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Mini Review

Application of Nano Drugs in Treatment of Leishmaniasis

Abstract

Objective: Leishmaniasis is endemic in 88 countries with incidence rate of 1.5-2 million; the most common form of leishmaniasis is cutaneous leishmaniasis (CL) with 1.5 million new cases per year. Correct diagnosis and characterization of the particular parasite is important for evaluating prognosis and prescribing appropriate treatment. The current management of leishmaniasis is drug treatment of patients, to alleviate disease and vector control to reduce its transmission. Also, current treatments for visceral leishmaniasis are unsatisfactory because of their toxicity, resistance and high cost. The purpose of the present study was to review the application of nano drugs in treatment of leishmaniasis.

Materials and Methods: it was used as source of research the following databases: MEDLINE, Cochrane Library, Scielo, PubMed and the database of CAPES.

Results: It has been proved nanosilver particles with highly small sizes, have a good penetration into the cutaneous lesions and a good efficacy on leishmaniasis.

Introduction

Protozoan parasitic diseases stay an unsolved public health difficulty, especially in tropical regions [1]. The major death toll is due to malaria, leishmaniasis, and African and American trypanosomiasis, whose high mortality rates in developing countries are associated to poor sanitary conditions and lack of efficient prophylactic measures [1-4]. Despite the remarkable amount of research aimed at the production of protective vaccines, the success is still elusive and chemotherapy remains the mainstay for the treatment of these diseases [4-6].

Leishmaniasis is an infection that is caused by an obligate intracellular protozoon of the genus *Leishmania* [6-8]. The natural transmission of *Leishmania* parasites is carried out by sandflies of the genus *Phlebotomus* or *Lutzomyia* [8]. These parasites cause three forms of leishmaniasis according to the localization of the parasites in mammalian tissues, notably visceral, cutaneous, and mucosal leishmaniasis [8].

Leishmaniasis is reported from 88 countries and estimated that 350 million world-wide are at risk of acquiring one form of the diseases, and 12 million are infected with annual occurrence rate of about 1.5 to 2 million [8-10]. According to findings ~15,000 people are affected annually in Iran. The real rate of incidence is 4 to 5 times higher than the reported prevalence [10-12].

The current management of leishmaniasis is drug treatment of patients, to alleviate disease and vector control to reduce its transmission [12-14]. Pentavalent antimonials (namely, sodium stibogluconate (SSG) and meglumine antimoniate) are the mainstay of anti-leishmanial therapy [14-17]. Although glucantime is commonly used for the treatment of leishmaniasis, it has some side effects including increased liver enzymes and electrocardiogram changes [17]. In addition, the drug is expensive, the injection is painful, and research shows that resistance of parasite to glucantime is growing in different parts of the world [17-20]. The use of nanotechnology is ever-expanding in today's technologically advanced world. This form of technology has many advantages over existing ones in many fields and medicine is one of them [20]. There are numerous devices and mechanisms developed with the aid of nanotechnology that can help cure diseases/disorders in a much better and more efficient manner [21]. The usefulness of nanotechnology can especially be seen in the treatment of infectious diseases [21,22]. This review has investigated the treatment of leishmaniasis by nano drugs.

Nano drugs against leishmaniasis

Nanotechnology must be applied for curing infectious disease like leishmaniasis [22]. Many drugs have been made and are still being discovered, but the protozoan re-emerges showing drug resistance to the effective medications [23]. Nanotechnology has just managed to show its promise in developing a liposomal formulation called amphotericin B for leishmaniasis but has serious side effects and is not cost effective in developing countries [23-25]. Initial, nanodelivery systems for delivering chemotherapeutics were nanodisks impregnated with amphotericin B, polymeric-nanoparticle loaded with pentamidine, primaquine, and niosomes, which still need validation at the clinical level [25-28]. There is an urgent need to take up assignments to use effective nanotechnology devices in combating this infectious disease [25-28].

