Original Article

A Systemic Review On Treatment Of Neglected Tropical Disease Using Nanoparticulate Drug Delivery System

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Abstract

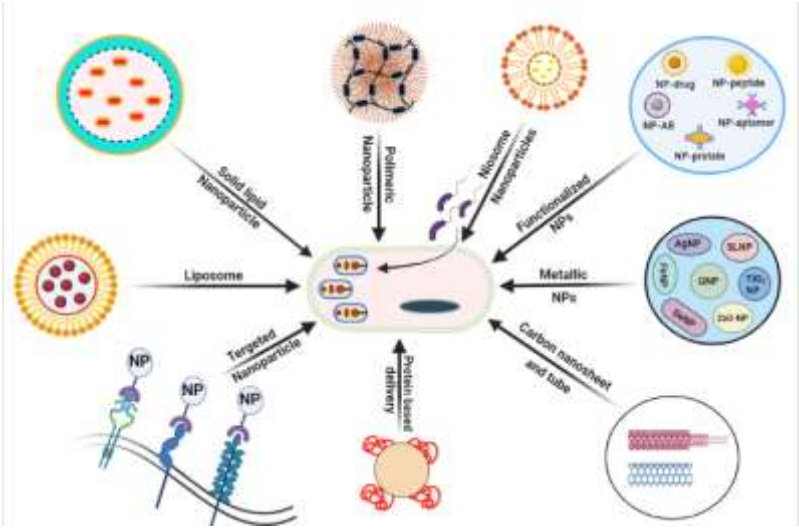
Vectors are biological organisms that can spread infectious pathogens from animals to individuals or between individuals. Human health issues are called vector-borne diseases when germs, parasites, and viruses are released by vectors. The presence of these diseases is extreme in the tropical and subtropical zone, and they mainly affect the poorest populations. Every year there are more than 700,000 deaths occurred by Vector-borne diseases. Leishmaniasis is an extensively transmitted protozoan vector-borne disease and it has been one of the most neglected tropical diseases for decades. *Leishmania donovani* and *Leishmania infantum* have been the most common species out of 20 intracellular protozoan parasites of genus *Leishmania* that causes visceral leishmaniasis (VL), the deadliest form. Due to the lack of a potent vaccine and effective vector control plan, chemotherapy has been considered a prime tool for the treatment of leishmaniasis. The antileishmanial drugs widely used are highly toxic, injectable (painful and require hospitalization), very expensive, and inferior efficacy for HIV co-infected VL patients. At present antimonials come in first-line therapy and failure of which the second-line drug Amphotericin B is generally considered. Miltefosine, an antineoplastic agent, had been emerged as the only oral anti-leishmanial drug. Unfortunately, the parasites introduce unavoidably resistance toward most of these antileishmanial drugs. Many resistance mechanisms that arise by these parasites are associated with a minimum uptake or increased efflux of the drug due to modification or altered expression of membrane transporters. Therefore, up-to-date strategies are required to discover more effective and less toxic nanomedicines that could specifically solve drug resistance associated with *Leishmania* chemotherapy. The Leishmania parasites completely contaminate highly phagocytic cells (macrophages), this aspect can be utilized for the targeted delivery formulation of nanoparticles. A number of nanotechnology-based approaches and products have come to light as anti-leishmanial drugs. These approaches are polymeric nanoparticles, liposomes, metallic oxide nanoparticles, lipid nano-capsules, nanosuspension, nanotube, and nano vaccines. These nanoparticles have exclusive inherent properties such as large pore size, high surface area, good biocompatibility and biodegradability, stable aqueous dispersion, etc. This review offers an overview of the present leishmania disease situation globally, its traditional pharmacological treatments, and how the usage of various nanoparticles can help to solve the issue of drug resistance.

