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Review article

A review of current treatment strategies based on cisplatin for leishmaniosis

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ABSTRACT. Neglected tropical diseases as termed by World Health Organization include a group of 20 diverse infectious diseases in the tropical and subtropical regions of the world. Amongst these diseases, high mortality rate is mostly associated with Chagas disease and leishmaniosis due to limited drugs, severe toxicity caused by the available drugs and drug resistance. The above hitches have triggered the researchers to focus on the development of novel alternative therapeutics. Studies reveal that several target-based drugs have emerged which affect the biochemical pathways of the causative parasite. An anti-cancerous molecule and its derivatives might be used as antiprotozoal agents due to biochemical similarities affecting DNA metabolism. Cisplatin is a widely used drug for the treatment of testicular, ovarian, head and neck cancers, melanoma, lymphomas and several others. It exerts anticancer activity via multiple mechanisms but most effective mechanism is binding with DNA, formation of intrastrand and interstrand cross-links and generation of DNA lesions. However, side effects of cisplatin limit its application and effectiveness in the cancer treatment. Moreover, to minimize the side effects of cisplatin, combination therapies are used and have proven to be effective against cancers. Thus, current review is aimed at highlighting potential of cisplatin alone and in combination therapies as an antileishmanial agent.

Keywords: antileishmanial, cisplatin, *Withania somnifera*, *Asparagus racemosus*, *Tinospora cordifolia*, immunotherapy

Introduction

Leishmaniosis

Leishmaniosis is one of the neglected tropical diseases (NTD) caused by an obligate intracellular agent of genus *Leishmania*. It is endemic in 98 nations of the world, where more than 350 million people are at risk and more than 12 million cases of infection have been reported [1,2]. *Leishmania* are transmitted to mammals through the bite of infected female sandflies belonging to genus *Lutzomyia* and *Phlebotomus* [3]. Based on the species and intensity of infection to the host, it has been classified into cutaneous leishmaniosis (CL), mucocutaneous leishmaniosis (MCL), and visceral leishmaniosis (VL) [4]. Visceral leishmaniosis, the most severe form, is fatal if untreated [5]. This disease is caused by *Leishmania donovani*, which is endemic to Africa and Asia, causes anthroponotic visceral leishmaniosis, and is associated with high mortality rates [6].

The resolution from leishmanial infection is dependent on the coordinated interactions between the components of the cell mediated immune system and the activation of T-cell population into appropriate cytokine production and the activation of macrophages [7]. However, the major immunological dysfunction observed in VL is the inability of T cells to produce cytokines upon stimulation with *Leishmania* antigen to activate macrophages and kill *Leishmania* parasites. Resistance to VL involves both CD4+, CD8+ T cells, interleukin IL-2, interferon (IFN)-gamma and IL-12. However, susceptibility involves IL-10 [8] but not IL-4, and B cells [9]. CD4+ T cells are responsible for the production of cytokines critical for the activation of macrophages and are required for optimal host response to infection [10]. Cytotoxic CD8+ T cells also play a host protective role, and are required for the effective clearance of parasites [11] and the generation of memory responses [12]. CD8+ T cells have been shown to

maintain immunity against infection through IFN-gamma production and regulation of the same by CD4+ T cells. CD8+ T cells have been found to participate in the control of *Leishmania* infection through various cytotoxic mechanisms [13].

The drugs for the treatment of visceral leishmaniosis such as pentavalent antimonials, pentamidine, amphotericin B and lipid formulations, paromomycin, allopurinol and miltefosine have limitations including development of resistance, parenteral administration, long courses of treatment, toxic side effects, and high costs [14,15]. Pentavalent antimonials administrated at the dose of 20 mg/kg/day (28–30 days) via intravenous, intramuscular, and intralymphatic routes showed potential of 35–95%. But its excessive use leads to nephrotoxicity, hepatotoxicity, cardiotoxicity, and pancreatitis [16]. Administration of miltefosine orally exhibited nephrotoxicity, teratogenicity, vomiting, diarrhoea and hepatotoxicity [17]. Use of paromomycin also showed severe nephrotoxicity, hepatotoxicity, and ototoxicity [18]. Treatment with pentamidine with the dose of 3 mg/kg/day can cause retardation of *Leishmania* growth but with some severe antagonistic effects such as hypotension, elevated rate of hyperglycemia, tachycardia, pancreatic damage, and electrocardiographic changes [15]. Hence, there is an instantaneous necessity to innovate new, harmless, and efficient prevention therapies to overcome these limitations [19].

