

In Silico Prediction and Structural Mapping of Candidate Linear B-Cell Epitopes in Andes Virus Glycoprotein

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ABSTRACT

Andes virus (ANDV), a pathogenic orthohantavirus associated with hantavirus cardiopulmonary syndrome, remains a public health concern because of its severe clinical outcomes and the absence of broadly approved vaccines for human use. The viral glycoprotein is a relevant antigenic target because of its surface localization and role in viral entry. This study aimed to identify and prioritize candidate linear B-cell epitopes in the ANDV glycoprotein using an integrated immunoinformatics approach. The ANDV glycoprotein sequence was retrieved from UniProt, and linear B-cell epitopes were predicted using BepiPred 3.0 with a threshold of 0.030. Candidate peptides were evaluated for antigenicity, allergenicity, and toxicity using VaxiJen v2.0, AllerTOP v2.1, and ToxinPred, respectively. The three-dimensional glycoprotein model was generated using AlphaFold, refined with GalaxyWEB, and validated using ERRAT and Ramachandran plot analysis. Surface-localized candidates were further assessed through molecular docking with a B-cell receptor structure using ClusPro 2.0, followed by binding free energy estimation using PRODIGY. E1 (EWRKKSDTTDTTNAASTTFE), E2 (QTKTVNLRGT), and E4 (PSTSSTDT) showed favorable antigenicity, non-allergenic and non-toxic profiles, and surface localization on the glycoprotein model. Docking analysis further supported their prioritization, with predicted binding free energies of -10.0, -9.4, and -9.1 kcal/mol for E1, E2, and E4, respectively. Overall, E1 emerged as the strongest candidate, while E2 and E4 represent additional candidates for further validation. These findings provide preliminary computational evidence for candidate linear B-cell epitopes in ANDV glycoprotein, although experimental confirmation remains necessary.

Keywords: Andes virus; B-cell epitope; glycoprotein; immunoinformatics; structural mapping; candidate linear B-cell epitope

Introduction

A recent cluster of Andes virus infections associated with the cruise ship MV Hondius has heightened international concern regarding the public health significance of pathogenic orthohantaviruses (Koopmans et al., 2026). Andes virus (ANDV), a zoonotic pathogen within the genus Orthohantavirus and family Hantaviridae, typically infects humans through inhalation of aerosolized particles contaminated with urine, feces, or saliva from infected rodent reservoirs. Notably, ANDV is epidemiologically unique due

to documented instances of limited person-to-person transmission, particularly among close contacts (Chediack et al., 2026; Martinez-Valdebenito et al., 2014). This transmission feature, combined with its association with severe cardiopulmonary disease, underscores the importance of ANDV for public health surveillance, outbreak preparedness, and vaccine development.

ANDV is a primary etiological agent of hantavirus

cardiopulmonary syndrome (HCPS), a severe disease marked by increased pulmonary vascular permeability, pulmonary edema, acute respiratory failure, and cardiogenic shock (Warner et al., 2025). While the incidence of HCPS is generally lower than that of hemorrhagic fever with renal syndrome caused by Old World hantaviruses, HCPS exhibits a substantially higher case-fatality rate, typically reported at 30–40% (Angulo et al., 2017; Barrera et al., 2025; Quarleri et al., 2026). Despite the clinical severity of ANDV infection, no specific antiviral therapy or widely approved vaccine is currently available for human use. This lack of medical countermeasures is particularly concerning given ecological disturbances, climate variability, and habitat changes that may influence rodent population dynamics and elevate the risk of human exposure to infected reservoirs (Moirano et al., 2024).

Structurally, ANDV is an enveloped, negative-sense RNA virus with a tripartite genome consisting of small, medium, and large segments. The small segment encodes the nucleocapsid protein, the medium segment encodes a glycoprotein precursor processed into Gn and Gc, and the large segment encodes the RNA-dependent RNA polymerase (Beltrán-Ortiz et al., 2017). The envelope glycoproteins Gn and Gc are of particular interest for vaccine development because they are displayed on the virion surface and mediate host-cell attachment, receptor engagement, endocytic entry, and membrane fusion. Their surface exposure facilitates antibody recognition, supporting their selection as antigenic targets for epitope-based vaccine research (Banerjee & Mukhopadhyay, 2016; Cifuentes-Muñoz et al., 2014).

