

Title: Potential Inhibitors from Natural Compounds against SARS-CoV-2 Main Protease: A Systematic Molecular Modelling Approach

Author: Kannan Raman, Rajagopal Kalirajan, Fahadul Islam, Mehrukh Zehravi, Laliteshwar Pratap Singh, Ritesh Rana, Sankaranarayanan Murugesan, Srikanth Jupudi, Shopnil Akash, Gowramma Byran, Firzan Nainu, Talha Bin Emran, Turki M. Dawoud, Mohammed Bourhia, Rashu Barua

Abstract: The COVID-19 outbreak poses a significant threat to the world's human population in 2020. Finding new drugs rapidly during this pandemic is quite challenging. Thus, in silico drug screening experiments may provide effective therapeutic alternatives for better assessing natural remedies in preventing and treating COVID-19. The main protease (Mpro) is an important drug target that is essential and ubiquitous for the survival of SARS-CoV-2. In this study, we performed in silico high-throughput virtual screening to identify potential hits employing a database of 3 million natural compounds (supernatural-II database). The initially obtained top 100 virtual hits were subjected to a standard SP and XP docking protocol, achieving the top 30 hits. Compounds SN00340755 (glide score: -16.0 kcal/mol and ΔG_{bind} : -134.29 kcal/mol) and SN00213037 (glide score: -13.30 kcal/mol and ΔG_{bind} : -81.18 kcal/mol) exhibited significant binding energy against Mpro (PDB ID: 6XQS). The ligands SN00340755 and SN00213037 formed multiple hydrogen bonds with the catalytic residues, especially with the functionally important residue GLU166, which plays a significant role in protomer dimerization. Further post-docking minimization studies (MM-GBSA) were performed to estimate the ligand-protein affinity. From MM-GBSA studies, it was observed that Coulombic (-140.70 to -37.66 kcal/mol) and van der Waals (-79.32 to -20.59 kcal/mol) energies, favoring the binding of ligands to the Mpro target protein. The ADMET properties were predicted using Qikprop, Chem Axon, and Data Warrior tools, demonstrating the beneficial pharmacokinetic parameters of these natural compounds. The 100 ns molecular dynamics simulation study revealed minor protein fluctuations, indicating the stability of the protein-ligand complex.

Keywords: COVID-19 drug discovery, In silico drug screening, Natural compound inhibitors, SuperNatural-II database, Molecular dynamics simulation (100 ns), Structure-based drug design

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