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In Silico Analysis of G Glycoprotein of Hendra virus as potential drug target against Hendra disease

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Abstract

Hendra virus (HeV) is a zoonotic, highly pathogenic member of the genus Henipavirus (family Paramyxoviridae) and is a significant public health risk due to its high mortality and lack of antiviral drugs. The viral attachment glycoprotein (G protein) is a key molecule in the recognition of host cells and viral entry, and is an appealing molecule for antiviral drug screening due to its ability to recognize ephrin-B2 and ephrin-B3 receptor molecules. The present study involved an integrated in silico analysis of Hendra virus G glycoprotein (PDB ID: 7SYY) to account for its structural reliability, physicochemical properties and receptor binding regions. The three dimensional structure of the glycoprotein was obtained from the RCSB Protein Data Bank and validated by PROCHECK, ERRAT and Verify3D. Structural validation showed that the structure is of good stereochemistry, with 86.4% of residues in the most favored regions of the Ramachandran plot, and an ERRAT quality score of 90.130, which indicates that the structure is reliable for computational studies. Physicochemical characterization was performed using ProtParam indicating a molecular weight of 67.25 kDa, theoretical pI of 8.64 and an instability index of 36.52, which indicates stability of the protein for docking simulation. A number of biologically relevant active site residues including Asp257, Asp260, Gly439, Lys443, Gly449, Lys465 and Asp468, involved in receptor recognition and viral attachment, were identified using binding pocket analysis.. In sum, these results provide a solid computational basis to target Hendra virus G glycoprotein for disease treatment.

Introduction

Hendra virus (HeV) is a very dangerous zoonotic virus that is a member of the genus Henipavirus and family Paramyxoviridae (Gazal *et al.*, 2022). Hendra virus was initially discovered in an outbreak in Brisbane in 1994, now known to be a severe emerging infectious agent in animals and human beings (Broder, 2012). Horses and consequently people are infected by fruit bats of the genus Pteropus which serve as natural reservoirs of the virus (Broder, 2012). The severity of respiratory disease and lethal encephalitis are common in human infections, and high mortality rates in documented outbreaks have been reported (Ganguly et al., 2025). Hendra virus is a biosafety level-4 (BSL-4) pathogen, because it is highly pathogenic and has no approved antiviral therapeutics (van den Hurk *et al.*, 2025).

The viral entry into host cells occurs through two surface glycoproteins, attachment glycoprotein (G) and the fusion glycoprotein (F) (Salleh, 2025). The G glycoprotein is a key factor in viral pathogenesis, binding to ephrin-B2 and ephrin-B3 receptors on host

endothelial and neuronal cells, thus triggering changes in conformational modifications of the F protein that initiates membrane fusion and viral entry (Xu *et al.,* 2011).

Inhibition of G glycoprotein -receptor interaction is a logical antiviral approach to this entry mechanism because it is possible to prevent viral binding and subsequent infection with this antiviral strategy (Maheden *et al.,* 2021). The discovery of antiviral drugs has been greatly enhanced by the progresses in computational biology (Du *et al.,* 2026; Yang & Kar, 2023).

The study analyzes the Hendra virus entry protein G glycoprotein (PDB ID: 7SYY) based on these proven strategies. (Ahmad et al., 2022). Recently solved crystal structure of the Hendra virus G glycoprotein (PDB ID: 7SYY), which is available in the RCSB Protein Data Bank, offers insight into the details of its receptor-binding domain, and a useful template to structure-based drug discovery.

Materials and Methods

Structure Retrieval

The UniProt database (https://www.uniprot.org) was the main reference tool employed in order to gain a profound structural and functional knowledge regarding the target protein. UniProt is a highly curated and well-known database that gives a detailed annotation on protein sequences, functional domains, physicochemical properties, and biological functions. The G glycoprotein (uniport id O89343) contains about 604 amino acids and weighs about 67 kDa and plays a vital role in triggering the membrane fusion in liaison with the viral fusion (F) protein.

