Parasite Epidemiology and Control 10 (2020) e00156

Contents lists available at ScienceDirect

Parasite Epidemiology and Control

journal homepage: www.elsevier.com/locate/parepi

Nanoparticles: New agents toward treatment of leishmaniasis

Amir Nafari [a], Koroush Cheraghipour [b], Maryam Sepahvand [a], Ghazal Shahrokhi [a], Esraa Gabal [c], Hossein Mahmoudvand [b,*]

[a] Student Research Committee, Lorestan University of Medical Sciences, Khorramabad, Iran
[b] Razi Herbal Medicines Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran
[c] Agricultural Science and Resource Management in the Tropics and Subtropics, Bonn University, Germany

ARTICLE INFO

Article history:
Received 28 February 2020
Received in revised form 17 April 2020
Accepted 16 May 2020

Keywords:
Leishmaniasis
Nano drugs
Treatment
Leishmania
Parasite
Nanotechnology

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.

Contents

* Corresponding author.
E-mail address: dmahmodvand@gmail.com. (H. Mahmoudvand).

https://doi.org/10.1016/j.parepi.2020.e00156

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 (Chávez-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 hamsters 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 (Coukell and Brogden, 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, nanospheres 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

Table 1
Some nanoparticles used to treat leishmaniasis.

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 Mice	Promastigote Amastigote	(Papagiannaros et al., 2005)
	Liposomal amphotericin B [LAB]	*L. infantum*	VL	BALB/c mice	Promastigote	(Coukell and Brogden, 1998)
		L. major		Murine	Amastigote	
		L. donovani	VL	BALB/c	Amastigote	(V1 and Croft, 2000)
		L. major	CL	mice		
		L. infantum	VL	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)
	Bovine serum albumin nanoparticles containing amphotericin B [AmB-loaded BSA nanoparticles]	*L. amazonnsis*	CL	BALB/c mice	Promastigote Amastigote	(Casa et al., 2018)
Polymeric nanoparticles	Primaquine-loaded polyisohexylcyanoacrylate nanoparticles [PIHCA]	*L. donovani infantum*	VL	Culture	Amastigote	(Gaspar et al., 1992a)
	Amphotericin B-loaded nanoparticles [AMB NPs]	*L. major*	CL	BALB/c mice	Promastigote Amastigote	(Abu Ammar et al., 2019)
	Pluronics® P-123 and F-127	*L. amazonnsis*	CL	BALB/c mice	Promastigote Amastigote	(Oyama et al., 2019)
	Nanoparticles loaded with meglumine antimoniate	*L. amazonnsis*	CL	BALB/c	Amastigote	(AJ1 et al., n.d..)
		L. infantum	VL	mice		
	Mannose-anchored thiolated amphotericin B nanocarriers [(MTC AmB]	*L. donovani*	VL	Culture	Amastigote	(Shahnaz et al., 2017)
	Primaquine-loaded poly (d,L-lactide) nanoparticles [PQ-loaded PLA nanoparticles]	*L. donovani*	VL	BALB/c mice	Amastigote	(Rodrigues et al., 1994)
	MDG	*L. donovani*	VL	Murine	Promastigote	(Corpas-López et al., 2019)
		L. infantum			Amastigote	
	Mannosylated thiolated paromomycin-loaded PLGA nanoparticles [nanovaccine of pVAX1-NH36]	*L. donovani*	VL	Culture BALB/c mice	Amastigote	(Afzal et al., 2019a)
	NP-CpG	*L. (V.) panamensis*	–	Mice	Amastigote	(Siefert et al., 2016)
	Gold nanoparticles	*L. donovini*	VL	Culture	Amastigote	(Das et al., 2013)
	Biogenic selenium nanoparticles [Se NPs]	*L. major*	CL	Culture BALB/c mice	Promastigote Amastigote	(Mahmoudvand et al., 2014c)
Lipid nanoparticles	Lipid nanoparticles containing oryzalin	*L. infantum*	VL	Culture BALB/c mice	Promastigote Amastigote	(Lopes et al., 2012)
	Artemisinin-loaded poly lactic co-glycolic acid nanoparticles [ALPLGA]	*L. donovini*	VL	BALB/c mice	Amastigote	(Want et al., 2015)
	Biogenic silver nanoparticle	*L. amazonensis*	CL	Culture BALB/c mice	Promastigote Amastigote	(Tomiotto-Pellissier et al., 2020)
	Andrographolide nanoparticles [AGnp]	*L. donovani*	VL	Culture	Amastigote	(Roy et al., 2010)
	Qcquercetin in nano-capsules containing LNC [LNC-Qc]	*L. amazonensis*	CL	BALB/c mice	Amastigote	(Sousa-Batista et al., 2017)
	Amphotericin B –loaded Solid lipid nanoparticles [AmB-SLNs]	*L. donovani*	VL	Culture	Amastigote	(Jain et al., 2014)
	Paromomycin loaded in solid lipid nanoparticles [PM-SLN]	*L. major*	CL	BALB/c mice	Amastigote	(Heidari-Kharaji et al., 2016)
TiO2 and Ag2O nanoparticles	TiO2Ag nanoparticles –loaded meglumine antimoniate [TiAgNps-MA]	L.tropica	CL	Culture	Promastigote Amastigote	(Abamor et al., 2017)
	Silver nanoparticles [Ag-NPs]	L.tropica	CL	Culture	Promastigote Amastigote	(Allahverdiyev et al., 2011b)
	Iron oxide magnetic nanoparticles	*L. mexicana*	CL	Culture	Amastigote	(Berry et al., 2019)
ZnO nanoparticles	ZnO Nanoparticles	*L. major*	CL	Culture	Promastigote Amastigote	(Delavari et al., 2014)
	PEGylated silver doped zinc oxide nanoparticles	L.tropica	CL	Culture	Promastigote Amastigote	(Nadhman et al., 2014)
	ZnO nanoparticle	L.tropica	CL	Culture	Promastigote	(Nadhman 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 2019 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 therapeutic productiveness 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 leishmaniasis 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-leishmaniasis (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 TiAgNp 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 (Allahverdiyev 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

