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in silico Docking Analysis of Small Molecule Inhibitors from *Nyctanthes arbor-tristis* against Nipah Virus Infection

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ABSTRACT

Nipah virus is a highly pathogenic paramyxovirus belonging to the genus Henipavirus, classified as Biosafety Level 4 (BSL4) agents. The virus causes severe illness characterized by encephalitis or respiratory disease in human. The case-lethality rate of Nipah was reported to be 70 % in India, since year 2001. Despite the high pathogenicity of virus, no therapeutics are currently approved for use in human. But, ribavirin, favipiravir and human mono clonal antibody was found to reduce the intensity in early stage. Medicinal plants serve as a rich source of therapeutically active compounds. *Nyctanthus arbor-tristis* Linn or pavizhamalli (Harsinger) is traditionally known to have activity against Nipha virus. In this study, therapeutic activity of phytochemicals arbortristoside A and arbortristoside C present in pavizhamalli plant against Nipha virus target was investigated by computational docking simulation. Computational docking analysis was performed using Schrodinger Suite. The phytochemicals arbortristoside A and arbortristoside C show promising binding affinity with the target Nipah virus than the reference drugs. Results of the study could be advantageous to develop a new lead molecule against Nipah virus infection.

KEYWORDS

Nipah virus infection, *Nyctanthes arbor-tristis*, Docking, Phytochemicals, Ribavirin, Favipiravir.

INTRODUCTION

Nipah virus is a zoonotic virus of the genus of Henipavirus, within the family Paramyxoviridae. Nipah virus causes severe encephalitis (inflammation of brain) and respiratory disease in mammalians including humans [1]. The name Nipah virus was introduced from the name of a village Sungai Nipah in Malaysia, where the first isolates were obtained [2]. The human Nipah virus infection was first reported in a large outbreak of 276 cases in peninsular Malaysia and Singapore from September 1998 through May 1999. In year 2001, Nipah virus was again identified as an outbreak of human disease occurring in Bangladesh and India. About 160 cases with 106 fatalities have been recognized in various districts of Bangladesh. Nipah virus infection had re emerged in Kozhikode, Kerala in year 2018, where the morality rate was very high (above 80 %).

Pteropus genus of large fruit bats appears to be the natural reservoir of Nipah virus. The route of infection of Nipah virus

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from bats to humans is by ingestion and consumption of Nipah virus contaminated or partially eaten fruits, or by contact with infected animals such as pigs, cattle and goats. Nipah virus infection can also be transmitted from person to person. The symptoms are high fever, headache, vomiting, unconsciousness and sudden death [3]. The virus infection was seen both in pigs and humans, during the first outbreak of Nipah virus.

Recently, there are no known approved therapies or vaccines against Nipah virus. Though there is no known cure for Nipah virus infection, antiviral drugs ribavirin, favipiravir and human monoclonal antibodies were found to reduce the symptoms in the early stage [4]. Because of high mortality rate and high pathogenic properties, there is an urgent need to find inhibitors for Nipah virus infection.

Medicinal plants contain a wide spectrum of therapeutically active compounds which can be investigated for drug discovery. Apart from the traditional and ethnic values, herbal medicines are also promising for highly efficient novel bioactive molecules [5]. Herein, we have chosen *Nyctanthes arbortristis* Linn. as a medicinal plant for the study. *Nyctanthes arbortristis* Linn. is also known as night jasmine, Harsingar plant or Parijat, belongs to the family Oleaceae. It is loaded with beneficial qualities and is native to Southeast Asia [6]. The plant is well known for its medicinal value and can be exploited commercially [7]. This plant also has significant pharmacological actions like as antileishmaniasis, antiviral, antifungal, antipyretic, antihistaminic, antimalarial, antioxidant, anti-inflammatory, *etc*. [8]. Several studies [9] reported that the secondary metabolites like arbortristoside A and arbortristoside C show promising antiviral activity.

Nowadays, computational methods and bioinformatics play a crucial role in modern drug discovery process. Drug designing relies on computer modeling techniques often referred to as Computer Aided Drug Discovery (CADD) [10]. Drug is usually a small molecule which activates or inhibits the function of a biomolecule like proteins, resulting in therapeutic effect. Hence, drug discovery involve the designing of small molecules with desirable pharmacological effect against the target to which they interact and bind [11]. Thus, the development of new, effective and useful agents called lead molecules is important in drug discovery. *in silico* Approaches attained considerable attention because it is a low cost and less time consuming method than that of experimental methods [12].

Nipah virus possesses non-segmented single stranded linear negative sense RNA virus of a genome size 18246 with six structural proteins, which include the nucleocapsid protein, phosphoprotein, matrix protein, fusion protein, glycoprotein and RNA polymerase [13]. Herein, binding affinity and inhibitory action of arbortristoside A and arbortristoside C present in *Nyctanthes arbortristis* Linn. against Nipah G attachment Glycoprotein by computational docking analysis are investigated.