Different mechanisms were proposed for antimicrobial property of nanoparticles [28]. One mechanism is binding of nanoparticle to sulfur/ phosphorus-containing biomolecules such as proteins and DNA, which leads to impairment of cell membrane, enzymes, and DNA [28-31]. Some nanoparticles are deposited within mitochondria and impair oxidative stress pathway [28-31]. On the other hand, adenosine triphosphate (ATP) synthesis is inhibited when mitochondrial proteins are damaged [28-31]. Additionally, antimicrobial nanoparticles can impair glycoprotein and lipophosphoglycan molecules, which are responsible for infectivity of bacteria and parasites [31]. Another mechanism is ion release from nanoparticles [31]. These ions interact with cysteine-containing proteins, and inhibit protein functions [31-33].

Before penicillin, colloidal silver was a treatment of choice for many illnesses and infections. There are many reports that show colloidal silver is effective on about 650 different micro-organisms [27-29]. Therefore, it seemed Nanosilver particles with highly small sizes, have a good penetration into the cutaneous lesions and a good efficacy on *Leishmania* spp [27-33].

Silver has been used to treat different infections for many years; silver nano-particle form usage has opened new ways of treatment with development of nano-technology [1-3]. Nanosilver compounds show impact on a wide range of microorganisms including bacteria, viruses, fungi, and even protect against protozoa and influenza [1-3]. Nanosilver solution is a new drug with anti-bacterial, antifungal and antiviral properties [3]. Advantages of this drug compared to other drugs are efficacy at low concentration and long life duration [34-36]. Studies showed that nanosilver cement has high antibacterial activity and high effectiveness against multi resistant bacteria without cytotoxicity *in vitro*. Recently, findings have demonstrated that nanosilver has anti-inflammatory effects and increases wound healing and dressings of wounds [1,2,37]. If these results are confirmed *in vivo*, nanosilver may be appropriate for ulcer treatment [1]. Nanosilver damage DNA, denature proteins and enzymes and produce free radicals and some studies showed that nanosilver is cytotoxic to several different cell lines [1,38]. The teratogenicity of nanosilver in humans is indistinctive and is not reported in the literature but *in vivo* (animal studies) and *in vitro* studies showed nanosilver can exhibit a significant level of toxicity [39].

Nano-mediated drug delivery of plant-derived products is one of the most important strategies for the treatment of visceral leishmaniasis (VL) in the absence of adequate anti-leishmanial drugs. Artemisinin has been traditionally used for the treatment of malaria and has been reported to exhibit anti leishmanial and antitumor activities [2,38-40]. Earlier, it has been proved that formulation of artemisinin-loaded nanoparticles improved its activity against *L. donovani* amastigotes ex vivo [17].

Nanoparticles of amphotericin B have greater efficacy than conventional amphotericin B. This formulation may have a good safety profile, and if production costs are low, it may prove to be a feasible alternative to conventional amphotericin B in the treatment of VL [17,25-29].

If nanoparticles are systemically administered, they will be agglomerated after exposure to plasma, and their efficacy will be decreased [17]. Anti-leishmanial nanoparticles must be conjugated with biological compounds such as antibody or lectin, which bind to specific targets, in order to exert more toxicity for parasites and less toxicity for normal cells [21-32].

Some nanoparticles have high cytotoxicity on macrophages, which must be considered [17]. The use of nanoparticles for treatment of CL may have both positive and negative consequences. Some reports indicate that gold nanoparticles (Au NPs), titanium dioxide nanoparticles (TiO2 NPs), zinc oxide nanoparticles (ZnO NPs), magnesium oxide nanoparticles (MgO NPs), etc. have antibacterial properties [30-33].

On the other hand, some nanoparticles have photo thermal effect after exposure to near infra-red (NIR) light [31-33]. These nanoparticles absorb NIR energy, and alter it to heat [31]. Then, temperature is increased and cells will be damaged [31]. It is stated that leishmania parasites are sensitive to heat, and heat therapy has been used as a new way with nanoparticles [31-36].

Vaccine development in leishmaniasis is another major area where DNA nanotechnology may have an important contribution [26]. Till date, many efforts have been undertaken to develop a successful vaccine, but realizing them into the clinics has been a bottle neck [26].

Conclusions

Nanotechnology being applied to treat leishmaniasis is a relatively new area of research and a lot still needs to be done to set up merge the available datasets with new data that will arise when nanotechnology will be applied to various aspects of the leishmanial disease

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