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Homology modelling and docking studies on Neuraminidase enzyme as a natural product target for combating influenza

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Abstract

Influenza remains to be dreadful with yearly epidemics and sudden pandemic outbreaks causing significant mortality, even in nations with the most advanced health care systems. Thus, there has been a long-standing interest to develop effective and safe antiviral agents to treat infected individuals. Attempt to identify suitable molecular targets as antiviral compounds have focused recently on the influenza virus neuraminidase (NA), a key enzyme in viral replication [1]. In this research, virtual screening was done on a total of 600 natural compounds from 22 ethno medicinal Indian herbs for activity against neuraminidase enzyme exploiting representative protein conformations selected from molecular dynamics simulations. Neuraminidase enzyme sequences from different existing strains available on National Center of Biotechnology Information [2] (NCBI) protein database were aligned using Clustal W [3] and CLC workbench 10 [4] to find the conserved residues. Neuraminidase protein sequence from H1N1 strain available on NCBI was used to structure 3D target model predicted against dataset from Protein data bank using modeller [5]. The target model was validated on different parameter at SAVES Server [6]. Using this target model a pharmacophore model was developed using ligand based strategy exploiting the three known inhibitors. The docking parameters were validated by redocking Zanamivir to its co-complex 2009 H1N1 NA crystal structure (PDB ID: 3TI5) generating best pose with a RMSD value of 0.7543 A°. This model was then used for *in silico* analysis of a library of natural compounds from 22 ethno medicinal Indian herbs known to have antiviral activity taken downloaded from PubChem database and selected on the basis of drug likeliness. All the compounds were docked in the binding pocket of neuraminidase. Top compounds having binding affinity better than or comparable to the control drug Zanamivir were selected and analysed for their ADME and toxicity. Their binding pattern in the 150 loop was studied along with their interaction with the active site conserved residues. Electrostatic interactions were the main driving force in the binding affinity of the potential inhibitors. These hit compounds will provide direction for further *in- vivo* and *in -vitro* validation and may play an important role in finding novel Neuraminidase inhibitors against influenza.

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