For leishmaniosis, various targets like nucleoside analogs, inhibitors targeting nucleoside phosphate kinases of the parasite's purine salvage pathway, 20S proteasome of *Leishmania*, mitochondria, and the associated proteins are reviewed along with the chemical structures of potential drug candidates [20]. Therefore, search of new therapeutic strategies for NTDs involves combining existing drugs to enhance the efficacy of the available therapeutics [21]. It has been a pharmacological observation that certain anticancerous molecules and their derivatives might also be used as antiprotozoal agents. It has been hypothesized that cytotoxic activity of antitumor drugs against protozoan parasites may be associated with the shared biochemical similarities affecting DNA metabolism, protein kinases pathways, glucose catabolism enzymes, and polyamine metabolism between parasites and cancer cells [22]. In addition growth in the case of trypanosomatid parasites in their respective host and also in the cancer cells, share common features for example being capable of rapid cell divisions, immune system evasion mechanisms and defense [23]. The molecular mechanism behind programmed cell death (PCD) of *Leishmania* parasites shares few similarities with the apoptotic mechanism of multicellular organisms. Such kind of PCD mechanisms involves proteins with caspase-like activity, cytochrome C release and DNA fragmentation [24]. Thus, the leishmanicidal activity of some anticancer drugs may be due to the induction of programmed cell death.

Cisplatin and mechanism of action

Cisplatin is a major antineoplastic drug used for the treatment of various types of solid cancers such as testicular, ovarian, head and neck, bladder, lung, cervical cancer, melanoma, lymphomas etc. [25]. It is an organic complex formed by an atom of platinum surrounded by chloride and ammonium atoms in the cis position of a horizontal plane [26]. Upon its absorption into cancer cells, it reacts with macromolecules and exerts its cytotoxic effect by binding to DNA, forming intra-strand DNA adducts, thus inhibiting DNA synthesis, cell growth and induces apoptotic cell death [27]. When cisplatin enters cytoplasm, it gets activated by displacing chloride atoms with water molecules forming an electrophile with affinity towards sulfhydryl groups on proteins and nitrogen donor atoms on nucleic acids [28]. The reactive complex formed after chloride disposal reacts with water and then interacts with DNA. It causes intrastrand cross-linking, probably between N^7 and O^6 of the adjacent guanine molecules resulting in local denaturation of the DNA chain [29,30] (Fig. 1).

Side effects of cisplatin and prevention

In vitro studies indicated that interaction between the cisplatin molecule and the DNA may contribute to the generation of superoxide radicals, causing toxicity to cancer cells [31]. Cisplatin given both intravenously or intraperitoneally, binds to serum proteins and gets distributed to most tissues [32] however, in the first hour, it accumulates in the kidney, liver, muscle and skin [33]. However, despite its clinical usefulness, cisplatin treatment is associated with several toxic side effects including nephrotoxicity [34,35], neurotoxicity and ototoxicity [36,37]. The kidney accumulates cisplatin to large extent than other organs and it is the major route for its excretion. The concentration of cisplatin in proximal tubular epithelial cells is 5

