Chapter 03

Nanoparticles as a Potential Drug Candidate for the Treatment of Leishmaniasis

Rana Saleh Al-Difaie

Assistant Professor, Biotechnology College, University of Al-Qadisiyah, Iraq
*Corresponding author: rana.rana@qu.edu.iq

ABSTRACT

One common parasitic infection that is included in the category of neglected tropical diseases is leishmaniasis. It is to blame for rising rates of sickness and mortality, particularly in low- and middle-income nations. The three most common types of leishmaniasis are visceral, mucocutaneous, and cutaneous. Since the present anti-leishmanial drugs have various drawbacks, such as limited efficacy, toxicity, negative side effects, drug resistance, length of treatment, and cost lines, chemotherapy for leishmaniasis has remained unsatisfactory. Moreover, the absence of efficacious preventive vaccinations impedes the management of the illness. As such, the quest for novel anti-leishmanial compounds is urgently needed. Nanoparticles have been shown in numerous recent studies to be a viable therapeutic agent for the treatment of anti-leishmanial disease. They can also be included with chemical medications to increase their quality, efficiency, and sustainability while also lowering their cost. The goal of this study is to present a thorough analysis of the various nanoparticles that may be employed in the future to treat leishmaniasis.

KEYWORDS
leishmaniasis, Chemotherapy, Alternative treatment, Nanoparticles, Anti-leishmanial

Received: 08-Jun-2024
Revised: 12-Jul-2024
Accepted: 09-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Al-Difaie RS, 2024. Nanoparticles as a potential drug candidate for the treatment of leishmaniasis. In: Rubio VGG, Khan A, Altaf S, Saeed Z and Qamar W (eds), Complementary and Alternative Medicine: Nanotechnology-I. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 21-28. https://doi.org/10.47278/book.CAM/2024.022

INTRODUCTION

Leishmania is genus of the protozoan species. It infects humans, carnivores, and rodents that spreads by sandflies bites and Leishmania parasite has 2 forms, amastigotes and promastigotes. Amastigotes are intracellular, without flagellum, spherical, and non-motile forms, which proliferate within the phagolysosomes of phagocytic cells like macrophages of the vertebrate host. The other form, promastigotes, is inside the sandflies, extracellular, spindle-shape, motile, and flagellated, as show in (Fig .1).

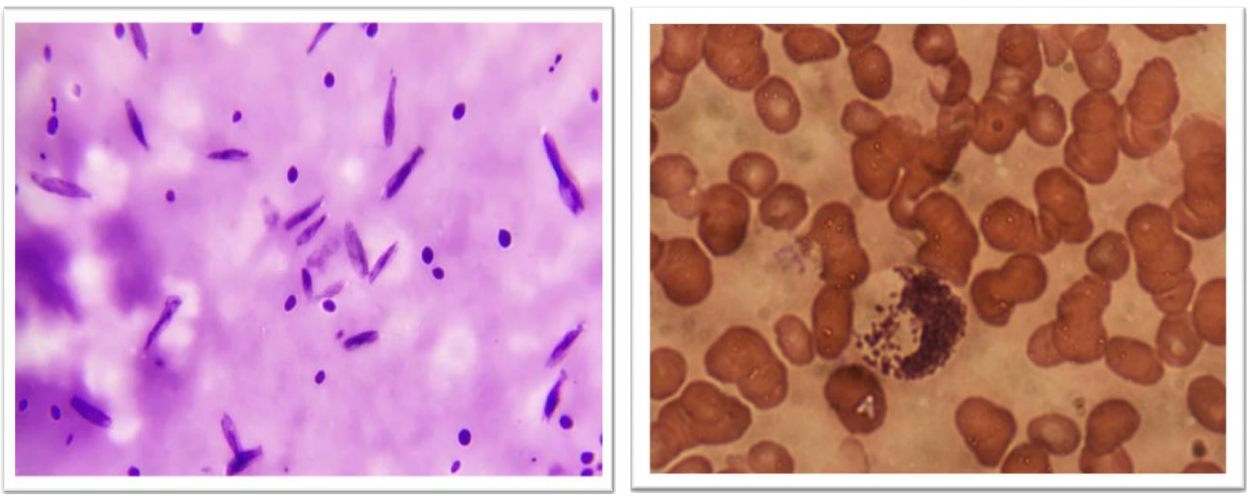

Fig. 1: The promastigote and amastigote of the Leishmania parasite (Giemsa stain, 100x)

There are three primary varieties of leishmaniasis that can occur: the most frequent variety, cutaneous leishmaniasis (CL); the deadliest type, visceral leishmaniasis (Kala-azar) (VL); and finally, mucosal leishmaniasis (ML) (Alvar et al., 2012). It occurs more frequently in rural areas than in cities. However, due to deforestation and climate change, leishmanian vectors have colonized metropolitan areas, spreading the illness to formerly uninfected areas (de Barros Dias et al., 2020; Oliveira et al., 2020). It is estimated that 12–15 million individuals globally suffer from this illness, with the majority of cases occurring in impoverished and/or developing nations because of inadequate cleanliness, a lack of preventative measures (such as nets, vector control and curtains), and a lack of health infrastructure (Saleem et al., 2019; Volpedo et al., 2019; Oliveira et al., 2020). Due to its high rates of infection and mortality, leishmaniasis has recently drawn more attention (Vaghela et al., 2017; Nafari et al., 2020; Ahmad et al., 2020). Unfortunately, there is still no effective chemical treatment to fight the disease, nor a vaccination or safe medication to inhibition parasite and other kinds of it (Mahmoudvand et al., 2017).

