SCREENING OF POTENTIAL ANTIMICROBIAL PEPTIDES FOR CYSTIC FIBROSIS USING NETWORK AND DYNAMIC STUDIES

A PROJECT REPORT

Submitted by

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ABSTRACT

Cystic Fibrosis (CF) is a severe autosomal recessive disorder caused by mutations in the CFTR gene, primarily the ΔF508 mutation, resulting in dysfunctional chloride and bicarbonate ion transport. This leads to thick mucus accumulation, chronic inflammation, and persistent bacterial infections—mainly by *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The biofilm-forming nature of these pathogens limits antibiotic effectiveness, necessitating alternative therapies. This study explores Antimicrobial Peptides (AMPs) as potential therapeutic agents due to their broad-spectrum activity, biofilm disruption, and possible CFTR-modulating capabilities. Using a computational pipeline, key CF-related regulatory genes were identified via UniProt and analyzed through STRING and Cytoscape to construct PPI networks. Centrality analysis confirmed CFTR as a crucial hub. Ten AMPs from the APD3 database were screened based on hemolytic activity, toxicity, biofilm activity, length, and antimicrobial potency. Scolopendin 2 emerged as top candidate. Molecular docking revealed strong binding affinities and interactions with key CFTR residues. Subsequent 100 ns molecular dynamics simulations evaluated the stability of AMP–CFTR complexes under physiological conditions. Analyses including RMSD, RMSF, Rg, hydrogen bonding, potential energy and SASA indicated superior structural stability and consistent binding. This study presents a comprehensive in silico framework for identifying AMP-based therapeutics against CF and proposes Scolopendin 2 as a promising candidate for modulating CFTR function. Further experimental validation is recommended to translate these findings into viable treatments.

Keywords: Antimicrobial Peptides, Biofilm Disruption, Computational Drug Discovery, Cystic Fibrosis, CFTR Protein, Molecular Dynamics Simulations, Network Pharmacology.

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LIST OF SYMBOLS AND ABBREVIATIONS

°	Degree
ns	Nanosecond
%	Percentage
M	Molarity
kJ/mol	kiloJoule per mole
kcal/mol	kilocalorie per mole
Å	Angstrom
nm	Nanometer
nm^2	Nanometer square
CF	Cystic Fibrosis
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
AMPs	Anti-Microbial Peptides
MD	Molecular Dynamics
MRD	Multi-Drug Resistance
STRING	Search Tool for the Retrieval of Interacting Genes/Proteins
PPI	Protein-Protein Interactions
APD3	Antimicrobial Peptide Database
CAMPR3	Collection of Antimicrobial Peptides Resource – Version 3
dPABBs	Design Peptide Against Bacterial Bio-films
dBAASP	Database of Antimicrobial Activity and Structure of Peptides
HPC	High-Performance Computing

PME	Particle Mesh Ewald method
LC-MS	Liquid Chromatography-Mass Spectrometry
PDB	Protein Data Bank
RCSB	Research Collaboratory for Structural Bioinformatics
SDG	Sustainable Development Goals
SWISS	Swiss Modeling of Integrated Structural Systems
TASSER	Threading ASSEmbly Refinement
SCFBio	Supercomputing Facility for Bioinformatics and Computational Biology
GROMACS	GROningen MAchine for Chemical Simulations
CHARMM	Chemistry at HARvard Macromolecular Mechanics
AMBER	Assisted Model Building with Energy Refinement
ACPYPE	Antechamber PYthon Parser Interface
TIP3P	Transferable Intermolecular Potential with 3 Points
RMSD	Root Mean Square Deviation
RMSF	Root Mean Square Fluctuation
Rg	Radius of Gyration
SASA	Solvent Accessible Surface Area

