

**CHEMOTHERAPY OF LEISHMANIASIS – A REVIEW****BORAH UTTAM\*, DASH BISWAJIT, DASH SUVAKANTA**

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**ABSTRACT**

Leishmaniasis is a dismissed vector-borne tropical contamination thought to be an ailment of poor people. It is a standout among the most ignored tropical sickness as far as medication disclosure and improvement. Moved in neediness stricken nations inside Southeast Asia, East Africa, and Latin America, it is likewise endemic in a few Mediterranean nations. The administration of the heterogeneous disorders controlled by parasites having a place with the genus *Leishmania* is, especially troublesome in created, non-endemic nations attributable to the newness of doctors with clinical side effects, demonstrative conceivable outcomes, and accessible treatment choices. Most antileishmanial medications are very lethal and introduce resistance issues or require hospitalization, being along these lines not sufficient to the field. As of late changes have been accomplished by blend treatment, decreasing the time, and cost of treatment. Regardless, new medications are still direly required. This overview highlights the chemotherapeutic operators against leishmaniasis, their science, method of activity and the component of resistance in the parasite. Future viewpoints in the territory of new hostile to leishmanial sedate targets are likewise specified.

**Keywords:** Visceral leishmaniasis, Cutaneous leishmaniasis, Chemotherapy, Antileishmanial drugs.

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**INTRODUCTION**

Chemotherapy is the only compelling approach to treat leishmaniasis [1]. Chemotherapy against leishmaniasis is constructed primarily on toxic pentavalent antimonial created during the main portion of the most recent century. Amid the most recent decade, elective medications have turned out to be accessible and enlisted for use in a few nations; be that as it may, most improvements in chemotherapy against leishmaniasis have originated from re-definition and rescreening of officially recognized medicaments instead of from reasonable outline of medications. This is on the grounds that both the science of the parasite and the immunological reaction of the host are not yet surely knew [2].

The primary medication medicines prescribed for both visceral leishmaniasis (VL) and cutaneous leishmaniasis (CL) were initially presented more than 50 years prior. In any case, the position is changing and some new treatments are getting to be noticeably accessible. Lamentably, it now appears to be evident that the past desire to build up a solitary medication or medication plan to be viable against all types of leishmaniasis was excessively hopeful. *Leishmanial* species very inherently in their medication affectability; additionally the instinctive and cutaneous locales of disease force contrasting pharmacokinetic necessities on the medications to be utilized. The objective for chemotherapy is the intracellular amastigote that survives and partitions in tissue macrophages whereby bringing about the sickness. The requests for new antileishmanial drugs have been bolstered as of late by the exhibit of gained imperviousness to the pentavalent antimonial medications, the principal line chemotherapy. The most extreme issue answered to date is in Bihar, India. The idea of medication resistance in leishmaniasis is not clear - affectability to drugs must be assessed deliberately and considered in connection to the distinctions in inherent medication affectability among species and circumstances where leishmaniasis is an anthroponotic infection instead of a zoonotic illness. Be that as it may, there is trouble when a standard medication regimen stops to powerful. Treatment viability is additionally traded off when there is immunosuppression, specifically because of HIV co-contamination. This can prompt fuel of malady or rising up out of dormant contamination - the exhausted insusceptible capacity implies that standard chemotherapy is as often as possible unsuccessful [3].

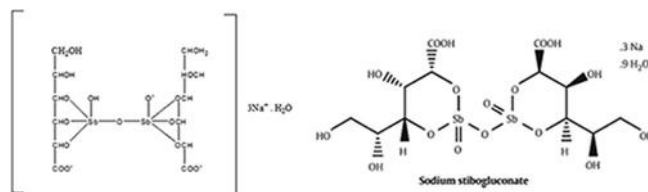
Sodium stibogluconate (SSG) (pentostam) and meglumine antimoniate (glucantime) are kept on being utilized as the first-line parenteral treatment for a long time for a wide range of leishmaniasis. The fundamental symptom related with antimonials is medication resistance. In 1975 and 1996, there are 1223 new clinical entities which have entered the market yet just 11 were utilized for the treatment of diseases. As per as regular sources is worried, there are many medications have been discovered, such as lapachol (hydroxy naphthoquinone derivative), plumbagin, and biplumbagin (naphthoquinoid subordinate). Dispyrin, a naphthoquinoid subsidiary acquired from *Diospyros montana* Roxb., is utilized against *Leishmania donovani*. The primary component related with this is that it is DNA topoisomerase-1 [4].