Leishmaniasis Treatment

Traditional Treatment of Leishmaniasis

The treatments for leishmaniasis consist of many of anti-leishmanial agents such as (Sodium stibogluconate, Meglumine antimoniate, Amphotericin B deoxycholate, Liposomal amphotericin B, Micellar amphotericin B, Pentamidine, Miltefosine, Paromomycin, Sitamaquine), These treatments are toxic and need a long-term treatment, which results in low patient compliance and drug resistance. Moreover, they usually incur considerable costs and necessitate cure (Akbari et al., 2017; de Souza et al., 2018). Finally, individuals with compromised cellular immune function, such as those infected with the human immunodeficiency virus (HIV), experience treatment failure and higher rates of relapse (Bruni et al., 2017). Moreover, vaccines have not succeeded in reaching clinical trials, and chemotherapy remains the only available treatment option for the time being. Therefore, in order to replace or enhance the current medications, and should develop new, more potent medications with enhanced features.

New or Alternative Treatment of Leishmaniasis

A nanoparticle is a small particle with a size (1-100) Nm. NPs is invisible, but it could detect by many of characteristics (physical and chemicals) from their larger material counterparts (Joudeh and Linke, 2022). The vast topic of nanomedicine has surfaced as a potential solution to problems pertaining to the side effects of older medications (Keyhani et al., 2020). This discontent stems from insufficient drug biodistribution, which results in a restricted therapeutic response and a range of adverse effects on healthy organs (Barratt, 2003; Beija et al., 2012). Additional observations point to the significance of nano-dimensionality in enhancing the efficiency of procedures like cellular absorption and biological barrier crossing, which can aid in the development of medications that are efficient in addressing infected tissues (Maeski, 2002; Couvreur and Vauthier, 2006; Huh and Kwon, 2011). In recent years, the use of nanoparticles in medicine, particularly for parasitic illnesses, has gained particular attention. Whereas the costly, energy-intensive, and potentially hazardous physical and chemical synthesis methods were being replaced with more ecologically friendly ones, nanoparticles were being created "biologically" through the use of plant- or microorganism-mediated reduction processes (Bhardwaj et al., 2020). In addition to being less costly and more ecologically friendly than chemically produced compounds, experiments have demonstrated their biological efficacy against diseases and may even be somewhat superior to them. To get rid of parasites, nanoparticles can be applied alone or in conjunction with other materials. Because of their destructive and inhibitory properties, it is therefore advised to utilize nanoparticles to eradicate parasites, improve the safety and efficacy of medications, and create efficient vaccines to prevent and combat parasites, particularly the Leishmania parasite (van Griensven and Diro, 2019). The NPs are believed to use a variety of methods to destroy microorganisms, including microbial membrane disintegration that results in oxidative stress, cell damage caused by ROS that damage DNA and leading into death of the cell by protein and lipid oxidation, and release of the ions that inhibit enzyme activity by displacing metal from metalloenzymes. These mechanisms are thought to prevent pathogens from evolving resistance (Ahmad et al., 2020). These new combinations can decrease side effects and the number of doses at a fair cost, increasing the likelihood of producing effective leishmaniasis treatments, regardless of production costs (Chávez-Fumagalli et al., 2015). Various metal and metal oxide nanoparticles have emerged as potent anti-leishmanial agents thus far such as:

- **Silver Nanoparticle (AgNPs)**

Since silver nanoparticles have a wide range of antibacterial activities, they are very important. As a result, silver nanoparticles have been employed as a substitute therapeutic agent to combat different types of leishmaniasis resistance. *Leishmania spp.* are relatively sensitive to ROS, which is the primary source of silver nanoparticles' antibacterial action (Allahverdiyev et al., 2011). Similar to antimony in its mode of action, silver is inhibitor of trypanothione/trypanothione reductase (Zahir et al., 2015; Baiocco et al., 2011). For promote the NPs accumulation in *L. major*-infected, the delivery of a small amount of silver NPs with electroporation. It causes high toxicity on macrophage and Leishmania (Dolat et al., 2015). Bioactive phytochemicals like flavonoids and alkaloids give biogenic metal nanoparticles (Metal NPs manufactured by use different plants) their extra antibacterial activity (Ahmad et al., 2020), As a result, these NPs may hold promise as anti-leishmanial medications.

Several articles address how biogenic silver nanoparticles can be used to treat leishmaniasis (Bagirova et al., 2020) By significantly lowering the promastigotes' rate of proliferation and the amastigotes' metabolic activity, they were

demonstrated that both chemically and biosynthesized (using cumin seed extract) silver NPs significantly inhibited *L. tropica* promastigotes and intracellular amastigotes, In addition, Bio-AgNPs induced the release of NO by macrophages, which killed Leishmania parasites. As a result, Bio-AgNPs were discovered to be more efficient than AgNPs against both kinds of Leishmania parasites, the results showed that green nanoparticles have a strong antileishmanial potential against *L. tropica* parasites, which are the cause of Cutaneous Leishmaniasis. Similarly, when evaluated in vitro, silver nanoparticles which using a *Mentha longifolia* (L.) (Aqueous Extract). The leaves can cause death of 66% of Leishmania (Javed et al., 2020). In order to produce silver nanoparticles, (Awad et al., 2021) used myrrh (*Commiphora molmol*). The antiparasitic efficacy of the MSNPs was evaluated on *L. major*, and both in vivo and in vitro experiments showed that MSNPs were superior to pentostam and CNPs. Thus, MSNPs may be excellent choices for a range of nanomedicine applications. The effect of Ag-NPs that generated from ginger rhizome extract on *L. major* promastigotes and amastigotes was to be effective, and it exhibited an inverse relationship with concentration, Ag-NPs caused programed cell death in *L. major* promastigotes and showed 60.18% of apoptosis (Mohammadi et al., 2021). Additionally, it was discovered that silver nanoparticles phytosynthesized with *Sechium edule* were effective in killing *L. donovani* that their activity was dosage dependent (Baranwal et al., 2018). Silver NPs showed dose-dependent cytotoxic activity against *L. tropica* by use of *Flammulina velutipes* (Faisal et al., 2021).

