Acta Scientific Pharmaceutical Sciences (ISSN: 2581-5423)

Volume 8 Issue 3 March 2024

Research Article

The Inhibition Potentials of Selected Plant Phytochemicals from *Nyctanthes arbor-tristis* Against Nipah Virus: A Molecular Docking, ADMET Analysis and Molecular Dynamic Simulation

Akash J[1]*, Subhiksha S[1], Ramesh V[1], Jaishree M[1], Abishek M[1], Harish Kumar S[1], B Siva Kumar[2] and K Ilango[3]

[1]*Department of Pharmaceutical Chemistry, SRM College of Pharmacy, SRM Institute of Science and Technology, Tamil Nadu, India*

[2]*Department of Pharmacrutical Chemistry, PERI College of Pharmacy, Chennai, India*

[3]*Department of Pharmacrutical Chemistry, Tagore College of Pharmacy, Chennai, India*

***Corresponding Author:** Akash J, Department of Pharmaceutical Chemistry, SRM College of Pharmacy, SRM Institute of Science and Technology, Tamil Nadu, India.

Received: January 17, 2024

Published: February 12, 2024

© All rights are reserved by **Akash J.*, et al.***

Abstract

The *Nipah virus* (NiV) is a member of the Paramyxoviridae family, specifically the Henipavirus genus. There is currently no more effective medication to treat the Nipha virus. Therefore, in our search for the NiV molecule, we identified 15 phyto-compounds derived from *Nyctanthes arbor-tristis*, a polyherbal plant that is helpful against the flu, cough, sore throat, and shortness of breath (symptoms that match viral infections). The PDB database provided the structure of the NiV attachment glycoprotein in relation to the human cell surface receptor ephrinB2, which was used in the current study. PYMOL was used to predict the beta-sitosterol docking structure with NiV. Autodock Vina estimated the ligand's active site-pocket, and the Hex dock was used to determine the binding energy. With a binding energy of 8.7 kcal/mol, the beta-sterol had the greatest binding energy, according to the data. A compound of beta sitosteroside, NiPas, and Human Cell Surface Receptor B2 (EphRinB2) was simulated using molecular dynamic theory, which revealed a stable and long-lasting binding relationship for a simulation duration of 50 nanoseconds. Additionally, beta-sterol had drug-likeness characteristics and complied with the Lipinski rule of 5, indicating that it may have use as a NiV inhibitor.

Keywords: NiV-Nipah Virus; In Silico; Molecular Dynamics; Beta-Sitosterol; Anti-viral; Dynamics

Introduction

The *Nipah virus* (NiV) is a member of the Paramyxoviridae family, specifically the Henipavirus genus. It is categorised as a zoonotic virus and is linked to a high fatality rate. Henipaviruses naturally occur in bats [1]. The first instances started in late September 1998 in the West Malaysian state of Perak, close to the city of Ipoh, where pig breeding was a significant business. This area had cases up to the beginning of February 1999. In December 1998 and January 1999, the second cluster was located in the adjacent state of Negri Sembilan, not far from the little town of Sikamat. The third and largest cluster began in December 1998 in the same state, near the city of Bukit Pelandok [2]. Initially, the cases were attributed to Japanese Encephalitis (JE), a disease that had previously led to outbreaks associated with pigs in Malaysia. This attribution was based on the detection of JE-specific IgM in four serum samples out of 28 patients in the affected area, as well as the identification of JE nucleic acids in some of the patient's blood samples [3]. The name "Nipah" was given to the virus due to its connection to Kampung Sungai Nipah, a village close to the Nipah River, where the first viral isolates were discovered in patient specimens. Subsequently, a few

instances were recorded originating from the regions of Sepang and Sungei Buloh, as well as from abattoirs located in the adjacent city-state of Singapore. NiV infection was included as one of the top 10 priority diseases in the World Health Organization's 2018 Research and Development Blueprint, acknowledging its potential to cause public health problems.