B-cell epitopes are specific antigenic regions recognized by antibodies and contribute to humoral immune responses (Caoili, 2022). In vaccine design, identifying B-cell epitopes is essential because antibody-mediated immunity and immunological memory are critical for protection against viral reinfection. Linear B-cell epitopes are particularly valuable in immunoinformatics-based screening, as they can be derived from the primary amino acid sequence, assessed for antigenicity and safety, and mapped onto three-dimensional antigen structures (Riswana & Punjungsari, 2025). However, sequence-based prediction alone does not adequately determine biological accessibility or

immunogenic potential. Structural mapping is therefore required to establish whether predicted epitopes are located on solvent-exposed regions of the target protein, where they are more likely to be accessible to antibody binding (Afnani & Purnama, 2025; Francino-Urdaniz & Whitehead, 2021). Although B-cell epitope prediction, multiepitope vaccine design, and structural evaluation have been applied in viral vaccine-related studies, including hantavirus targets, most previous hantavirus immunoinformatics studies have emphasized broad whole-proteome screening or multiepitope vaccine construct design rather than a focused prioritization of linear B-cell epitopes derived specifically from the ANDV glycoprotein (Abdulla et al., 2021).

The novelty of the present study therefore does not rely on the use of individual computational tools, which are well-established in immunoinformatics research, but on the ANDV-specific integration of linear B-cell epitope prediction, antigenicity and safety screening, three-dimensional structural mapping, and molecular docking with a B-cell receptor structure for candidate prioritization. This integrated approach allows predicted epitopes to be evaluated not only on the basis of sequence-level epitope propensity, but also according to their predicted antigenicity, safety profile, structural localization, and interaction potential with an antigen-recognition model. Such a focused framework is particularly relevant for glycoprotein antigens, in which not all sequence-predicted epitopes are necessarily exposed or available for antibody recognition on the folded protein surface.

Therefore, this study aimed to identify and prioritize linear B-cell epitope candidates in the Andes virus glycoprotein through an integrated immunoinformatics approach combining sequence-based prediction, antigenicity and safety screening, three-dimensional structural mapping, and molecular docking with a B-cell receptor structure. Candidate epitopes were further assessed for antigenicity, allergenicity, toxicity, structural localization, and predicted BCR-binding affinity. The results provide preliminary computational evidence for prioritized surface-accessible linear B-cell epitope candidates that may inform future experimental evaluation for Andes virus vaccine-associated or diagnostic applications. However, as this study is

entirely computational, the predicted epitopes should be regarded as potential candidates requiring further experimental validation through *in vitro* and *in vivo* studies.

Materials and Methods

Retrieval and Curation of Andes Virus Glycoprotein Sequence

The ANDV glycoprotein sequence was retrieved from the UniProt Knowledgebase using the taxonomic identifier and protein accession as search criteria. The UniProt entry Q9E006, annotated as ANDV glycoprotein and consisting of 1138 amino acids, was selected as the reference sequence for downstream analysis (Shimizu et al., 2013). The FASTA sequence and associated metadata, including accession number, organism name, protein length, and database source, were recorded to ensure sequence traceability and reproducibility. UniProtKB provides curated protein sequence and functional annotation resources, supporting its use as a primary source for protein sequence retrieval.

Linear B-Cell Epitope Prediction

Linear B-cell epitope prediction was performed using BepiPred 3.0, a sequence-based epitope prediction tool developed for identifying residues with potential B-cell epitope propensity (Clifford et al., 2022). The higher-confidence prediction option was selected. In this study, a threshold of ≥ 0.030 was used as a sequence-specific operational cutoff based on the score distribution observed across the ANDV glycoprotein. This cutoff was selected to balance epitope recovery and prediction stringency. Higher cutoff values retained only a very limited number of short epitope regions and reduced the ability to capture biologically plausible contiguous peptide segments, whereas lower cutoff values increased the inclusion of low-scoring regions that may represent less reliable predictions.