There are many studies on the biosynthesis of AgNPs from other microorganisms (fungi) and their anti-leishmanial effect of which study the effects of *Fusarium graminarum* AgNPs on *L. tropica* , where found that these particles have a significant impact on number of parasites; the number of parasites decreased after 24, 48, and 72 hours compared to pentostam and the control(Mohammed et al., 2019).In a second study, the same fungus was used to synthesize AgNP and study their effect on *Leishmania donovani*, where results recorded a significant gradual decrease in viability of the parasite within infected macrophage cells with the concentrations and the time (Ghadi et al., 2018). In another study, silver NPs biosynthesized with *Fusarium oxysporium* fungus killed *L. amazonensis* promastigotes and amastigotes in vitro due to increased ROS formation, loss of mitochondrial integrity, destruction of membrane, reduction of infected macrophages, and decrease of intracellular amastigotes. Another research used corn-extracted nanoxylan-containing silver NPs. Compared to free nanoxylan, NPs reduced *L. amazonensis* promastigotes' vitality (Viana et al., 2020). Additionally, (Jebali and Kazemi, 2013) showed that visible light, IR ray, and UV increased the anti-leishmanial activity of many inorganic NPs. UV light suppressed *L. tropica* promastigotes' growth and metabolic activity, a leishmanicidal effect of silver NPS (Allahverdiyev et al., 2011).

- **Gold nanoparticels (AuNPS)**

AuNPs have the potential to treat a number of illnesses (Dykman, 2020). AuNPs can be quite effective against different pathogenic parasites important for public health, among them there are protistias (Benellei, 2018). One experiment spotted in the area of skin injuries, AuNP-integrated into natural rubber membranes targeted leishmania promastigotes. The experiments had an outcome consisting of a retardation in the proliferation rate, changed behavior and reduction in lifespan of the organisms (Barboza-Filho et al., 2013). Effect of gold NPs treatment simulated with microwave at (2450 MHz) on *L. major* promastigotes and intracellular amastigotes as opposed for thermotherapy revealed that gold NPs alone significantly reduced the parasite survival rate of promastigotes after 48 hours of incubation and those of intra- J744 cell amastigotes after 24 hours The investigation conducted in conjunction with the other concerned the interactions of the Gold NPs prepared utilizing the plant species *Rhazya stricta decne* with the intra cellular amastigot cells of *L. tropica*. After two days of incubation, these Gold NPs were found to be inhibiting the intracellular amastigotes growth while being non-cytotoxic to the THP-1 cells (Uniform sized gold NPs were initially expected with use of polyphenolic substances. This inhibits growth of *L. donovani* in all forms, wild type as well as both sodium stibogluconate and paromomycin resistant. The NPs were shown to be low toxic and macrophages carry them in less than one hour. Furthermore, their effectiveness against drug-resistant strains (SSG, paromomycin) was demonstrated, and they demonstrated a high selectivity index (Das et al., 2013).

- **Selenium nanoparticles (SeNPs)**

In the recent studies,some protozoa including Trypanosoma and Leishmania, have been found to require trace levels of selenium ions as potential drugs, with encouraging results (Lobanov et al., 2006). According to Beheshti et al. (2013), biogenic selenium nanoparticles may be employed as a potential therapeutic agent to treat the local lesions associated with cutaneous leishmaniasis, In vitro and in animal models, the growth of *L. major* amastigote and promastigote forms is inhibited by selenium nanoparticles. Furthermore, Se NPS can prevent *L. tropica's* promastigote and amastigote growth (Mahmoudvand et al., 2014).

- **Metal Oxide Nanoparticles**

Zinc Oxide Nanoparticles (ZnONPs)

GRAS (generally regarded as safe) substance zinc oxide being ZnO NPs bring along the use of zinc oxide nanoparticles (ZnO NPs) in lipstick, moisturizers, sunscreen creams and deodorants. However, many researchers have been involved in creating considerable volumes of ZnO NPs and using them in different biomedical applications (Hameed et al., 2019). ZnO rod-shape NPs of L. ledebourii tuber was helpful in mitigation of *L. major* growth in in vitro; similar to other previous

studies on plant extract the effect also depended on the dose (Khatami et al., 2020). The in vitro culture medium also contained different levels of ZnONPs (0.18 µg/mL, 0.37 µg/mL and 0.75 µg/mL and 1.5 µg/mL) where the treatment was done on the *L. donovani* amastigote forms. Using the colorimetric assay to assess the cell viability data, it was revealed that the ZnONPs treated amastigote cells had a cytotoxic effect, and impeded their proliferation whose activity also got suppressed by *L. donovani*. As given in the study, ZnONPs would generate a unique and lightweight formation for anti-leishmanial medications (Delavari et al., 2014). The plants (*Verbena officinalis* and *Verbena tenuisecta*) leaf extracts were produced by Sumaira et al. (2018) to obtain ZnONPs , and the evaluation of their superb anti-Leishmanias efficiency demonstrated that the ZnONPs derived from the leaf extract of the *V. officinalis* was a better option because of its higher phenolic amount as In addition, a synergistic effect was observed when the ZnO NPs were decorated with *Geranium wallichianum* leaf extracts increasing the leishmanicidal activity of the nanozymes, (Abbasi et al., 2020). In further the like manner, the *Sageretia thea* water-based extract derived ZnO NPs were proven to be effective against *L. tropica* both promastigote and amastigote stage (Khalil et al., 2017). Zn NPs mixed in carbon or nitrogen to examine ability to kill *L. tropica* promastigote, it have ability to limitation of the growth by ROS generation. It has anti leishmanial effects (Nazir et al., 2019). Zn NPs biosynthetic in water and some solutions showed anti leishmanial effects (Ali et al., 2017).