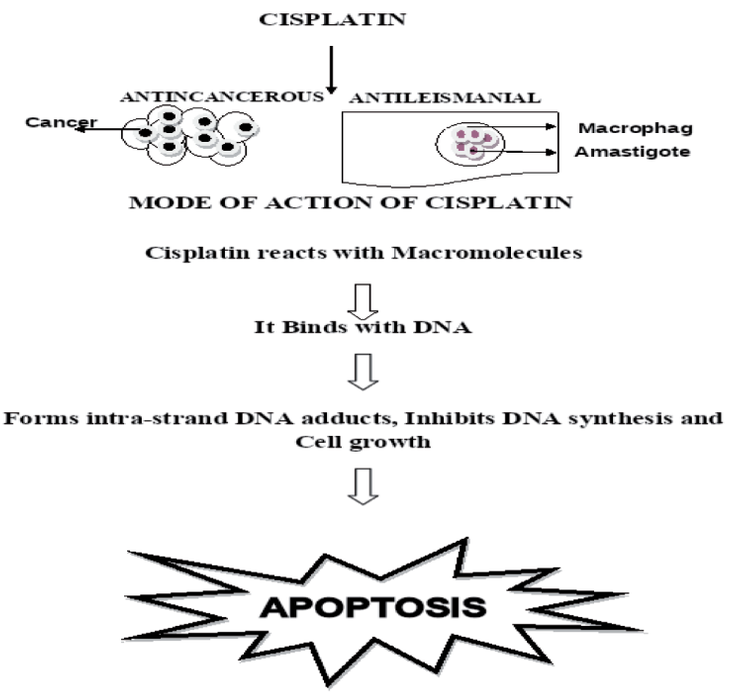

Figure 1. Common apoptotic pathway for antileishmanial and anticancer targets

times the serum concentration [38]. In the S3 segment of the proximal tubule highest concentration of cisplatin accumulates, followed by the distal collecting tubule and the S1 segment in the proximal tubule [39]. The critical transporter for the uptake of cisplatin in proximal tubules is organic cation transporter (OCT 2) in both animals and humans [40]. Cisplatin is conjugated to glutathione and then metabolized through a gamma glutamyl transpeptidase and a cysteine *S*-conjugate beta-lyase–dependent pathways to a potent nephrotoxin. The mitogen-activated protein kinase (MAPK) intracellular signaling pathways also mediate cisplatin induced nephrotoxicity [41]. The mechanisms of cisplatin nephrotoxicity are complex and involve oxidative stress, apoptosis, inflammation, and fibrogenesis also. Oxidative stress injury is actively involved in the pathogenesis of cisplatin-induced acute kidney damage. Reactive oxygen species (ROS) directly act on cell components, including lipids, proteins, and DNA, and destroy their structure [42,43].

However, various studies have shown that the administration of several agents extracted from plants and dietary components may reduce some of the side effects of cisplatin [44–46]. Among the antioxidants that have been tried against nephrotoxicity of cisplatin are those that have been extracted from natural products (mainly medicinal plants and dietary components) [44,47]. Many examples have been reported and the agents that have been reported to either ameliorate or prevent the nephrotoxicity of these drugs include soybean [48], alpha lipoic acid [49], *Heliotropium eichwaldii* [50], flavones luteolin [51], red ginseng [52], icariin [53], flavonoids [54], galangin [55], mangiferin [56], N-acetylcysteine [57], dietary isoflavone daidzein [58], gallic acid [59] etc.

During the effective tumor suppression treatment protocols, higher doses of cisplatin may lead to hepatotoxicity [60]. High doses of cisplatin have been found to accumulate in significant amounts in hepatic tissue [61]. There has been found an increase in lipid peroxidation status and decrease in glutathione levels in hepatic tissue of rat after cisplatin treatment. [62,63]. Oxidative stress appears to play an important role in cisplatin induced hepatotoxicity. Many cellular pathways have been suggested to contribute to induction of oxidative stress during cisplatin treatment. Cytochrome P450 2E1 (CYP2E1) is mainly expressed in liver and in small amounts in brain, kidneys, lungs, gastrointestinal tract, and lymphocytes [64].

Previous findings have suggested that side effects of cisplatin could be protected by drugs and micronutrients [65–70]. Lee and his colleagues [71] studied the protective effect of pericarp extract of (peach) *Prunus persica* (PPE) against cispatin induced acute toxicity in mice. Abdelmeguid et al.

[72] studied the ameliorative effect of silymarin, a plant extract on cisplatin induced hepatotoxicity in rats. They found that pretreatment with silymarin 2 h before cisplatin significantly decreased the pathological changes induced by cisplatin. Cayir et al. [73] studied the protective effects of pomegranate seed extracts (PSE) against oxidative stress caused by cisplatin injury in kidneys and liver. Naqshbandi et al. [74] found the protective effect of flaxseed oil on cisplatin induced hepatotoxicity. Bhattacharyya and Mehta [75] studied the potential of spirulina and vitamin C supplementation in cisplatin toxicity. *Sorghum* leaf sheath dye [76], pine bark extract [77], apocynin [78], green tea [79], *Zingiber officinale* [80], *Nigella sativa* [81], hydroalcholoic leaf extract of *Origanum vulgare* [82], curcumin nanoparticles [83], rutin [84] have been found to be effective against cisplatin induced toxicity.

Methods

The database of PubMed was used. The review included the studies that had used drug cisplatin against *Leishmania* parasites. Following the initial research paper, all those papers were included which were identified as being related from 2007 to 2019.