The lack of antibodies or therapeutics to combat this illness is a significant factor driving global scientific efforts to develop an effective NiV immunisation and therapy strategy [4]. Many antiviral drugs have been investigated for their possible use in treating NiV infection. But it's crucial to remember that very few of these drugs have been tested in trials using animal models. Remdesivir, favipiravir, and ribavirin are a few well-known antibiotics. One of the initial antiviral medications that was employed in the battle against NiV was ribavirin. In the period from 1998 to 1999, an outbreak occurred in Malaysia. During this outbreak, the administration of ribavirin treatment yielded a noteworthy outcome. Specifically, among a group of 140 patients infected with the Nipah virus (NiV), the mortality rate was reduced by 36% [5]. Among the various options, remdesivir, an antiviral drug belonging to the adenosine nucleoside class, has demonstrated potential in preclinical studies conducted on African green monkeys. It's important to note that only two of the four African green monkeys treated with remdesivir had moderate respiratory problems. On the other hand, each animal that remained untreated had significant respiratory issues. This observation highlights remdesivir's possible efficacy in treating NiV infection [6]. On the other hand, Avigan, commercially known as favipiravir, has exhibited inhibitory properties against NiV replication in i*n vitro* investigations [7]. In addition, favipiravir exhibited the most antiviral effectiveness towards NiV infection when compared to other drugs in research that used a hamster model [8]. At now, the existing *in vitro* and *in vivo* investigations are limited in their scope. Given the limited array of therapies currently available for NiV, current research efforts are concentrated on investigating the potential of alternative antiviral medications [9]. It may take a long time12 to 15 years to create an innovative drug from the initial concept to the final product's release [10]. In the field of early pharmaceutical research, in silico methodologies play a substantial role and have particular significance in the processes of target identification and lead development [11]. Using in silico analysis, we evaluate a ligand's capacity to bind to a protein at an active site and contrast the ways in which various ligands bind to the active site-pocket.

In this research, 2VSM was identified as a potential target site for NiV treatment. Previous research discovered the main protease (PDB ID:2VSM), a glycoprotein that binds the Nipah virus to the human cell surface receptor ephrinB2 [12].

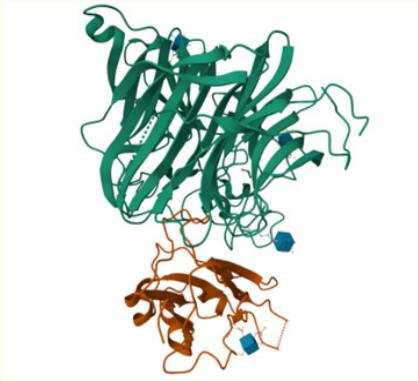


Figure 1: The crystal structure of Nipah virus attachment glycoprotein in complex with human cell surface receptor ephrinB2 PBD ID (2VSM).

Fifteen Phyto-compounds from *Nyctanthes arbor-tristis*, a polyherbal plant that is beneficial against the flu, cough, sore throat and shortness of breath (symptoms that resemble viral infections), were chosen in our search for the NiV compound. Thus, the aim of the present research is to discover strong natural compounds that are anti-NiV by using structure-based in silico molecular docking to analyse 15 phytocompounds and choose a lead compound from Nyctanthes arbor-tristis against the structure of NiV (2VSM).

Material and Methods

Preparation of protein

The crystal structure of the Nipah virus attachment glycoprotein in connection with the human cell surface receptor ephrinB2 (NiV) was obtained from the PDB database employing PDB ID (2VSM), and it was used in this investigation. It has a molecular weight of 63.83 kDa and a resolution of 1.80 Å. The following are three chains in total: A, B, C, D, E, F, and G. The derived structure's energy was minimised by using the SWISS PDB reader. It is used to reduce the energy of proteins and aids mend altered geometrics by rearranging atoms to eliminate internal constraints.

Preparation of ligand

Based on journal publications, antiviral agents from specific plant have been found. Using the SWISS ADME server, compounds with anti-viral qualities were filtered according to their drug-likeliness and ADME characteristics. 15 phytocompounds were chosen from Nyctanthes arbor-tristis. The PubChem database included the phytoligand and drug structures in SDF format. Following that, open-Babel was used to convert the phytoligands from SDF to PDB format. A docking study was carried out utilising eight phytoligands and the target protein, that is the glycoprotein attachment of the Nipah virus that is attached to the ephrinB2 receptor on the human cell surface. Autodock Vina was used in blind docking mode for the purpose of this study.

