nanoparticles and nanostructured lipid carriers are known as second-generation colloid carriers. These carriers that are used in anti-parasitic drugs are highly popular due to their structures and properties. Jain et al. (2014) conjugated amphotericin B and SLNs and examined them on leishmanial infections. The results showed that AmB-SLN successfully managed macrophages to activate the immune system and produced TNF-α and IL-12, which ultimately resulted in better drug delivery and higher anti-leishmanial (Jain et al., 2014).

Findings of Sousa-Batista suggest that when taking quercetin (Qc) in nanocapsules containing LNC orally, PQc can easily multiply the antileishmanial effects of this drug and even increase the effectiveness of the drug at lower doses (Sousa-Batista et al., 2017). The 6Gnp structure has been used because of its low toxicity in the treatment of infected macrophages. It has also proven its value in chemotherapy for tropical diseases such as leishmaniasis (Roy et al., 2010). Other studies have shown promising methods. For example, AgNp-bio obtained from Fusarium exosporium has a direct effect on L. amazonensis species and the ability of immunomodulation on infected macrophages (Tomiotto-Pellissier et al., 2020). The results of nanoparticle drug studies indicate that new horizons may be opened to find better, more efficient antileishmania drugs. For example, the effect of ALPLGA nanoparticles was tested in research, and the data showed a promising future for using these particles in safer drugs (Want et al., 2015).

1.4. TiO2 and Ag2O nanoparticles and Leishmania

Titanium dioxide (TiO2) has attracted many scientists, leading to a very large resource of information on its properties and functionality (Endo-Kimura et al., 2019). Researchers recently have turned their attention to modified TiO2 nanoparticles due to their specific physical and chemical properties. This increase in attention has led to the movement of TiO2 nanoparticles to more effective uses in various sciences, including the science of therapy and medicine. Emrah Sefik Abamor (2017) conducted a study with the purpose of generating less toxic drugs. Abamor used TiAgNps combined with meglumine antimoniate and specified that TiAgNps-MA exhibited an effective response as an antileishmania drug and could lead a massive road to find new methods of treatment for diseases involving parasites (Abamor et al., 2017).

Nowadays, many researchers have studied metal oxide nanoparticles as a new therapeutic solution for the treatment of parasitic diseases. In this regard, two nanoparticles of TiO2 and Ag2O are particularly popular (Allahverdijev et al., 2011a). The results of one study showed that Ag-NPs can be combined with chemical drugs as a suitable substitute for high toxicity drugs...
A comprehensive analysis of the absorption, distribution, and metabolism of nanoparticles is required for the development of efficient and safe nanoparticles (Yuksel et al., 2019). In the targeted drug delivery systems, smart nanoparticles can be combined with chemotherapy drugs and predictably respond to external and internal stimuli (Singh et al., 2019; Nikolić and AT-... and B of, 2019). The absorption and distribution profile of a nanoparticle is highly controlled by physicochemical properties and objective cells. In this regard, certain properties are conditioned on the variety of the delivery system (Card et al., 2011; Borel and Sabliov, 2014). For example, in a review by Wan Seob Cho (2013), the absorption and distribution of ZnO and TiO2 nanoparticles were examined and compared based on their delivery systems (Cho et al., 2013). Other studies also detected that metallic nanoparticles have other potential uses in various scientific fields, such as medicine (Zhong and Huang, 2019). The pathway for intracellular drug delivery to the target cell can vary with the characteristics and type of nanoparticle and the target cell’s character. This delivery has two forms of either phagocytosis or other endocytic pathways (Hillaireau and Couvreur, 2009; Lembo and Cavalli, 2010).

2. Cost-effectiveness analysis of therapy-based nanotechnology and its drawbacks

The evolving approach of the last fifty years includes a drug’s covalent attachment to a polymeric scaffold or a macromolecule to facilitate and improve drug delivery and overcome physiological barriers. In carriers linked to precursors in carrier-linked protein drugs, a non-toxic agent playing a protective role attaches to the active drug molecule to help improve the drug’s mobility and effectiveness. Typically, after activation, the progenitor core is rapidly expelled from the body. The platform for the application of precursors promotes medication’s efficacy and effectiveness by improving water solubility, minimizing toxic effects, increasing targeted release, increasing cellular absorption, and reducing the effects of explosive release common in many delivery systems (Banik et al., 2016).