(Allahverdiyev et al., 2011b). A 2019 study on killing parasites using iron oxide magnetic nanoparticles reported promising results in making better drugs (Berry et al., 2019).

1.5. Absorption and distribution of nanoparticles

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 (Jeevanandam 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 (Chaubey 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

prepare biogenic silver nanoparticles (AgNPs) and amphotericin B-bound biogenic silver nanoparticles (AmB-AgNPs) by *Isatis tinctoria*, which showed enhanced results (Ahmad et al., 2016). Another study showed the same promising result using zinc oxide nanostructure green synthesis by natural sweetener (Stevia) extract (Khatami et al., 2018). Also, *Olax nana* Wall. ex aqueous extract was used as an effective stabilizing agent to produce biogenic silver and gold nanoparticles, which also showed promising results toward the new treatment (Ovais et al., 2018). Other studies showed the same findings, such as green synthesis of cobalt oxide nanoparticles using *Geranium wallichianum* leaves extract, green synthesis of silver oxide nanoparticles using *Ficus benghalensis* prop root extract, or green synthesis of nickel oxide nanoparticles using the leaf extract of *Rhamnus virgate* (Iqbal et al., 2019a; Ismail et al., 2019; Iqbal et al., 2019b).

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 (Athanasiou 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 TNFα versus 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-depended 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 uility in making useful vaccines to prevent and fight against parasites.