**CLASSIFICATION OF ANTILEISHMANIASIS DRUGS [5]**

The brief classification of anti-leishmaniasis drugs is given in Table 1.

**First-line treatment***Pentavalent antimonials*

The antimonial was initially marketed at 1945 [3]. The principal operators with a great remedial file, the *P. antimonials* (SbV), were presented in the 1940s as yet the backbone of treatment for all types of leishmaniasis [1]. The primary restriction related with pentavalent antimonial is resistance; however, the prerequisite for up to 28 days of parenteral administration, the variable viability against VL and CL, and the rise of critical resistance is all components constraining the medications' helpfulness [3].

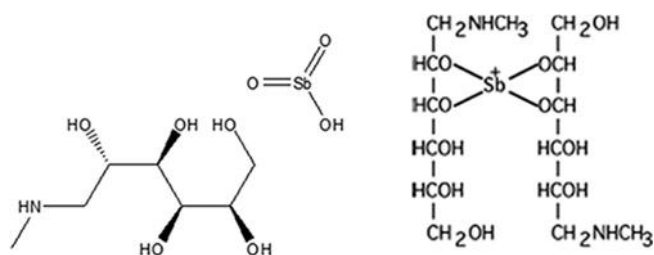
**CLASSIFICATION OF ANTIMONIAL****SSG (Pentostam)**

**Table 1: Current drug used in the treatment of leishmaniasis**

VL	
First-line drugs	SSG, meglumine antimoniate, Amp B, pentamidine
Clinical trails	MT, paromomycin, sitamaquine, other Amp B formulations
CL	
First-line drugs	SSG, meglumine antimoniate, Amp B, pentamidine
Clinical trails	Paromomycin tropical formulation MT, paromomycin Imiquimod Antifungal azoles, i.e., ketoconazole, fluconazole, etc.

VL: Visceral leishmaniasis, CL: Cutaneous leishmaniasis, MT: Miltefosine, SSG: Sodium stibogluconate, Amp B: Amphotericin B

### Meglumine antimonite (glucantime)



Antimonial is essentially used to be as first-line parenteral treatment for a wide range of leishmaniasis [6]. Essentially, they are utilized for the treatment of CL and instinctive leishmaniasis [7]. The primary reaction related with antimonial is medication resistance. There is an absence of viability [6].

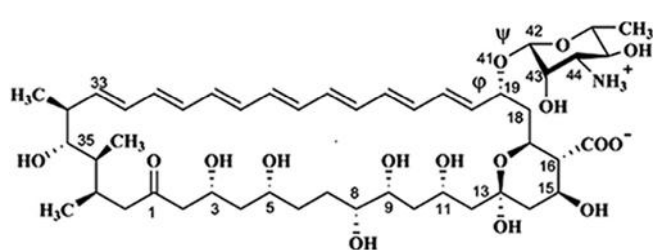
These medications are related with extreme reactions, for example, cardiotoxicity, reversible renal inadequacy, pancreatitis, weakness, leukopenia, rashes, migraine, stomach torment, queasiness, spewing, thrombocytopenia, and transaminase height [8].

Poisonous pentavalent antimonial, which constitutes the backbone of treatment for leishmaniasis, has practically been deserted in India attributable to the absence of reaction of *L. donovani* against glucantime and N-methyl glucamine, in spite of the fact that they are as yet valuable in whatever is left of the world [2].