EXPERIMENTAL

Docking analysis has been carried out with the help of Glide module of Schrodinger LLC software.

Target identification and preparation: X-ray crystal structure of the target protein, Nipah G attachment glycoprotein retrieved from RCSB Protein Data Bank (PDB) with the pdb id 3D118. The selected protein was prepared by using Protein Preparation Wizard which is available in the Schrodinger software. First step in the protein preparation, wizard is pre-process and it was completed by addition of polar hydrogen, removal of co-crystallized water molecule and metal ions. The optimal protonation states for histidine residues correct potentially transposed heavy atoms in arginine. Glutamine and histidine side chains can also be determined using this application. Then the optimization of protein′s hydrogen bond network was done by means of a systematic, cluster-based approach, which greatly decreased preparation time and allowed to perform a restrained minimization that let hydrogen atoms to be freely minimized, while allowing for sufficient heavy-atom movement to relax strained bonds, angles and clashes.

Active site prediction: Understanding the structure and exploiting the function of protein active sites is a cornerstone of drug design. The active site is the region of protein, where the ligand molecule binds and a chemical reaction takes place. The amino acid residues present in the active site of target will bind to the ligand molecule and results in the therapeutic effect. Thus, identification of active site of target protein is an important step in the docking procedure. Site Map application can help us to locate binding sites with a high degree of confidence and predict the druggability of those sites.

Ligand preparation: The phytochemicals present in *Nyctanthes arbor-tristis* is selected to find out the inhibitory activity towards Nipah virus target. The inhibitory activity of the phytochemicals is compared with the FDA approved drugs ribavirin and favipiravir.

The phytochemicals from *Nyctanthes arbor-tristis* along with the reference drugs were downloaded from the pubchem database [14]. The downloaded structures are prepared by Ligprep module of Schrodinger software. LigPrep application is used to generate the 3D structure of ligand molecules. It also helps in generating the tautomeric, stereo and ionization variation. Then the ligand molecules were optimized and minimized for further analysis.

Docking analysis: Once the protein and ligand were prepared, the next and the important step is to generate a grid box to pre-calculate the binding interaction at different positions within the binding site. After the grid generation, the docking has been carried out by Ligand docking application of the Schrodinger suite. Ligand docking is done with XP mode for the accurate docking. The ligand molecule binds with the target active site with different forms of interaction. Identifying and analyzing the interaction between protein-ligand complex is one of the major steps in the docking procedure.

Toxicity studies: Ligand molecule and the FDA approved drug candidates were checked for their ADME calculation using QikProp module [15]. It helps in calculating the pharmacokinetic and pharmacodynamic properties by assessing the drug-likeness. QikProp rapidly screens compound libraries for hits. It identifies molecules with computed properties that fall outside the normal range of known drugs, making it simple to filter out candidates with unsuitable ADME properties. The predicted descriptors are molecular weight (m.w.), H-bond donor, H-bond acceptor and log $P_{o/w}$, *etc*.

RESULTS AND DISCUSSION

Inhibitory effect of arbortristoside A and arbortristoside C presnt in *Nyctanthes arbor-tristis* against Nipah virus target protein is investigated by molecular docking studies using Glide module of Schrodinger LLC. Initially, the target was subjected to geometry optimization with protein preparation wizard of Schrodinger software. Then, 3D ligand molecule is generated using LigPrep followed by energy minimization. The minimized ligands and proteins are then used for the docking procedure by Glide Module of Schrodinger Software.

Docking results revealed the protein-ligand interaction and the amino acid residues involved in the complex. The docking results are shown in Table-1. From the results obtained, it has been observed that both arbortristoside A and C will interact with target better than the drug candidates. Arbortristoside A and arbortristoside C have better docking score with the target than the standard drugs. Binding interactions revealed that arbortristoside A interacts with the amino acid residues ARG 235, ASP 302, ARG 242, ASP 219 and also arbortristoside C interact with the amino acid residues ILE 401,ASP 219 ,GLU 579, ASP. The amino acid residue interacts with the ligand molecule by means of hydrogen bonding. The hydrogen bonding distance is also evaluated and shown in Table-1. This hydrogen bonding is actually responsible for the stability of protein-ligand complex.

The 3D interaction bondings of arbortristoside A and arbortristoside C within the binding site of 3D11 are shown in Fig. 1. It can be observed that the presence of four hydrogen bondings and one π-π interaction are responsible for holding the ligand mole-cule within the binding site with high stability and this stability is measured by docking score. Arbortristoside A showed a docking score of -5.914. kcal/mol, while arbortristoside C has docking score of - 6.201 kcal/mol (Fig. 2). The drugs ribavirin and favipiravir have a docking score of -5.04 and -2.55 kcal/mol, respectively. The ligand interaction diagram of the drugs are shown in Fig. 3.