Titanium Dioxide (TiO2)

The material with a semiconductor property, namely titanium dioxide (TiO2), induces antibacterial and photocatalytic features under UV radiation (Lopera et al., 2018). Moreover, the nanoparticles show enhanced the toxic effects of the particles when IR and UV light will be used together. It is by the production of the heat and the reactive oxygen species. The next option for CL is the application of photodynamic therapy where TiO2 NPs combined with UV light causes killing of the viruses. In this regard, prophylactic treatment should use different concentrations of TiO2 NPs (Rutile, Anatase) together with UVA and UVB to attain photodynamic treatment; the performance should be measured by variation in the death of promastigotes as the result of the various levels of TiO2 NPs and the types of UV light (Dolat et al. 2020). Through the strategic association between them, Lopera and associates came up with TiO2 nanostructure doped with multiple metals such as Zn, Fe, and Pt to induce ROS upon exposing light to visible light spectrum. When macropthages that were engaged with morpholonnate *L. amazonensis* amastigotes were treated by using different TiO2 respect to palladium and zinc, and then exposed to visible light, both doped Pt and Zn TiO2 showed a strong antiamastigote potential that was accompanied by elevation in ROS production (Lopera et al., 2018). Adding to that, findings of Jebali and Kazemi (2013) showed that TiO2 NPs change significantly features of *L. major* promastigotes as well as possessing antileishmanial activity. While blue light is a good source of producer of the Saharan haze, the effect of UV and IR rays on this issue is also noticeable.

Iron Oxide Nanoparticles (Fe3O4)

Iron oxides engineered nanoparticles (NPs) that have a wide utility in biomedical applications have even obtained FDA and EU approval as iron replacements or as contrast agents (Bobo et al., 2016). In this type of applications, hydrophilic decorating agents such as ligands are typically used to improve the stability of the nanoparticles in aqueous media (Moise et al., 2017). Fe3O4 NPs that is functionalized by citric acid for the elimination of *L. Mexicana* amastigotes in the cell culture medium were achieved, and magnetic hyperthermia evaluation was done using nanoparticles. The results revealed the potential therapeutic effect of this form of treatment in the obliteration of intracellular amastigotes in a heat-dependent manner. Furthermore, it elaborated a theoretical framework of the potential mechanism through which amastigotes respond to the host system challenged by heat (Berry et al., 2019). Where kind, Rosmarinus officinalis based NPs were synthesized in the presence of Fe3O4 and tested for antileishmanial efficacy (the efficacy of the newly synthesized nanoparticles against *L. major* promastigotes), the antileishmanial activity was dose dependent (Khatami et al., 2017). Finally, Trigonella foenum-graecum-synthesised ferromagnetic iron oxide nanorods (FIONs) demonstrated considerably greater leishmanicidal capabilities against *L. tropica* forms when exposed to LED light than when co-administered with AmB in the dark. ROS production was shown to cause growth impedance (Islam et al., 2020).

Magnesium Oxide Nanoparticles (MgONPs)

MgONPs are a desirable substitute for heavy metal-based NPS like ZnO because they are metabolized easily. Furthermore, renal function is normal, the body can effectively remove the products of Mg2+ and OH- ions, allaying worries about excessive metal accumulation (Nguyen et al., 2018). So Bafghi et al. (2015) investigated the impact of glucose-coated MgONPs) on *L.major* by the gene analysis of (GP63, CPB). It was demonstrated that longer incubation times and higher NP concentrations reduced cell viability while increased concentration also resulted in a decrease in gene expression, but not incubation time. Surprisingly, gene silencing was accomplished using NPs at non-toxic quantities. Also, in vitro research was also done on *L. major* and the impact of lectin-coated MgO NPs, The results showed that the functionalized NPs had high levels of macrophage activation and leishmanicidal action (Jebali et al., 2014). As for Tavakoli and his co-workers they have demonstrated that Mn2O3 NPs are advantageous effect to *L. major* promastigotes both in vitro and in vivo, and they may be a good option for treating this illness. According to flow cytometry studies, Mn2O3 NPs in vitro caused apoptosis in almost 57% of the promastigotes. In vivo investigations, the

mice's survival rate was higher than that of the control group and the ulcers' size was dramatically decreased (Tavakoli et al., 2019).

Nickel Oxide Nanoparticles (NiO NPs)

NiO NPs are widely used in biomedical applications due to their excellent qualities, tiny size, and biocompatibility. The greatest thing is the fact that they have a very good outcome in fighting the bacteria and they post the hope that they will one day be selected as the drugs against leishmaniasis. A recent work involving the antileishmanial activity of NiO NPs synthesised bio-chemically at *Sageretia thea* aqueous leaf extract level was evaluated and compared against *L. tropica* amastigote and promastigote cultures. A mastigotes and promastigotes were all found to be dose-dependently decreased (Khalil et al., 2018). Nevertheless, there is another evidence which is very informative where (NiONPs) biosynthesised with floral extracts from *Callistemon viminalis* persistently prevent the growth and even act on the kill *L. tropica* promastigotes (Sani et al., 2020). Artificial tulips of Iqbal and his team along with *Rhamnus virgata* extraction can lead to NiO NPs, this results in antileishmanial potential with the values of amastigotes and promastigotes of *L. tropica* being 10.62 µg/mL and 27.58 µg/mL, respectively (Iqbal et al., 2019).

Chromium Oxide Nanoparticles (Cr_2O_3NPs)

Cr_2O_3Nps are useful for treatment many of medical conditions, such as leishmanial (Thakur et al., 2023). Cr_2O_3-NPs were formed from *Rhamnus virgata* leaf extract and when *L. tropica* promastigotes and amastigotes were treated with NPs, the higher dose is leading into increased cytotoxicity (Iqbal et al., 2020).

Conclusions

The misuse and contraindications of leishmaniosis chemotherapeutic treatments have restricted their usage; hence parasitologists have researched NPs to control the parasite. NPs' non-toxicity and parasite resistance make them a better therapy than others. To create safe parasite treatments, additional study is required to understand nanoparticle modes of action. NPs produced in various ways may kill or limit parasite development. Nanoparticles may revolutionize Leishmania parasite therapy and management.

