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Review article

The improvement of Cutaneous leishmaniasis treatment by Nanomedicine-based strategies

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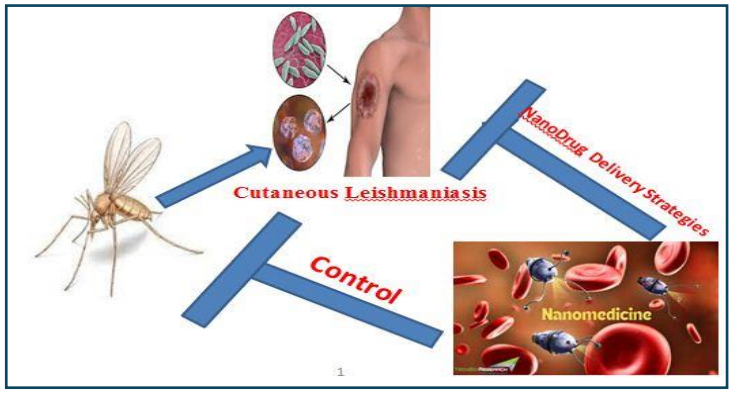
Abstract

Nowadays, Nanomedicine strategies become the selective drug of choice that were modified and effectively applied in clinical settings for several diseases. Leishmania is a parasite that has zoonotic effect through animals and human. This neglected of leishmaniasis disease result in a rise of new million cases per year. The most common two forms are the cutaneous form, which causes skin sores, and the visceral form, which affects internal organs. Accelerated wound healing, less scarring, prevention of parasite transmission and relapse are the goals of treatment for cutaneous leishmaniasis. Regretfully, none of the available medications were created effectiveness to this disease condition due to high toxicity, low efficiency, resistant strains, adverse effects, high costs, and long treatments. Nanomedicine devices with drug delivery are considered a promising tool to accelerate tissue
regeneration to various diseases. While these delivery devices help in decreasing secondary bacterial infection through targeting antileishmanial effect . Thus, in this review, we addressed nanomedicine-based strategies to
achieve scarless wound healing, low disease transmission, and reduce drug toxicity.

Key words:

Nanomedicine, Leishmania, zoonotic , secondary infection, prevention

Graphical abstract: Leishmaniasis



Introduction

Leishmaniasis caused by leishmania parasite that widespread distribution in the developing countries **(Figure1).**[1]

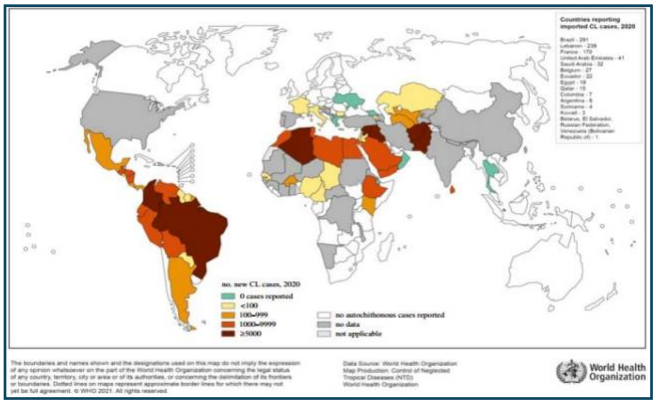


Figure 1. Cutaneous Leishmaniasis map around the World[8]

Leishmania (L.) is a zoonotic disease that hosted in different animal species and humans through the bite of sand fly at phlebotomine stage as a vector**.**[2] The danger of the disease as the result of their natural reservoirs reach to 70 animal species including humans**.**[3] Leishmaniasis has three forms according to the clinical features include: visceral ,cutaneous, and mucocutaneous. Cutaneous leishmaniasis (CL) is the most endemic form that widespread mainly in developing countries ; characterized by skin sores that lead to social stigmatization as always heal on their own leaving scars**.**[3] CL classified into two groups: New World species, like L. amazonensis, L. mexicana, L. braziliensis, and L. guyanensis, which are endemic in South and Central America and Old World species, such as L. major, L. tropica, and L. aethiopica, which are common throughout the Mediterranean Basin, the Middle East, the Horn of Africa, or the Indian subcontinent**.**[4] Humans, animals, and sandflies can all serve as hosts for the spread of leishmaniasis**.**[5]

In sandflies, the parasites multiply in the hind gut then proliferate in the blood meal at mid gut in the form of promastigote that transfer to anterior mid gut follow continuous differentiation into metacyclic form ready to transmission into vertebrates**.**[6] In vertebrates, promastigote convert into a mastigotes that multiply within macrophages**.**[7] After that, macrophage lysed and releasing mastigotes that engulfed by dendritic cells (DC) and neutrophils resulting in influx of neutrophils with inflammatory macrophage that mark the beginning of the inflammation **(Figure 2).**