Antigenicity, Allergenicity, and Toxicity Screening

The predicted linear B-cell epitope candidates were further evaluated for antigenicity, allergenicity, and toxicity. Antigenicity was assessed using VaxiJen v2.0 with a threshold value of 0.400; peptides with antigenicity scores above this threshold were considered potentially antigenic (Afnani, Kharisma, et al., 2026). VaxiJen is an alignment-independent antigen

prediction server that classifies antigens based on the physicochemical properties of protein sequences (Doytchinova & Flower, 2007). Allergenicity was predicted using AllerTOP v2.1, and only peptides classified as non-allergenic were retained. AllerTOP is an alignment-free allergenicity prediction server based on physicochemical properties and machine-learning classification (Dimitrov et al., 2014). Toxicity was evaluated using ToxinPred, and peptides predicted as non-toxic were prioritized for further structural mapping. ToxinPred is designed to classify peptides as toxic or non-toxic based on computational sequence-derived features (Rathore et al., 2024).

Prediction, Refinement, and 3D Structure Validation

The three-dimensional (3D) structure of the Andes virus glycoprotein was predicted using the AlphaFold Server (Kovalevskiy et al., 2024; Prastika et al., 2026). The predicted structure was then refined using the GalaxyWEB server to improve local structural geometry and reduce potential modeling artifacts. The refined model was validated using structure quality assessment parameters (Ko et al., 2012). The ERRAT score was calculated using the Structure Validation Server, and stereochemical quality was assessed using Ramachandran plot analysis through RamPlot (Afnani, Emilia, et al., 2026; Laskowski et al., 2013). The validated model was subsequently used as the structural template for mapping the selected linear B-cell epitope candidates.

Structural Mapping and Visualization of Linear B-Cell Epitope Candidates

The selected linear B-cell epitope candidates were mapped onto the refined 3D structure of the ANDV glycoprotein using PyMOL under an academic license. Epitope positions were identified based on their amino acid coordinates in the full-length glycoprotein sequence and visualized on the 3D model using distinct colors. Both cartoon and surface representations were generated to assess the spatial distribution and surface exposure of each candidate epitope (Riswana & Punjungsari, 2025). Epitope candidates located on surface-exposed regions were prioritized because B-cell epitopes are more likely to be accessible to antibody recognition when positioned on the external surface of the antigen. In contrast, epitopes located within

buried, transmembrane, or structurally uncertain regions were interpreted with caution and were not prioritized for further analysis.

Molecular Docking with B-Cell Receptor The prioritized linear B-cell epitopes, were further evaluated through molecular docking with the B-cell receptor (BCR). The BCR structure was obtained from the RCSB Protein Data Bank using PDB ID 5IFH (Riswana & Punjungsari, 2025). Molecular docking was performed using the ClusPro 2.0, with BCR designated as the receptor and each epitope peptide as the ligand (Arapa et al., 2026). The best-ranked docking complex from each epitope-BCR interaction was selected for further evaluation. The predicted binding free energy (ΔG) of each complex was then assessed using the PRODIGY web server, where more negative ΔG values indicate stronger predicted binding affinity (Xue et al., 2016). The resulting

docking complexes were visualized using PyMOL to examine the interaction orientation and spatial positioning of each epitope on the BCR surface.

