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DETERMINATION OF PHARMACOLOGICAL ACTIVITY OF BIOACTIVES IN ALLIUM SATIVUM USING COMPUTATIONAL ANALYSIS

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ABSTRACT

Both qualitative and quantitative studies were done in this study. Quantitative data was generated in form of binding energies when binding of ligands to the receptors as well as probability scores in toxicity profiles predictions. Qualitative data was generated from pharmacokinetics predictions using SwissADME. This tool assessed the chance of a molecule to have drug–likeness, which is an important parameter when evaluating the chance of high bioavailability with oral drugs. Drug-likeness is the physico-chemical and structural features desired and SWISS ADME analysed these properties based on the Lipinski rule of five. Qualitative data therefore, was generated in form of ‘yes or no ‘in determining the inhibitors of the cytochrome P450 enzymes as well as substrates of p-glycoprotein efflux system.

Keywords: Allium sativum, alliin, allicin, ajoene, diallyl sulphide, diallyl disulphide, diallyl trisulphide, swiss target prediction, molecular docking, ProTox ii and SwissADME.

1 Determining possible targets

Bioactive agents in Allium sativum namely z-ajoene, e-ajoene, alliin, allicin, S-allyl-cysteine, diallyl sulphide, diallyl disulphide and diallyl trisulphide were searched in PubChem tool and their canonical smiles were copied. Swiss target prediction tool was opened where Canonical smiles copied were pasted. A red button (predict targets) was clicked and results were generated *http://www.swisstargetprediction.ch/*. The results generated downloaded and saved in a one folder in the desktop of the laptop. Each bioactive agent had its own subfolder. Generated results had specific uniprot codes. Uniprot was opened using google chrome and codes generated in Swiss target page were searched in uniprot. Uniprot generated specific Protein Data Bank codes. Protein Data Bank was searched using google chrome and those specific receptor codes were searched. This generated specific receptors which were downloaded as pdf format and saved in the subfolders. Five receptors of each bioactive agents were downloaded and saved in the subfolders each receptor having different subfolders.

2 Bioactives and standard ligands retrieval

PubChem online tool were searched using google chrome and specific bioactives were searched. Each bioactive were then downloaded as SDF format and saved in specific folders. Standard drugs were accessed from Gene Card database, which generated specific ligands for specific receptors. The ligands were downloaded from PubChem (RRID:SCR_004284) and saved as SDF format to the subfolders.

3 Molecular Docking

Avogadro software (RRID:SCR_015983) was opened and the standard ligands as well as bioactives were opened one by one. Auto-optimization of the ligands was done by changing the force field to MFF94S and allowing fixed atoms to be movable followed by clicking the ‘ok’ button. Auto-optimization of the ligands and bioactives occurred automatically until the energy force was 0.0kj/mol. The ligands and the bioactives were then saved as optimized mol2 to the folders. Chimera software (RRID:SCR_004097) was opened and the optimized ligands and bioactives were opened. Minimization of these molecules was done by clicking structure editing then minimize the structure. The minimized bioactive agents and ligands were saved as optimized-minimized mol2 compounds to the respective folders. The activities were closed by clicking ‘close session’ button in chimera software.

Receptors were opened in chimera and standardised by removing all the non-standard residues. The receptors were saved to the folders as PDB format and the session was closed.

Standardized receptor was opened first in Chimera followed by optimized-minimized bioactives and ligands respectively. Surface binding analysis in Chimera was clicked which brought the popup allowing setting the output location. The output location was set and saved as PDBQT format to the same solders. The ligands and the receptors were specified. The binding site at the receptor was determined by setting random values at ‘search volumes’ which automatically

generated the grid box at the receptor. The box was made to fit the receptor through frequent adjustments. Once the box fitted, the executable location was specified where 'local' output file was browsed and vina.exe software present in each of the subfolders was clicked on and the 'open' button was tapped.'Ok' button was clicked allowing docking of the ligands to specific receptors to occur. The binding results were generated as a popup and they were compared between the bioactive agents in *Allium sativum* and the standard compounds.

4 Determination of pharmacokinetic properties

SwissADME (*http://www.swissadme.ch/*), online tool was searched in google chrome where the canonical smiles of both the bioactives in *Allium sativum* as well as standard molecules will be pasted. The red button was clicked to allow pharmacokinetics profiles generation. The results were downloaded and saved to the folder.

5 Toxicity predictions

The canonical Smiles of the bioactive agents as well as the reference drugs were copied from PubChem and pasted to ProTox II server (RRID:SCR_018506) . The predictions were done.