Exploring actinomycetes natural products to identify potential multi-target inhibitors against *Leishmania donovani*

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ABSTRACT: The neglected tropical disease visceral leishmaniasis (VL) disproportionately affects impoverished populations in the Indian, African, and South American subcontinent. However, the increasing resistance and the toxicity to antimonials, miltefosine, and amphotericin B underscores the pressing need to develop a safe and effective anti-leishmanial drug. To address this, we conducted a study and screened 6519 secondary metabolites from an actinomycetes source against five key proteins involved in the metabolic pathway of *Leishmania donovani* using three sequential docking protocols (HTVS, SP, and XP). These proteins included adenine phosphoribosyltransferase (PDB ID: 1QB7), trypanothione reductase (PDB ID: 2JK6), N-myristoyl transferase (PDB ID: 2WUU), pteridine reductase (PDB ID: 2XOX), and MAP kinase (PDB ID: 4QNY). The study predicted the binding energy of the top ligands using the MM-GBSA module of the Schrödinger suite, and SP and XP docking modes identified 55 multi-targeted ligands against *L. donovani*. The top 18 ligands with good-binding affinity and binding-free energy for four of the targeted proteins (compared to miltefosine, paromomycin, and a reference ligand for each target selected as positive control) were selected using MM-GBSA analysis. Finally, molecular dynamics simulation trajectory analysis (RMSD, RMSF, SASA, Rg, and H-bondong), post-MD-binding-free energy (MM-PBSA), and principal component analysis (PCA) identified three ligands (Adenosine pentaphosphate, Atetra P, and GDP-4-keto-6-deoxymannose) that met the screening parameters and were considered potential drug candidates to combat *L. donovani* parasites.