Funding

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

AA1, Date, Joshi, M.D., Patravale, V.B., 2007. Parasitic diseases: liposomes and polymeric nanoparticles versus lipid nanoparticles. Adv. Drug Deliv. Rev. 10 (59(6)), 505–521.
Abamor, E., Allahverdiyev, A., tropica, M.B.-A., 2017. Meglumine antımoniate-TiO2@ Ag Nanoparticle Combinations Reduce Toxicity of the Drug While Enhancing Its Antileishmanial Effect.
Abdollahimajd, F., Moravvej, H., Dadkhahfar, S., Mahdavi, H., Mohebali, M., Mirzadeh, H., 2019. Chitosan-based biocompatible dressing for treatment of recalcitrant lesions of cutaneous leishmaniasis: a pilot clinical study. Indian Journal of Dermatology, Venereology, and Leprology 85 (6), 609 Nov 1.
Abu Ammar, A., Nasereddin, A., Ereqat, S., Dan-Goor, M., Jaffe, C.L., Zussman, E., et al., 2019. Amphotericin B-loaded nanoparticles for local treatment of cutaneous leishmaniasis. Drug Deliv Transl Res 9 (1), 76–84 Feb 15.
Afzal, I., Sarwar, H.S., Sohail, M.F., Varikuti, S., Jahan, S., Akhtar, S., et al., 2019a. Mannosylated thiolated paromomycin-loaded PLGA nanoparticles for the oral therapy of visceral leishmaniasis. Nanomedicine 14 (4), 387–406 Feb 1.
Afzal, I., Sarwar, H.S., Sohail, M.F., Varikuti, S., Jahan, S., Akhtar, S., Yasinzai, M., Satoskar, A.R., Shahnaz, G., 2019b. Mannosylated thiolated paromomycin-loaded PLGA nanoparticles for the oral therapy of visceral leishmaniasis. Nanomedicine 14 (4), 387–406 Jan 28.
Agallou, M., Margaroni, M., Athanasiou, E., Toubanaki, D.K., Kontonikola, K., Karidi, K., Kammona, O., Kiparissides, C., Karagouni, E., 2017. Identification of BALB/c immune markers correlated with a partial protection to Leishmania infantum after vaccination with a rationally designed multi-epitope cysteine protease a peptide-based nanovaccine. PLoS Negl. Trop. Dis. 11 (1), e0005311 Jan 23.
Ahmad, A., Wei, Y., Syed, F., Khan, S., Khan, G.M., Tahir, K., Khan, A.U., Raza, M., Khan, F.U., Yuan, Q., 2016. Isatis tinctoria mediated synthesis of amphotericin B-bound silver nanoparticles with enhanced photoinduced antileishmanial activity: a novel green approach. J. Photochem. Photobiol. B Biol. 161, 17–24 Aug 1.
Akhlagh, A, Salehzadeh, A, ... AZ-F in public, 2019. 10-Year Trends in Epidemiology, Diagnosis, and Treatment of Cutaneous Leishmaniasis in Hamadan Province, West of Iran (2007–2016).
Alavi, M., 2019. Therapy MH-D metabolism and personalized. Passive and Active Targeting in Cancer Therapy by Liposomes and Lipid Nanoparticles.
Allahverdiyev, A.M., Abamor, E.S., Bagirova, M., Rafailovich, M., 2011a. Antimicrobial effects of TiO(2) and Ag(2)O nanoparticles against drug-resistant bacteria and leishmania parasites. Future Microbiol. 6, 933–940.
Allahverdiyev, A., Abamor, E., journal, M.B.-I., 2011b. Antileishmanial Effect of Silver Nanoparticles and Their Enhanced Antiparasitic Activity Under Ultraviolet Light.
Alvar, J., Vélez, I.D., Bern, C., Herrero, M., Desjeux, P., Cano, J., et al., 2012. Leishmaniasis worldwide and global estimates of its incidence. PLoS One 7 (5), e35671.
Amato, V.S., Rabello, A., Rotondo-Silva, A., Kono, A., Maldonado, T.P., Alves, I.C., Floeter-Winter, L.M., Neto, V.A., Shikanai-Yasuda, M.A., 2004. Successful treatment of cutaneous leishmaniasis with lipid formulations of amphotericin B in two immunocompromised patients. Acta Trop. 92 (2), 127–132 Oct.
Athanasiou, E., Agallou, M., Tastsoglou, S., Kammona, O., Hatzigeorgiou, A., Kiparissides, C., Karagouni, E., 2017 Jun 13. A poly (lactic-co-glycolic) acid nanovaccine based on chimeric peptides from different Leishmania infantum proteins induces dendritic cells maturation and promotes peptide-specific IFNγ-producing CD8+ T cells essential for the protection against experimental visceral leishmaniasis. Front. Immunol. 8, 684.
Banik, B.L., Fattahi, P., Brown, J.L., 2016. Polymeric nanoparticles: The future of nanomedicine. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology. 8. Wiley-Blackwell, pp. 271–299.
Barratt, G., 2003. Colloidal drug carriers: Achievements and perspectives. Cellular and Molecular Life Sciences. 60. Birkhauser Verlag Basel, pp. 21–37.