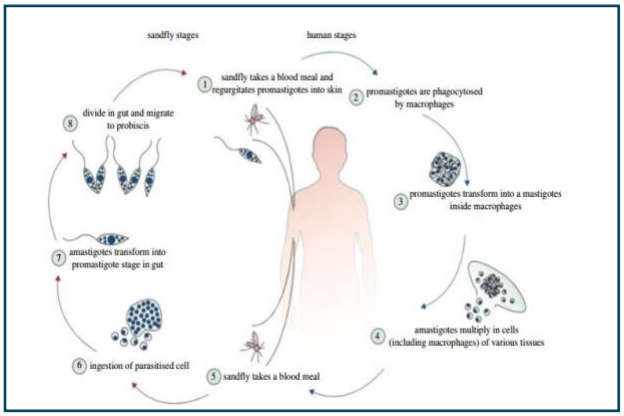


Figure 2. Leishmania parasites transmission by sandfly vector or the human host[8]

At this stage of infection skin sores begin to observe clinically. In which, interferon gamma

(IFNγ) produced by T cells ultimately affects lesion resolution by starting the parasite killing process. The adaptive immune response against Leishmania is then triggered by DC priming and activating antigen-specific T cells.[9] This process may take up to 18 months if no treatment is received. These immune response T cells play crucial function in the progress of the disease that provoke several inflammatory responses that trigger the expression of the disease from symptomless or subclinical to chronic or self-healing leishmaniasis.[2] Sand fly like other haematophagous insects which hold bioactive molecules that have immunomodulatory and anti-inflammatory effect that stimulate blood feeding, modulate host's immune response and parasitic infection.[10]

CL characterized by skin damage starting with erythema then become papule that converted into ulcerative nodule ended with scare formation. Also, mucocutaneous leishmania can affect and destroy mucous membranes that found in nose, mouth , and throat then enter to viscera resulting sever fatal feature called kala-azar **(Figure 3).**[11]

There are five phases of lesion development that include inflammatory, silent, active, ulcerative , and healing phases.[2] In inflammatory phase, no pathological appearance on the skin that may last about five months[12], Follow by the immigration of the macrophages at the point of the insect bite in which amastigote inhabitant inside.[13] Silent phase; characterized by parasitic proliferation without any activity or skin lesion. At active phase, skin lesion start to be occurred by forming nodules with infiltration of T-cells and DC.[14]

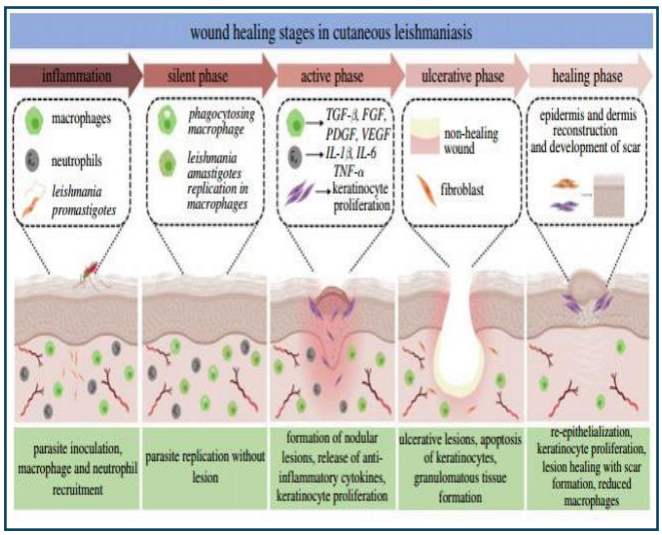


Figure 3. Scheme different phases of CL.[8]

Ulcerative phase , characterized by ulcerative development that converted into granuloma.[15] Finally at the healing phase the response of immune system of the host play a vital role in which cytokines such as transforming growth factor- beta (TGF-β) and interleukin 10 (IL-10) are infiltrated to enhance wound healing through parasitic elimination.[16] Thus, identifying the particular form of Leishmania and its corresponding causative microorganism, as well as distinguishing it from other skin diseases with comparable clinical features, like tuberculosis , malaria and, typhoid are the two primary challenges in diagnosing cutaneous leishmaniasis.[17]

There is currently no safe medication or vaccination to stop the parasite's growth. Since direct microscopic examination or molecular analysis are used to determine whether Leishmania amastigotes resides within phagocytes, are present in clinical specimens or not. The lack of microscopy in many countries' basic healthcare facilities consider as a significant obstacle in diagnosing leishmaniasis. The challenge of targeting the parasite within their resides with specific drugs is the goal of scientists to get rid of this parasite . Besides, different forms of CL challenging to find a specific drug against this disease.[18]

Nanomedicine is a modern technology that scientist praises its ability to address challenges of infectious and non-infectious diseases.[19] It enhances drug efficacy and reducing their toxic effects ,has good tolerance, and safe . Nanomedicine can be taken by oral, S/C or IV.[8] Regarding tissue regeneration , parasite , and inflammation management; nanomedicine-based strategies are targeted to be used at clinics for treatments of CL. Although, there are significant drawbacks in translating nanomedicine into clinical applications.[17]

-Diagnosis of C L:

Early laboratory identification is essential for selecting the right treatment and so halting the progression of the disease . Meanwhile , Infrastructure and resources are usually more crucial when selecting a diagnostic test than test accuracy.[4] The vulnerability of primary health care services in many affected countries, which faces issues including a limited infrastructure, lack of human capital and capital resources, an uncompromised system, and uncontrolled population expansion, are the most major barriers to the clinical management of leishmaniasis **(Figure 4).** [20]

