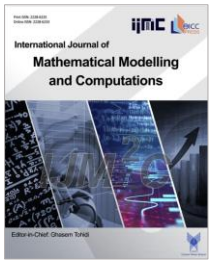

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Advanced Computational Design of Targeted Anticancer Peptides Using Docking, Molecular Dynamics and Deep Learning

Seyedeh Fatemeh Ahmadi[1], Hamidreza Samadikhah[1,2,*], Seyed Shahriar Arab[3]

[1]*Department of Biology, CT.C. Islamic Azad University, Tehran, Iran*

[2]*Department of Tissue Engineering and Regenerative Medicine Institute, Central Tehran Branch, Islamic Azad University, Tehran, Iran*

[3]*Center for Molecular Medicine, University of Georgia, Athens, USA*

***Corresponding author:** h.samadikhah.sci@iauctb.ac.ir

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Abstract

The computational design of peptides is increasingly employed in anticancer drug development, particularly by targeting protein–protein interactions (PPIs). In this study, we utilized structure-based modeling integrated with deep learning approaches, including AlphaFold, to accurately predict peptide structures. The anticancer peptides were designed as conjugates with cell-penetrating peptides (CPPs) to enhance cellular uptake.YASARA was used for structural inspection, and its FoldX plugin enabled the introduction of rational mutations and energy minimization. Chimera and AlphaFold were further employed for visualization and structural modeling of the anticancer peptides. The designed peptides were thoroughly evaluated using molecular docking, molecular dynamics (MD) simulations with GROMACS, and binding energy calculations via gmx_MMPBSA. Notably, the mutated peptide demonstrated a significantly improved binding affinity and structural stability compared to the non-mutated peptide, underscoring its potential therapeutic value. Despite the inherent computational complexity, our approach highlights the effectiveness of in silico peptide engineering for developing targeted anticancer therapeutics. Specifically, the designed peptide targets Survivin, a member of the inhibitor of apoptosis (IAP) family, which is frequently overexpressed in cancer cells and plays a critical role in tumor progression and therapy resistance.

Keywords: Computational peptide design, Anticancer peptide optimization, Molecular dynamics simulations, Protein-protein docking, Deep learning in structural biology, Mathematical modeling of Survivin inhibition, Binding free energy calculations (MM/PBSA).

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1. Introduction

The computational design of peptides has become a powerful tool in drug discovery, enabling the exploration of vast amino acid sequence spaces for the development of anticancer and antimicrobial agents [1][2]. Despite these advances, designing peptide inhibitors that specifically target protein–protein interactions (PPIs) remains a challenging and emerging area [3]. PPIs are fundamental to numerous biological processes, and their dysregulation

is often associated with diseases such as cancer. Therefore, modulating PPIs offers a promising therapeutic strategy. Two main computational approaches, structure-based and sequence-based methods [4], have been developed to design peptide inhibitors. These methods enable the rational engineering of peptides by identifying interaction interfaces, optimizing binding affinities, and evaluating structural stability [5]. In this study, we employ a structure-based design strategy utilizing AlphaFold deep learning algorithms [6] to model anticancer peptides targeting a specific protein: Survivin (BIRC5), a member of the inhibitor of apoptosis (IAP) family that plays a crucial role in cell division and cancer progression. Survivin's expression pattern is unique, being highly expressed during embryonic and fetal development but largely absent in normal, differentiated adult tissues [6][7][8][9][10]. However, it is markedly overexpressed in various human cancers, making it an attractive and selective therapeutic target [11][12][13].

This study follows a three-stage computational workflow. First, we analyze the three-dimensional structure of Survivin and its interaction interfaces using YASARA and Chimera. Second, peptides targeting functional Survivin regions involved in PPIs are designed. To enhance binding affinity, mutations are introduced using the FoldX plugin, based on energy calculations that include van der Waals, hydrogen bonding, electrostatics, and torsional strain. The $\Delta\Delta G$ value, reflecting changes in free energy, serves as a key criterion for predicting the structural stability of mutated peptides [14]. Third, to facilitate cellular uptake, a cell-penetrating peptide (CPP) containing arginine residues is conjugated to the N-terminus of the designed peptide.