REFERENCES

Abbasi, B.A., Iqbal, J., Ahmad, R., Zia, L., Kanwal, S., Mahmood, T., Wang, C. and Chen, J. T. (2020). Bioactivities of Geranium wallichianum Leaf Extracts Conjugated with Zinc Oxide Nanoparticles. *Biomolecules,* 10, 38. https://doi.org/10.3390/biom10010038

Ahmad, A., Ullah, S., Syed, F., Tahir, K., Khan, A.U. and Yuan, Q. (2020). Biogenic metal nanoparticles as a potential class of antileishmanial agents: mechanisms and molecular targets. *Nanomedicine (Lond*.), 15 (8), 809–828. https://doi.org/10.2217/ nnm-2019-0413.

Ahmad, A., Wei, Y., Ullah, S., Shah, S.I., Nasir, F., Shah, A., Iqbal, Z., Tahir, K., Khan, U. A. and Yuan, Q. (2017). Synthesis of phytochemicals-stabilized gold nanoparticles and their biological activities against bacteria and Leishmania. *Microbiology Pathogene*, 110, 304–312. https://doi.org/10.1016/j.micpath.2017.07.009.

Akbari, M., Oryan, A. and Hatam, G. (2017). Application of nanotechnology in treatment of leishmaniasis: A Review. *Acta Tropical,* 172, 86–90. https://doi.org/10.1016/j. actatropica.2017.04.029.

Ali, A., Ambreen, S., Javed, R., Tabassum, S., Ul-Haq, I.and Zia, M. (2017). ZnO nanostructure fabrication in different solvents transforms physio-chemical, biological and photodegradable properties. *Mater Science Eng, C* 74, 137–145. https:// doi.org/10.1016/j.msec.2017.01.004.

Allahverdiyev, A.M., Abamor, E.S., Bagirova, M. and Rafailovich, M. (2011). Antimicrobial effects of TiO2 and Ag2O nanoparticles against drug-resistant bacteria and leishmania parasites. *Future Microbiology,* 6 (8), 933–940. https://doi.org/10.2217/ FMB.11.78.

Almayouf, M. A., El-Khadragy, M., Awad, M. A., & Alolayan, E. M. (2020). The effects of silver nanoparticles biosynthesized using fig and olive extracts on cutaneous leishmaniasis-induced inflammation in female balb/c mice. *Bioscience Reports*, 40(12), BSR20202672. https://doi.org/10.1042/BSR20202672.

Alvar, J., Vélez, I.D., Bern, C., Herrero, M., Desjeux, P. and Cano, J., (2012). Leishmaniasis worldwide and global estimates of its incidence. *PLoS One,* 7 (5), e35671.

Awad, M. A., Al Olayan, E. M., Siddiqui, M. I., Merghani, N. M., Alsaif, S. S. A. L., and Aloufi, A. S. (2021). Antileishmanial effect of silver nanoparticles:Green synthesis, characterization, in vivo and in vitro assessment. *Biomedicine and Pharmacotherapy*, 137, 111294.

Bafghi, A.F., Daghighi, M., Daliri, K. and Jebali, A. (2015). Magnesium oxide nanoparticles coated with glucose can silenceimportant genes of Leishmania major at sub-toxic concentrations. Colloids Surf. *B Biointerfaces*, 136, 300–304. https://doi.org/ 10.1016/j.colsurfb.2015.09.029.

Bagirova, M., Dinparvar, S., Allahverdiyev, A.M., Unal, K., Abamor, E.S. and Novruzova, M. (2020). Investigation of antileshmanial activities of Cuminum cyminum based green silver nanoparticles on L. tropica promastigotes and amastigotes in vitro. *Acta Tropicla,* 208, 105498. https://doi.org/10.1016/j.actatropica.2020.105498.

Baiocco, P., Ilari, A., Ceci, P., Orsini, S., Gramiccia, M., Di Muccio, T., and Colotti, G. (2011). Inhibitory effect of silver nanoparticles on trypanothione reductase activity and Leishmania infantum proliferation. *ACS Medicinal Chemistry Letters*, 2(3), 230-233.

Baranwal, A., Chiranjivi, A.K., Kumar, A., Dubey, V.K. and Chandra, P. (2018). Design of commercially comparable nanotherapeutic agent against human disease-causing parasite. Leishmania. *Science Rep*, 8, 8814. https://doi.org/10.1038/s41598-018- 27170-1.

Barboza-Filho, C. G., Cabrera, F. C., Dos Santos, R. J., Saez, J. A. D. S., and Job, A. E. (2012). The influence of natural rubber/Au nanoparticle membranes on the physiology of Leishmania brasiliensis. *Experimental Parasitology*, 130(2), 152-158.

Barratt, G. (2003). Colloidal drug carriers: Achievements and perspectives. Cellular and Molecular Life Sciences. 60. Birkhauser Verlag Basel, pp. 21–37.

Beheshti, N., Soflaei, S., Shakibaie, M., Yazdi, M.H., Ghaffarifar, F., Dalimi, A. and Shahverdi, A.R. (2013). Efficacy of biogenic selenium nanoparticles against Leishmania major: in vitro and in vivo studies. *Journal Trace Element Medicine Biology,* 27, 203–207.

Beija, M., Salvayre, R., Lauth-de Viguerie, N., and Marty, J. D. (2012). Colloidal systems for drug delivery: from design to therapy. *Trends in Biotechnology*, *30*(9), 485-496.

Benelli, G. (2018).Gold nanoparticles–against parasites and insect vectors. Acta Tropica, 178, 73-80. https://doi.org/10.1016/j.actatropica.2017.10.021

Berhe, M. G., and Gebreslassie, Y. T. (2023). Biomedical applications of biosynthesized nickel oxide nanoparticles. *International Journal of Nanomedicine*, 4229-4251. https://doi.org/10.2147/IJN.S410668

Berry, S. L., Walker, K., Hoskins, C., Telling, N. D., and Price, H. P. (2019). Nanoparticle-mediated magnetic hyperthermia is an effective method for killing the human-infective protozoan parasite Leishmania mexicana in vitro. *Scientific Reports*, *9*(1), 1059.