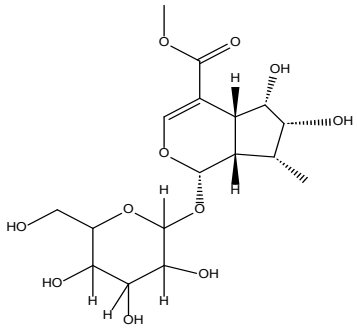
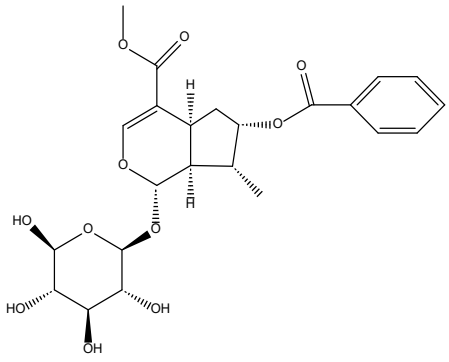
Molecular dynamic simulation of beta sitosterol

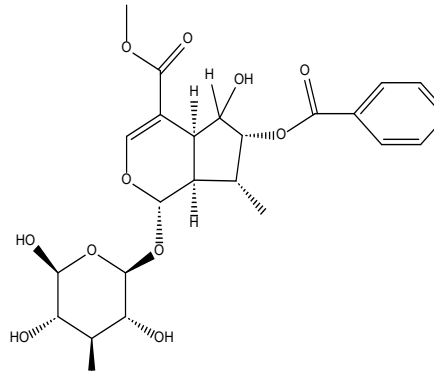
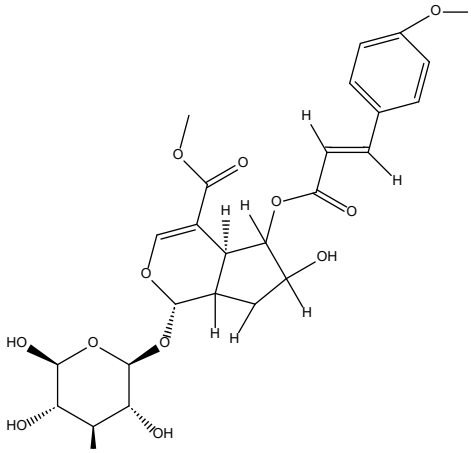
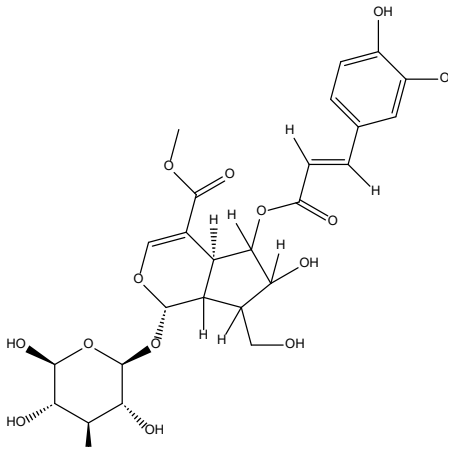
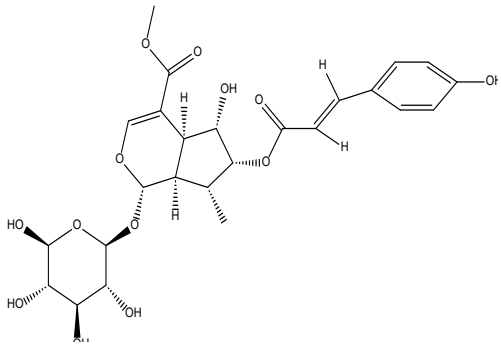
A molecular dynamic simulation of a compound including beta sitosterol, the human cell surface receptor ephrinB2, and the glycoprotein which attaches to the Nipah virus was carried out. MD simulation was used, and the simulation ran for 50 ns. Both the ligand's reduction in energy and topology emergence was accomplished via the Hex dock.