The three-dimensional (3D) structure of the Hendra virus G glycoprotein is available in the RCSB Protein Data Bank (https://www.rcsb.org/), which is the main world-wide repository of experimentally determined macromolecular structures. The chosen crystal structure (PDB ID: 7SYY) was identified via X-ray crystallography at high resolution, which gives a more detailed structural information about the receptor-binding domain of the glycoprotein. The Protein Data Bank has wide application in structural bioinformatics, molecular modeling, and drug discovery studies in various fields of science.

The structure retrieved was thoroughly checked in terms of completeness, chain selection, deleted residues and structural integrity before subsequent computational studies. Preprocessing was done to remove any heteroatoms, co-crystallized ligands or water molecules that were not necessary in docking studies. The quality of the structure was assessed and validated with the help of standard structure evaluation to guarantee reliability of further molecular docking and density functional theory (DFT) studies.

Structure Verification

Structure validation of the selected three-dimensional model of the Hendra virus G glycoprotein (PDB ID: 7SYY) to ensure the reliability and structural integrity of the model was done using the stereochemical quality of the protein structure through PROCHECK. PROCHECK is used to create a Ramachandran plot to analyze backbone dihedral angles (φ and ψ) of amino acid residues, which can be used to identify residues found in favored, allowed and disallowed regions. The large ratio of residues in the hottest and also permitted areas signifies excellent stereochemical quality and structural dependability of computational research (*SAVESv6.1 - Structure Validation Server*, n.d.).

The general quality parameter of the model which uses non-bonded atomic interactions was evaluated using ERRAT. ERRAT examines the statistics of non-bonded atom-atom interactions and gives an overall quality score; a score of more than 50 is usually deemed acceptable with high-resolution structures, whereas higher scores reflect superior structural reliability (*SAVESv6.1 - Structure Validation Server*, n.d.).

Also, the compatibility between the 3D atomic models with its own amino acid sequence (1D profile) was analyzed by Verify3D. Verify3D checks the consistency of the environmental profile of each residue in the 3D structure with known structural parameters. Good structural compatibility is indicated by high percentage of residues with an average 3D1D score 0.2 or above. The overall validation of the PROCHECK, ERRAT and Verify3D showed that the chosen structure of Hendra virus G glycoprotein is of reasonable quality and can be further analyzed by molecular docking and density functional theory (DFT). Give PROCHECK, ERRAT and Verify 3d results in supplementary data).

Binding Site Determination

The binding site of the Hendra virus G glycoprotein (PDB ID: 7SYY) was identified by thorough literature review using a combined approach and computational pocket prediction analysis. In silico analysis of known structural data from other deposited G glycoproteins revealed the residues significant for receptor recognition, and were checked against published structural studies describing Hendra virus-glycoprotein-ephrin-host-receptor interaction within the globular head domain (Bishop *et al.,* 2008). The three-dimensional structure was then analyzed with PrankWeb and CASTp, ligand binding cavity predictors which utilize geometric, physicochemical, and topographical features of the protein surface. The identified high-probability pockets were further cross-compared with regions interacting with the receptor reported in literature to ensure relevance biologically.

Given this combined analysis, the active site residues used for grid box generation and docking simulations were identified as Asp257 (D257), Asp260 (D2 60), Gly439 (G439), Lys443 (K443), Gly449 (G449), Lys465 (K465), and Asp468 (D468), which collectively define the functional receptor-binding interface targeted in this study (Halder *et al.*, 2023).

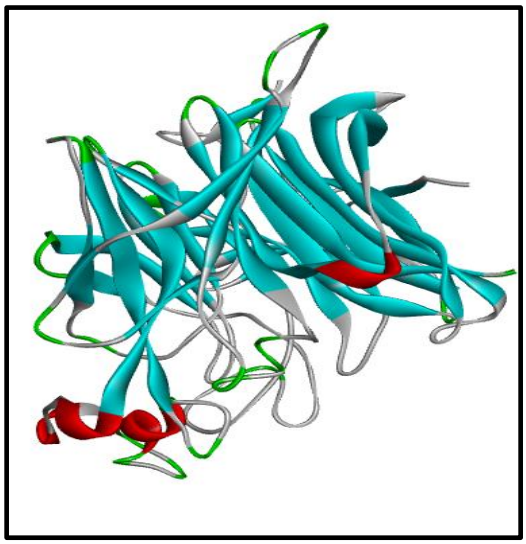


Figure 1: 3D structure of G glycoprotein (PDB ID: 7SYY) of the HeV.

