Newsletter
Year 2017 Volume 1: Issue 1

A STUDY ON THE POTENTIAL OF ACTIVE CONSTITUENT FROM *Senna spectabilis* IN TREATING *Leishmania major* INFECTION.

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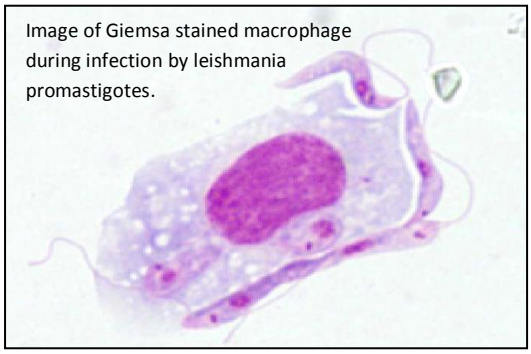

Image of Giemsa stained macrophage during infection by leishmania promastigotes.

Leishmaniasis affects millions of people each year. It consists of a group of tropical infections that are effecting human populations in mainly low-income countries. Visceral Leishmaniasis (VL) and Cutaneous Leishmaniasis (CL) are the main forms of Leishmaniasis which cause mortality, chronic disability and poverty. Leishmanasis is among three of most neglected diseases in the world, together with Human African Trypanosomiasis (HAT) and Chagas' disease. These diseases are termed as neglected diseases because they are receiving very limited press attention as well as research funding as compared to HIV/AIDS, tuberculosis and malaria. In 2003, Drugs for Neglected Diseases Initiative (DNDi) which is a non-profit drug R&D agency focusing on developing new treatments for neglected diseases was established. Malaysia is one of seven founding partners from around the world who had joined the force, indicating our interest in tackling this global health issue. Cutaneous Leishmaniasis (CL), the most common form of leishmaniasis is a disease with a varied spectrum of clinical manifestations, which range from small cutaneous nodules to gross mucosal destruction. Leishmania major is the most commonly studied parasite for CL, and distributed in wide area of the world which are Central Asia, North Africa, Middle East and East Africa.

It is also commonly used in in vitro and animal models in antiparasite drug discovery studies as it is the first Leishmania species which the genome had been fully sequenced back in 2005. In the natural life cycle of Leishmania species, it is transmitted through the bites of infected female sandflies. When a sandfly takes a blood meal from the host, promastigotes are released (via saliva) into the skin and bloodstream which subsequently invade the host macrophage. Thus, the target for chemotherapy of leishmaniasis is the intracellular amastigotes in the mammalian host. Alternative approaches are needed because the majority of those infected live in countries which are not financially capable in market-driven drug discovery. Current treatments come together with side effects such as cardiotoxicity and nephrotoxicity, besides requiring a long course of treatment leading to the development of resistance on the parasites.

In this study, antileishmanial properties from the constituents of a medicinal plant, *Senna spectabilis* were investigated using *in vitro* antileishmanial assays which were the first one established in Malaysia. Bioassay-guided isolation approach in this work resulted in further fractionation of the ethyl acetate extract with a series of chromatography processes which involved VLC, CC and flash CC which finally yielded the bioactive constituent against *L. major* with EC_{50} = 20.584 ± 1.65 µg/mL. The bioactive constituent was determined as piperidine alkaloid named (+)-spectaline based on the spectroscopic analysis mainly mass spectrometry (MS), infrared spectral (IR) and nuclear magnetic resonance (NMR). This natural compound showed cytotoxicity IC_{50} = 45.57 µg/mL or 0.14 ± 1.06 µM and selectivity index, SI = 2.22 From this work, we have demonstrated that the compound (+)-spectaline isolated from *S. spectabili*s is active against *in vitro L. major* infection, via antileishmanial bioassay-guided isolation method developed in-house. The finding from this work hopefully will aid the drug development efforts for leishmaniasis treatment.This work has been published in the International Journal of Pharmacology, Phytochemistry and Ethnomedicine (IJPPE) , Vol 3, year 2016 with the title '(+)-Spectaline, a Piperidine Alkaloid from *Senna spectabilis* DC. Effective in Reducing the *In Vitro* Infection of *Leishmania major*'.

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