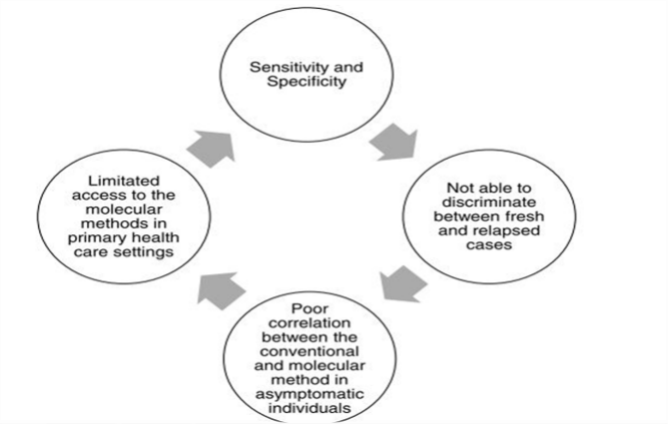


Figure 4 . Challenges of Leishmania diagnostics: Limitations for the detection of Leishmania parasites using current conventional diagnostics.[17]

There are different diagnostic tools for identification and quantification of parasitic disease such as microscopic identification of amastigotes, histopathological examination. Serological and molecular diagnosis; PCR considered a sensitive molecular test especially at mucosal lesions in which parasite with low recruitments. Recently, Loop-mediated isothermal amplification (LAMP) technique is one of the real-time kinetoplast DNA PCR

(KDNA PCR) showed high sensitivity(98%) on 40 CL patients.[21] Besides , chemiluminescent ELISA for detection of L. tropica or L. major infections through quantification of anti-α-galactosyl antibodies.[22] Pena et al (2020) reported the accuracy of the PCR for leishmanial diagnosis that must be used as basic technique in. As well as ELISA screening of suspicious cases is recommended with attention of cross-reactivity.[23] Recently, an immunochromatographic rapid diagnostic kit (IC-RDT); for amastigotes detection from skin lesions that depend on parasite count and peroxidioxin antigen expression which different between Leishmania species.[24]

The coupling of nanoscience with nanotechnology encourages sensitive and specific diagnosis of leishmania parasite. Gold nanoparticles are designed for detection of the disease through quantification of nucleic acids even in asymptomatic infection.[25] Serological detection by nanogold due to aggregation as a result of antigen antibodies recognition promastigote surface peptide.[26] Leishmanial genomic DNA differentially diagnosed from other parasite by well-designed gold nanoparticles.[27] Besides, Gas sensors for volatile organic compounds analysis from exhaled breath were designed with a molecular organic ligand (2-mercaptobenzoxazole) and six sensors of metal nanoparticles (Au or CUNPs) and. This sensor test is highly sensitive , specific and accurate for cutaneous leishmaniasis differentiation.[28]

-Treatment options of Cutaneous leishmaniasis:

There is no effective and specific available treatment strategies for treatment of CL. Effective long-term immunity development is challenging due to the diversity of Leishmania species and the intricacies of the parasite-host interaction.[29] WHO recommendation for treatment of CL depends on geographical location, species of parasite, and the clinical manifestations .In this context, the success of treatment protocols depend on (i) parasite factors (strain, species, virulence, resistance gene involved ,Leishmania RNA virus), (ii) host factors (age, immune system, sex, compliance), (iii) drug factors (dose, drug dynamics, drug kinetics, preservation), and (iv) drug resistance.[8]

Therefore , the treatment of leishmaniasis depend on two drug administration categories: The first line of treatment is administration of sodium stibogluconate at 20 mg kg−1 per day for 20–28 consecutive days ,that require hospitalization due to its toxic effect. The second-line treatment such as amphotericin B with liposome (AmBisome®, single-dose 10 mg kg−1), miltefosine (MILT) (Impavido®, 28 days with 1.5–2.5 mg kg−1 d−1), pentamidine (Pentam®, 3–5 days with 4

mg kg−1), paromomycin (PRM) (Humatin®, 21 days with 15 mg kg−1 d−1), and amphotericin B (AMB) deoxycholate (Fungizone®, 30 days with 1 mg kg−1), all are recommended for non respoders complicated cases and immunocompromised patients.[30] These drugs have toxic effect such as nausea, diarrhea ,vomiting, high blood sugar. Other local therapy is used directly on skin sores depend on thermosensitivity of the parasites such as thermotherapy and cryotherapy.[31] Regarding these medications is only successful and lasts more than six months especially for persistent, multiple and large lesions of immunocompetent patients while relapse occurred in immunocompromised patients.[1]

The issue of Drug resistance (DR) is the major challenge that occurs due to genetic mutations that diminished parasite's response through reduce uptake of certain drug by macrophages, and modification in drug/target interaction **(Figure 5)**.[32] Subsequently, Drug targeting and personalization be approached through complete genome sequence availability and understanding biological pathways of Leishmania ; which is a valuable strategy to overwhelms drug resistance .