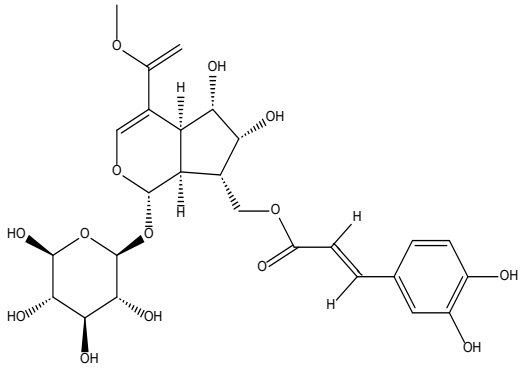
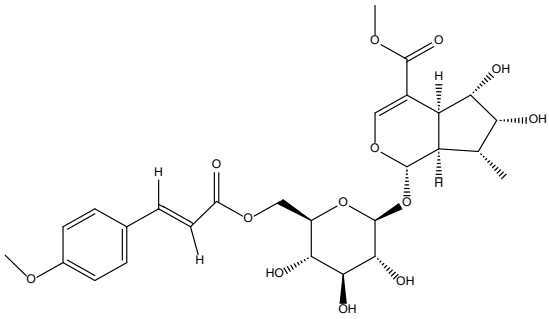
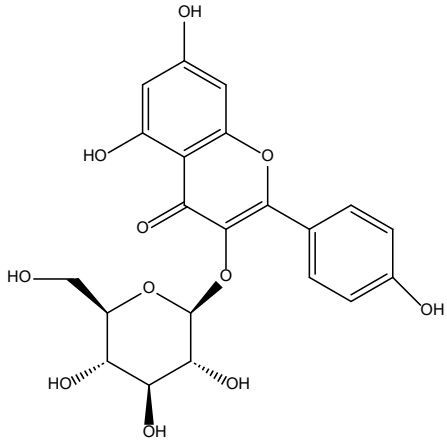
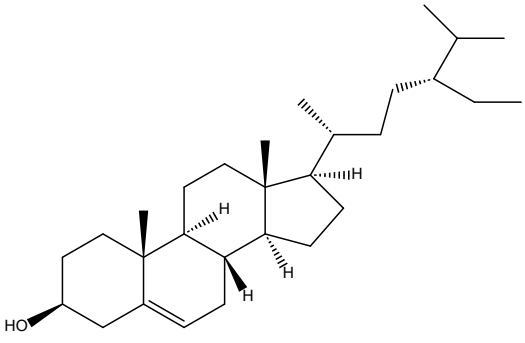
Results and Discussion

Molecular docking analysis

The range of binding energies observed for 15 phytoligands against the main protease, namely the glycoprotein responsible for binding the Nipah virus to the human cell surface receptor ephrinB2 (2VSM), varied from -10.2 kcal/mol (Arbortristoside D) to -5.7 kcal/mol (Rengyolone). Calceolarioside and Beta-Sitosterol had the highest binding affinity for the NiV. An additional MD simulation was performed on beta-sitostirol to examine the stability of its binding. (Table 1) included a variety of phytochemicals along with their docking scores. Table 2 presents the pharmacokinetic properties of the ligands that obtained the highest docking scores.

S no.	Phytochemicals	Structure	PUBCHEM ID	Docking score (kcal/mol)
1	6-beta-hydroxy-Loganin		341846	-7.6
2	Arborside B		182903	-8.5

3	Arborside C		182904	-8.3
4	Arbortristoside A		6442162	-8.0
5	Arbortristoside B		6442163	-10.0
6	Arbortristoside C		23955893	-8.7

7	Arbortristoside D		14632886	-10.2
8	Arbortristoside E		14632884	-9.0
9	Astragalin		5282102	-8.5
10	Beta-Sitosterol		222284	-8.7