Results

Ramachandran Plot Analysis

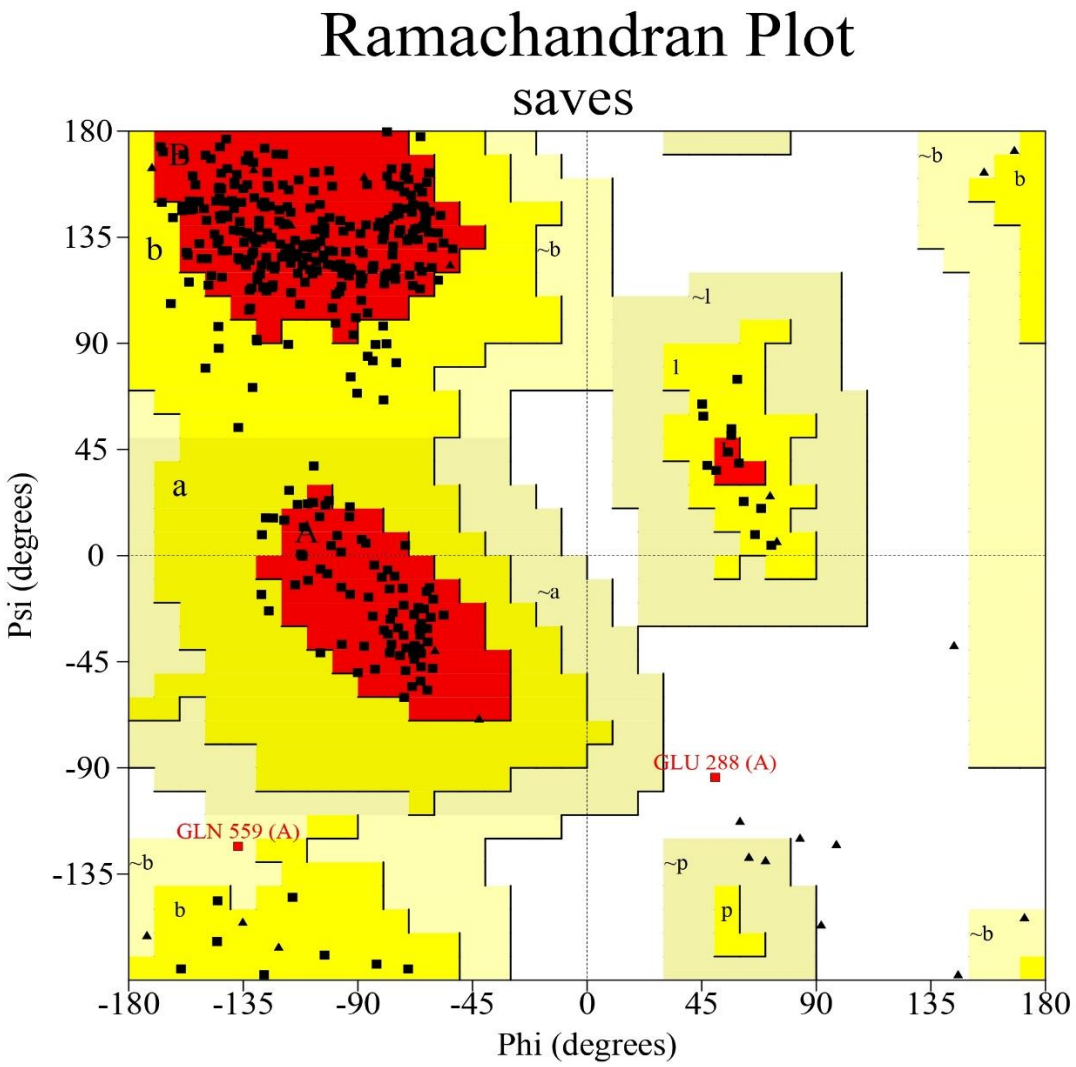
The Ramachandran plot analysis of Hendra virus G glycoprotein was used to evaluate the stereochemical quality and backbone conformation (Figure 1). The analysis showed that 86.4% of the amino acid residues (310 residues) had their residues in most favored regions [A, B, L] and 13.1% in the additionally allowed regions [a, b, l, p]. In addition, very few of the residues were found in the generous allowances (0.3%), and very little in the disallowed area (0.3%) and that was residue GLU 288 (A). The number of residues in the allowed region of the confirmed structure is in excess of the 99.5% mark, which is a good indicator of the stereochemical stability and reliability of the protein structure. The results obtained support the fact that the structure obtained is of good geometric quality and can be used for further computational and molecular interaction studies.