Keyword: Neglected disease, Leishmania, Antileishmanial drugs, Nanoparticles, Treatment

INTRODUCTION

A set of infectious disorders known as neglected tropical diseases (NTDs) predominates in underdeveloped regions of the world, particularly in developing nations. These types of infectious diseases are spreading rapidly in tropical and subtropical areas due to taking unsafe water, poor sanitation systems, poor housing conditions, and insufficient health infrastructures [1]. Around 1.4 billion people in 149 countries are affected by 20 different types of Neglected tropical diseases [2]. One of the most deadly neglected tropical illnesses, leishmaniasis affects about 12 million people worldwide and 350 million people are at risk of contracting it in 98 different countries[3]. Two million new leishmania cases occur each year. An obligate intracellular parasitic protozoan of the genus Leishmania is responsible for vector-borne zoonotic disease Leishmaniasis [4]. About 20 Leishmania species (*L. donovani*, *L. infantum*, *L. amazonensis*, *L. mexicana*) are responsible for leishmaniasis diseases [5]. There are two life forms present in the Leishmania parasite, i.e. promastigotes and amastigotes. Promastigotes are elongated, flagellated, and generally present in the mid gut of the female sandfly (insect vector). Amastigotes are small, rounded, non-motile forms and generally present in macrophages, antigen-presenting cells like dendritic cells, neutrophils [6]. Female sand fly needed high protein during the egg-laying period and they take blood meals of humans or domestic animals. When a female sand fly suckers blood from a person who has leishmaniasis, a leishmania parasite transformation takes place (human or animal) [7]. At the moment of sand fly

bite for taking a meal, the Leishmania parasites attack the local phagocytic host cells. After that, the promastigotes form converted to amastigotes form and multiply by simple division until bursting the host cell. There are three major types of the disease: cutaneous leishmaniasis (CL), which is the most prevalent type, visceral leishmaniasis (Kala-azar) (VL), which is the most severe type, and lastly, mucosal leishmaniasis (ML). About 90% of VL global cases occurred in Brazil, Ethiopia, India, Bangladesh, Sudan, Somalia, Kenya, and Nepal. On the other hand, 70% of CL cases occurred in Brazil, Colombia, Costa Rica, Ethiopia, Iran, Afghanistan, and Algeria [8]. The Leishmania parasites show extraordinary ability, that affected people's complete immune system comes under their control. The parasites show unmanageable proliferation inside the macrophages, which mainly imbalances the host immunity [9]. Macrophage's phagolysosomes are the primary focus of antileishmanial treatment because amastigotes are living inside it. But it is not a simple task because a lot of structural barriers are present to inhibit which are need to overcome by antileishmanial drugs. Available marketed antileishmanial drugs are very expensive, highly toxic and parasite resistance developed [10]. Unavailability of an efficient vaccination and vector control strategy, chemotherapy is a prime tool for treating leishmaniasis. At present antimonials come in first-line therapy, which is a costly, painful, and toxic chemotherapy with reducing effectiveness caused by parasitic resistances [11]. After the failure of first-line treatment amphotericin B (AmB) is considered for second-line drug therapy. It is a macrolide antifungal agent. Generally, poor people and developing countries are not able to use these intravenous drugs widely due to the high cost and it required hospitalization for administration [12]. Another optimistic drug is alkylphosphocholine derivative miltefosine. This drug was first synthesized as an antineoplastic drug, later it is used in the treatment of leishmaniasis. Miltefosine is the only orally available antileishmanial drug, which is used to treat visceral leishmaniasis [13]. Miltefosine shows several side effects like vomiting, diarrhea, and gastrointestinal disturbance. Miltefosine shows teratogenic effects, due to this reason it is not prescribed for pregnant women. Another antileishmanial drug is paromomycin and it is isolated from the cultures of *Streptomyces rimosus.* It comes under the aminocyclitol aminoglycosides category. Apart from these drugs, other compounds show anti-leishmanial activity like aromatic diamidine pentamidine, antifungal azole fluconazole. Unfortunately, the parasites introduce unavoidably resistance toward most of these antileishmanial drugs. The crucial obstacle associated with leishmaniasis treatment is parasite infects the macrophage. Due to this reason conventional antileishmanial drugs facing trouble entering inside the macrophages to kill the parasite[14]. Therefore, up-to-date strategies are required to discover more effective and less toxic nanomedicines that could specifically solve drug resistance associated with Leishmania chemotherapy. For this reason, anti-leishmanial drugs are combined with suitable nanocarriers, which have shown promising effects in leishmania treatment. Anti-leishmanial drug-loaded nanocarriers are having the potency to penetrate macrophages and then release the drug inside the cell. As a result, the high concentration of drugs killed the protozoa. These way nanocarriers are used in the treatment of leishmania. The fundamental method of treating leishmaniasis is to use suitable nanocarriers, which have the potential to cross biological barriers, to deliver the medications directly to macrophages [15]. Nanocarriers have some exclusive inherent properties like they reduce the toxicity of the drug, improve selectivity, regulate drug pharmacokinetics factors, boost drug solubilization in the body, give safeguard the drug from degradation, stimulate a sustained drug release straight to the target site[16]. Nanocarriers have also other advantages like more than one drug can be used; surface modification can be done to increase parasite selectivity. Different nanoparticles like polymers, nanospheres, liposomes are already proven very important drug delivery nanocarriers. In the field of leishmaniasis treatment nanotechnology shows optimistic results. The goal of this review is to discuss the current leishmaniasis treatment and to draw attention to a recent study on nanotechnology-based alternatives for the treatment of leishmaniasis that use polymers, metal nanoparticles, liposomes, a carbon-based material, polymeric nanoparticles, solid lipid-based nanoparticles, nanotubes, and nitric oxide-releasing nanoparticles.