The key of drug personalization to host is to understand the mechanism which stimulate protection of immune and mediate immunopathological responses, modulating disease severity, inflammation and restraining parasite replication.[8] In this context, different cytokines such as IL-12 or IL4, IFN-y, Tumor necrotic factor- alpha (TNF-a) and IL-1ß show parasitic growth control and enhance wound healing by increasing protective immunity through macrophage activation.[33]

Nano-drug delivery systems (nano-DDS) such as niosomes, liposomes, transfersomes and polymeric nano-DDS are tools of drug targeting at topical and oral delivery in CL by using drug-loaded surface-modified nano-DDS systems (thiolated or mannosylated) to avoid Parasitic resistance.[33] Besides, Gold nanoparticles have anti-leishmanial effect that exhibited activity of immune response, thioredoxin reductase inhibition and imbalance of redox species.[34]

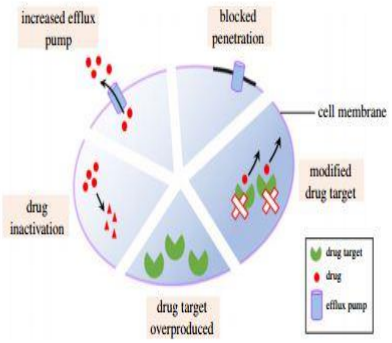


Figure 5. Drug resistance mechanism in infected macrophages.[17]

-Approaches for Drug nanonization based therapies

New drugs production which can be phagocytosed as foreign bodies by macrophages to be delivery for Leishmania parasites in their resides. Several nanodrugs have been discovered to follow the mechanism of target drug delivery includes Niosomes, polymeric , metallic nanoparticles, ethosomes and liposomes are studied for their potential effect as antileishmanial drug delivery **(Figure 6).**[28]

-Niosomes

Niosomes have been produced by non-ionic surfactants hydration to be one of drug delivery system.[35] Niosomes nanoparticles are characterized by less toxicity, low cost, biogradable, more stable, well skin penetration ,immune-modulatory and can be used instead of liposomes.[36] Different literatures demonstrate the potential effect of these nanoparticles for drug delivery against cutaneous leishmaniasis.[37]

-Metal and Metallic oxide nanoparticles

The production of gold (AuNPs) and silver (AgNPs) nanoparticles become promising leishmaniasis treatment due to their eye-catching nanoscale structure (size , shape, thermal, high surface/volume ratio) that make them more selective than raw one.[38] Au and Ag Metal NPs have the ability to damage cell membranes through metal oxidation that has anti-leishmanial effect.[39]

Green synthesis of metallic nanoparticles stimulates their active role as antimicrobial properties due to their eye-catching nanoscale structure. For instance, role of reactive oxygen species (ROS) production, inhibit parasite proliferation ,and biogenic metal nanoparticle with nanosize enable it to carry low concentration of drug but promote their penetration and reduce their toxicity because of low concentration needed.[40,41]

-Liposomes

Liposomes are colloidal bilipid layer of cholesterol and phospholipid in the presence of excess water enclosing aqueous compartment. It can be used in delivery of the drug in various dermatological lesions.[42] Liposomes have attractive characteristic features includes its ability to incorporates all physical types of molecules (hydrophilic, hydrophobic, and amphiphilic). As well as they can be coupled with antibodies or ligands or probes in order to targeting the region to be treated.[43]

Liposomes trigger the attention to become one of drug delivery strategy for treatment of leishmaniasis that commercially designed as topical ointment consist of liposomal amphotericin B.[44] Different studies were tested the efficacy of nanoliposomes as a drug delivery in vivo model (BALB/c mice infected by L. major.[45,46], and irritancy assessment in rabbit,[47]