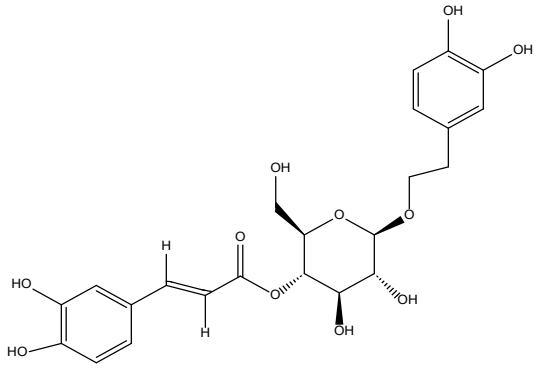
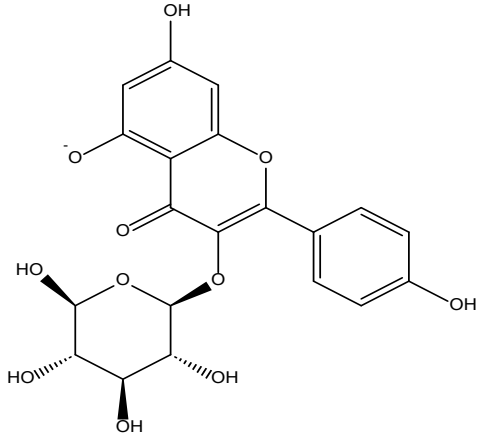
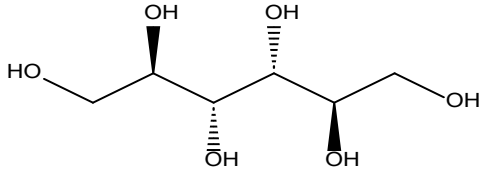
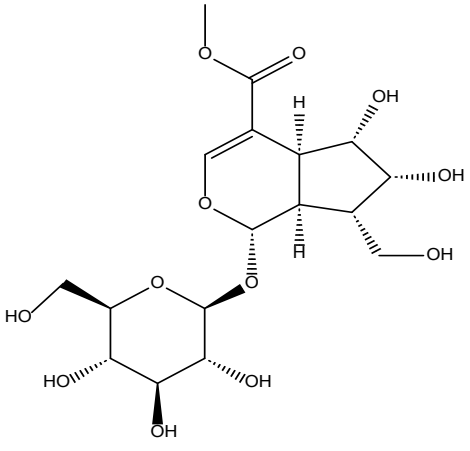
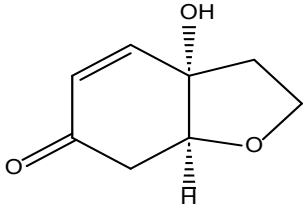
11	Calceolarioside A		5273566	-8.7
12	kaempferol 3-O-beta-D-glucoside (1-)		25203515	-8.5
13	Mannitol		6251	-5.9
14	Nyctanthoside		95224501	-8.5
15	(+)-Rengyolone		10725564	-5.7

Table 1: Docking scores of Phytochemicals, Molecular formula and PUBCHEM ID.

Table 2: ADME analysis of selected compounds.

S no	Ligand	Mol. Wt (g/mol)	No of hydrogen donors	No of hydrogen acceptors	Drug likeliness
1	Beta-Sitosterol	414.7	1	1	Yes
2	Calceolarioside A	478.4	7	11	No
3	Arbortristoside D	584.5	8	15	No
4	Arbortristoside B	584.5	8	15	No
5	Nyctanthoside	422.4	7	12	No

Prediction of active site of beta-sitosterol

PyMOL was used to identify the likely binding pockets or active sites of beta-sitosterol. The protein NiV is composed of two distinct chains, identified as A and B. Figure 2 illustrates the interaction between the binding complex of Beta-Sitosterol and the active site of NiV. Interaction analysis was performed by using Maestro software was shown in Figure 3.

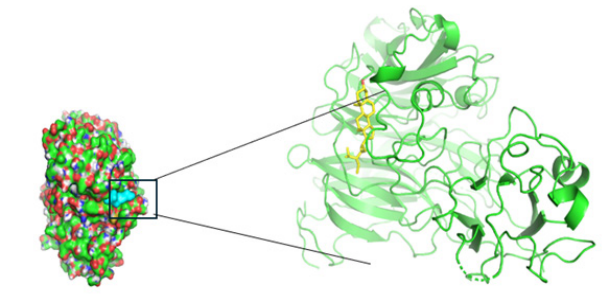


Figure 2: Active site of Beta-Sitosterol was predicted using PYMOL and docked structure of Beta-Sitosterol with NiV.