A representative figure of different NPs (liposomal, niosomal, SLN, Polymeric, metallic etc.) that is used for leishmaniasis delivery.

ANTIMONIALS:

Professor Upendranath Brahmachari first synthesized the pentavalent antimonials (Sb-V) in 1920 [17]. For the treatment of leishmaniasis, pentavalent antimonials are used as a chemotherapeutic agent for over 60 years. Usually, trivalent antimony (Sb-III) is active against Leishmania species but this form is toxic to the human body. Due to this reason pentavalent antimony forms are used. The pentavalent antimony comes in the form of complexation with meglumine (Glucantime) or sodium stibogluconate (Pentostam). This antimonial pentavalent form enters the host cells and crosses the phagolysosomal membrane and then converts to trivalent antimonial form inside the macrophages. The pentavalent antimony form is converted to the trivalent form inside the macrophage using thiols from the parasite and host cell surfaces, which acts on the amastigote forms of the parasite [18]. A parenteral route like intravenous (IV), intramuscular (IM), Intralymphatic (IL) are used for administering pentavalent antimonial drugs. Generally, the parasite's energy metabolism process is get hampered by antimonial drugs. These drugs are blocked the glycolytic pathway and fatty acid oxidation process, which causes inhibition of the biosynthesis of essential macromolecules in the amastigotes [19]. Some study report shows that antimonial drug-induced apoptosis-like process for treating amastigotes, which involves DNA fragmentation and externalization of phosphatidylserine on the outer surface of the plasma membrane [20]. Antimonial drugs are showed several adverse effects like hepatotoxicity, reversible renal failure, headache, nausea, pancreatitis, myalgia, asthenia, cardiotoxicity, and blood disorders due to their high toxicity [21]. That's why patients treated with the antimonial drugs are required hospitalization for monitoring different physiological parameters like renal function, amylase level, liver enzyme level, etc. Antimonial drugs are used worldwide as a first-line treatment for leishmaniasis for several decades [22]. When HIV co-infected patients are treated with antimonial drugs, it shows increased side effects and mortality rates [23]. Recently, Leishmania parasites develop a strong resistance towards antimonial drugs. Generally, different factors are responsible for developing resistance in antimonial drugs. These factors are gene amplification, decreased drug uptake, increased efflux mechanism, inhibition of drug activation, reduced drug concentration inside the parasite, etc. Another important factor is thiol metabolism which has a significant impact on the development of resistance [24]. Glutathione formation is inhibited by the thiol molecule, the macrophage's internal oxidative stress is increased, and pentavalent antimonials are converted to trivalent form. That's why an increased number of intracellular thiol levels are associated with high antimonial resistance.