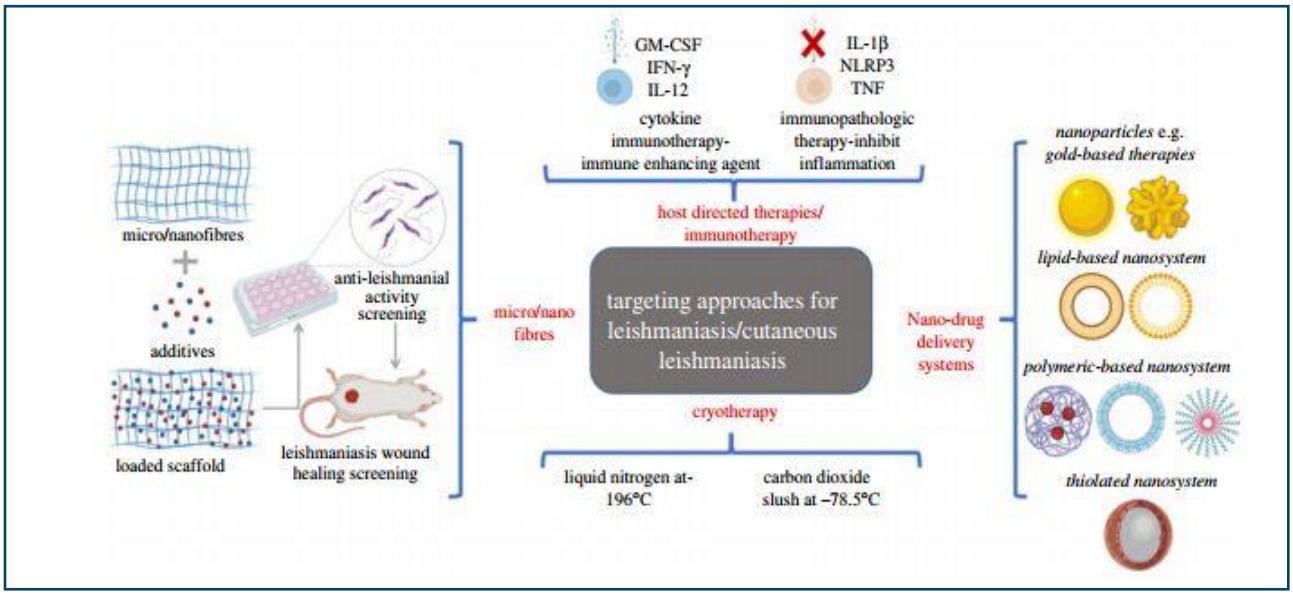


Figure 6.Targeted approaches for the treatment of CL. [17]

and healthy volunteers.[48] The potential formulations of the liposomes represent the

initial promise to be used as ideal drug targeting system for dermatological lesion.[49,50]

-Other lipid nanosystems

Nanoemulsions , solid lipid nanoparticles (SLN), nanostructures lipid carriers(NLC), and ethosomes are lipid-based drug targeting delivery system that share the same properties in term of solid matrix structure as polymeric and in term of lipid form as liposomes and overcome their drawbacks.[51] They characterized by their ability to encapsulated drug that insoluble in water, while being biodegradable and biocompatible.[52]

1- Nanoemulsions

Nanoemulsions are simple prepared emulsions with 100nm droplet size that used as drug delivery for lipophilic molecules such as essential oils to easily penetrate at the deepest region of the skin layers.[53]

2- Solid lipid nanoparticles (SLN)

They are one of nanoparticles with solid lipid core of size less than 1000nm ,which responsible for regulatory release of drug at target size.[54] They are one of the best choices for drug delivery as they can carry both lipophilic and hydrophobic active principles ,easy to prepare, stable and low cost.[55]

3- Nanostructures lipid carriers(NLC)

They are the second generation of SLNs, with improved features such as less organized lipid

nucleus with long lasting loading of the drugs.[56] Scientist focused on preparation of oral delivery of antileishmanial drugs to target lymphatic system with no topical application.[57]

4- Ethosomes

Ethosomes are lipid nanoparticles formed of ethanol and phospholipid that give them the ideal ability to deliver drug to the deepest area of the skin because of ethanol action that make them more selective than conventional liposomes.[58] Nevertheless, few studies reported the efficacy, high encapsulation and low toxicity in treatment of leishmaniasis.[59,60]

-Polymeric nanoparticles

These type of nanoparticles are trapped inside circulation a time and rapidly evacuated through phagocytosis ; thus can be administrated as drug delivery with reduction in the dose number.[61] Polymeric nanoparticles are less than 1 µm solid colloidal biodegradable matrix that used in several disease treatment like leishmaniasis due to trespass tissue barriers, tolerate physiological tension with high biological stability.[62, 63, 64] The stability of the drug depends on its adsorption ,dissolving , or retaining in polymeric matrix . There are two different types of polymeric matrices: synthetic polymers like Poly (butyl cyanoacrylate) (PBCA),poly (alkyl cyanoacrylate) (PACA), Polycaprolactone (PCL), polylactide (PLA), poly (glycolic acid) (PGA), ,Poly Lactic-co-glycolic acid (PLGA), poly (amino acid) and natural polymers such as chitosan, albumin, gelatin, and alginate.[65] Chitosan considered one of natural polymeric nanoparticles that have antileishmanial activity. [64]

Nanostructures encapsulation of anti-leishmanial drugs

Application of nanobased medications delivery strategy have been assessed for treatment of cutaneous leishmaniasis that extend to tissue regeneration. There are different techniques have designed as nanobased drug delivery such as nanoparticles, nano/microfibers and hydrogels.[8]

Nanoparticles

The biological constraints that therapeutic modalities confront, such as the parasite's intramacrophage location, Lack of oral bioavailability, active efflux of the drug, and permeability across skin tissue promote the dissemination of the disease. Subsequently, drug delivery nanoparticles tool inhibits the barrier obstacles of drug availability through improving drug loading, stability, solubility, and distribution all over the body. L. parasite is loaded in DC and macrophages , mucosal cells and lymph nodes in both mucosal and cutaneous

CL. Regards, multiple drugs delivery to targeted regions depend on exploitation of NPs.[39]

because of the negative charge[69], also it has antileishmanial activity inside the body.[70]