Leishmanicidal potential of cisplatin

As per literature *in vitro* antileishmanial potential of cisplatin was reported on promastigote and amastigote stages at a concentration of 0.25–0.64 μM [85]. The IC50, determined by flow cytometry, after 72 hour of drug incubation was 7.73+/–1.03 μM in the case of promastigotes and 1.88+/–0.10 μM in axenic amastigotes. In intracellular amastigotes the IC50, determined by counting the parasite index was 1.85+/–0.22 μM. By using flow cytometric analysis it was found that cis-DDP treated promastigotes and amastigotes accumulated in S phase and G2 phase. The cis-DDP response was also found to involve an „apoptosis-like" death in both promastigotes and amastigotes. However, DNA fragmentation was only detected in promastigote forms. In contrast mitochondrial transmembrane potential loss was observed for both stages of the parasite. Upon incubation of parasites with the drug an increase on GSH and GSSG levels and reactive oxygen species was detected. Thus, the study indicated that amastigotes are more sensitive to cis-DDP when compared to promastigotes. The *in vivo* antileishmanial efficacy of cisplatin was studied by Kaur et al. [86]. Two low doses of cisplatin 0.5 mg and 1 mg/kg body weight (b.wt.) were given intraperitoneally (i.p.) for five days in *L. donovani* infected BALB/c mice after 30 post infection days. Cisplatin treatment in infected mice resulted in significant reduction in hepatic parasite load with heightened DTH responses, leucopenia, mild hepatotoxicity and nephrotoxicity. It has been found that these doses of cisplatin reduced the parasite burden to some extent but not completely. Therefore, further higher doses of cisplatin were tried along with antioxidants with an aim to further reduce the parasite load with minimal side effects.

The antileishmanial effect of cisplatin at higher doses of 5 mg and 2.5 mg/kg body weight and its combination with different antioxidants (vitamin C, vitamin E and silibinin) was evaluated by Sharma et al. [87]. The combination therapy reduced the parasite load significantly with higher levels of IgG2a, lower IgG1 levels and enhanced DTH responses. The greater concentration of Th1 cytokines viz. IFN-γ, IL-2 was also observed. Moreover, combination therapy of cisplatin with antioxidants provided nephro and hepatoprotection.

Sachdeva and Kaur [88] did a combination study with cisplatin and *Withania somnifera*. When cisplatin (5t.) daily for 5 days, i.p.) was administered in *L. donovani* infected BALB/c after 30 post infection days, it reduced the parasite load to great extent but liver and kidney damage was also reported. Biochemically it was evidenced by an increase in SGOT, SGPT, serum creatinine, and blood urea nitrogen levels respectively. The biochemical observations were further supported by histopathological changes induced in the liver and kidney. The cisplatin induced changes were ameliorated by *W. somnifera* (350 mg/kg b.wt. daily for 15 days, orally) when given along with cisplatin. The results also indicate that *W. somnifera* in combination with cisplatin resulted in increased production of helper cell (Th1)1 cytokines, IFN-gamma and IL-2; augmented levels of IgG2a over IgG1; heightened DTH (delayed type hyper-sensitivity) responses were observed while Th2 cytokines, IL-4, and IL-10 were downregulated. Flow cytometric analysis of *W. somnifera* and cisplatin-treated animals showed an increase in the percentage of T cells (CD4+, CD8+) and NK1.1 suggesting its effect on activation of T cells.

Sharma and Kaur [89] studied the effect of cisplatin on gonads of *Leishmania donovani*

Table 1. Antileishmanial effect of cisplatin alone and in combination with other drugs

