Assessment of Protein-Ligand binding affinity with Molecular docking approach and Application.

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Abstract

Molecular docking determines the affinity of the ligand molecule towards a target whose 3D structure is known. The most important goals of molecular docking are: **1.** Characterization of the binding sites **2.** Positioning of the ligand into the binding site and **3.** Evaluating the strength of interaction for a specific ligand receptor complex [1]. During the docking process, the ligand generates multiple binding geometries (binding modes) in relation to the receptor. Only the stable conformation of the ligand binds with the receptor [2]. However, the main drawback in the docking process is to account for the flexibility of both, protein and receptor molecule. Therefore, in our work, we study performance of the docking process for deriving protein-ligand affinity.

Firstly, we used molecular docking approach to find alternative inhibitor for Thymidine kinase enzyme of HSV-1. A total of 62 antiviral plant metabolites and 13 drug molecules were docked against both the chains of Thymidine kinase enzyme using Patchdock tool. The plant metabolite Geraniin has produced higher score (5680 (chain A), 6562 (chain B)) than the commercially known anti-herpes compound Acyclovir (3504 (chain A), 3264 (chain B)). In addition, Gemdockv2.0 also produced the lower best fitness values for Geraniin (-130.123226 (chain A), -132.309075 (chain B)) as compared to Acyclovir (-102.182402 (chain A), -84.599474 (chain B)). Furthermore, docking through Autodock4 also produced lowest docking energy of -13.40 kcal/mol (chain A), -15.17kcal/mol (chain B) for Geraniin compound in comparison to Acyclovir -7.48kcal/mol (chain A), -7.96kcal/mol (chain B).

Further, the docking study is extended to analyze binding affinity of 7-azaindole-scaffolds inhibitors against Renin enzyme. One of the 7-azaindole-scaffold with 6-methoxy and methyl substituent is proven to be a potent inhibitor of Renin enzyme with IC50 of 3nM [3]. This affinity is also predicted by computational docking approach with docking energy of -15.85 kcal/mol. However, the other substituents are failed to reproduce binding affinity by computational means. Therefore, we implemented a novel molecular dynamics approach to derive binding affinity for 7-azaindole-scaffolds inhibitors against Renin enzyme. This approach accounts for fully flexible docking favorable protein-ligand arrangements.

Reference:

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