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Molecular docking studies on naturally occurring selected flavones against protease enzyme of Dengue virus.

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ABSTRACT:
Dengue is a prevalent disease affecting the citizens of both developed and developing countries. Dengue is transmitted by several species of mosquito within the genus *Aedes*, principally *Aedes aegypti* which bites during daylight hours. The dengue virus belongs to the Flaviviridae family of viruses that cause diseases in humans. Despite considerable progress in the treatment of dengue by antiviral agents, search for newer drugs continues because the existing synthetic drugs have several limitations. The herbal drugs with antiviral activity are yet to be commercially formulated as modern medicines, even though they have been acclaimed for their therapeutic properties in the traditional systems of medicine. The present work deals with the analysis of binding mechanism of some selected natural compounds from different Azardhicta and Swertia species against the novel targets for dengue namely viral protease NS3. The results revealed that most of the selected herbal lead compounds were effective targets against the receptors. These compounds showed favourable interactions with the amino acid residues thereby substantiating their proven efficacy as antiviral compounds. The resulting data of receptor-ligand interactions demonstrates that in silico screening method is highly efficient for identifying potential lead compounds against major disorders/diseases. The paper reports the *in-silico* docking results of some naturally occurring flavones on protease enzyme, which is a druggable target in the replication of dengue virus. One natural flavones bellidifolin has been reported to be active against it. The presence of hydroxy moiety in the side unit of the flavones seems to be instrumental in binding.

KEYWORDS: Protease, docking, *in-silico*, Dengue virus, flavones.

INTRODUCTION:

Dengue is an infectious disease caused by a Dengue virus. Dengue fever also known as break bone fever and it is a mosquito-borne tropical disease. Dengue is transmitted by several species of mosquito within the genus *Aedes*, principally *Aedes aegypti* which bites during daylight hours. The dengue virus belongs to the Flaviviridae family of viruses that cause diseases in humans. It is also known as arboviral illnesses.

The dengue virus genome (genetic material) contains about 11,000 nucleotide bases, which code for the three different types of protein molecules (C, prM and E) that form the virus particle and seven other types of protein molecules (NS1, NS2a, NS2b, NS3, NS4a, NS4b, NS5) that are only found in infected host cells and are required for replication of the virus. There are five strains of the virus, called serotypes, of which the first four are referred to as DENV-1, DENV-2, DENV-3 and DENV-4.When the binding of small molecule to the receptor ained. Such protein-ligand interaction is comparable to the lock-and-key pr and the key resembles the ligand. The most important driving force for bin e specificity is however controlled by hydrogen bonding interactions. There said to have antiviral property against dengue. Hence phytocompounds from this species were selected and further investigated for its binding efficiency to evaluate the best fit molecule using MVD. The DENV NS3 is a serine protease, as well as an RNA helicase and RTPase/NTPase. Viral proteases are excellent antiviral targets, as evidenced by the nine protease inhibitors of human immunodeficiency virus (HIV) currently in clinical use and the numerous protease inhibitors of hepatitis C virus (HCV) in clinical trials. By analogy with the successes of HIV and HCV protease inhibitors, efforts have been made to design inhibitors against DENV using dengue virus NS2B/NS3 protease as a molecular target. Various pharmacognostical and folklore claims have listed the dengue curing potential of the plant. The main active constituents of the plant are xanthone alkaloids. The aim of this study is to investigate the NS3 protease inhibitory potential of active constituents of *Swertia chirayita* by insilico molecular docking analysis.

MATERIAL AND METHODS:

Molecular docking studies:

Preparation of Ligand:

The major active constituents are identified from the selected medicinal plant namely *Swertia chirata and Azadirachta indica* which possess anti viral properties according to traditional claims and the 3D structures of the active constituents

indica which possess anti-viral properties according to traditional claims and the 3D structures of the active constituents (Apigenin, Bellidifolin, Bicalein, Chrysin, Gelangin, Globuxanthone, Quercetin, Rhamnazin, Rutin, Wogonin, Isomericillin and Nigrolineaxanthone P) were retrieved either from PubChem chemical databases [1]or drawn using Chemdraw software [2] and saved in .mol2 format. The ligands are imported to the workspace and preparation of them is done.

Retrieval of Crystal Structure and Target Preparation:
The high resolution crystal structure of Dengue NS3 protease was retrieved from the protein data bank (PDB ID: 3U1I). It is well known that PDB files often have poor or missing assignments of explicit hydrogens, and the PDB file format cannot accommodate bond order information. Therefore, proper bonds, bond orders, hybridization and charges were assigned using the MVD. The potential binding sites of both the targets were calculated using the built-in cavity detection algorithm implemented in MVD. The search space of the simulation exploited in the docking studies was studied as a subset region of 25.0 Angstroms around the active side cleft. The water molecules are also taken in to consideration and the replaceable water molecules were given a score of 0.50.

Energy minimization:
CHARMM is a general and flexible program for macromolecular energy minimization and dynamics calculations that utilizes both classical and quantum mechanical energy functions for molecular systems. Energy minimization of both the wild type and mutant targets were carried out under CHARMM force field. Gradient was set to 0.05.