Berman, J.D., Hanson, W.L., Chapman, W.L., Alving, C.R., Lopez-Berestein, G., 1986 Dec. Antileishmanial activity of liposome-encapsulated amphotericin B in hamsters and monkeys. Am Soc Microbiol. Antimicrob Agents Chemother. 30 (6), 847–851.
Berry, S., Walker, K., Hoskins, C., Telling, N., reports, H.P.-S., 2019. Nanoparticle-mediated magnetic hyperthermia is an effective method for killing the human-infective protozoan parasite Leishmania mexicana in vitro.
Borel, T., Sabliov, C.M., 2014. Nanodelivery of bioactive components for food applications: types of delivery systems, properties, and their effect on ADME profiles and toxicity of nanoparticles. Annu. Rev. Food Sci. Technol. 5 (1), 197–213 Feb 28.
Card, J.W., Jonaitis, T.S., Tafazoli, S., Magnuson, B.A., 2011. An appraisal of the published literature on the safety and toxicity of food-related nanomaterials. Crit. Rev. Toxicol. 41, 22–51.
Carvalho, S.H., Frézard, F., Pereira, N.P., Moura, A.S., Ramos, L.M.Q.C., Carvalho, G.B., et al., 2019. American tegumentary leishmaniasis in Brazil: a critical review of the current therapeutic approach with systemic meglumine antimoniate and short-term possibilities for an alternative treatment. Trop Med Int Heal 24 (4), 380–391 Apr 1.
Casa, D.M., Scariot, D.B., Khalil, N.M., Nakamura, C.V., Mainardes, R.M., 2018. Bovine serum albumin nanoparticles containing amphotericin B were effective in treating murine cutaneous leishmaniasis and reduced the drug toxicity. Exp. Parasitol. 192, 12–18 Sep.
Cauchetier, E., Paul, M., Rivollet, D., Fessi, H., Astier, A., Deniau, M., 2000 May 1. Therapeutic evaluation of free and liposome-encapsulated atovaquone in the treatment of murine leishmaniasis. Int. J. Parasitol. 30 (6), 777–783.
Chaubey, P1., Mishra, B., 2014. Mannose-conjugated chitosan nanoparticles loaded with rifampicin for the treatment of visceral leishmaniasis. Carbohydr. Polym. 101, 1101–1108 Jan 30.
Chaubey, P., Patel, R.R., Mishra, B., 2014. Development and optimization of curcumin-loaded mannosylated chitosan nanoparticles using response surface methodology in the treatment of visceral leishmaniasis. Expert Opin Drug Deliv 11 (8), 1163–1181.
Chaubey, P., Mishra, B., Mudavath, S.L., Patel, R.R., Chaurasia, S., Sundar, S., Suvarna, V., Monteiro, M., 2018. Mannose-conjugated curcumin-chitosan nanoparticles: efficacy and toxicity assessments against Leishmania donovani. Int. J. Biol. Macromol. 111, 109–120 May 1.
Chávez-Fumagalli, M.A., Ribeiro, T.G., Castilho, R.O., Fernandes, S.O., Cardoso, V.N., Coelho, C.S., Mendonça, D.V., Soto, M., Tavares, C.A., Faraco, A.A., Coelho, E.A., 2015. New delivery systems for amphotericin B applied to the improvement of leishmaniasis treatment. Rev. Soc. Bras. Med. Trop. 48 (3), 235–242 May-Jun.
Cho, W.S., Kang, B.C., Lee, J.K., Jeong, J., Che, J.H., Seok, S.H., 2013. Comparative absorption, distribution, and excretion of titanium dioxide and zinc oxide nanoparticles after repeated oral administration. Part Fibre Toxicol 10 (1) Mar 26.
Corpas-López, V., Díaz-Gavilán, M., Franco-Montalbán, F., Merino-Espinosa, G., López-Viota, M., López-Viota, J., Belmonte-Reche, E., Pérez-del Palacio, J., de Pedro, N., Gómez-Vidal JA, M.-M.F., 2019. A nanodelivered Vorinostat derivative is a promising oral compound for the treatment of visceral leishmaniasis.
Coukell, A.J., Brogden, R.N., 1998. Liposomal amphotericin B: therapeutic use in the management of fungal infections and visceral leishmaniasis. Drugs 55 (4), 585–612.
Couvreur, P., Vauthier, C., 2006. Nanotechnology: Intelligent design to treat complex disease. Pharmaceutical Research. 23. Springer Science and Business Media Deutschland GmbH, pp. 1417–1450.
Danesh-Bahreini, M.A., Shokri, J., Samiei, A., Kamali-Sarvestani, E., Barzegar-Jalali, M., Mohammadi-Samani, S., 2011. Nanovaccine for leishmaniasis: preparation of chitosan nanoparticles containing Leishmania superoxide dismutase and evaluation of its immunogenicity in BALB/c mice. Int. J. Nanomedicine 6, 835.