The structure of this conjugate is modeled using I-TASSER, MODELLER, and AlphaFold. Final structures are selected based on superimposition with the Survivin surface. Peptides are then ranked by stability and affinity, with top candidates undergoing molecular docking via ClusPro, followed by molecular dynamics (MD) simulations for validation [15]. Docking studies predict optimal protein-peptide binding orientations and identify promising complexes based on energy scores and geometric fit [16]. Given the complexity of peptide folding and PPI interfaces, MD simulations capture the dynamic behavior of protein–peptide complexes under near-physiological conditions. These simulations, performed and allow detailed atomic tracking over time, considering solvation, pH, and ionic conditions [5][15][17].

1.1. Docking

Protein-protein interactions (PPIs) regulate numerous cellular functions, but understanding which proteins interact and how these interactions govern specific biological processes remains a major challenge. Modeling three-dimensional structures of protein-protein complexes at atomic resolution provides valuable insights into these interactions, which are critical for drug design, protein engineering, and systems biology. Docking methods simulate how proteins bind and interact by predicting optimal binding orientations and interfaces. In this study, we use the ClusPro web server, a widely used protein-protein docking tool that requires only two Protein data bank (PDB) files as input. Docking algorithms identify the most favorable binding sites and orientations based on energetic and geometric criteria, facilitating the prediction of stable complexes. Docking approaches can be categorized into macromolecule-small molecule and macromolecule-macromolecule docking [1] ClusPro offers both basic and advanced options, such as excluding flexible or unstructured protein regions, selecting specific protein chains, and retrieving structures using PDB IDs, thereby enhancing docking accuracy and flexibility.

1.2. Molecular Dynamics (MD) simulations

Understanding the mechanisms of protein-protein interactions, as well as the interactions between proteins and other biomolecules, presents a significant challenge in biology. While having an atomic-level structure by docking provides immense clarity and often reveals valuable insights into a biomolecule's functionality, it does not tell the whole story. Biomolecules are dynamic, with their atoms in constant motion, and their functions and interactions are deeply influenced by this dynamism. Instead of relying solely on a static view, scientists need to observe these molecules in action, manipulate them at the atomic scale, and study their responses to such changes. However, tracking individual atomic movements and precisely modifying them is a complex task[15][18][32]. A compelling alternative is to utilize computer simulations that model these biomolecules at the atomic level. MD simulations offer predictions about the movements of every atom in a protein or molecular system over time, based on the physical principles governing interatomic forces. These simulations enable researchers to investigate a broad range of biomolecular phenomena, such as conformational shifts, ligand binding, and protein folding, while providing detailed atomic positions with femtosecond-level temporal accuracy. Moreover, MD simulations allow predictions of how biomolecules respond at the atomic level to various perturbations, such as mutations, changes in phosphorylation or protonation states, or the presence or absence of ligands. These simulations are often used in conjunction with experimental methods in structural biology, such as x-ray crystallography, cryo-electron microscopy (cryo-EM), nuclear magnetic resonance (NMR), electron paramagnetic resonance (EPR), and Förster resonance energy transfer (FRET) [14][30]. In this study, MD simulations are conducted using GROMACS 2023. The simulation workflow includes energy minimization, pressure and temperature equilibration, and production runs. System stability is monitored via root mean square deviation (RMSD), radius of gyration (Rg). Binding free energies of protein-peptide complexes are evaluated using M/PBSAcalculations, providing quantitative insights into interaction strength (Table1).

2. Computational Methods

In this section, we have focused on the computation almethods of designing anticancer peptideswith greater

precision.

2.1. Peptide design

The initial step in designing an inhibitory peptide involved identifying key interface residues mediating interactions between Survivin and its protein partners. [25].

Table 1. Presenting the steps involved in MD simulation, including system preparation, energy minimization, equilibration, and data production, along with detailed descriptions for each step.

Steps in a GROMACS Simulation
System Preparation: Define molecular topology (bonds, angles, and parameters) and prepare initial structure files (Gro)
Energy Minimization: Reduce the system's initial energy using the Steepest Descent algorithm
Equilibration: Stabilize temperature and pressure using thermostats (Nose-Hoover) and barostats (Parrinello-Rahman).
Production Simulation: Perform long-term simulations to study system dynamics.
Result Analysis: Analyse trajectories, energies, radius of gyration, GROMACS, and gmx_MMPBSA interaction energy [28].