Preparation of Enzyme:
The target for docking studies is selected as dengue virus protease enzyme. Docking analysis is done by initially selecting the target for the disease and followed by obtaining the 3D structure of dengue virus protease enzyme (PDB ID: 3U1I) from protein data bank in .pdb format [3, 4]. It is well known that PDB files often have poor or missing assignments of explicit hydrogens, and the PDB file format cannot accommodate bond order information. Therefore, proper bonds, bond orders, hybridization and charges were assigned using the MVD. The potential binding sites of both the targets were calculated using the built-in cavity detection algorithm implemented in MVD. The search space of the simulation exploited in the docking studies was studied as a subset region of 25.0 Angstroms around the active side cleft. The water molecules are also taken in to consideration and the replaceable water molecules were given a score of 0.50.

MolegroVirtual Docker's docking search algorithms and scoring functions:
Ligand docking studies were performed by Molegro Virtual Docker(MVD), which has recently been introduced and gained attention among medicinal chemists. MVD is a fast and flexible docking program that gives the most likely conformation of ligand binding to a macromolecule. MolDock software is based on a new heuristic search algorithm that combines differential evolution with a cavity prediction algorithm [5]. It has an interactive optimization technique inspired by Darwinian Evolution Theory (Evolutionary Algorithms - EA), in which a population of individuals is exposed to competitive selection that weeds out poor solutions. Recombination and mutation are used to generate new solutions. The scoring function of MolDock is based on the Piecewise Linear Potential (PLP), which is a simplified potential whose parameters are fit to protein-ligand structures and a binding data scoring function [6, 7] that is further extended in GEMDOCK (Generic Evolutionary Method for molecular DOCK) [8] with a new hydrogen bonding term and charge schemes.

MolDock Optimizer:
In MVD, selected parameters were used for the guided differential evolution algorithm: number of runs =5 by checking constrain poses to cavity option), population size=50, maximum interactions =2000, cross over rate=0.9, and scaling factor=0.5. Ao variance-based termination scheme was selected rather than root mean square deviation (RMSD).To ensure the most suitable binding mode in the binding cavity, Pose clustering was employed, which lead to multiple binding modes.

RESULTS AND DISCUSSIONS:

The Molecular Docking analysis of the selected natural compounds from different Azardhicta and Swertia speices and the receptor protease involved in the replication of dengue viru ɔility of the compounds was evaluated using their GOLD scores generated ions GOLD score for each compound was considered. The GOLD software teracts with the receptor. The results were evaluated based on the binding co s).

Table 1: MOLECULAR DOCKING ANALYSIS OF FLAVONES AGAINST DENGUE NS3 PROTEASE

Compounds	Binding energy (Kcal/mol)	Ki Inhibition Constant (µm)	Intermolecular energy	Internal Energy	Torsional energy	Hydrogen Bonding
Apigenin	-6.62	14.05	-7.51	-0.21	0.89	5 – ASN 416, ALA 316, GLN 456, LYS 199,GLU 230
Bellidifolin	-5.07	193.03	-6.26	-0.55	1.19	2 – ASN 416, ASP 284
Bicalein	-5.91	46.49	-7.1	-1.28	1.19	2 – LYS 199, ASN 416
Chrysin	-6.51	17.04	-7.1	-0.25	0.6	2 – LYS 199, ASN 416
Gelangin	-6.42	19.71	-7.31	-0.7	0.89	1 – LEU 193
Globuxanthone	-3.93	1.31mM	-5.42	1.99	1.49	5 – THR 200, GLN456, ARG 460
Quercetin	-6.24	26.86	-8.03	-1.18	1.79	3 – GLU 230, LEU 193, ARG 460
Rhamnazin	-6.16	30.49	-7.35	-0.84	1.19	2 – ARG 463
Rutin	-6.82	10.05	-8.01	-0.76	1.19	4 – ARG 463, GLU 230, LEU 193

Wogonin	-6.12	32.41	-7.32	-1.05	1.19	2 – ARG 463

Graph 1: Binding energy data of various flavones

Figure 1: Bellidifolin Docked to the Active Site of Dengue NS3 Protease

Figure 2: Isomericillin Docked to the Active Site of Dengue NS3 Protease

Figure 3: Nigrolineaxanthone bound with Dengue NS3 protease

Figure 4: Ligand interaction map of Bellidifolin

Figure 5: Ligand interaction map of Isomericillin

Figure 6: Ligand interaction map of Nigrolineaxanthone P

CONCLUSION:

Novel therapeutic molecules can be designed using computer aided drug design. In the present study the selected compounds from different Azardhicta and Swertia species have been docked with the promising target namely protease for dengue. The interaction of the receptor and inhibitors were analyzed using GOLD and the best interacting inhibitor were screened. The receptor protease involved in the replication of dengue virus interacts with bellidifolin, bicaelin and globuxanthone with maximum fitness score. This study is also helpful for pharmaceutical sectors as computer aided screening would reduce the complexities involved in the discovery and development of new lead molecules.

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