

in silico evaluation for repositioning oral drugs in visceral leishmaniasis

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Molecular docking is a way of predicting the binding between a macromolecule and a ligand. It is a powerful tool for drug repositioning, a strategy that uses approved drugs for a new purpose. Considering that leishmaniasis is a neglected disease that, in its visceral form, leads to death in approximately 90% of nontreated patients, the quick development of an oral effective treatment would save thousands of lives. The redox balance is a key to *Leishmania spp.* survival inside the host cells. This work demonstrated a target-directed virtual trial to reposition oral drugs that are potential inhibitors for macromolecules involved in the survival of the parasite. A data library of approximately 4300 compounds was trialed and ranked by the binding affinity with a specific *Leishmania infantum* enzyme. The three-dimensional structures are available in the ZINC database. The graphical interface for AutoDockTools, Raccoon, was used for loading the ligands. Lipinski's rule-of-five filter was used. For the receptors, two physiological forms of the enzyme were obtained by RCSB-ProteinDataBank. The protonation state at pH 7.4 using the AMBER force field was normalized at the ProKa platform. The molecular docking was run at PyRx, a program that uses the AutoDockVina interface. Both states of the enzyme were tested by all the compounds binding in their active site, creating two rankings on the affinity values. The enzyme forms had 1.118 and 504 compounds in conformations with binding affinity values equal to or under -8 Kcal/mol. 475 compounds had conformations in this binding affinity range with both forms. The data around these 475 compounds were analyzed with the intent to filter which of them were orally administered drugs. Absorption, distribution, metabolism, excretion and toxicity properties were analyzed by the PkCSM platform. A total of 239 orally administered drugs were found, 54 of which were approved by the FDA and ANVISA. The analysis of the molecular mechanism of action shows that many of those interact in strong binding with important amino acids for the inhibition of the physiological function of the enzyme. Taken together, our data proposed that those drugs deserves prominence on the pursuit to improving the treatment of visceral leishmaniasis.