Crystal structures of Survivin in complex with other proteins (PDB IDs: 2QFA and 1E31) were used as templates. Binding interfaces were identified using the NCCFinder server, revealing a 14-residue segment as a candidate inhibitory peptide. To enhance the peptide's binding affinity, functional mutations were introduced using the FoldX plugin in YASARA software. A ΔΔG threshold of less than −1.0 kcal/mol was applied to define beneficial mutations [3].

Among the tested variants, a leucine-to-isoleucine substitution at a critical position (Leu 65 to Ile) showed the most favorable predicted stability. This approach allowed the prioritization of mutations likely to enhance binding energy without compromising structural integrity.

2.2. Homology modeling

Peptide 3D structure modeling was performed using the MODELLER software, the I-TASSER server, and AlphaFold2, implemented via Google Colab. The best model was chosen based on the lowest DOPE score and optimal folding characteristics. The structural quality and consistency of models were evaluated using Chimera software, with attention paid to potential limitations in flexible regions [24].

2.3. Cluspro docking

Docking of the peptides to Survivin was performed using the ClusPro server. **The interaction models were analyzed with LigPlot+ to identify key binding residues and interactions.** ClusPro's docking protocol includes: **Extensive Sampling:** 70,000 ligand rotations with translations across a 3D grid; best scores are retained.

- **Filtering and Clustering:** The top 1,000 docked poses are clustered based on 9 Å Cα RMSD; the densest clusters represent the most likely binding modes.
- **Scoring:** The ClusPro scoring function combines van der Waals repulsion/attraction, electrostatics, and desolvation energy.
- **Model Selection:** Final models are ranked by **cluster population, not energy scores**, as entropic factors are not included.

The top-ranked cluster centers were selected as representative binding poses for further dynamic analysis [1][7][17][21][27] .

2.4. Molecular Dynamics simulations using GROMACS

To evaluate the dynamic stability of the protein–peptide complex, MD simulations were conducted using GROMACS 2023 with the CHARMM27 force field. The system was solvated in a cubic box with water molecules, and neutralizing ions were added. After energy minimization, the system was equilibrated under NVT and NPT conditions at 300 K and 1 atm for 100 ps each. A 100-nanosecond production run was then performed. Trajectory analysis included assessment of structural stability via RMSD and compactness via the radius of gyration. Protein–peptide interactions were further examined using the gmx_MMPBSA tool and the GROMACS protein–ligand interaction module, with results visualized through YASARA. The 100 ns simulation duration was selected based on prior studies indicating this timeframe is sufficient to observe convergence and assess interaction stability. RMSD plots confirmed structural stabilization after 10 ns, supporting the validity of the simulation results. It is important to note that computational models are inherently limited by the accuracy of the force fields and sampling time. The results should therefore be interpreted within the context of these constraints [13][18][31] .
Governing Equations of MD simulations solve Newton's equations of motion for atomic systems:

$$m_i \frac{d^2 r_i}{dt^2} = F_i$$

Forces are derived from the gradient of the potential energy:
$F_i = -\nabla_{r_i} U(r_1, r_2, \ldots, r_N)$

The potential energy U is divided into bonded and non-bonded interactions:

$$U = U_{\text{bonded}} + U_{\text{non-bonded}}$$

Bonds

$$U_{\text{bond}} = \sum_{\text{bonds}} k_b(r - r_0)^2$$

Angles

$$U_{\text{angle}} = \sum_{\text{angles}} k_\theta(\theta - \theta_0)^2$$

Dihedrals

$$U_{\text{dihedral}} = \sum_{\text{dihedrals}} \frac{1}{2} V_n[1 + \cos(n\phi - \gamma)]$$

Electrostatic

$$U_{\text{coulomb}} = \sum_{i<j} \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}}$$