Results and Discussion

Linear B-cell epitope prediction was conducted to identify continuous amino acid regions with potential antibody-binding capacity in the analyzed ANDV protein sequence. This analysis is significant because B-cell epitopes represent antigenic regions recognized by antibodies and may serve as preliminary targets for vaccine-associated evaluation, immunodiagnostic development, and immune-reactivity assessment. (Caoili, 2022). In silico screening serves as a preliminary pipeline to prioritize these regions

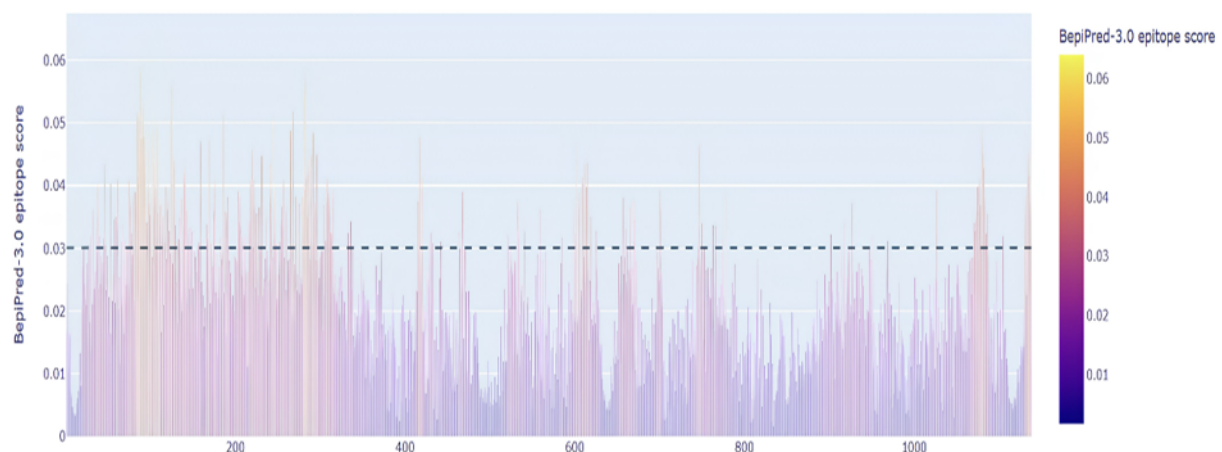


Figure 1. Predicted linear B-cell epitope score distribution across the ANDV glycoprotein sequence using a threshold value of 0.030.

boundaries require careful interpretation due to the inherent complexity of immune interactions (Cia et al., 2023). In this analysis, residues with epitope scores above the threshold value of 0.030 were considered to meet the initial criterion for potential linear B-cell epitope regions (**Figure 1**). Several regions of the ANDV glycoprotein exhibited epitope prediction scores above the predefined threshold, indicating the presence of localized candidate linear B-cell epitope regions (**Figure 1**). The threshold of 0.030 was selected as an operational cutoff because it provided a practical balance between sensitivity and specificity for this particular ANDV glycoprotein sequence. Based on the score distribution shown in Figure 1, more stringent thresholds resulted in very few retained peptide regions, which could

exclude potentially relevant epitopes, whereas lower thresholds included broader low-score regions that might increase false-positive candidate selection. The threshold of 0.030 was selected as an operational cutoff because it provided a practical balance between sensitivity and specificity for this particular ANDV glycoprotein sequence. Based on the score distribution, more stringent thresholds resulted in very few retained peptide regions, which could exclude potentially relevant epitopes, whereas lower thresholds included broader low-score regions that might increase false-positive candidate selection. The non-uniform distribution of these scores implies that potential binding sites are localized within specific clusters, which biologically correlates with flexible and

accessible segments in native viral proteins (Galanis et al., 2021; Jespersen et al., 2019; Zeng et al., 2023).

The predicted linear B-cell epitopes were designated as E1–E5, each corresponding to a specific peptide region within the target protein. E1 corresponds to the peptide sequence EWRKKSDDTTNAASTTFE at positions 82–101, while E2 corresponds to QTKTVNLRGT at positions 103–112. E3 and E4 represent the peptide sequences HPRGEDHD and PSTSSTDT,

located at positions 279–286 and 306–313, respectively. E5 corresponds to FNQIDSDKVYDDGAPP at positions 1071–1086. The complete properties of these predicted candidates are detailed across subsequent evaluation criteria **Table 1**.

Five candidate linear B-cell epitopes were identified, of which E1–E4 fulfilled the predefined antigenicity criterion, while E5 showed a score below the cutoff (**Table 1**).