Das, S., Roy, P., Mondal, S., Bera, T., B AM-C and S, 2013. One Pot Synthesis of Gold Nanoparticles and Application in Chemotherapy of Wild and Resistant Type Visceral Leishmaniasis.
de Souza, R.M., Maranhão, R.C., Tavares, E.R., Filippin-Monteiro, F.B., Nicodemo, A.C., Morikawa, A.T., Kanashiro, E.H., Amato, V.S., 2019 Nov 7. Lipid nanoparticles for amphotericin delivery in the treatment of American tegumentary leishmaniasis. Drug delivery and translational research 1–0.
Delavari, M., Dalimi, A., Ghaffarifar, F., Sadraei, J., 2014 Mar. In vitro study on cytotoxic effects of ZnO nanoparticles on promastigote and amastigote forms of Leishmania major (MRHO/IR/75/ER). Iran. J. Parasitol. 9 (1), 6.
Ebrahimi, K., Shiravand, M., Mahmoudvand, H., 2017. Biosynthesis of copper nanoparticles using aqueous extract of Capparis spinosa fruit and investigation of its antibacterial activity. Marmara Pharm J 21 (4), 866–8717.
Endo-Kimura, M., Janczarek, M., Bielan, Z., Zhang, D., Wang, K., Markowska-Szczupak, A., et al., 2019. Chemengineering Photocatalytic and Antimicrobial Properties of Ag 2 O/TiO 2 Heterojunction.
Espuelas, M.S., Legrand, P., Loiseau, P.M., Bories, C., Barratt, G., Irache, J.M., 2002. In vitro antileishmanial activity of amphotericin B loaded in poly(ε-caprolactone) nanospheres. Vol. 10. Journal of Drug Targeting. Taylor and Francis Ltd. 593–599.
Gaspar, R., Opperdoes, F.R., Preat, V., Roland, M., 1992a. Drug targeting with polyalkylcyanoacrylate nanoparticles: in vitro activity of primaquine-loaded nanoparticles against intracellular Leishmania donovani. Ann. Trop. Med. Parasitol. 86 (1), 41–49.
Gaspar, R., Préat, V., Opperdoes, F.R., Roland, M., 1992b. Macrophage activation by polymeric nanoparticles of polyalkylcyanoacrylates: activity against intracellular Leishmania donovani associated with hydrogen peroxide production. Pharm Res An Off J Am Assoc Pharm Sci 9 (6), 782–787.
Heidari-Kharaji, M., Taheri, T., Doroud, D., Habibzadeh, S., Badirzadeh, A., Rafati, S., 2016. Enhanced paromomycin efficacy by solid lipid nanoparticle formulation against Leishmania in mice model. Parasite Immunol. 38 (10), 599–608 Oct 1.
Hillaireau, H., Couvreur, P., 2009. Nanocarriers' entry into the cell: relevance to drug delivery. Cellular and Molecular Life Sciences. 66. Birkhauser Verlag Basel, pp. 2873–2896.
Leishmaniasis. (n.d.). Retrieved from. https://www.who.int/news-room/fact-sheets/detail/leishmaniasis.
Huh, A., Kwon, Y.J., 2011 Dec 10. "Nanoantibiotics": a new paradigm for treating infectious diseases using nanomaterials in the antibiotics resistant era. J. Control. Release 156 (2), 128–145.
Iqbal, J., Abbasi, B.A., Batool, R., Khalil, A.T., Hameed, S., Kanwal, S., Ullah, I., Mahmood, T., 2019a. Biogenic synthesis of green and cost effective cobalt oxide nanoparticles using Geranium wallichianum leaves extract and evaluation of in vitro antioxidant, antimicrobial, cytotoxic and enzyme inhibition properties. Materials Research Express 6 (11), 115407 Oct 25.
Iqbal, J., Abbasi, B.A., Mahmood, T., Hameed, S., Munir, A., Kanwal, S., 2019b. Green synthesis and characterizations of nickel oxide nanoparticles using leaf extract of Rhamnus virgata and their potential biological applications. Appl. Organomet. Chem. 33, e4950.