Van der Waals (Lennard-Jones Potential)

$$U_{\text{LJ}} = \sum_{i<j} 4\epsilon \left[\left(\frac{\sigma}{r_{ij}} \right)^{12} - \left(\frac{\sigma}{r_{ij}} \right)^{6} \right]$$

2.4. Numerical Integration of Equations

The equations of motion are solved using numerical methods like the Verlet Algorithm

$$r(t + \Delta t) = 2r(t) - r(t - \Delta t) + \frac{F(t)}{m} \Delta t^2$$

3. Results

3.1. Peptide design

Based on the affinity data of the NCCFinder server (Fig1), an inhibitory peptide targeting the 90-100 region of the Survivin protein was designed. This region was chosen due to its significant interactions with other binding partners, suggesting its potential as a therapeutic target for disrupting protein-protein interactions.

3.2. Homology modeling

The results of peptide modeling using AlphaFold, a deep learning–based model, demonstrated superior accuracy compared to MODELLER and I-TASSER in predicting peptide structures. AlphaFold consistently provided more precise models with better alignment to experimental data, highlighting the power of deep learning in structural biology (Fig 2).

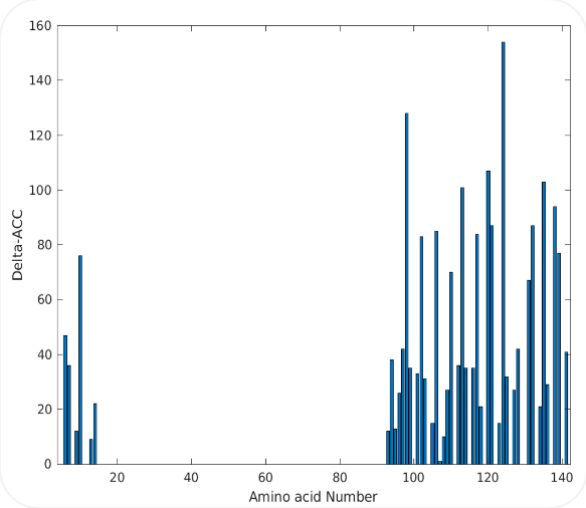

Figure1. Affinity diagram of the Survivin protein binding to other proteins, generated using the NCC-Finder server. This diagram illustrates the interactions between Survivin and its binding partners, highlighting the affinity strength and potential functional relationships.

3.3. Docking

Molecular docking analysis reveals that the peptides interact with the protein's common residues, obtaining a high score in cluster 0. As shown in Fig 3 and Table 2, the mutated peptide disrupts the functional region of the Survivin protein with a higher binding affinity compared to the non-mutated peptide.

3.4. MD simulations

3.4.1. *System equilibration*

The systems were equilibrated in NVT and NPT ensembles (each for 100 ps) at 300 K and 1 bar before the MD simulations were run, with electrostatic interactions calculated using the PME method (Fig 4).

3.4.2. *MD simulations product analysis*

Molecular dynamics simulations revealed that the mutated peptide, based on the RMSD (Fig 5), radius of gyration (Fig 6), GROMACS interaction energy analyses (Fig 7), and gmx_MMPBSA analysis (Table3), exhibited a higher binding affinity compared to the non-mutated protein-peptide throughout the 100-nanosecond simulation. Furthermore, the system's structure remained stable and properly folded during the simulation.

This included the use of the NVT ensemble (constant number of particles, volume, and temperature), where the temperature is maintained by a thermostat while the volume remains fixed, and the NPT ensemble (constant

Figure2.Structure of the non-mutated (cyan) and mutated peptides (purple) modeled by AlphaFold2