### Second-line treatment

#### Polyene macrolide group of antibiotics

Amphotericin B (Amp B) (Fungizone)

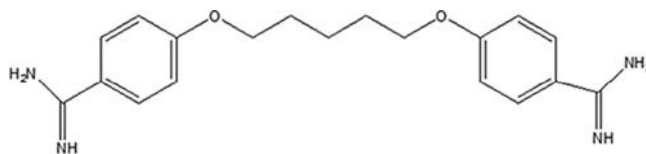


It is synthesized from actinomycetes microorganisms and compelling against pentavalent antimony-safe mucocutaneous ailment [9]. It follows up on sterols and phospholipids in cell films. It is compelling against parasites and leishmanial [10]. It has turned out to be exceptionally compelling for the treatment of antimonial-safe *L. donovani* VL [3]. Amp B is at present proposed as an option first-line treatment [11]. The principle restriction related with Amp B is harmfulness and its toxicity [6,10].

### Lipid formulation of Amp B

Middle Easterner plan is a colloidal scattering of lipid complex and is at first used to treat mycoses; however, nowadays, it is utilized for the treatment of instinctive leishmaniasis. It is for the most part follow-up on the reticuloendothelial arrangement of the body where leishmania reside. The fundamental favorable position of utilizing ARaB over Amp B is poisonous quality. It primarily decreases the poisonous quality altogether. It is 95% viable. However, the principle impediment is the high cost. It is for the most part utilized for the treatment of VL-related AIDS and post dermal kala-azar [1,12].

### Diamidine derivative: Pentamidine isethionate (pentam 300)



#### Pentamidine

It is presented in 1952 [3]. It is considered as second-line treatment for instances of lethargy to antimony, in VL and CL [12]. Diverse creators have told distinctive system of activity of this medication. As per Papadopoulou *et al.*, it might meddles with the vehicle and blend of polyamines which are required for the combination of trypanothione (N1, N8-bis-glutathionyl spermidine) [1]. Leandro have informed that it basically hinder DNA topoisomerase II [12]. Long haul regimen of high-dosage pentamidine is presumably more dangerous than antimonial regimens and is in this manner utilized just when it is probably going to be more successful than antimony [1]. The fundamental impediment is the harmful impact on pancreas, kidney, or bone marrow. It might incite diabetes mellitus [7].

### Broad spectrum antibiotics: Aminoglycoside antibiotics

#### Paromomycin sulfate: (Figure 1)

Paromomycin was initially isolated from filtrates of *Streptomyces krestomuceticus* in the 1950. At first, it was called as aminosidine. It is the main aminoglycoside with clinically essential antileishmanial movement. The antileishmanial properties of paromomycin were perceived by Kellina in 1961 and were affirmed by Neal *et al.* The fundamental instrument related with paromomycin is that it hinders protein amalgamation by communication with ribosomal RNA subunits [13]. Paromomycin in methylbenzethonium chloride ointment is utilized as a topical treatment for CL [7,14].

Paromomycin has been utilized as a part of clinical trials for VL, CL. Paromomycin is in stage 2 clinical trials in India and Kenya

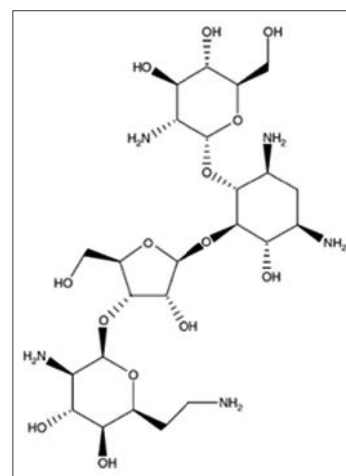


Fig. 1: Chemical structure of paromomycin

which demonstrates that 90% of patients cured of VL. For CL it is utilized as a topical operator. As per El-On and partners in 1984 detailing containing 15% PM and 12% methylbenzethonium chloride (a skin-infiltrating operator) was compelling, against test CL prompted clinical trials. Paromomycin is utilized for neighborhood treatment [6].