TABLE-1
DOCKING RESULTS OF PHYTOCHEMICALS IN *Nyctanthes arbor-tristis* WITH TARGET PROTEIN 3D11

Name	Docking score	Amino acid residues involved	H-Bond distance (Å)
Arbortristoside A	-5.914	ARG 235	2.34
		ASP 302	2.70
		ARG 242	1.65
		ASP 219	2.04
Arbortristoside C	-6.201	ILE 401	2.14
		ASP 219	1.75
		GLU 579	1.82
		ASP 219	1.84
		TRP 504	4.95
Ribavirin	-5.048	GLN 559	1.97
		ASP 302	2.05
Favipiravir	-2.555	ARG 236	2.08

The ADME properties of phytochemicals and drug molecules are illustrated in Table-2. ADME properties are calculated by using QuikProp module of Schrodinger software. Thus, the results revealed that ligand molecules have acceptable ADME properties and may be considered as a lead molecule.

Conclusion

in silico Docking methods are of great value in drug discovery, as they help in the preliminary screening of compounds as prospective drug candidates. Findings in this study, demonstrate the efficacy of arbortristoside A and arbortristoside C against highly pathogenic Nipah virus and worth further investigation to be applied as therapeutic agent.

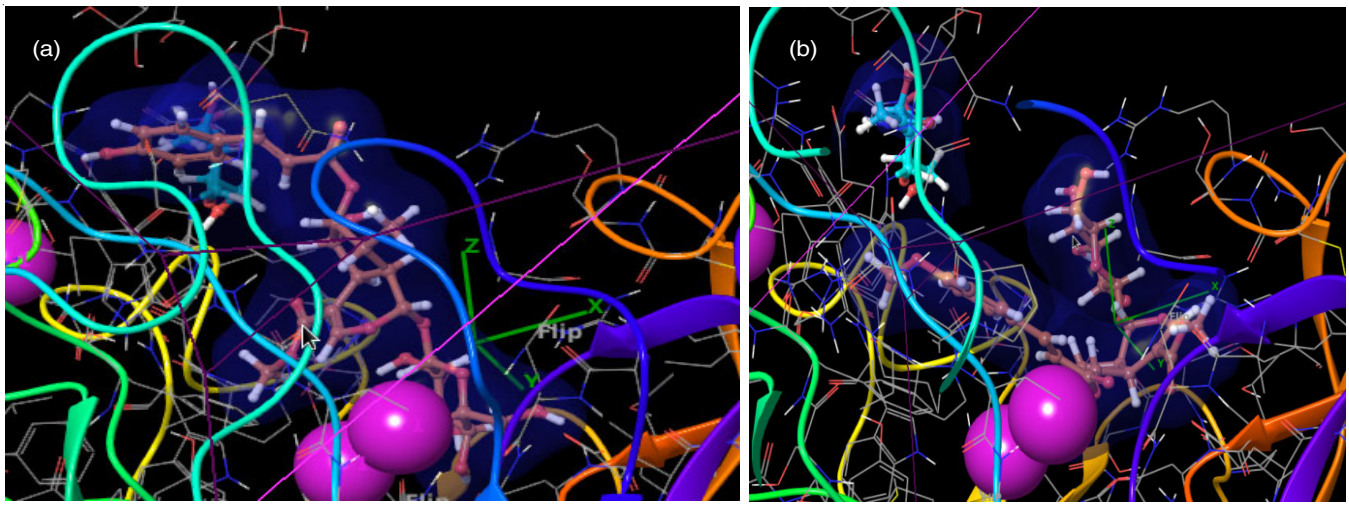

Fig. 1. 3D interaction of (a) arbortristoside A and (b) arbortristoside C within the binding site of 3D11

TABLE-2
ADME PROPERTIES OF LIGAND AND DRUG MOLECULE

Ligands	Star value of	Rule five	Donor-Hb	Acceptor-Hb	log p0/W	Rule of three	Human oral absorption (%)
Arbortristoside A	4	2	5	18.35	-0.098	2	24.67
Arbortristoside C	4	3	6	18.35	-0.807	2	0.581
Ribavirin	1	0	5	12.3	-2.74	0	30.5
Favipiravir	1	0	1	4	-0.921	0	60.4