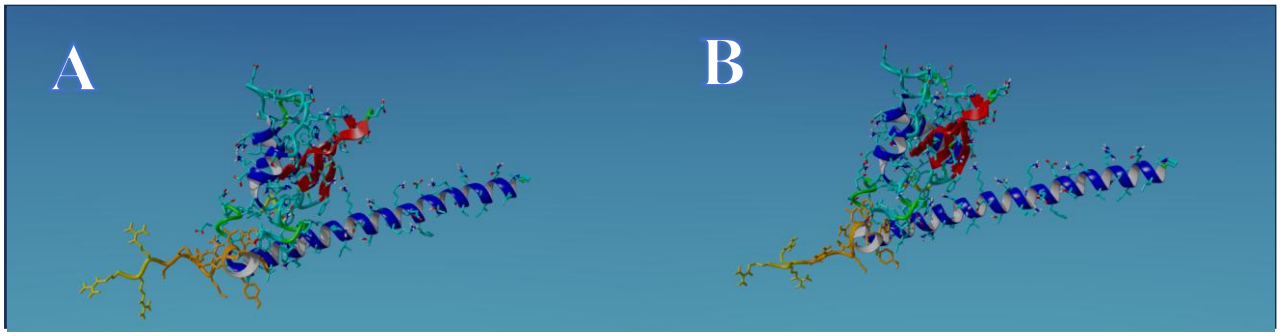

Figure 3. Illustration of the molecular docking process showing the binding of (A)a non-mutated peptide (orange) to the functional site of Survivin protein (blue), alongside (B) the binding of a mutated peptide(orange) to the functional site of Survivin protein(blue). In both cases, a cell-penetrating peptide (yellow) is conjugated as a tail to facilitate cell penetration. This tail does not participate in the binding interactions.

Table 2. The docking analysis results of the Survivin protein with the non-mutated peptide (A) and the Survivin protein with the mutated peptide (B) are displayed according to the scoring values.

A				B			
Cluster	Members	Representative	Weighted Score	Cluster	Members	Representative	Weighted Score
0	298	Center	-663.6	0	314	Center	-743.3
		Lowest Energy	-764.7			Lowest Energy	-784.7
1	233	Center	-721.1	1	279	Center	-723.5
		Lowest Energy	-735.6			Lowest Energy	-787.0
2	127	Center	-680.6	2	259	Center	-707.6
		Lowest Energy	-765.4			Lowest Energy	-786.1

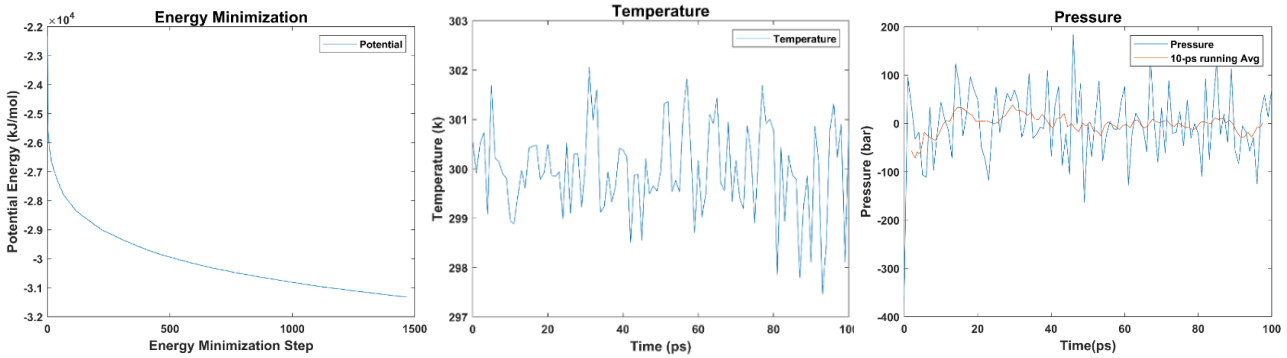

Figure 4. The parameters of potential energy, temperature, and pressure were carefully adjusted during the final stages of the MD simulations, specifically during the energy minimization process.

number of particles, pressure, and temperature), where pressure is regulated using a barostat, ensuring the system reaches thermodynamic equilibrium before proceeding with further simulation steps.