Bhardwaj, B., Singh, P., Kumar, A., Kumar, S., and Budhwar, V. (2020). Eco-friendly greener synthesis of nanoparticles. *Advanced Pharmaceutical Bulletin*, 10(4), 566.

Bobo, D., Robinson, K. J., Islam, J., Thurecht, K. J. and Corrie, S. R. (2016). Nanoparticle-based medicines: A review of FDA-approved materials and clinical trials to date. *Pharm Research,* 33, 2373–2387, https://doi.org/10.1007/s11095-016-1958-5 (2016).

Bruni, N., Stella, B., Giraudo, L., Della Pepa, C., Gastaldi, D. and Dosio, F. (2017). Nanostructured delivery systems with improved leishmanicidal activity: a critical review. *International Journal Nanomedicine,* 12, 5289–5311. https://doi.org/10.2147/IJN. S140363.

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. and Coelho, E.A. (2015). New delivery systems for amphotericin B applied to the improvement of leishmaniasis treatment. *Review Society Bras. Medicine Tropicla*, 48 (3), 235–242 May-Jun.

Couvreur, P. and Vauthier, C. (2006). Nanotechnology: Intelligent design to treat complex disease. Pharmaceutical Research. 23. Springer Science and Business Media Deutschland GmbH, pp. 1417–1450.

Das, S., Roy, P., Mondal, S., Bera, T. and Mukherjee, A. (2013). One pot synthesis of gold nanoparticles and application in chemotherapy of wild and resistant type visceral leishmaniasis, Colloids Surf. *B Biointerfaces,* 107, 27–34. https://doi.org/10.1016/j. colsurfb.2013.01.061.

de Barros Dias, M.C.H., Freitas, L.A.B., Dos Santos, I.R., de Almeida, V.S., do Amaral E Melo, R.T., de Melo Silva, V.G., de Fatima ´ Maia de Santana, B., da Conceiçao, ˜ J.M. and Leite, A.C.L. (2020). An Overview of the Compounds Tested In Vivo for Leishmania spp. of the Last 5 Years. *Current Medicine Chemistry*, 27, 1–33. https://doi.org/10.2174/0929867327999201116145408.

de Souza, A., Marins, D.S.S., Mathias, S.L., Monteiro, L.M., Yukuyama, M.N., Scarim, C. B., Lobenberg, R. and Bou-Chacra, N.A. (2018). Promising nanotherapy in treating leishmaniasis. *International Journal Pharmacy,* 547, 421–431. https://doi.org/10.1016/j. ijpharm.2018.06.018.

Delavari, M., Dalimi, A., Ghaffarifar, F. and Sadraei, J. (2014). In Vitro Study on Cytotoxic Effects of ZnO Nanoparticles on Promastigote and Amastigote Forms of Leishmania major (MRHO/IR/75/ER). *Iranian Journal Parasitology,* 9,6–13. [PubMed]

Dolat, E., Rajabi, O., Salarabadi, S.S., Yadegari-Dehkordi, S. and Sazgarnia, A. (2015). Silver Nanoparticles and Electroporation: Their Combinational Effect on Leishmania Major. *Bioelectromagnetics,* 36, 586–596. https://doi.org/10.1002/bem.21945.

Dolat, E., Salarabadi, S.S., Layegh, P., Jaafari, M.R., Sazgarnia, S. and Sazgarnia, A. (2020). The effect of UV radiation in the presence of TiO2-NPs on Leishmania major promastigotes. Biochim. Biophys. *Acta - General Subjects,* 1864, 129558. https://doi. org/10.1016/j.bbagen.2020.129558.

Dykman, L. A. (2020). Gold nanoparticles for preparation of antibodies and vaccines against infectious diseases. *Expert Review of Vaccines*, 19(5), 465-477.

Faisal, S., Khan, M.A., Jan, H., Shah, S.A., Shah, A.S., Rizwan, M., Ullah, W. and Akbar, M.T. (2021). Edible mushroom (Flammulina velutipes) as biosource for silver nanoparticles: from synthesis to diverse biomedical and environmental applications. *Nanotechnology,* 32, 065101. https://doi.org/10.1088/1361-6528/abc2eb.

Fanti, J.R., Tomiotto-Pellissier, F., Miranda-Sapla, M.M., Cataneo, A.H.D., Andrade, C.G. T.D.J., Panis, C., Rodrigues, J.H.S., Wowk, P.F., Kuczera, D., Costa, I.N., Nakamura, C.V., Nakazato, G., Duran, ´ N., Pavanelli, W.R. and Conchon-Costa, I. (2018). Biogenic silver nanoparticles inducing Leishmania amazonensis promastigote and amastigote death in vitro. *Acta Tropical*, 178, 46–54. https://doi.org/10.1016/j. actatropica.2017.10.027.

Ghadi, H. H., Mohamed, S. T., and Essa, R. H. (2018). Leishmanicidal activity of fusarium silver nanoparticles against leishmania donovani in vitro study. *Biochemical and Cellular Archives*, 18(1).

Hameed, S., Khalil, A.T., Ali, M., Numan, M., Khamlich, S., Shinwari, Z.K. and Maaza, M. (2019). Greener synthesis of ZnO and Ag–ZnO nanoparticles using Silybum marianum for diverse biomedical applications. *Nanomedicine (Lond.)*, 14 (6), 655–673. https:// doi.org/10.2217/nnm-2018-0279.

Huh, A. J., and Kwon, Y. J. (2011). "Nanoantibiotics": a new paradigm for treating infectious diseases using nanomaterials in the antibiotics resistant era. *Journal of Controlled Release*, 156(2), 128-145.