New treatments, such as nanotechnology-based ones, can be justified in contrast to the usual treatments that include high-cost purchases (Jeevanandanm et al., 2018). Nanotechnology in today’s world has been recognized as a key enabler technology (KET) for its various applications in science. However, despite the high benefits and frequent use of these particles, there are still concerns about their potential risks and side effects. There are particles that have boosted toxicology in this area, owing to the importance of trying to minimize the potential risks of these drugs and materials on human cells and tissues, as well as the environment (Oliveira et al., 2019).

3. New patents toward better treatments

In recent years, the scientific value of NPs in the treatment of leishmaniasis has increased due to the improvement of anti-leishmaniasis drugs. For example, the present study estimates the effectiveness of paromomycin (PM)-loaded mannosylated thiomeric NPs in oral therapy for visceral leishmaniasis. It shows MTC-PLGA-PM NPs as a promising strategy for visceral leishmaniasis. (Afzal et al., 2019b) Another promising research examines the effectiveness of manganese NPs against Leishmania major. Results showed the toxicity of Mn2O3 NPs against L. major promastigotes. The possible apoptosis of L. major by Mn2O3 NPs was evaluated with flow cytometry assay. As a result, Mn2O3 NPs have a salubrious effect on L. major promastigotes, and it is an outstanding candidate for treatment. (Tavakoli et al., 2019) Also, another recent study used Mannose-conjugated curcumin-chitosan NPs, which have shown a significantly higher suppression of replication in the spleen with Cur-MCN than unconjugated chitosan NPs. Also, in vitro shows much more cytotoxicity than unconjugated chitosan nanoparticles (Chaube, et al., 2018). New assuring research used Triglyceride-rich nanoparticles mimicking chylomicrons (TGNP) for the treatment of L. amazonensis. The TGNP-AB development achieved a high leishmanicidal activity with extraordinarily lower toxicity at high doses that, because of the toxicity-buffering features of the nanocarrier, became entirely tolerable (de Souza et al., 2019). Other studies have shown the same potential for an alternative treatment for leishmaniasis such as oral pentamidine-loaded poly (d,l-lactic-co-glycolic) acid nanoparticles, or gold nanoparticle–amphotericin B covalent conjugate and antimony sulfide nanoparticle (Valle et al., 2019; Kumar et al., 2019; Mohtasebi et al., 2019).

Various studies have shown Chitosan-Coated Poly Nanoparticle as another effective method to treat leishmaniasis (Abdollahimajd et al., 2019; Malli et al., 2019).

4. Green synthesis a safer treatment

There are currently few studies on the green synthesis of nanoparticles and their efficacy in controlling Leishmania parasites. Among the various biosynthetic methods, the use of plant extracts is preferred because they are easily accessible and safe. The use of plants as biological materials for nanoparticle synthesis could be one of the prospects for the treatment of leishmaniasis. In recent years, numerous studies have been done which have shown promising results, such as an article by Zahir in 2015 that Showed Shift from Apoptosis to G0/G1 Arrest followed by Necrotic Cell Death in L. donovani by green synthesis of silver and titanium dioxide nanoparticles using Euphorbia prostrata extract (Zahir et al., 2015). Another study developed a green protocol to
5. Nanovaccines and leishmaniasis

