Universität Basel

Research Project

From medicinal plant to mechanism: Target deconvolution of phytochemicals for Trypanosoma cruzi

Third-party funded project

Project title From medicinal plant to mechanism: Target deconvolution of phytochemicals for Trypanosoma cruzi

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Organisation / Research unit

Swiss Tropical and Public Health Institute (Swiss TPH)

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Department

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Status Completed

Plants have been the richest source of novel chemotherapeutics throughout the history of medicine. Lately, however, the use of natural products as starting points for the development of new drugs has been declining, mainly due to the lack of developability of natural molecules as compared to synthetic ones. The fact that natural compounds cannot easily be modified also hinders target identification, and for many antiparasitic phytochemicals the mode of action is unknown. We aim to overcome this roadblocks by combining phytochemistry and synthetic chemistry, supported by molecular modeling and cell biology. The primary focus is on the waltheriones from Waltheria indica, which are quinoline alkaloids we have previously isolated and shown to be highly active against Trypanosoma cruzi. This trypanosomatid parasite is the causative agent of Chagas' disease, a neglected tropical disease of the New World that, due to geographic mobility, has become of global importance and even affects Switzerland. Here we propose (i) to synthesize the most active molecules of the waltherione series and make derivatives thereof; (ii) to elucidate the mode of action of the waltheriones against T. cruzi by combining genomics, chemical proteomics, metabolomics and target space modeling; and (iii) to increase the chemical space by exploring other medicinal plants for trypanocidal molecules. The proposed research will unravel novel mechanisms for selective chemotherapy of T. cruzi and innovate the use of natural compounds for drug discovery. It will be carried out by a collaborative network involving the Swiss Tropical and Public Health Institute in Basel, the School of Pharmaceutical Sciences of the University of Geneva, the Dalle Molle Institute for Artificial Intelligence in Manno, and the Institute of Pharmaceutical Sciences of the ETH Zürich.

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