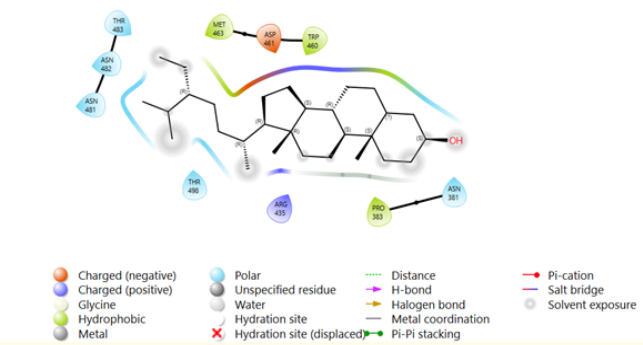


Figure 3: AInteraction of Beta-Sitosterol with NiV.

Table 3: Active site of Beta-Sitosterol with A and B chain of NiV.

Ligand	Beta-Sitosterol
Docking Score (kcal/ mol)	-8.7
A Chain	ASN 381
B Chain	-

Molecular dynamic simulation of Beta-Sitosterol with NiV

The docked complex of beta-sitosterol with NiV has been examined by molecular dynamic simulation. The conformation of the molecule binding the drug has been demonstrated to be stable with a mean RMSD value varying within the range of 0.1 nm when MD simulation was run for 50 ns. As may be seen in, the root mean square deviation (RMSD) value was visually shown as a function of the time frame (Figure 4). The fluctuation of the binding of Beta-Sitosterol with NiV, as seen in Figure 5, is indicative of RMSF.

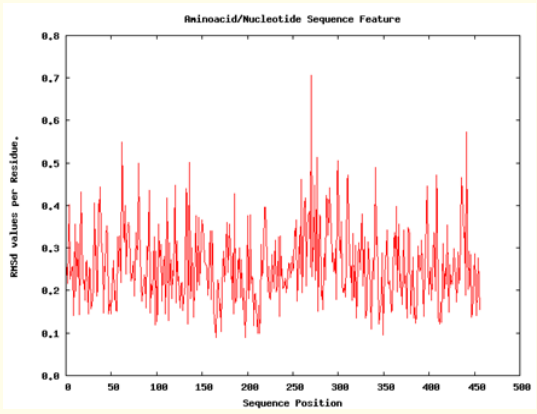


Figure 4: Time-dependent RMSD plot of Beta-Sitosterol binding with NiV using MD simulation.

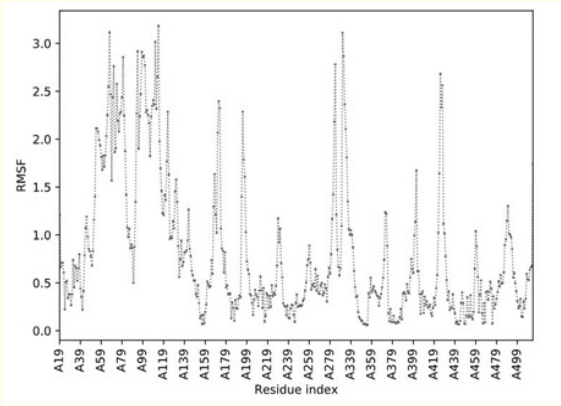


Figure 5: Time-dependent RMS fluctuation plot of Beta-Sitosterol binding to NiV using MD simulation.

Discussion

In the present investigation, Beta-Sitosterol obtained from the Nyctanthes arbor-tristis plant exhibited superior binding activity, as measured by Autodock Vina, with a binding energy of − 8.7 kcal/mol. Beta-sitosterol inhibits WSSV replication via viral genes, which is the first indication of a particular complement virus [13]. Beta-sitosterol has the ability to inhibit the immunological response that is regulated by RIG-I signalling and the generation of harmful interferons (IFNs), therefore suggesting its potential therapeutic use in the management of influenza [14]. It has been shown that β-sitosterol has the potential to augment immune response to SARS-CoV-2 infection and impede viral entry into host cells via angiotensin converting enzyme-2 (ACE-2) inhibition, specifically targeting spike glycoprotein. The modulation of immunity by increased dietary intake of β-sitosterol and other phytosterols is a contemporary strategy to address the challenges posed by the COVID-19 pandemic [15]. In this research, Beta-Sitosterol was selected as the primary chemical for analysis against the Nipah virus (NiV). The molecular dynamic simulation results using NiV and Beta-Sitosterol demonstrate a consistent and enduring binding interaction, as shown over the 50-nanosecond simulation period (Table 4).