Nanovaccines are emerging as a novel approach to the methodology of vaccination, having shown promising results in inducing both humoral and cell-mediated immune responses. These positive results have led to a promising path to more suitable treatment for several diseases, including leishmaniasis (Sekhon and Saluja, 2011). In a 2011 study, recombinant Leishmania superoxide dismutase (SODB1) was loaded onto chitosan nanoparticles by the ionotropic gelation method to develop a new nanovaccine that was experimented on BALB/c mice. The results showed that in single and triple doses of SODB1 nanoparticles, IgG2a and IgG2a/IgG1 were significantly higher than the other groups (P < 0.05), which shows the efficiency of chitosan nanoparticles in developing a nanovaccine for leishmaniasis (Danesh-Bahreini et al., 2011). Another study perused the effectiveness of chimeric peptides containing HLA-restricted epitopes from three immunogenic L. infantum proteins, in poly(lactic-co-glycolic) acid nanoparticles with or without the adjuvant monophosphoryl lipid A (MPLA) or surface modification. The nanovaccine induced Dendritic Cells Maturation and Promoted Peptide-Specific IFNγ-Producing CD8+ T Cells (Athanasio et al., 2017). Another study used a synthetic peptide-based nanovaccines along with MPLA adjuvant co-encapsulated in PLGA nanoparticles. The results demonstrated a strong spleen lymphoproliferative response and high levels of IL-2, IFN-γ, and TNF between low IL-4 and IL-10 secretion (Agallou et al., 2017). A 2019 study developed a process to prepare lipidic nanoparticles (NPs) loaded with plasmid pVAX1-NH36 for application as a leishmaniasis nanovaccine. The result presented stability >84% in all of the samples, which could be a promising approach for future studies (Ureña-Búrquez et al., 2019b).

6. ZnO nanoparticles

ZnO nanoparticles cause membrane permeability (Sirelkhatim et al., 2015). In another study, ZnO NPs induced apoptosis in L. major by dose and time-dependent manner in vitro condition (Delavari et al., 2014). Daylight-responsive silver doped semiconductor nanoparticles of zinc oxide were examined against Leishmania in a 2014 study. Results revealed that nanoparticles caused permeability of the cell membrane, leading to the death of parasites (Nadhman et al., 2014). A 2016 study investigated the effectiveness of synthesized photodynamic therapy-based doped and nondoped zinc oxide nanoparticles, which were activated in daylight to produce reactive oxygen species in the immediate environment. Results depicted a significant improvement in lipid and protein oxidation (Nadhman et al., 2016).

7. Conclusion

In this study, various aspects of the treatment of leishmaniasis as a universal disease were considered. Despite the rapid spread of parasitic diseases worldwide, the study of their treatment is very limited. This neglect has resulted in the continuation of a weak and harmful treatment process. The key to solving this problem is the effective use of drug delivery systems that increase the strength of drugs and simultaneously reduce adverse effects.

A new drug delivery system is a reliable approach to overcome the limitations associated with the current medication protocol. Today, the treatment of leishmaniasis involves many difficulties due to the toxicity and expense of first-line drugs. According to the obtained results, drug carriers such as nanoparticles can aid in reducing toxicity and enhancing the efficiency of the leishmaniasis drugs.

PM-loaded mannosylated thiomeric NPs, Mn2O3 NPs, mannose-conjugated curcumin-chitosan NPs, triglyceride-rich NPs, TGNP, pentamidine-loaded poly (d,L-lactic-co-glycolic) acid NPs, green synthesis, nanovaccines, and ZnO have shed new light on leishmaniasis treatment and have shown promising results; however, these new approaches are still at the beginning of a very long road and require more researchers' concentration and work on these topics.

Previous studies have shown that some metal oxide nanoparticles and metals have antimicrobial activity. Nanotechnology has been studied as a new research area for leishmaniasis treatment. Nanoparticles, as new drug delivery devices, divert anticoagulant drugs to targeted cells, in particular by minimizing toxic effects and increasing susceptibility. Findings show that nanoparticles of silver, gold, chitosan, and a metal oxide have a growth or inhibitory effect on different parasites such as Leishmania. Nanoparticles can be used alone or in combination to eliminate parasites. In the present study, we tried to find studies in different conditions that examined various nanoparticles' influence on various forms of leishmaniasis. In this way, we could compare the results and obtain a reliable conclusion of the most recent studies on this subject. Our review's results indicate that incorporating nanoparticles with chemical drugs improves the quality, efficiency, and sustainability of drugs and reduces their cost. Finally, further research is highly recommended on the use of nanoparticles in the destruction of parasites, their inhibitory effect (making drugs more effective and less harmful), and their utility in making useful vaccines to prevent and fight against parasites.
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