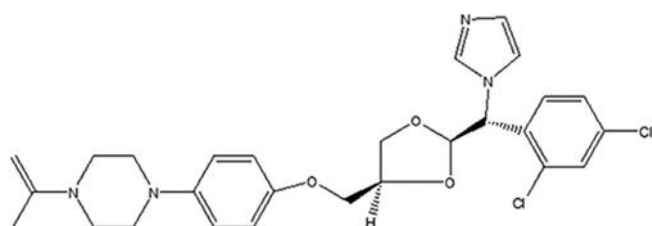
Topical paromomycin is used against *Leishmania major* and *Leishmania mexicana*. It can be conjugated with antimonials to reduce the number of injections [7]. Paromomycin is currently in phase IV clinical trials against leishmaniasis [13]. The main side effect of paromomycin is inflammation and pigmentation [10].

### Nucleoside analogs

#### 2,5 Azole derivatives

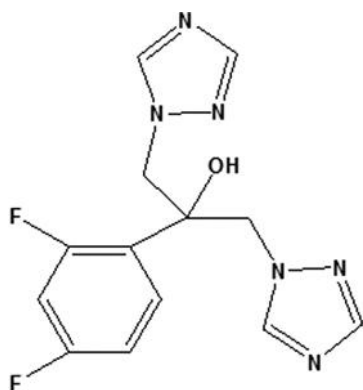
The azoles (ketoconazole, fluconazole, and itraconazole) are dynamic option drugs, offering an appealing plausibility for the treatment of VL. Be that as it may, they should be better assessed [15].

- Ketoconazole



Ketoconazole acted by interferes with cell wall biosynthesis, inhibiting the 14 alpha-demethylation of lanosterol to ergosterol [13]. It has a variable cure rate for New World CL [6].

- Fluconazole



inhibiting the cytochrome P-450-mediated 14 alpha-demethylation of lanosterol, blocking ergosterol synthesis, and causing accumulation of 14 alpha-methyl sterols. Fluconazole is utilized orally [16]. It is active against 79% of patients infected with uncomplicated CL produced by *L. major* in Saudi Arabia [6].

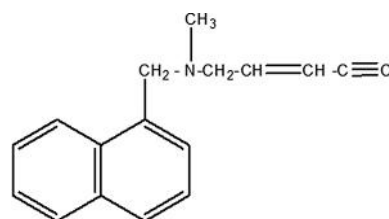
- Itraconazole

It is a fresher synthetic triazole dioxolane derivative [10]. The azole mixes have unavoidably weaker activity than amphotericin since they act prior in the blend of ergosterol, by repressing the demethylation of lanosterol. They have not been reliably successful

with allopurinol or pentavalent antimonial. Fluconazole has, be that as it may, been effectively utilized for CL diseases brought on by *L. major* [12].

### Allylamine derivative

- Terbinafine



Terbinafine is an engineered antifungal specialist of the allylamine class. Its antifungal action is because of impedance with ergosterol biosynthesis, particularly the profoundly specific hindrance of parasitic squalene epoxidase in contagious cell layers and the absence of resulting arrangement of lanosterol. Be that as it may, its utilization alone or with different medications in the treatment of cutaneous and instinctive VL, *in vitro* or *in vivo* (brought on by a few *Leishmania* animal categories), has created distinctive outcomes (Vannier-Santos *et al.*, 1995; Rangel *et al.*, 1996; Bahamdan *et al.*, 1997; Urbina, 1997; Gangneux *et al.*, 1999). As indicated by Melby *et al.* (2001), the hamster (*Mesocricetus auratus*) is a decent model for human VL. The medication had little or no leishmanicidal or leishmaniostatic impact on parasites display in the organs, for example, *Leishmania chagasi* and *Leishmania infantum*.

