INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

Name of the Student	:	SHALINI SINGH
Roll Number	:	11610628
Programme of Study	:	Ph.D.

Thesis Title: Exploring Leishmania Biochemistry to Understand Effect of Spermidine Starvation and Identification of Novel Drug Candidates

Name of Thesis Supervisor(s)	:	PROF. VIKASH KUMAR DUBEY
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SHORT ABSTRACT

Leishmaniasis is caused by different species of Leishmania. In order to develop a better drug candidate, we chose to explore two different pathways of *Leishmania*, redox metabolism and protein prenylation pathway. Spermidine synthase, a key enzyme for second step of redox metabolism pathway of parasite, catalyzes formation of spermidine. We have identified hypericin as a novel inhibitor of spermidine synthase of *Leishmania donovani*. Hypericin has shown significant antileishmanial activity with IC_{50} value of 18 μM. Spermidine starvation due to hyericin treatment has resulted in necrotic like death of the parasite. Elucidating the mechanism of hypericin induced parasite death has revealed a novel role of spermidine in processes other than redox metabolism of Leishmania. In Leishmania, the role of spermidine is only confirmed in redox metabolism pathway. However, the spermidine has found to play role in different pathways like hypusination of eIF5A, autophagy, etc. We have checked the alteration in expression of genes involved in these pathways by using quantitative real time PCR. These alterations were further confirmed by biochemical and cellular analysis. We observed that death of the parasite after hypericin treatment was due to alteration in translation initiation occurred due to defective hypusine modification of eIF5A. It has also suggested the novel role of spermidine in hypusine modification of eIF5A of *Leishmania donovani*. Further, hypericin treatment was also found to cause induction of certain events like autophagy, increase in NAD^+ and ATP pool, alteration in DNA repair enzyme as a cytoprotective event towards the ROS generated after hypericin treatment. We have also done quantitative proteome profiling of untreated and hypericin treated Leishmania promastigotes to understand the global effect of hypericin. The post-translational modifications of biological molecules are known to be crucial for their functional activation, regulation and localization. Prenylation is one such modification which is involved in post-translational modification of various important proteins like proteins of Ras superfamily which are involved in a variety of regulatory and signalling events in eukaryotes. We have modelled the structures of CAAX prenyl protease I & II and simulated them within DPPC membrane and explicit water solvent. We have further predicted the active site and electrostatic potential surface map of both CAAX prenyl protease I & II. We have screened the inhibitors against both CAAX prenyl protease I and II by using virtual screening.