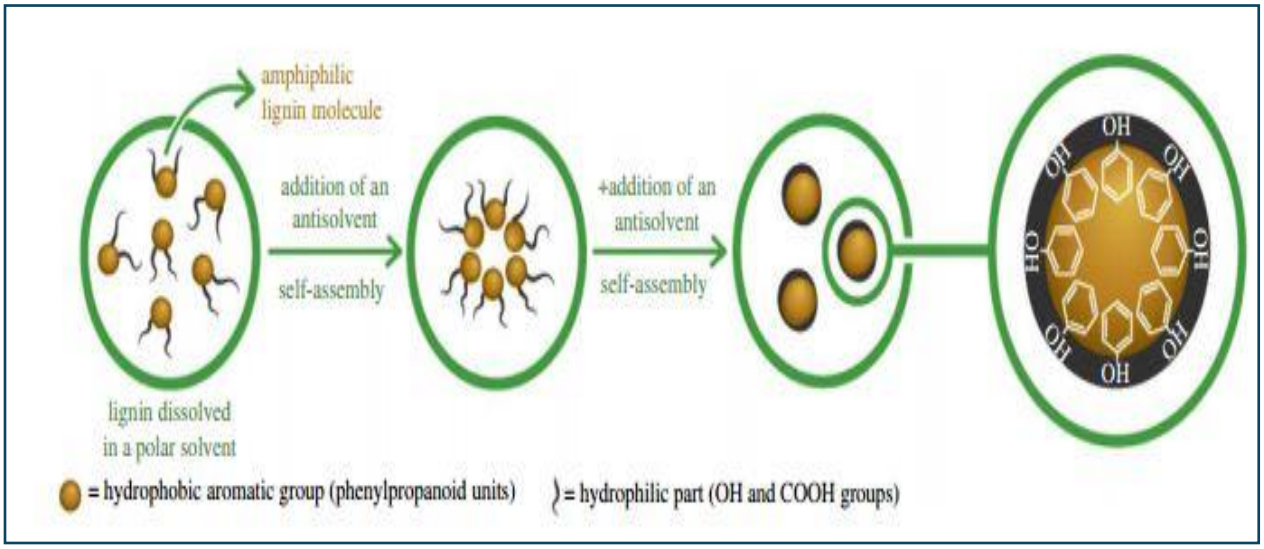


Figure 7. Lignin nanoparticle formation. [74]

Nanoparticles dimension and surface charge can be monitored for more particular biodistribution and accumulation . For instance, NPs are retained in spleen with size larger than 150 nm and in liver with smaller size.[66] Besides, +ve charged NPs are retained in spleen ,liver, and lung.[67] Different ligands (antibodies, peptides, lipids, carbohydrates and nucleic acid) that loaded on NPs allow recognition of leishmaniasis pathophysiological markers on infected cells or the parasites.[68] Chitosan (CS) NPs is one of chosen positively charged fabricant that easily attracted by cell membranes

Lignin is the second common numerous and renewable natural biopolymer that found in wood.[71] Lignin may be transformed into lignin-based LNP and/or hydrogel to control drug release of different types of molecules.[72] The most common method used for LNP are self-assembly technique and micelles by dialysis.[73]There are different prepared nanolignins anti-leishmaniasis such as alkyl LNP, enzymatically hydrolysable lignin and organosolv LNP **(Figure 7).**[74]

Micro/nanofibers

The anti-leishmanial drug loading of micro- and nanofibres (NF) has not been thoroughly studied in comparison to NP delivery technologies. Micro- and nanofibrous mats can be compressed

to create oral tablets with large surface area, which allows high drug encapsulation efficiency. This lowers expenses associated with hospitalization-based traditional chemotherapy and increases patient compliance. Compressed oral tablets containing cross-linked nanofibrous amphotericin B-loaded gelatin were successfully created and demonstrated outstanding release of the drug for long time (approximately 10 days).[75]

The ability of the drug breakthrough the dermis, where leishmania incorporated into macrophages, is necessary for the topical administration of drugs for CL. It was discovered that the nanosystem largely permitted drug retention in the topmost layer of the skin, whereas the nanoemulsion form penetrated significantly deeper using an electrospun mat based on polyvinyl alcohol (PVA). [76] Gonçalves et al.(2020) created core-shell nanofibres loaded with amphotericin B, which are composed of polyethylene glycol (PEG) and polylactic acid (PLA) .They demonstrated strong anti-leishmaniasis effectiveness against L. braziliensis and L. amazonensis in vitro.[77] Lignin NFs, that have appropriate viscosity to be utilized to improve the spreading of their topical application , were employed to create arginine-derived lignin NF. In comparison to lignin NFs and arginine, the arginine-based lignin NF promoted reepithelialization, collagen deposition, and angiogenesis while also speeding up wound healing.[78]

Regarding, electrospun wound dressing; Rahimi et al. (2020) evaluated the anti-leishmanial activity of an electrospun wound dressing composed of chitosan (CS)-polyethylene oxide (PEO) nanofibers in vitro, against L. major.[79] It was discovered that the nanofibres were biocompatible, non-toxic, and did not inhibit fibroblast cell proliferation. Furthermore, the nano-scaffolds exhibited a 14-day drug release capacity, releasing 50% of the drug in the first 18 hours and 80% on day 3. In a mouse model, the healing of Leishmania ulcers were expedited by CS-PEO-berberine nanofibres.[80]

Hydrogel

According to earlier reports, hydrogels are appropriate carriers for topical drug delivery**.** After developing well-established lesions that are extremely inflammatory, ulcerated with numerous damaged tissues, and have a high parasite load, patients typically seek medical assistance. Hydrogel formulations are easier to apply directly to the skin lesions than NP formulations, which are frequently given intravenously. Hydrogels have demonstrated high water content and good biocompatibility, that mimic tissues features and properties of body and closely resembling the extracellular matrix found in wounds.[81]