Rangel *et al.* (1996) have demonstrated the power of terbinafine against *Leishmania braziliensis*. As indicated by Vannier-Santos *et al.* (1995), terbinafine alongside ketoconazole is utilized against *L. amazonensis*. Urbina (1997) revealed the viability of terbinafine against *L. braziliensis*. The movement appeared by terbinafine is just *in vitro* [15].

### Phosphocholine analog: (Figure 2)

Miltefosine (MT): (Impavido) (n-hexadecylphosphocholine) MT is an alky-lphosphocholine (ALP) imitative which was previous used as an anticancer drug [3,17] but nowadays castoff as antileishmanial drug, i.e., operative against both CL and VL (oral treatment.) [3,18]. It is used in opposition to antimony resistant parasites [12,18]. The antileishmanial movement of MT was at first found in the mid-1980s and the consequent exhibit of its viability in a few exploratory models in the mid-1990s to clinical trials and co-improvement of MT for leishmaniasis by an association between Asta Medica (now Zentaris) and WHO/TDR. After a Phase 3 trial, in which 282 out of 299 (94%) VL patients were cured with an oral dosage of 2.5 mg/kg 21 of MT

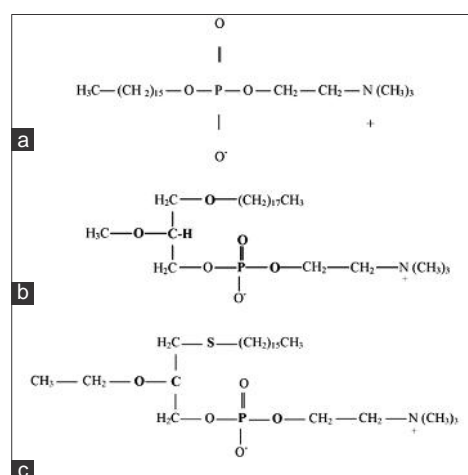


Fig. 2: Phospholipid drugs with antileishmanial activity. (a) Miltefosine, (b) edelfosine, (c) ilmofosine [19]

day by day for 28 days. The real constraint of MT is teratogenicity and this bars its utilization in females of youngster bearing age [3].

It is utilized for the treatment of instinctive leishmaniasis. It is likewise utilized for the treatment of CL which is created by *Leishmania vienna panamensis* [6]. As of now, the most encouraging new pharmaceutical specialists are ALPs, for example, MT and edelfosine. MT is the principal oral medication ended up being exceedingly powerful against VL, including antimony-resistant cases. As of late, it has been liable to stage IV trials. There are, in any case, a few disadvantages, for example, potential teratogenicity and the possible improvement of medication resistance. These may in the long run, prompt the untimely end of its utilization. The method of activity against Leishmania is not yet settled [12].

### MT analog

#### 16-mercaptohexadecylphosphocholine

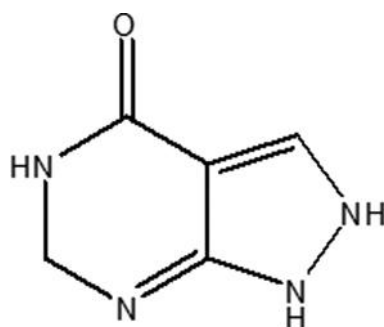
It is a thiol analog of MT. It is used for the oral treatment of human leishmaniasis. This simple exhibits the same leishmanicidal impact as the parent sedate against *L. donovani* promastigotes and *Leishmania pifanoi* axenic amastigotes. MT analogs with the lipophilic gatherings cyclohexylideneundecyl, adamantylideneundecyl, dodecylidene cyclohexyloxyethyl, or tetradecylidene-cyclohexyloxyethyl indicated more *in vitro* leishmanicidal movement than MT, and among them, just the two last mixes exhibited higher cytotoxicity *in vivo* than the parent tranquilize. Analogs with shorter chains, for example, phenoxyhexadecyl or 2-naphthyloxyethyl gatherings, were without activity. Regarding the polar head aggregate, it has been found that mixes with the terminal trimethylammonium assemble, as in phosphocholine, introduce higher *in vitro* action than the relating analogs with ammonium, N-methylpiperidinium, or N-methylmorpholinium terminal gatherings. Furthermore, couple phosphocholine subordinators have been synthesized which contain a particular columnist gather (test). That is the situation of MT analogs bearing the tetrafluorophenylazido photo labeling group or nitroxide paramagnetic gathering [18].