AMPHOTERICIN B:

Amphotericin B (AmB) constitute by a lactone ring known as macrolactone ring that is linked to a mycosamine by a glycosidic linkage. It was first isolated from the actinomycete *Streptomyces nodosus* in 1950. Due to its remarkable efficacy in treating parasitic fungi and protozoa (Leishmania species), Food and Drug Administration approved Amphotericin in 1960. It shows potent antileishmanial activity against visceral leishmaniasis, that's why it is used as a second-line treatment. In the cell membrane, AmB forms complexes with 24- substituted sterols, such as ergosterol. These complexes unchain pores which customize the ion balance and cause cell death [24]. The molecular weight of AmB is very high, due to this it shows poor bioavailability, poor solubility, and poor permeability. High toxicity profile and various side effects are associated with AmB. AmB forms toxic oligomeric aggregates in the bloodstream which accumulate in different organs after the administration through the IV route. Due to its acute toxicity, several side effects are also present like fever, nausea, cardiac alterations, liver damage, nephrotoxicity, etc. To beat this situation a new formulation was developed. Amphotericin B combined with lipid and formed liposomal Amphotericin B, which shows remarkable success. In this new formulation, drug release is controlled in the bloodstream, toxicity is reduced and therapeutic efficacy is also improved [25]. The concentration of liposomal AmB is very high in macrophages, which increases drug concentration in infected tissues, mainly in the liver and spleen [26]. This formulation is suggested by WHO due to its high efficacy but poor people are not accessing this formulation due to its high cost.

MILTEFOSINE:

It is a synthetic phospholipid analog and developed as an anticancer agent. From various in vitro and in vivo experimental models, it was confirmed that miltefosine having antileishmanial activity. In 1980, the first antileishmanial activity was found in miltefosine and after the clinical trial, it was approved for marketing in India in march 2002. It is the first orally available antileishmanial drug used to treat visceral leishmania and cutaneous leishmania. Miltefosine can cross the cellular plasma membrane due to its amphiphilic structure [27]. This drug works directly against the parasite through its mechanism of action, which alters lipid metabolism and causes parasite apoptosis. Another mechanism of action is also shown by miltefosine to kill the parasite. At the host cell level, it stimulates the production of nitric oxide synthetase- 2 ($iNOS_2$) that catalyzes the formation of nitric oxide (NO) that primarily destroys the parasite inside the macrophages [28]. Different types of side effects are associated with miltefosine like diarrhea, nausea, dizziness, vomiting, the elevation of liver enzyme, renal dysfunction, reduced reproductive capacity.

PAROMOMYCIN:

Paromomycin is isolated from *Streptomyces krestomuceticus* and it is a class of aminoglycoside antibiotics. In 1960 it was first identified but it was used for antileishmanial treatment in 2006 [29]. Paromomycin is used to treat visceral leishmania through the IV route. It is also used in cutaneous leishmania through tropical treatment. The mechanism of action of Paromomycin is not clear properly. But several study reports show that paromomycin can damage the cell's metabolism by hampering the mitochondrial membrane potential, inhibits protein synthesis and cell respiration, leading to the death of the parasite. It shows poor bioavailability and different adverse effects like nausea, diarrhea, nephrotoxicity [30].

Drug-Loaded Nanocarrier: A Systems For The Treatment Of Leishmaniasis

LIPOSOMES:

In the year 1965, Bangham et al., reported that these all closed vesicular structures comprising of lipid bilayers could be arched when phospholipids are hydrated by the addition of water [31]. First these structures were called as 'smectic mesophases' by Bangham and then it was called as 'liposomes' by Gerald Weissman. These liposomes are basically microscopic bilayered vesicular structures, which are biocompatible, biodegradable, and non-immunogenic in nature; which can be categorized as large unilamellar vesicles (LUVs), multilamellar vesicles (MLVs), and small unilamellar vesicles (SUVs). Generally occurring phospholipids are the vital components of the bilayers, which make them biodegradable and non-toxic Liposomes which have the ability to capture drugs both in a lipid and in an aqueous phase assembly, making themselves a striking delivery system for both the hydrophobic and hydrophilic drugs. Drugs entrapped into liposomes are not degraded by the body's external environment. High entrapment ability and concentrated drug toxicity further make them a similar carrier for drug delivery. They can set out the release of drugs by targeting the drugs to the site of action or by long-lasting circulation of drugs or by site evasion drug delivery. It has also been demonstrated that drugs absorbed in liposomes are primarily assigned to reticuloendothelial tissues, such as the lungs, liver, and spleen [32].