ERRAT Overall Quality Factor

The overall quality and non-bonded atomic interactions of the 7SYY structure of the protein were evaluated by ERRAT2 server. The quality of the Protein model for chain A was calculated by ERRAT as 90.130. Most of the residues had error values which were less than the 95% threshold, which suggested that the atomic interaction geometry was good in the majority of the structure. Minor deviations of relatively large error values were noticed around the residues 280, 330 and 380, but the deviations were within the acceptable limits for experimentally solved protein structures. High quality crystal structures with resolution range from 2.5 to 3 Å have ERRAT scores around 90% or higher. Thus the quality factor achieved supports the structural reliability and validity of the Hendra virus G glycoprotein model employed in the present study.

Verify3D Assessment

The server, called Verify3D, was used to assess the compatibility between the 3D structure and 1D sequence of the Hendra virus G glycoprotein (Figure 3). The Verify3D profile showed that most of the 3D–1D compatibility scores of the amino acid residues were greater than the known threshold value of 0.2. This result shows that most residues are in energetically favorable environments, reflecting their physicochemical characteristics, such as their polarity, hydrophobicity, and solvent accessibility. In addition, a very good compatibility score was obtained over the full length of the sequence (residues 11 to 413), further confirming the integrity and appropriate folding of the protein model. Overall, it is concluded that the 7SYY structure is suitable for the computational analysis and structural investigation in the downstream area.



Plot statistics

Residues in most favoured regions [A,B,L]	310	86.4%
Residues in additional allowed regions [a,b,l,p]	47	13.1%
Residues in generously allowed regions [~a,~b,~l,~p]	1	0.3%
Residues in disallowed regions	1	0.3%
Number of non-glycine and non-proline residues	359	100.0%
Number of end-residues (excl. Gly and Pro)	5	
Number of glycine residues (shown as triangles)	25	
Number of proline residues	24	
Total number of residues	413	

Based on an analysis of 118 structures of resolution of at least 2.0 Angstroms and R-factor no greater than 20%, a good quality model would be expected to have over 90% in the most favoured regions.