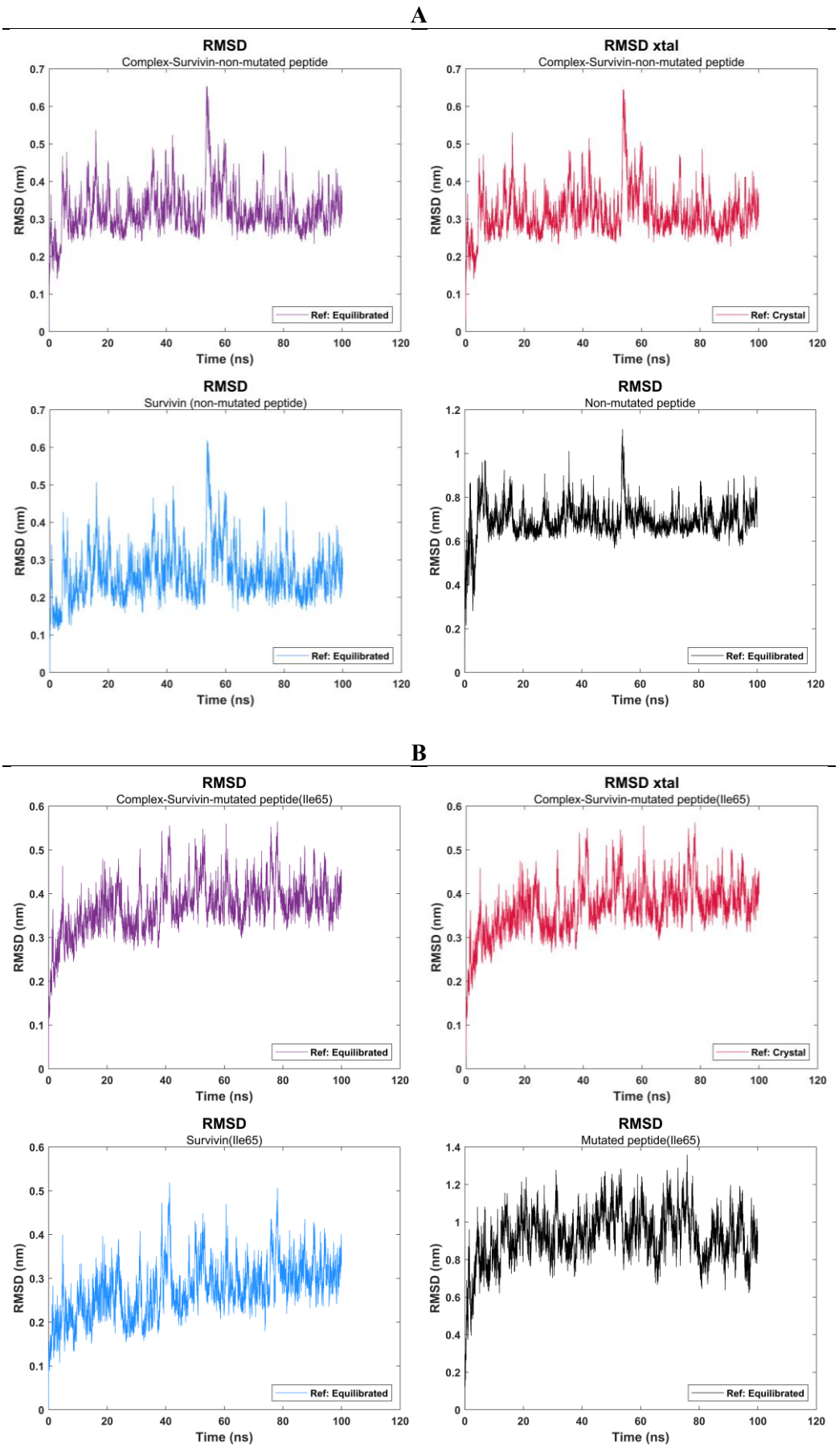

Figure 5. RMSD analysis was performed on (A) the Survivin–non-mutated peptide system, (B) the Survivin–mutated peptide system. Purple plots represent the RMSD of the Survivin–peptide systems, while the red plots indicate the RMSD of the crystal structure (xtal), i.e., the structure before simulation. The blue plots show the RMSD of the Survivin protein, and the black plots correspond to the RMSD of the peptides. The similar fluctuation patterns suggest stable binding and overall structural stability within the systems.