The usage of liposomes over conventional medications has several benefits because they have improved their ability to stay in the body and maintain blood flow for extended periods of time [33]. Drug release can be sustained by liposomes, including frequency of administration, control of the release, and dosage reduction [34]. Due to all of these qualities, liposomes are frequently used in leishmaniasis treatment research and hence, considered as the most trusted clinical drug. In the instance of anti-leishmanial therapy, the medications are sealed inside a liposomal layer, allowing for very effective intracellular delivery to the leishmanial amastigotes. These liposomes have the capacity to enter macrophages through the process of phagocytosis and deliver the medication directly to the parasite's location [35]. The usage of nanosized liposomes is becoming more common in many medical procedures for the treatment of illnesses, particularly when it comes to the administration of chemotherapy medications. A key benefit of the liposomes is their improved pharmacokinetic characteristics and target-specificity [36]. The AmB-liposome formulation, which lessens the negative effects brought on by amphotericin B, is the best illustration of a liposome [37]. The liposomal AmB has been shown to be the most effective among the several types of AmB formulation, including AmB lipid networks, AmB colloidal solutions, and AmB liposomes [38]. A study found that the liposome formulation can limit the negative effects of traditional medications. By adopting the freeze-drying method, various formulations, such as paromomycin, miltefosine, and meglumine antimoniate, have been created to combat leishmanial infections. [39]. It has been estimated in one of the studies that, on the surface of the macrophages are receptors that regulate cellular processes such secretion, activation, endocytosis, and recognition [40].

EMULSOMES:

Emulsomes are colloidal carriers made up of nano-emulsions of lipid-containing particles that are stabilised by at least one phospholipid envelope and have a lipid core that is in a liquid or solid crystalline phase at a temperature of at least 25°C. Emulsomes are reported to be used for the rectal, oral, intranasal, parenteral or topical delivery of both water-soluble and fat-soluble drugs [41]. These formulations have type that is halfway between oil-in-water and liposomes emulsions. Like a typical oil-in-water emulsion, particles have a hydrophobic core that is stabilised by one or more phospholipid bilayers. Liposomes are an example of a phospholipid-based particle. The internal lipid core is comprised of triglycerides (such as trilaurin, tristearin, trimyristin, tricaprin and tripalmitin) and the surrounding cover consists mainly of phospholipids (such as soybean or egg lecithin, phosphatidyl-choline, diphosphatidylglycerol, phosphatidyl ethanolamine, phosphatidyl glycerol, phosphatidylserine, etc.) Emulsomes have the advantage of high drug loading of lipophilic drugs such as AmB and also, owing to their colloidal nature. So, it can be very useful for the treatment of VL through targeting macrophages. Gupta et al., developed AmB-bearing emulsomes and evaluated the effect of it in the treatment of leishmaniasis. efficacy. When administered at a dose of 0.5 mg/kg intracardially on alternate days, AmB emulsomes produced better results in in vivo tests on L. donovani-infected hamsters (51.7 5.4 percent parasite inhibition) than AmB-Deoxycholate (AmB-Doc) (30.4 4.8 percent parasite inhibition) in the splenic macrophages [42].

SOLID LIPID NANOPARTICLES (SLNS):

Solid lipid-based nanoparticles are a more recent development in the field of nanocarriers. This class includes nanostructured lipid carriers (NLCs) and solid lipid nanoparticles (SLNs), and the way they differ from one another

depends on the composition of their respective matrices [43]. Emulsifiers are used to stabilize the lipid-based nanospheres known as SLNs, which remain solid at body temperature [44]. They have a size lesser than 1000 nm [45]. They also have a number of benefits, including simple large-scale manufacturing, the ability to shield drugs from harsh environmental conditions using a technique called high-pressure homogenization, and the fact that they are both biocompatible and biodegradable [46]. They do, however, have some restrictions due to its crystalline structure including low drug loading efficacy and during storage there are chances of drug expulsion of the crystalline structure due to which initial burst emission could take place [47]. In a trial, treatment for leishmania infection was administered using chitosan-coated SLNs containing AmB. The SLNs have a stronger effect than commercially available AmB-isome and Fungizone formulations, as demonstrated by their antileishmanial activity. Furthermore, SLNs are less harmful than market products, according to a mouse study on acute toxicity. [48]. Another study examined the effectiveness of paromomycin sulphate loaded with SLN against *L. tropica* using a mouse model.. It was discovered that utilizing PM loaded with SLNs was more effective at inhibiting parasite proliferation and transitioning to the Th1 response than using paromomycin sulphate alone [49].