Use of cisplatin alone or in combination	Observation	References
Cisplatin (0.25–0.64μM) against promastigotes and amastigotes stages *in vitro*	Cisplatin treated promastigotes and amastigotes accumulated in S phase and G2 phase, apoptosis like death	[85]
Cisplatin (0.5mg and 1mg) *in vivo*	Significant reduction in parasite load, DTH responses, leucopenia, mild hepatotoxicity and neprotoxicity	[86]
Cisplatin (5mg and 2.5 mg+Antioxidants (vitamin C 200 mg, vitamin E 100 mg 200 mg/kg b.wt. of silibinin) *in vivo*	Combination therapy reduced the parasite load significantly with higher levels of IgG2a, DTH responses, Th1 cytokines but lower IgG1 levels	[87]
Cisplatin (5mg/kg b.wt. of mice)+ *W. sominifera* (350mg/kg b.wt. of mice) *in vivo*	Combination group observed decreased parasite load, increased levels of Th1 cytokines, IgG2a, DTH responses, CD4+, CD8+ and NK 1.1 cells, improved biochemical and histological parameters	[88]
Cisplatin+Antioxidants effect on gonads (dose as mentioned in serial number 3)	Cisplatin treated animals had mild reduced spermatogenesis, antioxidants+cisplatin helped in suppression of drug-induced toxic effects	[89]
Cisplatin+*Leishmania* specific 78KDa antigen with or without adjuvant MPL-A	Animals treated with immunotherapy showed maximum curative potential	[90]
Cisplatin (5mg/kg b.wt. of mice)+*Asparagus racemosus* (650mg/kg b.wt)	Enhanced clearance in parasite load, increased production of Th-1 response (IFN-gamma, IL-2), heightened DTH, augmented levels of IgG2a, normal liver and kidney function test, attenuated histological parameters	[91]
Cisplatin (5mg/kg b.wt. of mice) +*T. cordifolia* (100 mg/kg b.wt.of mice)	Good antileismanial activity, enhanced levels of IFN-γ and IL-2, IgG2a, DTH, decline in cytokines IL-4 and IL-10. The flow cytometric analysis of lymphocyte surface markers of T cells (CD3+, CD4+ and CD8+), NK1.1 and B cells (CD19) indicated prominent enhancement in proliferation and differentiation of lymphocytes	[92]
Cisplatin+*T. cordifolia* or Cisplatin+*W. sominifera* or Cisplatin+*A. racemosus*	In the group of infected mice treated with cisplatin in combination with herbal drugs *T. cordifolia*, *W. somnifera* and *A. racemosus* daily for 15 days orally a significant reduction in the percentage of Treg cells.	[93]
In vitro cisplatin bonded carbon nanotubes against promastigotes and amastigotes of *L. major*	IC 50 of CP-MWCNT (0.11±0.09 μM) for amastigotes was 41-fold lower than that of Glucantime ® (4.52±1.31 μM).	[94]

infected BALB/c mice. In cisplatin treated animals, mild reduced spermatogenesis was observed but when antioxidants were supplemented along with cisplatin, the morphological characteristics of testes were comparable to those in control groups. Moreover, the ovary was also found to be normal in the oestrus phase with development of corpus luteum. The above findings showed that damage caused by cisplatin to gonads was ameliorated by administration of antioxidants.

Combination of *Leishmania*-specific 78 kDa antigen (with or without adjuvant MPL-A) along with a novel drug cisplatin was studied in infected BALB/c mice. Animals that were treated with immunochemotherapy showed maximum curative potential as demonstrated by a marked reduction in parasite load. Moreover, an increased delayed-type hypersensitivity (DTH) response was observed in animals given immunotherapy or chemotherapy or immunochemotherapy; however, maximum DTH response was observed in animals treated with cisplatin + 78 kDa + MPL-A. These animals were also found to exhibit higher IgG2a levels greater cytokine (IFN-γ and IL-2) concentrations suggesting the generation of a strong Th1 type of immune response which is responsible for

resolution of the disease [90].

A new therapeutic approach based on combination of *Asparagus racemosus* and cisplatin was evaluated in murine visceral leishmaniosis. The *L. donovani* infected BALB/c mice were given cisplatin (5 mg/kg b.wt./day for 5 days, intraperitoneally) and *A. racemosus* (650 mg/kg b.wt./day for 15 days, orally) 30 days post infection. In this study enhanced clearance in parasite load was achieved in the combination groups as determined by Giemsa-stained liver impression smears. This combination group also offered increased production of disease resolving Th-1 response (IFN-gamma, IL-2), heightened DTH (delayed type hypersensitivity) response and augmented levels of IgG2a. Moreover, normalization in the levels of liver and kidney function tests such as SGOT, SGPT, alkaline phosphatase, creatinine and urea with normal histological observations as compared to only cisplatin treated *L. donovani* infected BALB/c mice was also observed [91].

In another study, *T. cordifolia* (100 mg/kg b.wt. for 15 days daily) was used in combination with cisplatin (5 mg/kg body weight (b.wt.) daily for 5 days, i.p.) in *L. donovani* infected BALB/c mice. The combination showed good antileishmanial activity and augmented the cisplatin induced side effects. Moreover, this combination has selectively induced Th1 type of immune response as depicted by enhanced levels of IFN-γ and IL-2 whereas Th2 specific cytokines IL-4 and IL-10 showed a moderate decline. Confirmation of Th1 polarization was further obtained from augmented levels of IgG2a over IgG1 and heightened DTH (delayed type hypersensitivity) response. The flow cytometric analysis of lymphocyte surface markers of T cells (CD3+, CD4+ and CD8+), NK1.1 and B cells (CD19) indicated prominent enhancement in proliferation and differentiation of lymphocytes [92].

