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Subjects



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SESQUITERPENE LACTONES AFFECT THE REDOX SYSTEM OF *TRYPANOSOMA CRUZI*

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Chagas disease is caused by *Trypanosoma cruzi* (*T. cruzi*) and affects millions of people worldwide, mostly in Latin America. Despite its sanitary importance, there are currently only two drugs available for its treatment: benznidazole and nifurtimox, both exhibiting serious adverse effects on patients. In order to complete its life cycle, *T. cruzi* faces extreme environmental conditions –i.e. oxidative stress- as it propagates from an insect vector to a mammalian host, driving the transition from non-infective epimastigote to the infective form trypomastigote. It is known that the antioxidant defense system in the trypanosomatids is different from that in mammalian cells since the parasites have exclusive molecules and reducing enzymes. Because of this, the parasite redox machinery is an attractive target for antiparasitic therapies. The sesquiterpene lactone dehydroleucodine (DhL), is a trypanocidal molecule – containing an alpha-methylene group that could react with sulfhydryl groups of key redox enzymes. This study was focused on elucidating the DhL mechanism of action and extended to ten DhL derivatives (DC-X1 to DC-X10) obtained by chemical substitutions on the methylene group. We firstly confirmed an antiproliferative effect of DhL and its chemical derivatives, being DC-X6 one of the most active. The effect of DhL and DC-X6 was blocked by reduced glutathione, suggesting that compounds are reactive to sulfhydryl groups of certain molecules. Moreover, parasites overexpressing reducing enzymes, such as Tc-CPX, showed a protective effect against these STLs. Consistent with these results, both STLs increased ROS concentration in the wild type parasites. These results indicate that STLs induce oxidative stress on the parasites, possibly by affecting some crucial enzymes of the redox system.

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A SEMI-SYNTHETIC MOLECULE DERIVED FROM DEHYDROLEUCODINE AFFECTS THE *TRYPANOSOMA CRUZI* CELL CYCLE

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Trypanosoma cruzi is a parasite causing Chagas disease, which is endemic in Latin America, but in the last 20 years, it has expanded worldwide. The current treatment is restricted to Nifurtimox and Benznidazole, but both are relatively toxic and have limited efficacy on the patients. The development of new effective therapeutic agents is urgently needed. The sesquiterpene lactones (STLs) are natural compounds purified from native plants of Argentina with multiple pharmacological applications. The STL dehydroleucodine (DhL), has an alpha-methylene group that could react with multiple sulfhydryl group-containing proteins, affecting cellular functions such as proliferation, the activity mitochondrial, leading to the cell death/apoptosis. This study is focused on elucidating the action mechanisms of DhL and its derivative DC-X11, obtained by chemical substitution, on *T. cruzi* epimastigotes (strain Dm28c). We observed that DhL and DC-X11 have antiproliferative and cytostatic effects on the parasites. By morphological and ultrastructural studies, we observed an increase of parasites with multiple cell nuclei, kinetoplasts, or flagella after the treatment with DC-X11, suggesting an effect on late steps of the cell cycle (i.e., cellular division). These results were confirmed with parasites synchronized with hydroxyurea (HU 20 mM) for 24 h, and then they were treated with the compound. We concluded that the derivative DC-X11 inhibits *T. cruzi* proliferation by delaying the progression of the cell division. Further studies are necessary to identify the molecular targets affected by DC-X11.

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THE NEUROTOXIN OF AN AUTOCHTHONOUS *CLOSTRIDIUM BOTULINUM* AFFECTS THE ACTIN CYTOSKELETON IN BREAST CANCER CELLS

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Botulism is a neuroparalytic disease caused by botulinum neurotoxins (NTBo, serotypes A-G) produced by *Clostridium botulinum*, whose main reservoir is the soil (Su). Infant botulism is a toxi-infection, caused by the ingestion of spores, subsequent colonization, and the production of toxins *in situ*. The autochthonous NTBo would correspond to subtype A2 and have higher toxicity than A1