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BIOTRANSFORMATION AND EVALUATION OF THE LEISHMANICIDAL ACTIVITY OF QUINOLINIC ALKALOIDS AND DERIVATIVES

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Introduction: In recent years new compounds with anti-leishmanial activity derived from quinolinic alkaloids have been developed. **Objectives:** The aim of this work was to produce phenylquinoline alkaloid (PQ) derivatives by biotransformation using *Aspergillus fumigatus* and *Aspergillus flavus*, and compare their leishmanicidal potential with the original molecule. **Methods:** The microorganisms' cultures were shaken (150 rpm) for 7 days at 28° C, in medium (200 ml) enriched with glucose, malt and yeast extracts added of PQ (100 mg). The products were purified by chromatographic techniques and identified by MASS and NMR spectroscopy. *In vitro* leishmanicidal activity against *L. amazonensis*, *L. infantum,* and *L. braziliensis* promastigote forms of PQ and derivatives were performed using the MTT assay, and photodocumentated by transmission electronic microscopy (TEM). The effects were compared with standard drugs. **Results:** Two derivatives were obtained: DFQ1, from *A. fumigatus*; 8% yield, with two hydroxyl groups at C5 and C6 positions, originating a substance not reported to date; and DFQ2, from *A. flavus*; 5% yield, with a hydroxylation at the C4' position. The results demonstrated that the insertion of a hydroxyl group at the C4' position of the derivative DFQ2 favorably changed the anti-leishmania activity (IC_{50} > 100 μM), since it showed a cytotoxic activity at least five times higher than the activity observed for the original phenylquinoline compound (IC_{50} > 500 μM). However, the cytotoxic activity of the derivative DFQ2 was considerably lower than that observed for the derived DFQ1 (IC_{50} < 10 μM), demonstrating that the insertion of two hydroxyls at C5 and C6 positions was able to enhance the activity two thousand times more than the original molecule. Interestingly, the extra hydroxyl groups of DFQ1 enhanced the activity of the original molecule. TEM of the parasites showed mitochondrial swelling, increase of lipid inclusions, chromatin condensation, and changes in the plasma membrane. **Conclusion:** The results herein presented showed that PQ could be biotransformed by *A. fumigatus* producing DFQ1, a new unreported substance. *A. flavus* also produced DFQ2, and both quinolinic derivatives showed higher leishmanicidal potential than the parental molecule disrupting directly the cytoplasmatic, nuclear, and membrane components of the parasites.

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