The hydrogel drug delivery strategies is characterized by low cost manufactured, its easy administration in which 3D structure of microporous hydrogel matrix help the encapsulation of the drug .As well as, it increased skin permeability and has antileishmanial and antibacterial activity.[8]

Treatment of cutaneous Leishmania and wound repair by Multiple nano-drug delivery strategies

1- **Treatment of cutaneous Leishmania by Multiple nano-drug delivery**

-Efficacy improvement and toxicity reduction

Multiple loading of more than one drug specific for treatment of leishmaniasis on nanoparticles chitosan is more efficacy and has better therapeutic effect. For instance, chitosan promotes slow releasing of the drugs with increment of up taking to the cell, prevent site haemolysis , inhibit parasitic growth.[82] Besides, has no cytotoxic effect and is more stable through adhesion of nanoparticle at mucosal lining of gastrointestinal tract in comparison to administration of free drug.[83]

-Secondary bacterial infection targeting

Secondary bacterial and fungal infection occurred at ulcerative stage of the disease especially in low hygiene conditions that result in severe pain burning sensation , delay of epithelization and wound healing , and complication in diagnosis.[84] The skin flora in normal conditions has antimicrobial defense mechanism that accelerate wound healing . However, infected skin microbiota converted to dysbiotic skin microbiota that inhibit wound healing and assess wound infection with different bacterial species such *as Staphylococcus and or Streptococcus.*[85,86] Different studies have supported that nanodrug delivery that carried multiple drug which has antileishmanial and antimicrobial effect is more efficacy than use free drugs such as cu-SEDDS (Curcumin-loaded self-emulsifying drug delivery system) and Titanium dioxide (TiO2) and silver oxide (Ag2O) nanoparticles.[87, 88] The mechanism of metal nanodrug delivery through interaction with sulfur and phosphorous inside DNA of the bacteria result in inhibition of bacterial growth.[89] As well as increase the liberation of reactive oxygen species that destroy DNA, protein and lipid content of bacteria.[90]

2- **Wound healing by Multiple nano-drug delivery**

Flavonoids , Sesquiterpenes, Triterpenoids, and alkaloids are Small natural molecules have been proven to have antileishmanial activity and wound repair properties.

-Inflammatory phase:

1- Flavonoids

Curcumin is one of green food rich in flavonoids that responsible for wound repair by enhancing fibroblast proliferation , collagen deposition and granulation tissue formation.[91] Different studies have reported that curcumin nanodrug delivery system has cytotoxic effect toward the parasite by releasing reactive oxygen species that destroy parasitic DNA.[92]

2- Sesquiterpenes

Sesquiterpenes mechanism of action characterized by production of free radicals in the present of iron which induce parasitic death and accelerate wound repair through its antibacterial and anti-inflammatory effect.[93]

3- Triterpenoids

This natural molecules in nanoform inhibit parasitic burden in the macrophage through inhibition of COX-2 result in reduction of prostaglandins E2 biosynthesis result in increasing production of NO that damage parasitic cells.[94] Besides, their anti-inflammatory and proliferative effect through inhibition of proinflammatory cytokines and trigger ERK1/2 signaling pathway respectively. [95]

-Proliferative phase :

1- Alkaloids

Alkaloids found to have antileishmanial activity, antibacterial effect against gram positive and negative bacteria , ant-inflammatory effect by inhibiting different pro-inflammatory cytokines.[96] As well as provoke epithelization, angiogenesis ,and migration of fibroblast.[97]

2- Polyphenols

This compound accelerates wound repair through promoting granulation , fibroblast proliferation and migration , angiogenesis , collagen deposition anti-inflammatory effect and reduction of reactive oxygen species.[98]

-Future Vision on drug delivery strategies in combination with monitoring wound healing

In developing countries, the incidence of infection with leishmania is very high due to absence of trained medical persons at healthcare facilities , that give chance of disease dissemination with secondary bacterial infection. For instance, different diagnostic tools are time consuming and cost effective such as microbiological examination and PCR analysis , so any delay in these procedures resulting in generation of secondary bacterial infection at ulcerative biofilm.[99]

1- Nanotechnology-based vaccines

Nowadays , Scientists focus their efforts in production of vaccines to save hosts from

incidence of infection with leishmania parasite. Leishmanial vaccines have not reached to examined clinically due to several obstacles such as leishmania species , various consequences that developed after infection , adverse effect of vaccine. The main active component of the vaccine is the presence of a good adjuvant in which the active principle carries on and the present of an effective delivery system to potentiate the immune response for future standardization.[20]

- The assessment of a liposome nanoparticles with their beneficial properties as adjuvant encapsulation in different studies to be one of vaccine adjuvant targeting to activate Th1 immune response which triggers protection against leishmania parasite infected BALB/c mice.[100]
- Another type of liposomes archaeosomes were extracted from archaebacteria , that used as adjuvant topically applied as nano vaccination on antigen presenting cells invitro. [101]
- Another adjuvant nanoparticles is poly (D,L-lactide) an efficient adjuvant that stimulate immune system and ameliorated leishmania cutaneous ulceration and stop parasites spreading.[102]

