TITLE: *IN SILICO* CHEMOGENOMICS APPROACH FOR DRUG REPOSITIONING FOR PARACOCCIDIOIDOMYCOSIS

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ABSTRACT

Paracoccidioidomycosis (PCM) is a common systemic mycosis in Latin America caused by thermally dimorphic fungus *Paracoccidioides* spp. PCM treatment is long-term chemotherapeutic approach and causes several side effects. Aiming to discover new drugs for treating PCM, our group implemented an *in silico* chemogenomics approach for screening of *Paracoccidioides* spp. proteome, based on the concept that "proteins sharing enough similarity (orthology) have enhanced probability of sharing the same ligands". By using OrthoVenn web platform, we compared a list of 6743 proteins from *Pb*01 with orthologous from other two isolates (*Pb*03 and *Pb*18) (E-value $\leq 10^{-20}$). Then, to screen for drugs that could potentially have anti-PCM activity, protein sequences from *Pb*01, which orthologous were present in the other two isolates, were aligned against the sequences of drug target databases (DrugBank and TTD). Moreover, inclusion and exclusion criteria, such as consideration of FDA approved drugs or in phase II/III of the clinical trials, sequence identity $\geq 30\%$, and removal of nutraceuticals/peptides/antibodies, were also incorporated in the drug screening. Consequently, 254 proteins genes encoding potential *Pb*01 drug targets for a total of 982 approved drugs were identified. After, the essentiality of predicted targets was investigated by using the model microorganism *Saccharomyces cerevisiae*. As a result, we found that 46 proteins were homologous to the essential *S. cerevisiae* proteins. In the following, 3D structures of the predicted *Pb*01 targets were generated using homology modeling approach in SWISS-MODEL server. Built models were structurally optimized using KoBaMIN server, and their stereochemical and geometrical qualities were investigated MolProbity server. Finally, molecular docking studies were carried using the OEDocking suite to investigate the binding modes and scores energies between predicted Pb targets and their associated drugs. Consequently, we found that 58 drugs with acceptable score energies are promising candidates for further *in vitro* and *in vivo* evaluation. In addition, the top scored drugs belong to a wide range of pharmacological classes, including anticancer agents (dactolisib, tozasertib, and riviciclib) and bone resorption agents (incadronate and pamidronate). On the other hand, some of the top-scored drugs (*e.g.*, miconazole, itraconazole, and ketoconazole) are already used on PCM treatment, highlighting the accuracy of the developed *in silico* methodology.

Keywords: Paracoccidioidomycosis, drug repurposing, chemogenomics, orthology, molecular modeling.

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