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Recent advancement and treatment of leishmaniasis based on pharmacoinformatics approach: Current and future outlook

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ABSTRACT

The concept of rational treatment, target to therapy, is an old and interesting process in drug discovery that includes the entire step from target identification to successful treatments of disease and is based on new drug delivery approach. In this current review, we have tried to compile maximum data which are published in a recent journal and books from 2005 to 2017 in all areas related with treatment of leishmaniasis. During last decade (2005–2015), there are a number of preclinical drug(s) undergone into clinical phase (Ph-III) and our institute (RMRIMS, Patna) is dedicated to the basic and clinical research of leishmaniasis. Today, there are number of drugs of choice for the treatment of leishamaisis (AmBisome and miltefosine) and more are in a clinical trial (Phase IV), which have > 94% efficacy and success rates. Moreover, there are 98 candidates (drugs) in preclinical development stages and most of them are antleishmanial agents. The nine (9) antleishmanial agents are in Phase III (efficacy) trials (combination with first line drugs). The success rate of combination therapy are having > 98%. The chemical classification of all drugs which have under preclinical trial is classified as chalcones (18), azoles (15), and quinolines (9) compounds. The drug target is based on classifications of drugs or drug candidates that revealed that topoisomerase have higher success rate (42%) followed by cysteine protease (13%). This study suggest that the drug target against this site such as topoisomerase and cysteine proteases will have > 50% success rate. In this review, number of diagrams have been elucidated to understand overall and clear picture, and its structural group which is responsible for development of drug(s) against leishmaniasis.

1. Introduction

Leishmania, the causative agent of leishmaniasis, is a severe parasitic disease with considerable significance in terms of both diversity and complexity in their life cycle. There are a number of reports indicating approximately 350 million people are at risk and 2.3 million new cases are reported every year (Pearson and de Queiroz Sousa, 1996; Pearson et al., 1981; Rab, 1996). All *Leishmania* species have a digenetic life cycle in which one is flagellated that is mobile promastigotes and other is non-flagellated (amastigotes) (Chang et al., 1985; Chang et al., 2003; Wheeler et al., 2011) (Fig. 1). Visceral leishmaniasis (VL) is one of the most serious condition or severe form of the disease in which, protozoan targets and affects the visceral organ (spleen and liver). The condition is most serious and severe, if left untreated (Table 1). According to World health Organization (WHO) report (2015), this disease is the second largest parasitic killer and now it is responsible for an estimated 0.429 million new cases every year. *Leishmania* are a member of trypanosomatidae family that characteristic have presence of a single flagellum and have rich DNA contents called as kinetoplast and a mitochondrial like organelle. There are various species of *Leishmania* are responsible for a wide spectrum of disease termed leishmaniasis (Table 1) which includes cutaneous leishmaniasis, subcutaneous leishmaniasis and visceral leishmaniasis. This protozoan disease is also known as Orient Boils, Aleppo Boil, Baghdad Boil, kala azar, black

Abbreviations: VL, visceral leishmaniasis; PKDL, post-kala-azar dermal leishmaniasis; WHO, World Health Organization; TDR, Tropical Disease Research; HGPRT, hypoxanthine-guanine phosphoribosyltransferase; CDKs, cyclin dependent kinases

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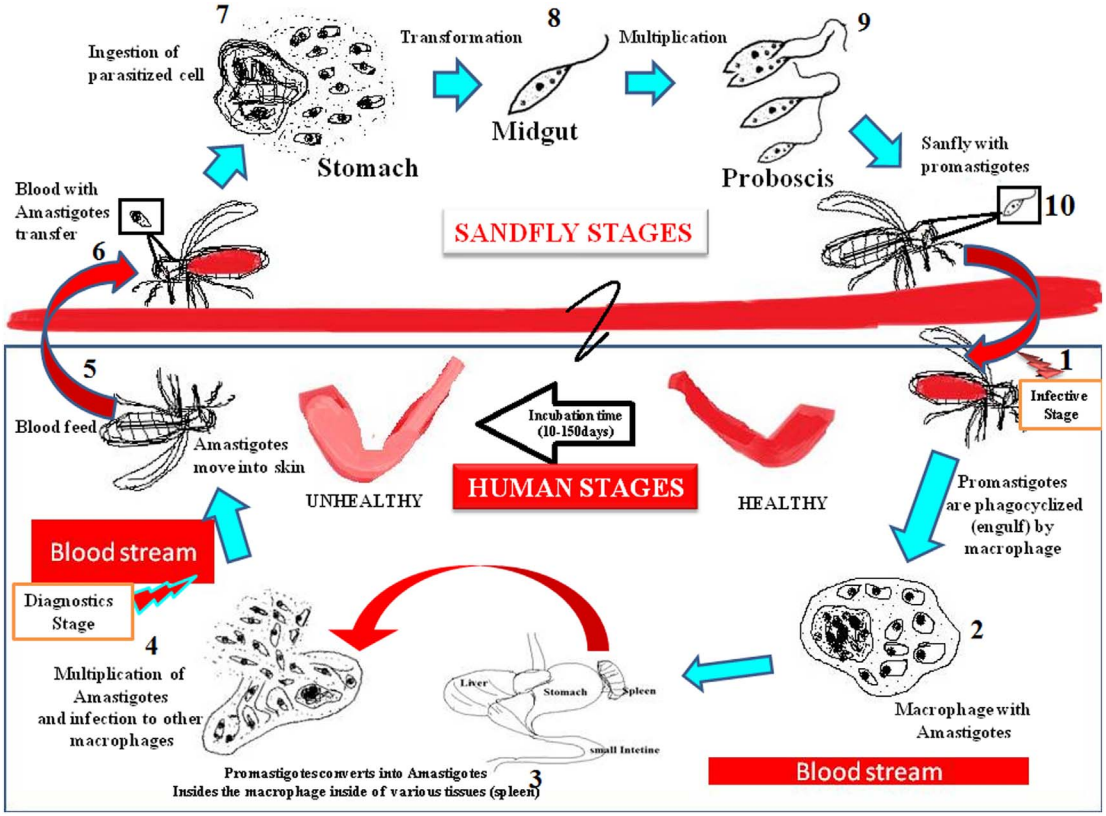