Ismail, H.H., Hasoon, S.A., Saheb, E.J., 2019. The anti-Leishmaniasis activity of green synthesis silver oxide nanoparticles. Annals of Tropical Medicine and Health 22, 28–38 Sep.
Jain, V., Gupta, A., Pawar, V.K., Asthana, S., Jaiswal, A.K., Dube, A., et al., 2014. Chitosan-assisted immunotherapy for intervention of experimental leishmaniasis via amphotericin B-loaded solid lipid nanoparticles. Appl. Biochem. Biotechnol. 174 (4), 1309–1330.
Jeevanandam, J., Barhoum, A., Chan, Y.S., Dufresne, A., Danquah, M.K., 2018. Review on nanoparticles and nanostructured materials: history, sources, toxicity and regulations. Beilstein J Nanotechnol 9, 1050–1074.
Keyhani, A., Ziaali, N., Shakibaie, M., Kareshk, A.T., Shojaee, S., Asadi-Shekaari, M., Sepahvand, M., Mahmoudvand, H., 2019 Dec 17. Biogenic selenium nanoparticles target chronic toxoplasmosis with minimal cytotoxicity in a mouse model. J. Med. Microbiol. https://doi.org/10.1099/jmm.0.001111 (Epub ahead of print).
Khatami, M., Alijani, H.Q., Heli, H., Sharifi, I., 2018. Rectangular shaped zinc oxide nanoparticles: green synthesis by Stevia and its biomedical efficiency. Ceram. Int. 44 (13), 15596–15602 Sep 1.
Kirchberger, M.C., Schliep, S., Bogdan, C., 2019. Rhinophyma-like cutaneous leishmaniasis due to Leishmania aethiopica treated successfully with liposomal amphotericin B. Am J Trop Med Hyg 100 (2), 231–232 Feb.
Kumar, P., Shivam, P., Mandal, S., Prasanna, P., Kumar, S., Prasad, S.R., Kumar, A., Das, P., Ali, V., Singh, S.K., Mandal, D., 2019. Synthesis, characterization, and mechanistic studies of a gold nanoparticle–amphotericin B covalent conjugate with enhanced antileishmanial efficacy and reduced cytotoxicity. Int. J. Nanomedicine 14, 6073.
Lembo, D., Cavalli, R., 2010. Nanoparticulate delivery systems for antiviral drugs. Antivir. Chem. Chemother. 21, 53–70.
Lopes, R, Eleutério, C, ... LG-EJ of, 2012. Lipid nanoparticles containing oryzalin for the treatment of leishmaniasis.
M1, Beija, Salvayre, R., Lauth-de Viguerie, N., Marty, J.D., 2012 Sep. Colloidal systems for drug delivery: from design to therapy. Trends Biotechnol. 30 (9), 485–496.
Maeski, S., 2002. Drug delivery system of anti-fungal and parasitic agents. Curr. Pharm. Des. 8 (6), 433–440.
Mahmoudvand, H., Fasihi Harandi, M., Shakibaie, M., Aflatoonian, M.R., ZiaAli, N., Makki, M.S., Jahanbakhsh, S., 2014a. Scolicidal effects of biogenic selenium nanoparticles against protoscolices of hydatid cysts. Int. J. Surg. 12 (5), 399–403.
Mahmoudvand, H., Sharififar, F., Sharifi, I., Ezatpour, B., Fasihi Harandi, M., Makki, M.S., Zia-Ali, N., Jahanbakhsh, S., 2014b. In vitro inhibitory effect of Berberis vulgaris (Berberidaceae) and its main component, berberine against different Leishmania species. Iran. J. Parasitol. 9 (1), 28–36.
Mahmoudvand, H., Shakibaie, M., Tavakoli, R., Jahanbakhsh, S., Sharifi, I., 2014c. In vitro study of leishmanicidal activity of biogenic selenium nanoparticles against Iranian isolate of sensitive and glucantime-resistant Leishmania tropica. Iran. J. Parasitol. 9 (4), 452–460.
Mahmoudvand, H., Kheirandish, F., Mirbadie, S.R., Kayedi, M.H., Rezaei Riabi, T., Ghasemi, A.A., Bamorovat, M., Sharifi, I., 2017. The potential use of methotrexate in the treatment of cutaneous leishmaniasis: in vitro assays against sensitive and meglumine antimoniate-resistant strains of Leishmania tropica. Iran. J. Parasitol. 12 (3), 339–347.