Figure 2: Ramachandran plot analysis of the G glycoprotein of Hendra virus

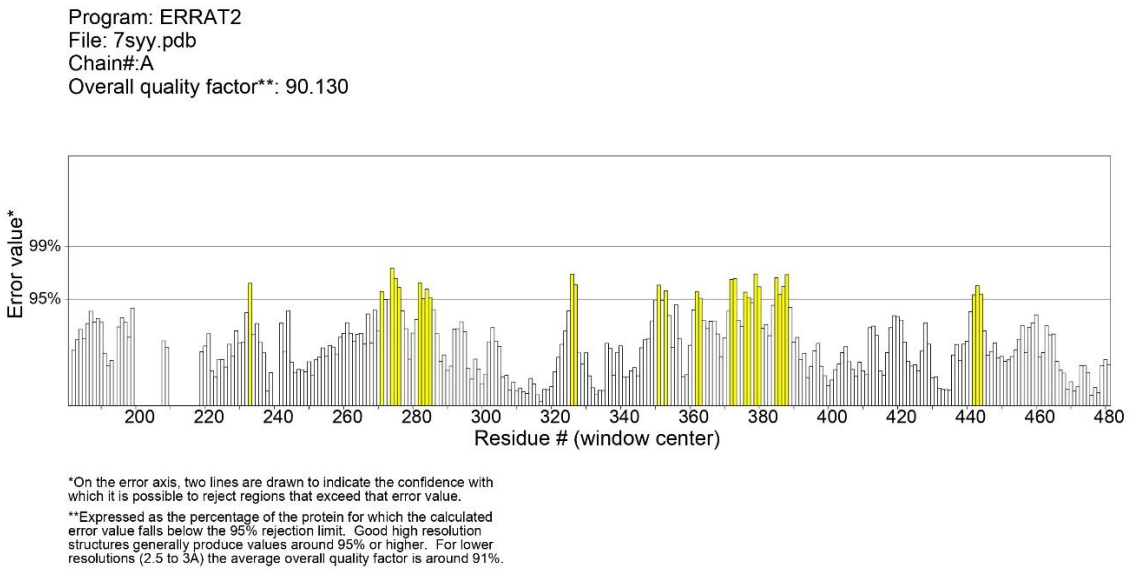


Figure 3: ERRAT analysis of the protein structure

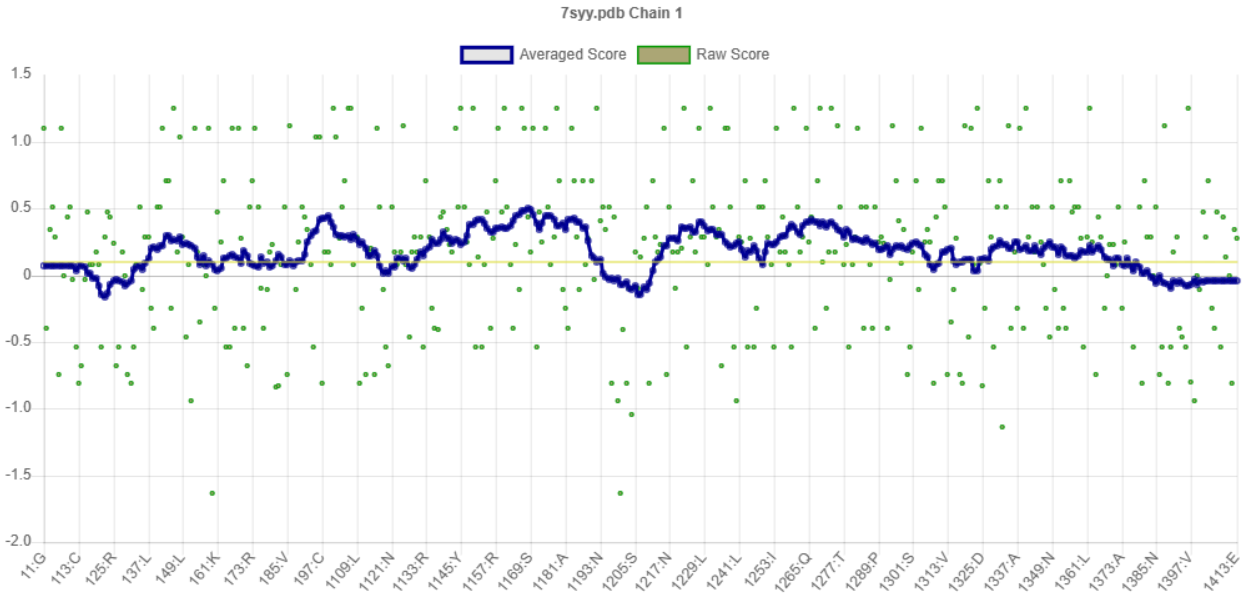


Figure 4: Verify 3D analysis of the protein

Table 1: Results of programs used for crystal structure verification of G glycoprotein