Iqbal, J., Abbasi, B.A., Mahmood, T., Hameed, S., Munir, A., and Kanwal, S., (2019). Green synthesis and characterizations of Nickel oxide nanoparticles using leaf extract of Rhamnus virgata and their potential biological applications. *Applied Organomet Chemistry*, 33(8): e4950. doi:10.1002/aoc.4950.

Iqbal, J., Abbasi, B.A., Munir, A., Uddin, S., Kanwal, S. and Mahmood, T. (2020). Facile green synthesis approach for the production of chromium oxide nanoparticles and their different in vitro biological activities. *Microsc. Research Technology*, 83 (6), 706–719. https:// doi.org/10.1002/jemt.23460.

Islam, A., Ain, Q., Munawar, A., Corrˆea-Junior, J.D., Khan, A., Ahmad, F., Demicheli, C., Shams, D.F., Ullah, I., Sohail, M.F., Yasinzai, M., Fr´ezard, F. and Nadhman, A. (2020). Reactive oxygen species generating photosynthesized ferromagnetic iron oxide nanorods as promising antileishmanial agent. *Nanomedicine (Lond.)*, 15 (8), 755–771. https://doi.org/10.2217/nnm-2019-0095.

Javed, B., Mashwani, Z.-R., Sarwer, A., Raja, N.I. and Nadhman, A. (2020). Synergistic response of physicochemical reaction parameters on biogenesis of silver nanoparticles and their action against colon cancer and leishmanial cells. *Artif. Cells Nanomedicine Biotechnology*, 48 (1), 1340–1353. https://doi.org/10.1080/ 21691401.2020.1850467.

Jebali, A., and Kazemi, B. (2013). Nano-based antileishmanial agents: a toxicological study on nanoparticles for future treatment of cutaneous leishmaniasis. *Toxicology in vitro*, 27(6), 1896-1904. https://doi.org/10.1016/j.tiv.2013.06.002.

Jebali, A., Hekmatimoghaddam, S., Kazemi, B., Allaveisie, A., Masoudi, A., Daliri, K., Sedighi, N.and Ranjbari, J. (2014). Lectin coated MgO nanoparticle: its toxicity, antileishmanial activity, and macrophage activation. *Drug Chemistry Toxicology*, 37 (4), 400–409. https://doi.org/10.3109/01480545.2013.870192.

Joudeh, N., and Linke, D. (2022). Nanoparticle classification, physicochemical properties, characterization, and applications: a comprehensive review for biologists. *Journal of Nanobiotechnology*, *20*(1), 262.

Keyhani, A., Ziaali, N., Shakibaie, M., Kareshk, A. T., Shojaee, S., Asadi-Shekaari, M., and Mahmoudvand, H. (2020). Biogenic selenium nanoparticles target chronic toxoplasmosis with minimal cytotoxicity in a mouse model. *Journal of Medical Microbiology*, 69(1), 104-110.

Khalil, A.T., Ovais, M., Ullah, I., Ali, M., Shinwari, Z.K., Hassan, D. and Maaza, M. (2018). Sageretia thea (Osbeck.) modulated biosynthesis of NiO nanoparticles and their in vitro pharmacognostic, antioxidant and cytotoxic potential. *Artif. Cells Nanomedicine Biotechnology,* 46 (4), 838–852. https://doi.org/10.1080/21691401.2017.1345928.

Khalil, A. T., Ovais, M., Ullah, I., Ali, M., Shinwari, Z. K., Khamlich, S., and Maaza, M. (2017). Sageretia thea (Osbeck.) mediated synthesis of zinc oxide nanoparticles and its biological applications. *Nanomedicine*, 12(15), 1767-1789.

Khatami, M., Alijani, H., Sharifi, I., Sharifi, F., Pourseyedi, S., Kharazi, S., Nobre, M.A.L. and Khatami, M. (2017). Leishmanicidal Activity of Biogenic Fe3O4 Nanoparticles. *Science Pharm*, 85 (4), 36. https://doi.org/10.3390/scipharm85040036.

Khatami, M., Khatami, S., Mosazade, F., Raisi, M., Haghighat, M., Sabaghan, M., and Varma, R. S. (2020). Greener synthesis of rod shaped zinc oxide nanoparticles using lilium ledebourii tuber and evaluation of their leishmanicidal activity. *Iranian Journal of Biotechnology*, 18(1), e2196.

Lobanov, A.V., Gromer, S., Salinas, G. and Gladyshev, V.N. (2006). Selenium metabolism in Trypanosoma: characterization of selenoproteomes and identification of aKinetoplastidspecific selenoprotein. *Nucleic Acids Research*, 34, 4012-4024.

Lopera, A. A., Velásquez, A. M. A., Clementino, L. C., Robledo, S., Montoya, A., de Freitas, L. M., and Graminha, M. A. S. (2018). Solution-combustion synthesis of doped TiO2 compounds and its potential antileishmanial activity mediated by photodynamic therapy. *Journal of Photochemistry and Photobiology B: Biology*, 183, 64-74.

Maeski, S. (2002). Drug delivery system of anti-fungal and parasitic agents. *Current Pharm Des*, 8 (6), 433–440.

Mahmoudvand, H., Kheirandish, F., Mirbadie, S.R., Kayedi, M.H., Rezaei Riabi, T., Ghasemi, A.A., Bamorovat, M. and 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. *Iranian Journal Parasitology,* 12 (3), 339–347.

Mahmoudvand, H., Shakibaie, M., Tavakoli, R., Jahanbakhsh, S. and Sharifi, I. (2014). In VitroStudy of Leishmanicidal Activity of Biogenic Selenium Nanoparticles against Iranian Isolate of Sensitive and Glucantime-Resistant Leishmania tropica. *Iranian Journal Parasitology,* 9, 452–460.