### 5, 8-aminoquinolone

#### Sitamaquine

The antileishmanial movement of this compound was initially distinguished in the 1970s at the Walter Reed Army Institute of Research. Sitamaquine is quickly used, shaping desethyl and 4-CH<sub>2</sub>OH subsidiaries, which may be in charge of its action. Poisonous quality gives off an impression of being generally gentle, it causes mellow methemoglobinemia [3].

### Purine analog: Allopurinol

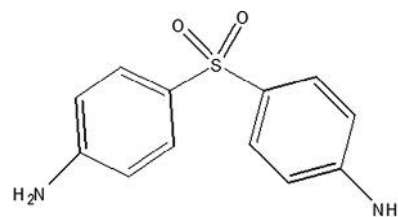


It was distinguished more than 30 years ago and on the grounds that it had oral bioavailability and was generally utilized for other clinical signs, it entered clinical trials for VL and CL. Be that as it may, the outcomes were frustrating. Allopurinol is utilized as a substrate by different proteins of the purine rescue pathway of trypanosomatids and is specifically fused into nucleotide intermediates and nucleic acids

in the parasite. As of late, allopurinol has been considered as a feature of a support treatment for canine leishmaniasis against which it has suppressive movement [3].

### Sulfonamide derivative

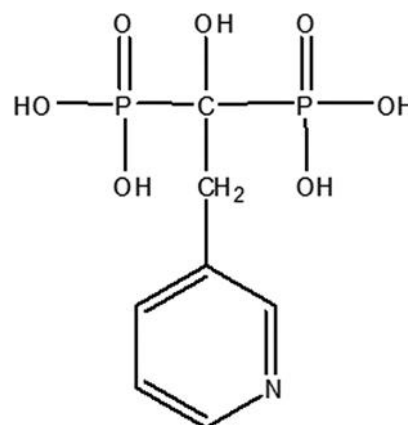
#### Dapsone



It is effective against Indian CL after 6 weeks of therapy. Sitamaquine is also utilized, as oral drug for the treatment of VL [6]. Dapsone perhaps act against leishmania by inhibition of choline incorporation into lecithin in the cell membrane, thus lessening phospholipid synthesis is first-line drug for the treatment of CL in India [10].

### Pyridinyl bisphosphonates

- Risedronate (actonel)



- Pamidronate  
These are in extensive use in the treatment of bone disorders such as osteoporosis, have also shown action against leishmaniasis in experimental representations [3].

Mechanism action of anti-leishmanial drugs: (Table 2)

### Biaryls

#### Arylanthranilodinitriles

Singh *et al.* have synthesized some arylanthranilodinitriles derivatives and exposed that a biaryl with trifluoromethyl group showed 83% hang-up against promastigotes and 70% inhibition against amastigotes of *L. donovani* [20].