Table 1. Predicted linear B-cell epitope candidates in ANDV glycoprotein and their antigenicity, allergenicity, and toxicity profiles.

Epitope	Peptide Sequence	Length	Position	Antigenicity (>0.400)	Allergenicity	Toxicity
E1	EWRKKSDDTTNAASTTFE	20	82-101	0.862	Non-allergen	-0.44 (Non-toxic)
E2	QTKTVNLRGT	10	103-112	1.052	Non-allergen	-0.58 (Non-toxic)
E3	HPRGEDHD	8	279-286	1.074	Non-allergen	-1.17 (Non-toxic)
E4	PSTSSTDT	8	306-313	0.5101	Non-allergen	-0.87 (Non-toxic)
E5	FNQIDSDKVYDDGAPP	16	1071-1086	-0.105	Non-allergen	-1.08 (Non-toxic)

Through this comparative screening using an antigenicity cutoff of 0.400, a clear hierarchy emerged among the valid candidates: E3 exhibited the highest score (1.074), followed closely by E2 (1.052), E1 (0.862), and E4 (0.5101). Notably, E1 and E2 are adjacent in the sequence, suggesting a highly dense antigenic region at residues 82–112.

Conversely, E5 was excluded due to a negative score (-0.105); despite its non-allergenic and non-toxic properties, a baseline antigenic capacity is mandatory for any candidate intended for vaccine or diagnostic applications (Dimitrov et al., 2014; Doytchinova & Flower, 2007; Rathore et al., 2024).

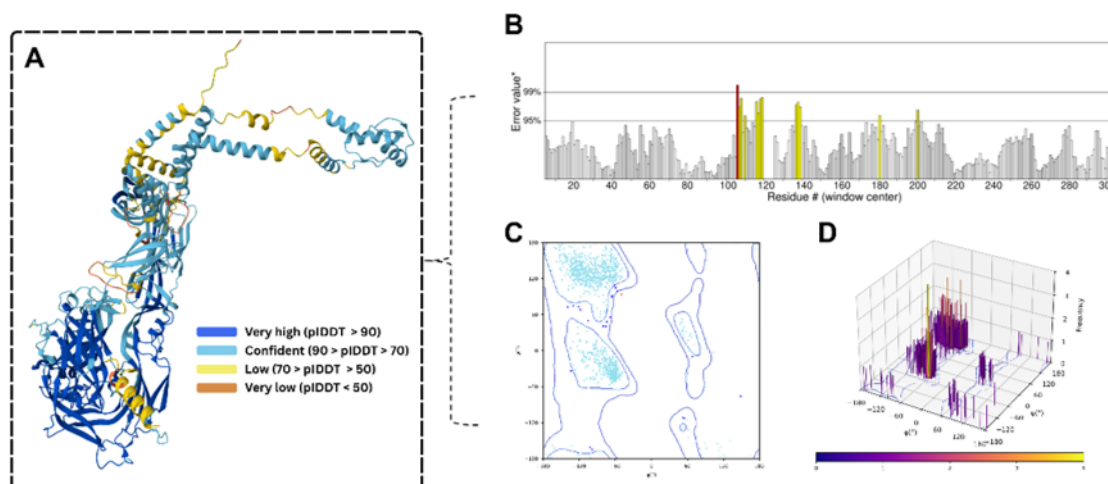


Figure 2. Predicted linear B-cell epitope score distribution across the ANDV glycoprotein sequence using a threshold value of 0.030.