Malli S, Pomel S, Ayadi Y, Delomenie C, Da Costa A, Loiseau PM, Bouchemal K. Topically applied chitosan-coated poly (isobutylcyanoacrylate) nanoparticles are active against cutaneous leishmaniasis by accelerating lesion healing and reducing the parasitic load. ACS Applied Bio Materials. 2019 May 8.
Mohtasebi, S., Mohebali, M., Elikaee, S., Akhoundi, B., Foroushani, A.R., Teimouri, A., Yarizadeh, H., 2019. In vitro and in vivo anti-parasitic activity of biogenic antimony sulfide nanoparticles on Leishmania major (MRHO/IR/75/ER). Parasitol. Res. 118 (9), 2669–2678 Sep 1.
Nadhman, A., Nazir, S., Khan, M.I., Arooj, S., Bakhtiar, M., Shahnaz, G., Yasinzai, M., 2014 Dec 1. PEGylated silver doped zinc oxide nanoparticles as novel photosensitizers for photodynamic therapy against Leishmania. Free Radic. Biol. Med. 77, 230–238.
Nadhman, A., Khan, M.I., Nazir, S., Khan, M., Shahnaz, G., Raza, A., Shams, D.F., Yasinzai, M., 2016. Annihilation of Leishmania by daylight responsive ZnO nanoparticles: a temporal relationship of reactive oxygen species-induced lipid and protein oxidation. Int. J. Nanomedicine 11, 2451.
Nanotherapeutics CV-PN, 2019. Polymeric Nanomaterials: Recent Developments, Properties and Medical Applications.
. Nikolić V, Ilić-Stojanović S, Petrović S, … AT-… and B of, 2019. Administration Routes for Nano Drugs and Characterization of Nano Drug Loading.
Oliveira, H., Bednarkiewicz, A., Falk, A., Fröhlich, E., Lisjak, D., Prina-Mello, A., et al., 2019. Critical considerations on the clinical translation of upconversion nanoparticles (UCNPs): recommendations from the European upconversion network (COST action CM1403). Advanced Healthcare Materials. 8. Wiley-VCH Verlag.
Ovais, M., Khalil, A.T., Raza, A., Islam, N.U., Ayaz, M., Saravanan, M., Ali, M., Ahmad, I., Shahid, M., Shinwari, Z.K., 2018. Multifunctional theranostic applications of biocompatible green-synthesized colloidal nanoparticles. Appl. Microbiol. Biotechnol. 102 (10), 4393–4408 May 1.
Oyama, J., Lera-Nonose, D., tropica, Á.R.-M.-A., 2019. Potential of Pluronics® P-123 and F-127 as Nanocarriers of Anti-Leishmania Chemotherapy.
Papagiannaros, A, Bories, C, ... CD-B, 2005. Antileishmanial and trypanocidal activities of new miltefosine liposomal formulations.
Rijal, S., Sundar, S., Mondal, D., Das, P., Alvar, J., Boelaert, M., 2019. Eliminating visceral leishmaniasis in South Asia: the road ahead. BMJ 22 (364), k5224.
Rodrigues, J., Croft, S., Fessi, H., CB-… : official organ of, 1994. The Activity and Ultrastructural Localization of Primaquine-Loaded Poly (d, l-lactide) Nanoparticles in Leishmania Donovani Infected Mice.
Roy, P., Das, S., Bera, T., SM-I journal of, 2010. Andrographolide Nanoparticles in Leishmaniasis: Characterization and In Vitro Evaluations.
Samuel Singh, N., Phillips Singh, D., 2019. A review on major risk factors and current status of visceral leishmaniasis in North India a review on major risk factors and current status of visceral leishmaniasis in. North India Am J Entomol. 3 (1), 6–14.
Sekhon, B.S., Saluja, V., 2011. Nanovaccines-an overview. Int J Pharm Front Res 1 (1), 101–109.
Shahnaz, G., Edagwa, B.J., McMillan, J., Akhtar, S., Raza, A., Qureshi, N.A., et al., 2017 Jan 1. Development of mannose-anchored thiolated amphotericin B nanocarriers for treatment of visceral leishmaniasis. Nanomedicine 12 (2), 99–115.