LIPID NANO CAPSULES:

Nanocarriers called lipid nano-capsules (LNs) that resemble lipoproteins and have sizes between 20 and 100 nm. Lipid nanocapsules are mostly made of lipids, with a surfactant membrane enclosing them. Liposomes and polymeric nanocapsules were combined to create the hybrid structure of lipid nanocapsules [50]. LNs are often produced using a solvent-free technique, increasing their bioavailability and stability. The key benefit of LNs is that they deliver the drug to the intended place, thus reducing the dosage and adverse side effects [51]. According to one of the research, LNs were developed by, hydrophobic olive oil and a hydrophilic component named chitosan was used to make the core and the outer shell, respectively [52]. Miltefosine is an alkyl-phospholipid that is primarily used to treat leishmaniasis by disrupting the parasite's Ca2+ homeostasis. The damage to the promastigotes suggested that the composition of NPs loaded with miltefosine boosted efficiency against leishmaniasis. The LNs also guaranteed stability and prolonged drug release. The LN oral drugs were created using modern technology [53].

NANOTUBES:

Nanotubes are cylindrical hollow molecules which are manufactured from inorganic and metallic materials. A number of studies proved that nanotubes are very good nanocarriers. A study investigated how carbon nanotubes (CNTs) are related to the anti-leishmanial effectiveness of AmB. Scientists found that this formulation have better killing efficacy of *L. donovani* than that with the formulation without AmB [54,55]. According to a study conducted from Established Betulin connected with CNTs as an anti-leishmanial formulation, the new anti-leishmanial preparation's cytotoxicity was determined to be superior to the control group [56]. Another study utilised linked AmB, an antileishmanial medication formulation, together with functionalized carbon nanotubes (f-CNTs), which minimized the toxicity of the medicine. Compared to AmB, this formulation was able to more effectively limit the proliferation of parasites. This medicine enhances the efficacy of the medication. Additionally, the liver and kidneys of mice exhibited harmful effects [57]. Although they are still in the preclinical stage, carbon nanotubes have not yet been created for drug delivery in humans.

MICROSPHERES:

Microspheres are matrix-type compound which is composed of synthetic or natural polymers in which drugs may be adsorbed at the surface, or may be entrapped or dissolved in it. These particles range in size from 1 to 1000 m. AmB-loaded microspheres resulted in higher drug concentrations in the liver, spleen, and bone marrow and lower amounts in the kidneys and lungs when administered into the body, hence reducing toxicity. Given that it can be found in pure form and is non-toxic, biodegradable, and immuneogenic, albumin is widely employed to repair microspheres. Dea-Ayuela et al., tested the anti-leishmanial activity of albumin microspheres filled with AmB in *L. infantum* infected golden hamsters [58]. They found that the encapsulated drug showed 88.8 and 87.2% reduction at the shorter stage of infection (day 32 p.i.) and of 66.7 and 54% reduction at the later stage of infection (day 135 p.i.) in liver and spleen parasite load. Gradually, at a dose of 1 mg/kg administered by the intra-cardiac route, was compared with untreated animals, whereas free AmB was found to be inactive. In an another study, Sanchez-Brunete et al., compared the albumin microspheres of AmB with AmB-Doc and found that acute toxicity of AmB loaded albumin microspheres was lower than that of the AmB-Doc in *L. infantum*-infected golden hamsters [59]. The AmB-loaded albumin microspheres increased the degree of antileishmanial activity in the spleen (72 percent PI) and liver (90 percent PI) compared to AmB-Doc at a dose of 2 mg/kg. Even a significantly higher dose of AmB microspheres administered as an intravenous bolus (40 mg/kg (body weight)) did not result in an Metals have been employed in medicines since ancient times. Antileishmanial activity requires the use of a wide range of metallic nanoparticles due to their low toxicity and great efficacy [60, 61]. Metal nanoparticles were initially theorised in the 1850s. A study was done using glycine-coated iron oxide (Fe3O4) nanoparticles that contained the AmB drug to treat visceral leishmaniasis. The use of nanoparticles with sizes between 10 and 15 nm allowed for the regulated release of AmB by lowering the parasite count in the treated participants' spleens [62]. Glycine-coated nanoparticles could be used further in leishmanial therapies. The production and use of zinc oxide nanoparticles (ZnONPs) is widespread. ZnONPs were used in a study against the amastigote type of leishmania at

