Abstract No: STEM 18 Science, Technology, Engineering and Mathematics

Identification of phytochemical inhibitors against papain-like protease of SARS-CoV-2: molecular docking, molecular dynamics and absorption, distribution, metabolism, excretion and toxicity (ADMET) study

Wadanambi P. M.[1*], Mannapperuma U.[2], Jayathilaka N.[1]

The COVID-19 outbreak has created a huge social and economic disruption worldwide due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Papain-like protease (PL^{pro}) of SARS-CoV-2 plays a crucial role in viral replication and host innate immunity suppression. Therefore, it is an ideal therapeutic target to develop inhibitors. Thus, the goal of this study was to use virtual screening methods to identify potential phytochemical inhibitors of this dual therapeutic target. Virtual docking was performed for 31 phytochemicals with documented anti-SARS-CoV-1 PL^{pro} activity and two positive controls using AutoDock 4.2 software to determine the binding affinity, inhibition constant and ligand efficiency of each compound within the S3/S4 binding pocket of SARS-CoV-2 PL^{pro} (PDB ID: 6WX4). Based on the docking results, top twelve compounds were subjected to protein-ligand interaction analysis utilizing the Discovery Studio Visualizer software. Physicochemical properties were analyzed using molinspiration web server. Moreover, pharmacokinetics and toxicity descriptors were assessed using pkCSM and StopTox web servers, respectively. Molecular dynamics simulations (MD) were carried out for 100 ns for each top docking complex and PL^{pro} of SARS-CoV-2 inhibitors. Hirsutenone (from *Alnus japonica*), broussoflavan A (from *Broussonetia papyrifera*) and broussochalcone A (from *Broussonetia papyrifera*) displayed the strongest binding affinities (-8.23 kcal/mol, -8.13 kcal/mol and -7.78 kcal/mol), the lowest inhibition constants (920.39 nM, 1.1 µM and 1.97 µM) and the highest ligand efficiencies (0.34, 0.26 and 0.31) among all phytochemicals towards the S3/S4 binding pocket of SARS-CoV-2 PL^{pro}, demonstrating superiority to positive control, GRL0617 while hirsutenone and broussoflavan A exhibited superiority to both positive controls, 3k and GRL0617. In addition, hirsutenone, broussoflavan A and broussochalcone A possessed favorable physicochemical properties satisfying Lipinski's and Veber's rules. Furthermore, *in silico* pharmacokinetics and toxicity predictions revealed that the three phytochemicals are water soluble, non-mutagenic, non-hepatotoxic. These compounds were not toxic for acute inhalation and acute dermal exposure. They also showed no eye irritation, skin irritation or corrosive properties. MD confirmed the stability of broussoflavan A and broussochalcone A. However, hirsutenone showed less stability due to fluctuations during the simulation period. Hence, broussoflavan A and broussochalcone A might be exploited to expedite the drug discovery process against the ongoing COVID-19 infection.

Keywords: COVID-19, Papain-like protease, ADMET, Molecular docking, Molecular dynamics

[1] Department of chemistry, Faculty of Science, University of Kelaniya, Sri Lanka
[2] Department of pharmacology, Faculty of Medicine, University of Colombo, Sri Lanka
* pwadanambi@gmail.com