Sharifi, I., Aflatoonian, M.R., Fekri, A.R., Hakimi Parizi, M., Aghaei Afshar, A., Khosravi, A., Sharifi, F., Aflatoonian, B., Khamesipour, A., Dowlati, Y., Modabber, F., Nadim, A., 2015. A comprehensive review of cutaneous leishmaniasis in Kerman province, southeastern Iran-narrative review article. Iran. J. Public Health 44 (3), 299–307 Mar.

Siefert, A., Ehrlich, A., Corral, M., KG-P, Biomaterials, 2016. Immunomodulatory Nanoparticles Ameliorate Disease in the Leishmania (Viannia) Panamensis Mouse Model.

Singh, A., Yadav, T., Pandey, B., VG-A of T, 2019. Engineering Nanomaterials for Smart Drug Release: Recent Advances and Challenges.

Sirelkhatim, A., Mahmud, S., Seeni, A., Kaus, N.H., Ann, L.C., Bakhori, S.K., Hasan, H., Mohamad, D., 2015. Review on zinc oxide nanoparticles: antibacterial activity and toxicity mechanism. Nano-Micro Letters 7 (3), 219–242 Jul 1.

Sousa-Batista, A., Poletto, F., Philipon, C., Parasitology, S.G., 2017. Lipid-Core Nanocapsules Increase the Oral Efficacy of Quercetin in Cutaneous Leishmaniasis.

Sousa-Batista, A.J., Cerqueira-Coutinho, C., do Carmo, F.S., Albernaz, M.S., Santos-Oliveira, R., 2019. Polycaprolactone antimony nanoparticles as drug delivery system for leishmaniasis. Am. J. Ther. 26 (1), e12–e17. https://doi.org/10.1097/MJT.0000000000000539 Jan/Feb.

Sundar, S., Chakravarty, J., Meena, L.P., 2019. Leishmaniasis: treatment, drug resistance and emerging therapies. Expert Opinion on Orphan Drugs. 7. Taylor and Francis Ltd, pp. 1–10.

Sunyoto, T., Boelaert, M., Meheus, F., 2019. Understanding the economic impact of leishmaniasis on households in endemic countries: a systematic review. Expert Review of Anti-Infective Therapy. 17. Taylor and Francis Ltd, pp. 57–69.

Tavakoli, P., Ghaffarifar, F., Delavari, H., Shahpari, N., 2019. Efficacy of manganese oxide (Mn2O3) nanoparticles against Leishmania major in vitro and in vivo. J. Trace Elem. Med. Biol. 56, 162–168 Dec 1.

Tomiotto-Pellissier, F., Menegazzo Miranda, M., Cataneo Fundação Carlos Chagas, A., Guadalupe Tardeli Andrade, C., Rodrigues Fanti, J., Menegazzo Miranda-Sapla, M., et al., 2020. Biogenic Silver Nanoparticles Inducing Leishmania Amazonensis Promastigote and Amastigote Death In Vitro.

Ureña-Búrquez, L., García-Rendón, A., Fuel, S.R.-W., 2019a. Preparation and Characterization of a Nanovaccine of pVAX1-NH36 for Leishmaniasis.

Ureña-Búrquez, L.A., García-Rendón, A., Rochín-Wong, S., Tejeda-Mansir, A., 2019b. Preparation and characterization of a nanovaccine of pVAX1-NH36 for leishmaniasis. Fuel 235, 1077–1082 Jan 1.

V1, Yardley, Croft, S.L., 2000. A comparison of the activities of three amphotericin B lipid formulations against experimental visceral and cutaneous leishmaniasis. Int. J. Antimicrob. Agents 13 (4), 243–248.

Valle, I.V., Machado, M.E., Araújo, C.D., da Cunha-Junior, E.F., da Silva Pacheco, J., Torres-Santos, E.C., da Silva, L.C., Cabral, L.M., do Carmo, F.A., Sathler, P.C., 2019. Oral pentamidine-loaded poly (d, l-lactic-co-glycolic) acid nanoparticles: an alternative approach for leishmaniasis treatment. Nanotechnology 30 (45), 455102 Aug 21.

van, Griensven J., Diro, E., 2019 Mar. Visceral leishmaniasis: recent advances in diagnostics and treatment regimens. Infect. Dis. Clin. N. Am. 33 (1), 79–99.

Want, M, Islamuddin, M, Chouhan, G, ... HO-C and SB, 2015. Therapeutic efficacy of artemisinin-loaded nanoparticles in experimental visceral leishmaniasis.

Wolfram, J., Zhu, M., Yang, Y., Shen, J., Gentile, E., Paolino, D., Fresta, M., Nie, G., Chen, C., Shen, H., Ferrari, M., Zhao, Y., 2015. Safety of nanoparticles in medicine. Curr. Drug Targets 16 (14), 1671–1681.

Yuksel, A., Edward, T., MC-J of P for, 2019. Effect of Particle Size Distribution on Near-Field Thermal Energy Transfer Within the Nanoparticle Packings.

Zahir, A.A., Chauhan, I.S., Bagavan, A., Kamaraj, C., Elango, G., Shankar, J., Arjaria, N., Roopan, S.M., Rahuman, A.A., Singh, N., 2015. Green synthesis of silver and titanium dioxide nanoparticles using Euphorbia prostrata extract shows shift from apoptosis to G0/G1 arrest followed by necrotic cell death in Leishmania donovani. Antimicrob. Agents Chemother. 59 (8), 4782–4799 Aug 1.

Zhong, J., Huang, C., 2019. Crowding effects of nanoparticles on energy absorption in solar absorption coatings. J. Appl. Phys. 125 (3) Jan 21.