The predicted and refined three-dimensional structure of the Andes virus glycoprotein was evaluated to determine whether the model possessed sufficient structural quality for subsequent epitope mapping, which serves as a crucial backbone verification process (**Figure 2**). This structural validation step is critical to verify the spatial orientation of the sequence, ensuring that down-stream analysis rests on a structurally sound model (Terwilliger et al., 2024; Varadi et al., 2022). The baseline refinement results and validation parameters confirm the structural integrity of the final model (Jumper et al., 2021). The refined three-dimensional structure of the Andes virus glycoprotein exhibited varying local confidence levels across different structural segments (**Figure 2A**). High-confidence regions correspond to residues with greater positional reliability, while lower-confidence regions are typically associated with flexible loops, terminal regions, intrinsically flexible segments, or structurally uncertain areas (Agarwal & McShan,

2024). In AlphaFold-based analyses, pLDDT values above 90 indicate very high-confidence regions, and values between 70 and 90 indicate confident backbone prediction (Varadi et al., 2022). However, pLDDT should be regarded as a local prediction-confidence metric rather than direct experimental evidence of the native biological conformation (Kovalevskiy et al., 2024). The Ramachandran plot revealed that 97.88% of residues were located in the favored region, with only 2.12% in other regions, indicating that most residues adopted energetically favorable backbone conformations. Since Ramachandran plot analysis evaluates phi (ϕ) and psi (ψ) backbone dihedral angles, a high proportion of residues in the favored region reflects good stereochemical quality (Laskowski et al., 2013). Thus, the 97.88% favored value demonstrates that the refined model possesses acceptable backbone geometry for further structural interpretation.