Mohammadi, M., Zaki, L., KarimiPourSaryazdi, A., Tavakoli, P., Tavajjohi, A., Poursalehi, R., and Ghaffarifar, F. (2021). Efficacy of green synthesized silver nanoparticles via ginger rhizome extract against Leishmania major in vitro. *PloS one*, *16*(8), e0255571.

Mohammed, O. T., Abdulkhaliq, R. J., and Mohammed, S. T. (2019). The effects of Fusarium graminarum silver nanoparticles on leishmania tropica. In *Journal of Physics: Conference Series* (Vol. 1294, No. 6, p. 062075). IOP Publishing.

Moise, S., Céspedes, E., Soukup, D., Byrne, J. M., El Haj, A. J., and Telling, N. D. (2017). The cellular magnetic response and biocompatibility of biogenic zinc-and cobalt-doped magnetite nanoparticles. *Scientific Reports*, 7(1), 39922.

Nafari, A., Cheraghipour, K., Sepahvand, M., Shahrokhi, G., Gabal, E. and Mahmoudvand, H. (2020). Nanoparticles: New agents toward treatment of leishmaniasis. *Parasite Epidemiology Control,* 10, e00156

Nazir, S., Rabbani, A., Mehmood, K., Maqbool, F., Shah, G.M., Khan, M.F. and Sajid, M. (2019). Antileishmanial activity and cytotoxicity of ZnO based nano-formulations. *International Journal Nanomedicine,* 14, 7809–7822. https://doi.org/10.2147/IJN.S203351.

Nguyen, N. Y. T., Grelling, N., Wetteland, C. L., Rosario, R., and Liu, H. (2018). Antimicrobial activities and mechanisms of magnesium oxide nanoparticles (nMgO) against pathogenic bacteria, yeasts, and biofilms. *Scientific Reports*, *8*(1), 16260.

Oliveira, S.S.C., Ferreira, C.S., Branquinha, M.H., Santos, A.L.S., Chaud, M.V., Jain, S., Cardoso, J.C., Kovaˇcevi´c, A.B., Soutod, E.B. and Severino, P. (2020). Overcoming multiresistant leishmania treatment by nanoencapsulation of potent antimicrobials. *Journal Chemistry Technology Biotechnology,* https://doi.org/10.1002/jctb.6633.

Saleem, K., Khursheed, Z., Hano, C., Anjum, I. and Anjum, S. (2019). Applications of Nanomaterials in Leishmaniasis: A Focus on Recent Advances and Challenges. *Nanomaterials* 9, 1749. https://doi.org/10.3390/nano9121749.

Sani, A., Hassan, D., Khalil, A.T., Mughal, A., El-Mallul, A., Ayaz, M., Yessimbekov, Z., Shinwari, Z.K. and Maaza, M. (2020). Floral extracts-mediated green synthesis of NiO nanoparticles and their diverse pharmacological evaluations. *Journal Biomol Struct Dyn*, 22, 1–15. https://doi.org/10.1080/07391102.2020.1775120.

Sazgarnia, A., Taheri, A. R., Soudmand, S., Parizi, A. J., Rajabi, O., and Darbandi, M. S. (2013). Antiparasitic effects of gold nanoparticles with microwave radiation on promastigotes and amastigotes of Leishmania major. *International Journal of Hyperthermia*, 29(1), 79-86. https:// doi/pdf/10.3109/02656736.2012.758875

Sumaira, Siddique Afridi, M., Salman Hashmi, S., Ali, G. S., Zia, M., and Haider Abbasi, B. (2018). Comparative antileishmanial efficacy of the biosynthesised ZnO NPs from genus Verbena. *IET Nanobiotechnology*, 12(8), 1067-1073.

Tavakoli, P., Ghaffarifar, F., Delavari, H., and Shahpari, N. (2019). Efficacy of manganese oxide (Mn2O3) nanoparticles against Leishmania major in vitro and in vivo. *Journal of Trace Elements in Medicine and Biology*, *56*, 162-168.

Thakur, T. M., Lokhande, R. S., Thigle, M. M., and Patil, V. R. (2023). Nanoparticles of chromium oxide by green synthesis using Eucalyptus globulous leaves extract; characterization and biological activity studies. *Materials Today: Proceedings*, *79*, 100-106.

Vaghela, R., Kulkarni, P.K., Osmani, R.A.M., Bhosale, R.R. and Varma, V.N.S.K. (2017). Recent Advances in Nanosystems and Strategies for Managing Leishmaniasis. *Curr. Drug Targets,* 18 (14), 1598–1621. https://doi.org/10.2174/1389450117666160401124133.

van Griensven, J., and Diro, E. (2019). Visceral leishmaniasis: recent advances in diagnostics and treatment regimens. *Infectious Disease Clinics*, *33*(1), 79-99.

Viana, R.L.S., Fidelis, G.P., Medeiros, M.J.C., Morgano, M.A., Alves, M.G.C.F., Passero, L. F.D., Pontes, D.L., Theodoro, R.C., Arantes, T.D., Sabry, D.A., Sassaki, G.L., MeloSilveira, R.F. and Rocha, H.A.O.(2020). Green Synthesis of Antileishmanial and Antifungal Silver Nanoparticles Using Corn Cob Xylan as a Reducing and Stabilizing Agent. *Biomolecules* 10, 1235. https://doi.org/10.3390/biom10091235.

Volpedo, G., Costa, L., Ryan, N., Halsey, G., Satoskar, A., and Oghumu, S. (2019). Nanoparticulate drug delivery systems for the treatment of neglected tropical protozoan diseases. *Journal Venom Animal Toxins Incl Tropical Disease*, 25, e144118. https://doi. org/10.1590/1678-9199-jvatitd-1441-18.

Zahir, A.A., Chauhan, I.S., Bagavan, A., Kamaraj, C., Elango, G., Shankar, J., Arjaria, N., Roopan, S.M., Rahuman, A.A. and 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.