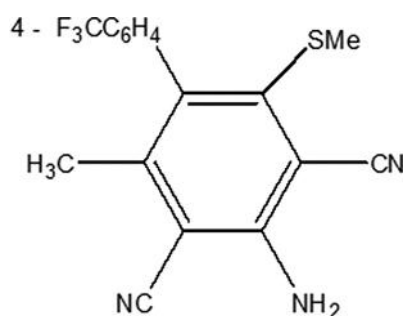


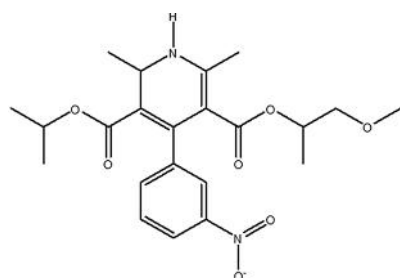
Table 2: MOA of antileishmanial drugs

Generic name of drug	Mechanism of action
Pentavalent antimonial such as SSG, meglumine	Structure of SSG is still not known despite its use for over 50 years. Activated within the amastigote, but not in the promastigote, by converting to a lethal trivalent form. Activation mechanism is not known. Antileishmanial activity might be due to action on host macrophage
Amphoterecin B	Complexes with 24-substituted sterols. Such as ergosterol in cell membrane, thus causing pores which alter ion balance and result in cell death
Pentamidine Paromomycin	Accumulated by the parasite; effects include binding to kinetoplast DNA Inhibit protein synthesis by binding to 30 seconds subunit of ribosomes, causing misleading and premature termination of mRNA translation
MT Sitamaquine	Possible inhibition of ether remodeling phosphatidylcholine biosynthesis Might affect mitochondrial electrons transport chain

SSG: Sodium stibogluconate, MT: Miltefosine

### Ca<sup>2+</sup> Channel Blocker: (1,4-dihydropyridine derivative)

#### Nimodipine



Nimodipine was highly effective against promastigotes and intracellular amastigotes of *L. chagasi*, with 50% inhibitory concentration values of 81.2 and 21.5  $\mu\text{M}$ , respectively. Nimodipine was about fourfold more effective than the standard pentavalent antimony against amastigotes and showed a selectivity index of 4.4 considering its mammalian cells toxicity. *L. amazonensis* and *L. major* promastigotes were also susceptible to nimodipine in a range concentration between 31 and 128  $\mu\text{M}$ . Tempone *et al.* (2009) in their report showed that nimodipine affects mitochondrial functions, as no oxidation of MTT by dehydrogenases could be detected. Inhibition of oxygen consumption causes an increase in the intracellular reactive oxygen species, leading to a loss of mitochondrial membrane potential. This could have been a possible effect of nimodipine in Leishmania, resulting in enlarged mitochondria as observed in transmission electron microscopy. Further assays must be conducted to elucidate this mechanism and also to investigate the possibility of Leishmania apoptosis [21].

Verapamil: Recently, it was established that verapamil could efficiently reverse antimony resistance in *L. donovani* (Valiathan *et al.*, 2006) [21].

### Macrolide antibiotics

#### Azithromycin

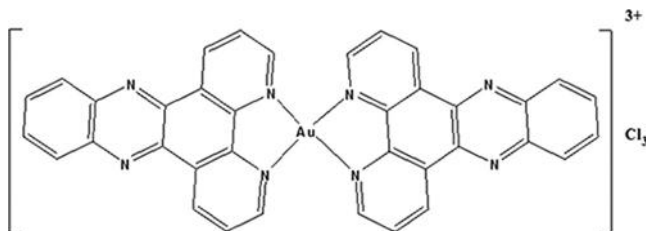
Azithromycin is a macrolide antibiotic utilized for more than 40 years in numerous irresistible conditions, particularly those that influence the respiratory tract and in sexually transmitted sicknesses, which has potential movement against leishmaniasis. The macrolide acted by hindering protein union, separating the peptide from the ribosome

Azithromycin has indicated activity against *L. major* *in vitro* and *in vivo*, despite the fact that there has been no comprehension of its activity component. Utilizing it to treat patients, it demonstrated activity against leishmaniasis with remedial reaction slower than for antimonial operators 5. *In vitro* analyses, azithromycin did not add to the phagocytosis of *L. major*, however it expanded the intracellular passing rate of amastigotes 8. Another probability is that azithromycin has an immunomodulating impact, diminishing the quantity of amastigotes and enacting the neutrophils, keeping the generation of go-betweenes

and proinflammatory cytokines 5, 9. *In vitro*, it has additionally demonstrated viability against *L. amazonensis*, *L. (V.) braziliensis*, and *L. chagasi* in the focus 150  $\mu\text{g}/\text{ml}$  [22].