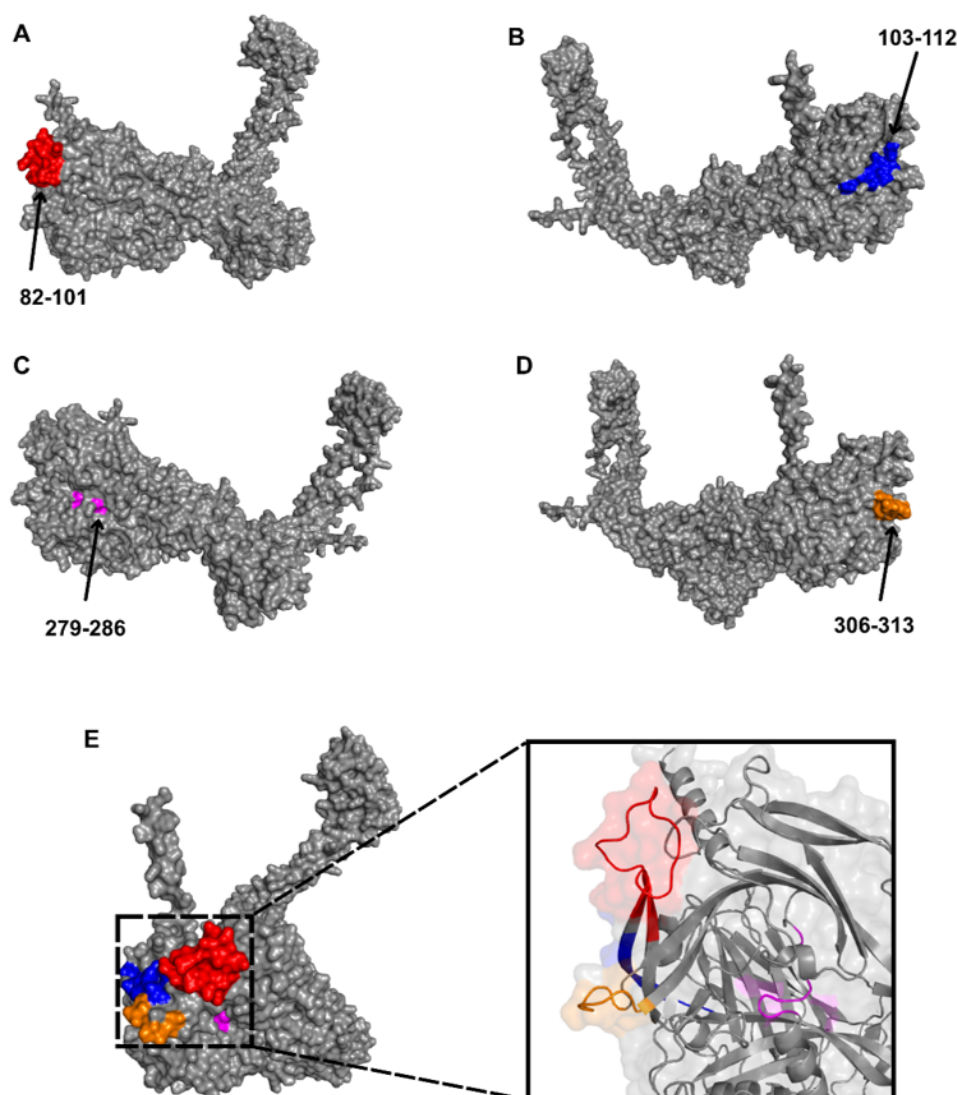


Figure 3. Mapping and visualization of selected linear B-cell epitope candidates on 3D ANDV glycoprotein model. E1 is shown at residues 82-101 (A), E2 at residues 103-112 (B), E3 at residues 279-286 (C), and E4 at residues 306-313 (D), combined localization of E1–E4 on the validated protein structure (E).

The ERRAT analysis yielded an overall quality score of 97.73, further supporting the reliability of the refined model. ERRAT evaluates protein structure quality by assessing non-bonded atom–atom interaction patterns, with higher scores indicating superior overall structural quality (Colovos & Yeates, 1993). A score above 95 is generally indicative of a good-quality model based on these interaction patterns. However, as a membrane-associated viral protein, the ANDV glycoprotein contains complex transmembrane domains and potential glycosylation sites that introduce inherent limitations to AlphaFold predictions compared to soluble proteins. Consequently, this model should be treated as a high-confidence structural hypothesis rather than

an absolute native conformation, necessitating a balanced interpretation during mapping (Agarwal & McShan, 2024; Kovalevskiy et al., 2024). Therefore, the validated 3D model is appropriate for mapping the selected linear B-cell epitope candidates, although experimental assays remain necessary to confirm antibody recognition and immunological relevance (Villanueva-Flores et al., 2025).

Mapping and visualization of the selected linear B-cell epitope candidates were conducted to assess their spatial distribution on the validated 3D structure of ANDV glycoprotein. Integrating structural context with primary sequence data is vital, as a candidate's biological relevance

depends heavily on its spatial accessibility within the folded glycoprotein (Choi & Kim, 2024; Riswana & Punjungsari, 2025). Four selected epitopes were successfully mapped onto the protein model, specifically E1 at residues 82–101, E2 at residues 103–112, E3 at residues 279–286, and E4 at residues 306–313 (**Figure 3**).

Structural visualization revealed a critical divergence between sequence scores and spatial reality: E1, E2, and E4 are clustered on the outer surface of the protein, which maximizes their biological availability for molecular interactions. The spatial proximity of E1 and E2 confirms that residues 82–112 form a highly exposed antigenic patch, making them premium choices for target design. E4 also remains structurally viable due to its external exposure, compensating for its lower initial screening score. In sharp contrast, E3 which yielded the highest sequence-based score is positioned internally within the folded glycoprotein. This structural burial represents a significant limitation, as internal residues are generally shielded from immune interaction unless exposed via major conformational shifts or denaturation (Potocnakova et al., 2016; Yao et al., 2013). This emphasizes that sequence-based values must always be filtered through structural localization data.

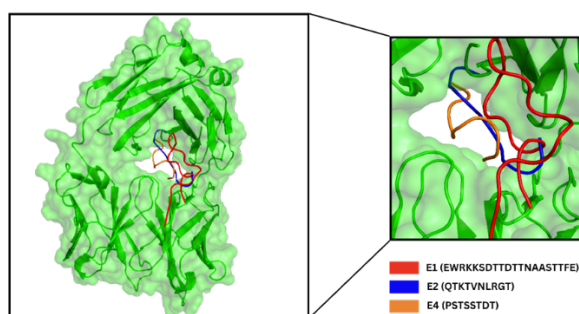


Figure 4. Molecular docking of prioritized linear B-cell epitopes with the B-cell receptor.