2- Smart hydrogel:

- To monitor the environmental condition of the infected wound by using chitosan hydrogel is a responsive smart biomaterial that responsible for detection of either bacterial enzymes and/or bacteria itself.[103]
- This smart biomaterial hydrogel is designed as multiplex plateform of different substrate for detection of different types of bacteria and its enzymes result in different colours readout or specific shape development.[102,104]
- These responsive biomaterial multiplex plateform can be used in leishmania's wound to monitor several bacterial infections at once.[105]
- The opportunity to detect different bacteria such as gram-positive bacteria like S,aures and gram-negative bacteria like E.coli by using colour-encoded chitosan hydrogels that depend on sensitive and rapid differentiate between both bacteria through detection of each specific enzyme.[106]
- In rural area of low income ; paper coated with colorimetric chitosan-based sensing hydrogel can be used to identify bacterial infection through assessment of specific bacterial enzymes that compatible with widely available smartphone camera readout.[107]
- Not only hydrogel bandage sense to bacterial infection but also triggered for secretion of specific antibiotics.[108]
- Easily to monitor skin wound bacterial infection with other beneficial effect in which ; hydrogel offer the wound with better

hydration, have the ability to absorb wound fluid, and good wound dressings.[109]

- For detection of bacterial and monitoring the lesion status; Smart hydrogel was engineered as a bandage for appropriate wound management through instu monitoring the healing of internal wound after infection.[110]

3- **Non-pharmacological treatment**

There are different non-pharmacological approaches to eradicate some diseases such as modeling studies which are also helpful for analyzing disease dynamics, monitoring disease, and identifying the risk factors and treatment strategies that are crucial for curing the disease [111], smartphone [112], and machine learning.[113] Also, Public campaigns to disseminate awareness of disease control, prevention and utilization of insecticides. [8]

- Because disease dynamics are influenced by social and economic factors, leishmaniasis dynamics are difficult to model. Based on historical data from Assam, India, models called discrete time were initially employed to investigate the dynamics of visceral leishmania between these epidemic countries and the effect of both intrinsic and extrinsic factors on disease effectiveness; in which this model exhibits one of these countries are the reservoir of the disease that outbreak occur[111], Other model is a compartmental delay-differential equation model is used to calculate the number of reproduction or single affected sandfly during illness outbreak.[112]
- Smartphone technology is frequently employed in low-resource environments and can capture, process, and save high-resolution images. Health professionals may find it easier to monitor wound healing and identify the presence and severity of various leishmaniasis types with the help of affordable and easy to use smartphone application software.[114]
- Artificial intelligence in the form of machine learning is helpful in completing tasks like pattern recognition algorithms for recognition of key features of certain disease that are simple for people to complete but challenging for conventional computational methods. Machine learning software with an image dataset of leishmaniasis wounds may be utilized to describe wounds of leishmaniasis, track wound repair, assess the effectiveness intervention techniques for wound healing, and solve the shortage of specialists in environments with low resource.[8]

4- **In-vivo model**

Currently, CL has no validated animal model because of the weak link between the

mechanisms underlying human and animal disease. Inbred mice (primary tests), rat, hamster, dog (secondary tests) and non-human primates (tertiary tests) have been utilized in different L. studies.[8]

- To realize pathogenicity of L. parasite , different studies work on dog because they act as of L. infantum. [115]
- The inbred mice model (BALB/c–L. major mice) have been exploit in different studies of the disease because of high sensitivity to Leishmania major infection and the outcomes easily to be evaluated.[8]
- Monkeys as non-human primate models are utilized as they are similar to humans physiological and biological conditions with the same disease mechanism and progression.[8]

5- Others

- Egypt is one of the developing countries in which leishmaniasis disease is spread as a zoonotic disease in which supported by molecular and bioinformatics analysis.[115]
- Public campaigns to disseminate awareness of control , prevention and consult the government about the endemic areas to overwhelms both sand fly and parasite
- This parasitic disease must be put in consideration to be eradicated ,in which Egypt will be Zero leishmania.
- Healthcare facilities at leishmania spreading areas should be well established with infrastructure and equipment , well trained physicians that used for early diagnosis , and treatment of the disease by nanodrug delivery system.

Abbreviations :

AgNPs: silver nanoparticles, AuNPs: gold nanoparticles, CL: Cutaneous Leishmania, CS: chitosan, cu-SEDDS: Curcumin-loaded self-emulsifying drug delivery system, DC: Dendritic cells, DR: Drug resistance, IFNγ :Interferon gamma, IL-10:interleukin 10, L: Leishmania, LNP: lignin-based, nano-DDS: Nano-drug delivery systems, NF: Nanofibers, NLC: Nanostructures lipid carriers, NPs: Nanoparticles, PACA: poly (alkyl cyanoacrylate), PBCA: butyl cyanoacrylate, PCL: Polycaprolactone, PEG: polyethylene glycol, PEO: polyethylene oxide, PGA: poly (glycolic acid), PLA: polylactide , PLA: polylactic acid, PLGA: Poly Lactic-co-glycolic acid , PVA: polyvinyl alcohol, SLN: Solid lipid nanoparticles, TGF-β: transforming growth factor- beta, TNF: Tumor necrotic factor

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