Extended Abstract Journal of Pharmacy and Pharmaceutical Research 2021
Vol.5 No.4

Pharmacophore base and 3D-QSAR studies in discovery and identification of natural product inhibitors that target Mitochondrial Complex I

Samira Norouzi
Shahid Beheshti University, Iran

Introduction:
Respiratory complex I (NADH- ubiquinone Oxidoreductase) is the largest protein complex of the respiratory chains that catalyzes the transfer of electrons from NADH to coenzyme Q10 (CoQ10). Dysfunction of this protein complex can cause many hereditary and degenerative diseases. Notwithstanding many types of research, the mechanism of action of this complex is not entirely understood.

Objectives:
Hence, increasing number of inhibitors of mammalian Complex I may bring about clues to the enzyme mechanism. In this study, a virtual screening method combined with pharmacophore modeling was utilized to search and identify new potential natural compounds acting on inhibition of mitochondrial complex I. To this aim, a 3D QSAR model was made and validated to be utilized in virtual screening in-order to identify a new scaffold.

Results:
Then the lead compounds were subsequently subjected to molecular docking studies for their binding to the X-ray structure of the biological target. Two different types of crystal structure of the target-structure of membrane arm and structure of membrane and peripheral arm-were selected to investigate the Interface between peripheral and membrane arm as well as ubiquinone access. For all molecular modeling, the small-Molecular Drug Discovery Suite 2015-2(Schrodinger, LLC, New York, NY, 2016) was used.

Conclusion:
DQA, 2-decyl-4-quinazolinylamine, was included as a positive control in this study. As result, several compounds showed good binding affinity to the targets and finally 10 compounds with the highest binding affinities, much more than DQA, were selected as potent compounds. Based on computed docking score these compounds, with the docking score range of -7.9 ??? -10.85 KJ/mol, have a high tendency to inhibit complex I. Also, all Inhibitors acted on the ubiquinone reduction site of this complex. It is hoped these compounds can be good candidates in the focus of biomedical researches, and their backbone structural scaffold can present as building blocks in designing drug-like molecules for respiratory complex I.