Ligand-Based Pharmacophore Modeling and Virtual Screening of Plant-Derived Ligands for the Alpha-Amylase and Alpha-Glycosidase

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Natural antioxidants compounds have been associated with reduction of postprandial hyperglycemia by blocking enzymes involved in the carbohydrates digestion, such as alpha-amylase and alpha-glycosidase. Furthermore, preventing or delaying the absorption of glucose by inhibiting glycoside hydrolases in the digestive organs may represent a promising approach in the treatment of diabetes and its complications. Thus, the aim of this work was search for new plant-derived compounds with pharmacological potential to inhibit this glycoside hydrolases based on the pharmacophore model. The pharmacophore modeling was performed with the aid of vROCS 3.2.0.4, this model contains information about shape and chemical properties extracted from the fluconazole molecule. The ligand library used in this research are originated from ZINC database, that have been carefully selected a natural compounds subset, totaling 180.303 compounds. In order to perform the virtual screening, the ligand library was prepared with the OMEGA 2.5.1.4, which was used to generate conformer libraries. Pharmacophore model validation and virtual screening of the conformer libraries were performing using vROCS. The pharmacophore model was previously validated using the ROC (receiver operating characteristic) curve and AUC (area under the curve). The AUC extract from the ROC curve graph it is simply the probability that randomly chosen bioactive compounds have a score higher than randomly chosen inactive compounds. In order to generate the ROC curve and the AUC value, biologically active ligands against alpha-amylase (PDB id: 1SMD) and alpha-glycosidase (PDB id: 1OBB) were obtained from ZINC database, and the decoys were generated on the DUD-E online platform. After validation, the conformer library previously generated was submitted to the pharmacophore model and the top 500 ligands of each, based on the TanimotoCombo score, were selected. The best-scored ligands will be used to perform a molecular docking against human alpha-amylase and alpha-glycosidase as the next step of this research.

Financial Support : Fapemig e CNPq.