To complement the structural mapping analysis, the three prioritized surface-accessible epitopes, E1, E2, and E4, were further evaluated through molecular docking with the BCR structure using ClusPro 2.0, followed by binding free energy estimation using PRODIGY. The results showed that all three epitope-BCR complexes produced negative ΔG values, indicating favorable predicted interactions in the computational model (Riswana & Punjungsari, 2025; Xue et al., 2016). Among them, E1-BCR showed the most favorable binding free energy with a ΔG value of -10.0 kcal/mol, followed by E2-BCR at -9.4 kcal/mol

and E4-BCR at -9.1 kcal/mol. Therefore, the predicted affinity ranking was $E1 > E2 > E4$ (**Figure 4**).

The docking results were consistent with the previous antigenicity, safety, and structural mapping analyses. E1 and E2 had previously been prioritized because both fulfilled the antigenicity criterion, were predicted to be non-allergenic and non-toxic, and were localized on exposed regions of the ANDV glycoprotein surface. The stronger predicted binding affinity of E1 further supports its prioritization as the most promising candidate linear B-cell epitope. E4 also remained relevant because it showed acceptable antigenicity, favorable safety prediction, external structural localization, and a negative ΔG value in the docking analysis.

The relatively stronger ΔG value observed for E1 may be partly influenced by its longer peptide sequence, consisting of 20 amino acids, compared with E2 and E4, which consist of 10 and 8 amino acids, respectively. A longer peptide may provide a broader interaction interface and form more intermolecular contacts, which can influence the binding free energy estimated by PRODIGY. Therefore, the differences in ΔG values among E1, E2, and E4 should be interpreted as a relative computational ranking rather than definitive evidence of biological binding strength.

Overall, the integration of sequence-based epitope prediction, antigenicity and safety screening, structural mapping, and epitope-BCR docking consistently identified E1 as the strongest candidate for further investigation. E2 and E4 may be retained as additional candidates because both showed favorable predicted interactions with the BCR structure. However, these docking results should be considered complementary computational evidence and not direct confirmation of natural antibody recognition. In addition, because the predicted epitopes were derived from a single reference ANDV glycoprotein sequence, the present findings should not be interpreted as evidence of conservation across different ANDV isolates or circulating strains. Future studies should therefore include multiple sequence alignment and conservation profiling to evaluate the broader applicability of E1, E2, and E4. Experimental validation, including peptide-specific antibody-binding assays, ELISA, B-cell activation assays,

and neutralization studies, is still required to confirm the immunological relevance of the predicted epitopes.

Conclusion

This study identified and prioritized potential linear B-cell epitope candidates in the Andes virus glycoprotein through an integrated immunoinformatics approach involving sequence-based epitope prediction, antigenicity, allergenicity, and toxicity screening, three-dimensional structural mapping, and molecular docking with a B-cell receptor structure. Among the predicted epitopes, E1 (sequence: EWRKKSDTTDTTNAASTTFE), E2 (sequence: QTKTVNLRGT), and E4 (sequence: PSTSSTDT) fulfilled the antigenicity criterion, exhibited non-allergenic and non-toxic profiles, and were positioned on exposed regions of the glycoprotein surface, supporting their potential accessibility for antibody recognition. Molecular docking further strengthened this prioritization, with all three epitopes showing favorable predicted interactions with the B-cell receptor structure, as indicated by negative binding free energy values. E1 demonstrated the strongest predicted binding affinity with a ΔG value of -10.0 kcal/mol, followed by E2 at -9.4 kcal/mol and E4 at -9.1 kcal/mol. Overall, the combined computational evidence suggests that E1 represents the strongest candidate for further investigation, while E2 and E4 may be retained as additional candidate linear B-cell epitopes. Nevertheless, these findings remain preliminary and require further conservation analysis across multiple ANDV isolates, as well as experimental validation through peptide-specific antibody-binding assays, B-cell activation studies, and neutralization assays, to confirm their broader applicability, immunological relevance, and potential use in Andes virus vaccine-associated or diagnostic studies.

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Conflict of Interest Statement

The authors declare no conflict of interest.

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