various concentrations (0.18, 0.37, 0.75, and 1.5 g/mL). ZnONPs were prepared by Sumaira et al. from plant leaf extracts of *Verbena tenuisecta* and *Verbena officinalis* [63]. Both biosynthesized ZnONPs were examined for their ability to combat leishmaniasis, but the *V. officinalis* ZnONPs performed better because to their smaller size and higher phenol content than the *V. tenuisecta* ZnONPs [64]. Since silver has long been a valuable ingredient in medicines, hence silver colloid solution has been used to treat about 650 different diseases and conditions [65, 66]. Later, as technology advanced, nanotechnology assisted in the creation of nanosilver or silver nanoparticles (AgNPs). Later, as technology developed, nanotechnology contributed to the production of silver nanoparticles (AgNPs) or nanosilver. Numerous studies have focused on the innate synthesis of silver AgNPs and their mechanisms of action in various biological applications. [67, 68]. A group of researchers tested and assessed the antileishmanial activity of AgNPs that were derived from the fungus Fusarium oxysporium [52]. The study findings were promised because AgNPs caused promastigotes to die, facilitating their apoptosis. According to other studies, AgNPs cause reactive oxygen species (ROS) that harm promastigotes' membranes. AgNPs caused a reduction in infected macrophages, in the case of amastigotes. AgNPs had direct anti-amastigote activity [52]. Another study on AgNP revealed that silver nanoparticles' anti-bacterial properties are highly helpful in the fight against leishmaniasis. The effects of AgNPs were examined in this work in relation to leishmanial parasite shape, proliferative rates, metabolic activity, and infectivity. AgNPs caused the parasite's morphological traits and infectivity rates to be destroyed. Additionally, there was a 1.5-fold decrease in metabolic activity and proliferation [51]. In general, the AgNPs may provide a fresh therapeutic source for the treatment of leishmaniasis [51, 69]. By producing ROS, the utilisation of nanoparticles under infrared (IR) and ultra-violet (UV) light has a significant toxicity that results in the death of the parasites. One study examined the antileishmanial effects of several nanoparticles, including gold nanoparticles (AuNPs), silver nanoparticles (AgNPs), zinc oxide nanoparticles (ZnONPs), magnesium oxide nanoparticles (MgONPs), and titanium dioxide nanoparticles (TiO2NPs) [70, 71]. Under UV and IR light circumstances compared to dark, AgNPs showed increased antileishmanial property, followed by AuNPs, ZnONPs, TiO2NPs, and MgONPs. Future research must take into account both of these nanoparticles' improved antileishmanial effects [28]. In a separate investigation, promastigote and amastigote forms of the parasite were successfully treated using TiO2NPs derived from chitosan. Meglumine antimoniate was added to TiO2NPs made from chitosan to boost their activity. UV spectrophotometer was used to check activity of nanoparticles. It was discovered that the mixture works well against the parasite's promastigote and amastigote forms. [72]. In general, metal oxide and metallic nanoparticles present an approach that is hopeful for the therapy and repression of all leishmanial activity [72, 73].

POLYMERIC NANOPARTICLES:

Many different kinds of biodegradable and biocompatible colloidal particle types are used to make these nanoparticles. They range from 10 to 1000 nm in size [74]. They transport drugs using a variety of strategies, including chemically bonding the drug to the surface of polymeric nanoparticles, encapsulation, adsorption, trapping, and dissolution (PNPs) [75].' Advanced physicochemical properties of PNP enables regulated drug administration, better cellular dynamics, and higher bioavailability and biodegradability [76]. Polymers are the primary type of carrier employed in nanomedicine research and investigations. Polyalkylcyanoacrylate nanoparticles were used to adsorb anti-cancer medicines for the first time in cancer therapy in 1979 [77]. PNPs are made up of both natural and synthetic polymers. Synthetic polymers include poly (glycolic acid), poly (lactic acid), poly (lactide-co-glycolide), poly (cyanoacrylate), and poly (caprolactone). Natural polymer such as albumin, gelatin, chitosan, and alginate are used [78, 79]. Among these type of polymers, PLGA has seen significant use in the transport of drugs and in tissue engineering. Nano capsules and nanospheres, reservoir or polymeric systems, respectively, come in two different shapes. In contrast to nanocapsules, which have a cavity surrounded by a polymer membrane, nanospheres have a uniform distribution of the medicine rather than a cavity [80, 81]. Because of their ease of permeation, PNPs are a fantastic option for delivering drugs and proteins to target cells. These polymers can be built into a variety of molecular patterns with numerous applications due to their small size [75]. Following are three mechanisms through which drugs are transported by PNPs to the targeted sites:

- By an enzymatic process that results in the polymer degrading at the targeted spot and releasing the drug.
- By diffusion based drug release, which happens through swelling of the PNPs which is followed by hydration.
- By drug and polymer detachment [3, 82].