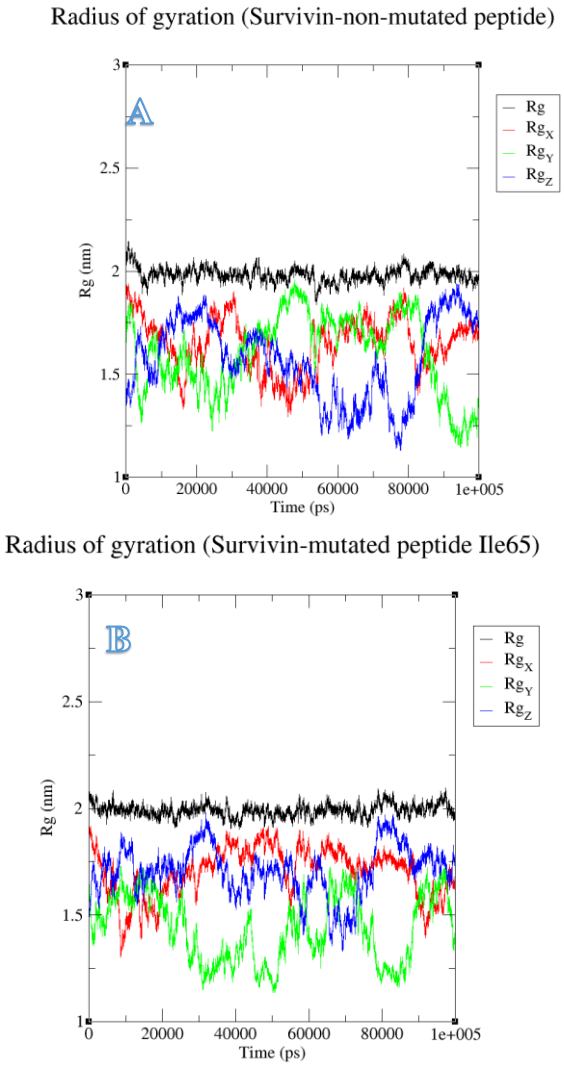

Figure 6. Radius of gyration analysis indicated that the folding and stability of the protein and peptide remained unchanged upon binding. The results show that both systems maintained a stable structure throughout the simulation. The radius of gyration was calculated as the average of the X (yellow), Y (green), and Z (red) dimensions, with the overall value represented in black. As shown, the Rg fluctuated within a very narrow range, suggesting structural stability. (A) The Survivin–non-mutated peptide complex; (B) the Survivin–mutated peptide system.

4. Conclusion and discussions

The anticancer peptide designed in this study demonstrated a high binding affinity for the target protein, effectively inhibiting its cancer-related functions, as confirmed through bioinformatics analyses[23][26][29]. These results provide strong evidence that the mutated peptide, developed using advanced bioinformatics techniques, has significant potential as a novel and effective targeted cancer therapy. The use of advanced bioinformatics tools such as YASARA, Chimera, AlphaFold, ClusPro, and GROMACS, along with interaction energy calculations, enabled an in-depth investigation of protein-peptide interactions at the molecular level. Notably, molecular docking revealed an improved binding free energy score of approximately -743.3 kcal/mol, and an increased number of interactions in the Survivin-mutated peptide complex compared to the non-mutated counterpart. This indicates a stronger and more favorable interaction between Survivin and the mutated peptide. During the 100-nanosecond simulation, RMSD and Rg analyses showed that the systems remained stable and the peptides did not dissociate from Survivin. Additionally, the peptide binding did not induce significant conformational changes in Survivin during the simulation, suggesting proper folding and stability.