Programs used for structure verification	**7syy (G glycoprotein of HeV)**
ERRAT	The overall quality factor was 90.130
Verify 3D	high quality as approximately **98%** of the residues have an averaged 3D-1D score ≥ **0.1**,

Ramachandran plot (PROCHECK)	**86.4%** in the most favoured regions **13.1%** in the additional allowed regions **0.3%** in the disallowed regions

Table 2: Physiochemical parameters of G glycoprotein of HeV computed by using ProtParam

Sr. No.	Parameters	G glycoprotein
1	Mol. weight	67,256.8 Da
2	No. of amino acids	604
3	Theoretical Pi	8.64
4	Instability index (II)	36.52
5	No. of negatively charged residues (Asp+Glu)	54
6	No. of positively charged residues (Arg+Lys)	59
7	Aliphatic index	78.91
8	Grand average of hydropathicity (GRAVY)	−0.212
9	Estimated half-life	30 h

Discussion

The G glycoprotein of the Hendra virus is a critical viral surface protein which is involved in membrane fusion and host receptor binding during viral entry (Bradel-Tretheway *et al.*, 2015). Due to the direct interaction with ephrin-B2 and ephrin-B3 receptors, the glycoprotein has become an attractive molecular target in antiviral drug discovery (Xu et al., 2011b). In this study, comprehensive pre-docking computational studies were performed to evaluate the structural integrity, physicochemical stability and receptor binding properties of the Hendra virus G glycoprotein (PDB ID: 7SYY). It is important to validate the structure of the target protein model. The selected crystal structure was analyzed stereo chemically with excellent results in PROCHEK, ERRAT and Verify3D. The Ramachandran plot showed that 86.4% of the residues were in favored regions, and there were no residues at all in disallowed regions, which meant there were no major steric clashes in the backbone and good backbone conformation. Likewise, high resolution of the protein structure and the reliability of non-bonded atomic interactions were confirmed by a ERRAT quality score of 90.130. The structural compatibility was also verified by the analysis of the residues using the software Verify3D; about 98% of the residues had an acceptable 3D–1D profile score. All these results indicate that the picked protein structure can be used for further molecular docking and computational drug design research. The glycoprotein was subjected to physicochemical analysis to gain additional information about its biochemical nature. The molecular weight of ~ 67.25 kDa and the number of 604 amino acid residues are similar to those of previously reported attachment glycoproteins of henipaviruses. A theoretical isoelectric point (pI) of 8.64 signifies a slightly basic protein and could affect receptor interaction and molecular stability in physiological conditions. The calculated instability index value of less than 40 indicates that the protein is stable and the aliphatic index of 78.91 is considered as favorable thermal stability (Gamage et al., 2019). Furthermore, the very low GRAVY score of the glycoprotein (−0.212) is also in favor of its surface display role as a viral attachment protein. The residues which were selected from the binding-site prediction analysis and found to be important for binding to the receptor included Asp257, Asp260, Gly439, Lys443, Gly449, Lys465 and Asp468. These residues are within the receptor-binding domain and are thought to play important roles in ephrin receptor recognition and viral attachment. The predicted active site was reported previously in the structural studies of Hendra and Nipah virus glycoproteins, indicating its biological relevance. Overall, the computational analyses conducted in this study are in agreement with the use of Hendra virus G glycoprotein as an attractive antiviral target. These results could help in the development of more specific anti-Hendra virus infection therapies in the future.

Conclusion

The present study could perform a detailed in silico analysis of Hendra virus G glycoprotein (7SYY) to evaluate their potential to be used as a target for antiviral drug development. The stereochemical quality, structural stability and reliability of the residue conformations selected for the protein structure were validated by structural validation analysis using PROCHECK, ERRAT and Verify3D. Physicochemical characterization also showed that the glycoprotein has stable properties and biologically

relevant properties consistent with its role in viral attachment and host-cell recognition. Using binding site prediction analysis, several key residues were identified that are involved in receptor recognition and viral entry, such as Asp257, Asp260, Gly439, Lys443, Gly449, Lys465, and Asp468, which could be targeted for inhibitor binding.

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