Fig. 1. Life cycle of *Leishmania*: (1) infective stage in which the metacyclic promastigotes were entered into blood stream of host (take blood and inject promastigotes); (2) blood steam having metacyclic promastigotes were phagocytozed by host macrophages; (3) reservoir of amastigotes which are differentiated from promastigotes (non flagellates); (4) all amastigotes are ready to enter the newly macrophage cells and infect to host cells (diagnostic stage); (5) rupture macrophage and promastigotes come out into blood steam (skin surface) (6) the carrier of amastigotes (sand fly) were sucked blood of host (including infected macrophages); (7) injection of macrophages cells having amastigotes; (8) during digestion, free amastigotes were differentiated into promastigotes (adaptation); (9) binary fission of promastigotes (asexual reproduction) and migrate to the proboscis; (10) promastigotes cells of *Leishmania* were differentiated into metacyclic promastigotes stage and ready to enter into host (take blood and inject amastigotes) (https://www.cdc.gov/parasites/leishmaniasis/biology.html).

fever, sand fly disease, Dum-Dum fever, chiclero ulcer or espundia based on geographical distribution and language (Thakur, 1984; Kenner et al., 1999). Although, the main concern of reservoirs have been incriminated in the epidemiological chain of human VL, such as wild canids, rodents, or marsupials, zoonotic VL epidemics. The life cycle of *Leishmania* (Fig. 1) has depicted its overall stages and duration time for complete survival.

2. Visceral leishmaniasis

When the parasites enter into blood, soon after it migrates to the visceral organ (internal organs include liver, spleen) and also to the bone marrow for their survival. A sand fly is the main carrier (or vector) of promastigotes form of *Leishmania* and become mature when it transfer to host organism including human. In the alimentary tract of sand fly, a number of parasites exist as a promastigotes form that is flagellated motile (Kumar et al., 2012). When the insect is sucking blood, the metacyclic promastigotes is injected into the dermis, then enters into host macrophages. Now metacyclic promastigotes are differentiated into a non-motile amastigote form and then later it multiplies by asexual reproduction to produce million of amastigotes Fig. 1.

2.1. Sign and symptoms of Leishmania infection

The first sign and symptoms of *Leishmania* infected person is having high fever, weight loss, mucosal ulcers, fatigue, mucosal and substantial swelling of the liver and spleen. According to WHO, this disease creates a major and emerging problem as HIV/VL co-infection (get more chances of secondary infection). The traditional treatment of leishmaniasis is use of pentavalent antimonials such as sodium-stibogluconate and meglumine antimoniate (success rate have shown in the Fig. 2) have shown unresponsiveness in India. Resistance is now common in India, and rates of resistance is increasing as high as 60% in major parts of Bihar, India (Mondal et al., 2009; Purkait et al., 2012).

2.2. Currently available drugs

There is currently no vaccine available for the treatment of any form of leishmaniasis, includes visceral leishmaniasis (VL). The VL causes when systemic infection with *L. infantum*, which occurs in Europe, North Africa, South and Central America, whereas *L. donovani* infection, which are found throughout East Africa, India, and some part of the Middle East (Gyapong and Boatin, 2016). Currently, there are a number of projects ongoing at RMRIMS with the collaboration of well reputed international organization includes Bill and Melinda Gates Foundation, Grand Challenge of Canada for designing and proper management of VL patient and their treatment with the help of ASHA workers (Das et al., 2014). There is limited number of drugs available for treatment and major problem is drug side effect and now most of them are resistant (Fig. 2). The combination therapy is also success nowadays for the *Leishmania* treatment. Recently, nanotechnology based drug delivery approach become more efficious with less side effects (Gutiérrez et al., 2016; Rishikesh et al., 2014; Kumar et al., 2015) and most of them are under pre-clinical trial phase (PLGA–PEG encapsulated miltefosine and amphotericin B drugs) (Kumar et al., 2016). Currently, available treatment is unsatisfactory in terms of safety and efficacy, which sharply contrasts with the therapeutic needs in terms of people at risk, a number of affected patients and associated deaths. This discrepancy is