For the treatment of leishmania PNPs are being researched as potential drug delivery carrier. On an in vitro mouse model, various PNP types are being researched as potential leishmaniasis treatments [83, 84]. Roy et al. [3,76] carried out a study in which they investigated the effects of andrographolide and nano-encapsulated diterpenoid lactone on albino mice. DL-lactide-co-glycolic acid and polyvinyl alcohol (PVA) nanoparticles were added in a ratio of 50:50. When 4% PVA was used instead of 1/4 of the pure chemical dosage, the results on mice models demonstrated powerful antileishmanial capabilities. The authors suggested that this procedure might offer a leishmaniasis treatment that is affordable. In a recent study, the efficiency of PLGA (poly lactide-co-glycolide) nanospheres functionalized with carbohydrates for the cure of therapeutic VL in mice was examined [85]. Three distinct forms of carbohydrates, including mannan, mannose, and mannosamine, were used to surface functionalize the PLGA nanospheres after they had been created using nanoprecipitation. When these PLGA nanospheres were co-cultured with macrophages, the host's immune-modulatory and pro-inflammatory responses were initiated, which resulted in the parasites being killed.

Mannan-functionalized PLGA nanospheres were found to be more efficient than VL parasites and mannose-functionalized PLGA nanospheres. [85].

NIOSOMES:

Niosomes (NIV) are mainly vesicular carriers made of mixes of non-ionic surfactants such dialkyl polyoxyethylene ether, monoalkyl, and sorbitan esters, as well as cholesterol. The hydrated surfactant monomers are self-assemble to form niosomes. Phospholipids are a realistic alternative to non-ionic surfactants with a wide range of structural variations in the construction of niosomes. These are advanced chemically stable controlled drug delivery systems (DDSs) [86]. Furthermore, it has been reported that using these carriers reduces systemic toxicity and improves site-specific delivery of the entrapped drug. These carriers does not require any special production, handling and storage conditions. It is also that when the cost of materials are relatively lesser, make it easier for the industrial manufacturing of niosomes [87].

CONCLUSION:

In this study, different possible options for the treatment of leishmaniasis have been discussed. From this study we find out that not even single efficient options would be effective to control the incidence of leishmaniasis [88]. Despite of the rapid spread of the disease worldwide, there has been very limited research done on their management. All the first liner anti leishmaniasis drugs such as, AmB, Sb-V, miltefosine, paromomycin face many side effect, toxicity, resistance to parasites and high cost of treatment create trouble for the treatment of people [89]. These demits could be overcome by Novel drug delivery system such as phytosome, nanosome, liposome, metallic nano compounds, etc. Different research study enlightens the uses of nanotechnology for the treatment of leishmaniasis. Various nanomaterial encapsulated drugs (AmB, Sb-V, paromomycin) being studied for the development of drugs for the treatment of different leishmania. This technology enhanced solubility, increase absorption rate, improve bioavailability and cell permeability of the active drug molecules into macrophages in host cell. Due small shape, size and uniform external texture, all nano-compounds can easily bind with the receptor present on the macrophages and inhibit their cellular function. Some metallic nanoparticles also active against promastigotes by generating reactive oxygen species (ROS) [60].

With the exception of nano-liposomal AmB gel which is commercially available, all leishmaniasis-related treatments based on nanotechnology are now in the preclinical and development stages. Cl and certain tropical diseases can now be treated in Iran with nano-liposomal AmB gel. Hence, Nano-technology is one of the alternative way to produce safe and cost effective medication for leishmania now a day. However, more advance studies should be required to prepare and develop more effective drugs on this promising technology as an antileishmanial drugs' arsenal [88, 89].

CONFLICT OF INTEREST:

Nil

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