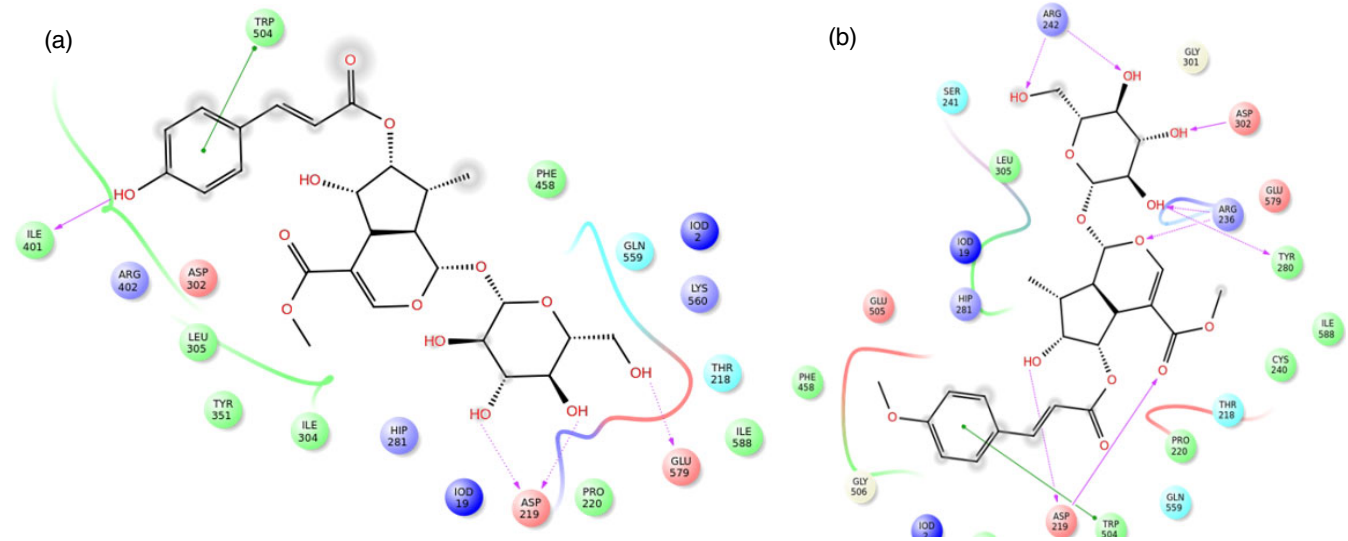

Fig. 2. 2D interaction of (a) arbortristoside A and (b) arbortristoside C with target protein 3D11

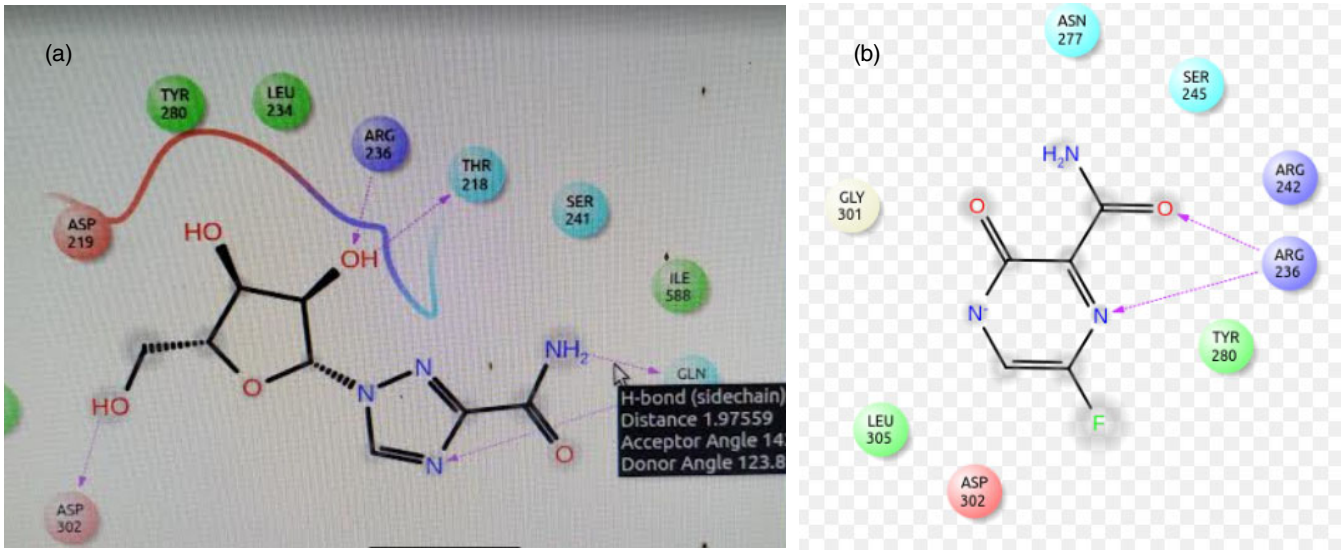

Fig. 3. Interaction of (a) ribavirin and (b) favipiravir with target protein 3D11

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