In addition, percentages of CD4+ CD25+ FoxP3+ T regulatory cells and ultra structural changes in kidney, liver and spleen were evaluated in various groups of mice. Cisplatin (5 mg/kg b.wt. daily for 5 days, i.p.) along with *Tinospora cordifolia* (100 mg/kg b.wt. daily for 15 days, p.o.) or *Withania somnifera* (350 mg/kg b.wt. daily for 15 days, p.o.) or *Asparagus racemosus* (650 mg/kg b.wt. daily for 15 days, p.o.) were administered to *L. donovani* infected BALB/c and 30 days post treatment mice were sacrificed. In the cisplatin treated *L. donovani* infected BALB/c mice significant (P<0.0001) decline in parasite load was observed compared with infected control. A percentage reduction of 96.7% was found. Also, infected mice treated with cisplatin along with *T. cordifolia*, *W. somnifera* and *A. racemosus* showed 97.1%, 97.2% and 97.2% percentage parasite decrease respectively.

The percentage of CD4+CD25+ Treg (19±2.1%) was found to be significantly higher in *L. donovani* infected BALB/c mice at 30 day post infection. However, it found to be decreased significantly in the group of infected mice treated with cisplatin alone at the dose of 5 mg/kg b.wt. daily for five days, i.p. (19±2.1% vs 6.9%). In the group of infected mice treated with cisplatin in combination with herbal drugs *T. cordifolia, W. somnifera* and *A. racemosus* daily for 15 days orally a significant reduction in the percentage of Treg cells was also observed (5.7±1.5%/5.1±0.7%/5.3±1.9% vs 19± 2.1%) as compared with infected controls.

In the cisplatin administered group of infected BALB/c mice, mitochondrial degeneration in proximal convoluted tubular cells was observed. However, aforementioned change was found to be reduced in the groups of infected mice treated with cisplatin along with herbal drugs. In the cisplatin treated infected group of mice cytoplasmic changes were observed in the micrographs of liver and dilation in space of Disse was found. However in the groups of infected mice treated with cisplatin along with herbal drugs, these changes were found to be ameliorated. The spleen sections showed heterochromatin condensation in the nucleus of plasma cells in cisplatin treated infected mice. However, cisplatin in combination with herbal drugs achieved normal architecture of spleen [93].

In vitro cytotoxic and antileishmanial activity of cisplatin-bonded carbon nanotubes was evaluated against promastigotes and amastigotes of *Leishmania major.* For the study, cisplatin-bonded single-walled carbon nanotubes (CP-SWCNT) and cisplatin-bonded multi-walled carbon nanotubes (CP-MWCNT) were taken as test compounds. The controls taken for the study were SWCNT, MWCNT, free cisplatin and meglumine antimoniate (Glucantime®). The effect of each compound was evaluated both on promastigote and amastigote stages of *L. major*. A statistically significant (P<0.05) difference was found between the half-maximal inhibitory concentration (IC_{50}) of CP-SWCNT and each of the controls, including

SWCNT, cisplatin and Glucantime®. In addition, IC_{50} values of CP-MWCNT and each of the controls, including MWCNT, cisplatin and Glucantime®, were significantly different both for promastigotes and amastigotes (P<0.05). However, the selectivity index (SI) of CP-SWCNT was <10 (5.23), indicating the selective effect of these two compounds on the parasite. Moreover, the SI values of CP-MWCNT (12.54) and Glucantime® (16.28) were >10, indicating the selective effect of these two compounds on the parasite. Moreover, the IC_{50} of CP-MWCNT (0.11±0.09 μM) for amastigotes was 41-fold lower than that of Glucantime® (4.52±1.31 μM), suggesting that a lower dose of CP-MWCNT in comparison with Glucantime® is required to kill 50% of amastigotes [94].

Hence, it is interesting that certain molecules are effective as both anticancer drugs and antiprotozoal agents. It suggests that this class of compounds and their derivatives might be useful as antileishmanial agents. Discovery of newer drug could involve high cost and time management. Moreover, choosing an already approved drug with known mode of action would be beneficial. Thus, in future cisplatin can be a drug of choice for treatment of leishmaniosis. However, various trials are required to be conducted to know the exact efficacy and doses.

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