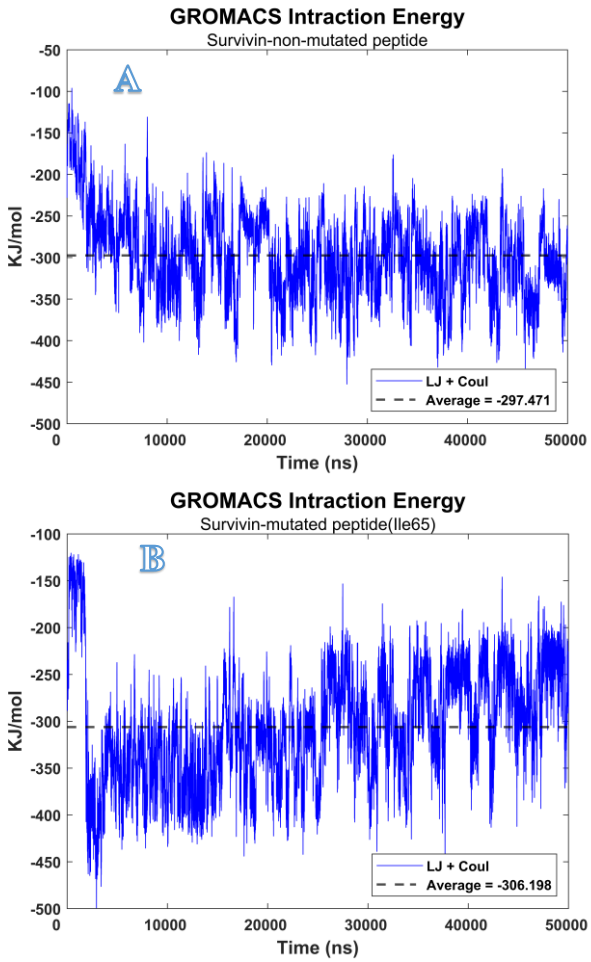

Figure 7. The average Coulombic interaction energy and Lennard-Jones interaction energy were calculated using protein–ligand analysis in GROMACS. (A) Interaction energy values of the Survivin–non-mutated peptide system. (B) Interaction energy values of the Survivin–mutated peptide system.

The mutated peptide maintained a stable structure and proper folding based on RMSD and Rg analyses, indicating its potential for reliable and sustained therapeutic application. Further analysis confirmed that the protein and peptide structures remained stable after binding, with no major structural alterations that could compromise function. Interaction energy calculations using GROMACS and gmx_MMPBSA, including electrostatic and van der Waals contributions, demonstrated that the binding affinity of the mutated protein–peptide system was superior to that of the non-mutated counterpart. The total interaction energy, as calculated by GROMACS, showed improvements in both Lennard-Jones and Coulomb energies, with a combined value of -306.198 kJ/mol, -8.727 kJ/mol better than that of the non-mutated Survivin–peptide system. Similarly, gmx_MMPBSA analysis revealed enhancements in van der Waals, electrostatic,

desolvation, and total interaction energies, with a total binding energy of -51.30 kJ/mol, which is -23.29 kJ/mol more favorable.

Table 3. gmx MMPBSA analysis. Free energy calculations were performed for two separate simulations using GROMACS-generated files. Input structures were prepared using both the Poisson–Boltzmann (PB) and Generalized Born (GB) approaches. Subsequently, interaction energies, including van der Waals, electrostatic, desolvation, and total contributions, were determined for each system. A summary of the binding affinities between protein and peptide complexes is provided in Table 3. Energy KJ/mol)

System	Total interaction	Van der Waals	Electrostatic	Desolvation
Survivin-non-mutated peptide	−28.01	−31.53	-229.60	233.12
Survivin-mutated peptide (Ile65)	−53.77	−5130	-378.16	375.69

These findings further highlight the mutated complex's enhanced potential as an effective therapeutic agent. This study not only identifies a novel anticancer peptide with promising therapeutic potential but also underscores the value of computational approaches in drug design and cancer therapy development. Utilizing advanced computational tools, we optimized the peptide structure and predicted its behavior within biological systems with high precision. Nevertheless, certain limitations must be acknowledged, such as the assumption of receptor rigidity and the simplified representation of the cellular environment inherent in molecular dynamics simulations. These constraints may impact the direct applicability of the computational results to real biological systems. Consequently, future research should focus on experimental validation, through laboratory-based binding assays and cell-based studies, to confirm the peptide's biological efficacy and safety. These findings provide a strong foundation for further experimental studies and potential clinical development, offering a promising path toward more effective and targeted cancer treatments. Furthermore, the results highlight the increasing significance of bioinformatics and computational modeling in modern biomedical research, paving the way for innovation and personalized therapies for cancer patients in the near future.

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Authors Contribution
All the authors have participated sufficiently in the intellectual content, conception and design of this work or the analysis and interpretation of the data (when applicable), as well as the writing of the manuscript.

Availability of data and materials
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Conflict of interests
The author states that there is no conflict of interest.

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