### INTERFERON-GAMMA (IFN - 7)

A few reviews have utilized IFN-gamma (IFN-7) as a subordinate to antimony treatment for instinctive leishmaniasis. Systemic IFN-7 is not viable by riser and has reactions, but rather it increases the adequacy of SbV treatment.



### TUFTSIN

Tuftsin a tetrapeptide has been found to take an interest in a few organic capacities related with the invulnerable framework. It is created in the body from a particular cytophilic division of the protein (leukokinin) through a two-stage enzymatic preparing instrument. The tetrapeptide improves the phagocytic action of monocytes and macrophages. Particular restricting destinations for tuftsin have been uncovered to exist on macrophages. Tuftsin only ties to macrophages and potentiates their common executioner movement against pathogens. This makes tuftsin an alluring contender to be utilized as a ligand for focusing on medications to different macrophage-related maladies. Tuftsin-based focusing of SSG stacked liposomes was considered by *L. donovani* tainted hamsters for VL [23].

### PYRIMIDINES

The library of substituted aryl pyrimidine subordinates was composed and incorporated at 2013. Every one of these mixes was screened *in vitro* by correspondent quality luciferase test for their antileishmanial property against intracellular amastigotes of *L. donovani*. Among them, 8 mixes indicated promising IC<sub>50</sub> values (0.5-12.9  $\mu\text{M}$ ) [24].

### CONCLUSION

Examine went for recognizing and approving new medication targets is in one regard the most Leishmania particular piece of the medication disclosure prepare, albeit near reviews on Leishmania and trypanosomes have been powered by the yearning to locate a wide range antitrypanosomatid tranquilize. The cell science of Leishmania and mammalian cells gives the guarantee that a considerable lot of the parasite's proteins ought to be adequately not the same as anything in the host to be effectively misused as medication targets.

Finding new subterranean insect leishmanial medications ought to be significantly less demanding than finding new anticancer medications. In this way, from the logical point of view there is much reason for positive thinking. To be sure, over numerous years, an entire exhibit of "intriguing medication targets" has been proposed - beyond any reasonable amount to list here. This claim has been made for some proteins that have been appeared to contrast from a mammalian partner in even a minor way. Shockingly, a few of these conceivable targets have been thoroughly approved. There are a few methodologies that can give such proof, the most capable being compound and hereditary approval.

*Leishmania* spp. has been creating wrecking dreariness and mortality since relic. Notwithstanding, in the 20<sup>th</sup> century, the causative operator was found and inside 2 many years of its revelation, fruitful remedial specialists were found. The first being the trivalent and pentavalent antimonials, which remained medication of leishmaniasis for the greater part a century. Shockingly, in late quarter of the twentieth century, lethargy to this medication began in *Leishmania*. The danger and expanding lethargy to antimonials proceeded. Amid, these years a few laborers kept looking more secure mixes; however, little achievement was accomplished. Just as of late, Amp B, ordinarily utilized as an antifungal operator, was discovered best; however, even this medication has its own particular burdens, for example, nephrotoxicity. To decrease its nephrotoxicity, lipid details were readied; however, their cost wound up plainly excessively expensive to underdeveloped nations. No oral medication was accessible till 2004, when MT, an ALP compound, was discovered exceedingly powerful. In any case, it cannot be utilized as a part of pregnant women and kids. Furthermore, reports of resistance have begun developing. In this manner, we are left with no perfect viable medication, which is oral, safe, and financially savvy and does not create resistance. There are recommendations for mix treatment like on account of tuberculosis; however, cost of these medications should be cut down. However, the present circumstance for chemotherapy of leishmaniasis is more encouraging than any other time in recent memory, yet a leap forward is yet to come. It gives enough degree for discovering more current medications through seeing new metabolic pathways and medication targets.

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