Table 4

Docking mode	Affinity (kcal/mol)	Distance from best mode rmsd l.b. rmsd u.b.
1	-8.7	0.000 0.000
2	-7.4	3.207 9.518
3	-7.3	28.816 31.515
4	-7.2	1.234 2.613
5	-7.1	1.865 3.936

Conclusion

The virtual screening of the NiV PDB ID (2VSM) was conducted using 15 phytoligands derived from *Nyctanthes arbor-tristis.* Among these compounds, Beta-Sitosterol exhibited a notable affinity of -8.7. Furthermore, Beta-Sitosterol adhered to the Lipinski rule of 5 and shown drug-likeness properties, suggesting its potential as a NiV inhibitor. The binding site between Beta-Sitosterol and its target, the NiV virus, has been determined to be ASN381 on chain A of the NiV protein. Hence, Beta-Sitosterol has promising potential as a viable inhibitor of NiV, as shown by the available evidence. Further *in vitro* and *in vivo* experiments are required.

Bibliography

1. Clayton BA., *et al*. "Henipaviruses: An Updated Review Focusing on the Pteropid Reservoir and Features of Transmission". *Zoonoses Public Health* 60.1 (2013): 69-83.

2. Ang BSP., *et al*. "Nipah Virus Infection". *Journal of Clinical Microbiology* 56.6 (2018).

3. Chua KB. "Nipah virus outbreak in Malaysia". *Journal of Clinical Virology* 26.3 (2003): 265-275.

4. Talukdar P., *et al*. "Molecular Pathogenesis of Nipah Virus". *Applied Biochemistry and Biotechnology* 195.4 (2023): 2451-2462.

5. Goh KJ., *et al*. "Clinical features of Nipah virus encephalitis among pig farmers in Malaysia". *The New England Journal of Medicine* 342.17 (2000): 1229-1235.

6. Lo MK., *et al*. "Remdesivir (GS-5734) protects African green monkeys from Nipah virus challenge". *Science Translational Medicine* 11.494 (2019).

7. Srinivasan K and Rao M. "Understanding the clinical utility of favipiravir (T-705) in coronavirus disease of 2019: a review". *Therapeutic Advances in Infectious Disease* 8 (2021): 20499361211063016.

8. Dawes BE., *et al*. "Favipiravir (T-705) protects against Nipah virus infection in the hamster model". *Scientific Report* 8.1 (2018): 7604.

9. Orosco FL. "Advancing the frontiers: Revolutionary control and prevention paradigms against Nipah virus". *Open Veterinary Journal* 13.9 (2023): 1056-1070.

10. Hughes JP., *et al*. "Principles of early drug discovery". *British Journal of Pharmacology* 162.6 (2011): 1239-1249.

11. Terstappen GC and Reggiani A. "*In silico* research in drug discovery". *Trends in Pharmacological Science* 22.1 (2001): 23-26.

12. Bowden TA., *et al*. "Structural basis of Nipah and Hendra virus attachment to their cell-surface receptor ephrin-B2". *Nature Structural and Molecular Biology* 15.6 (2008): 567-572.

13. Chen C., *et al*. "First Discovery of Beta-Sitosterol as a Novel Antiviral Agent against White Spot Syndrome Virus". *International Journal of Molecular Sciences* 23.18 (2022): 10448.

14. Zhou B Xian., *et al*. "β-sitosterol ameliorates influenza A virus-induced proinflammatory response and acute lung injury in mice by disrupting the cross-talk between RIG-I and IFN/STAT signaling". *Acta Pharmacologica Sinica* 41.9 (2020): 1178-1196.

15. "Beta-Sitosterol: As Immunostimulant, Antioxidant and Inhibitor of SARS-CoV-2 Spike Glycoprotein". *Archives of Pharmacology Therapy* 2.1 (2020).