1. INTRODUCTION

1.1 Cystic Fibrosis

Cystic Fibrosis (CF) is a life-threatening, autosomal recessive genetic disorder that significantly impacts multiple organ systems, most notably the respiratory and digestive tracts. The disease results from mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene, which encodes a membrane protein functioning as a chloride and bicarbonate ion channel in epithelial cells. The most common mutation, ΔF508, leads to a misfolded CFTR protein that is degraded prematurely and fails to reach the cell surface. This deficiency disrupts ion and water homeostasis, resulting in the production of thick, sticky mucus that clogs airways, pancreatic ducts, and other passageways. In the lungs, this viscous mucus impairs mucociliary clearance, creating a favourable environment for persistent bacterial infections and chronic inflammation. Over time, these infections lead to progressive lung damage, bronchiectasis, and respiratory failure, which are the primary causes of morbidity and mortality in CF patients. The digestive system is also severely affected, with mucus-induced blockages in the pancreas hindering enzyme secretion and leading to malnutrition and growth issues. While advances in therapy have improved life expectancy, CF remains a serious and incurable condition, necessitating ongoing research into novel therapeutic approaches that target the underlying molecular and microbial mechanisms of the disease (Terlizzi and Lopes-Pacheco, 2025).

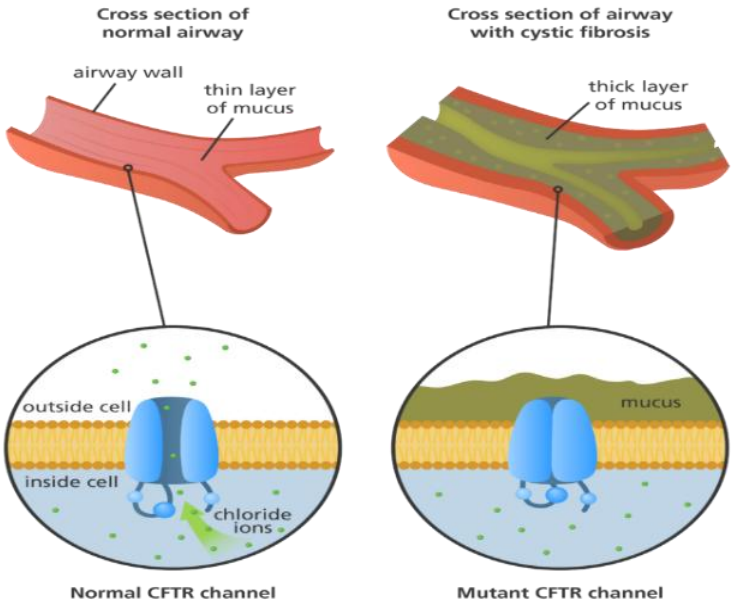


Figure 1.1 Comparison of Normal and Cystic Fibrosis Airway Epithelia Showing CFTR Channel Function

1.2. Pathogenesis and role of Biofilm

In CF, the defective CFTR protein leads to the accumulation of dehydrated, thick mucus in the airways, which impairs mucociliary clearance and creates an ideal environment for bacterial colonization. Opportunistic pathogens such as *Pseudomonas aeruginosa* and *Staphylococcus aureus* frequently infect CF lungs and form biofilms structured microbial communities encased in a self-produced extracellular polymeric matrix. Biofilm formation is a key factor in CF pathogenesis, as it protects bacteria from host immune responses and significantly reduces antibiotic efficacy. This leads to persistent, chronic infections that are difficult to eradicate. Over time, the inflammatory response to these infections results in tissue damage, airway obstruction, and a progressive decline in pulmonary function. The biofilm-mediated resistance to treatment poses a major clinical challenge in CF management. Understanding the role of biofilms is critical to developing new therapies that can effectively penetrate the biofilm barrier and clear bacterial infections in CF patients (Power, 2025).

1.3. Antimicrobial Peptides

The growing threat of antibiotic resistance has intensified the need for alternative therapeutic strategies, particularly in treating chronic and biofilm-associated infections. Antimicrobial peptides (AMPs) have emerged as promising candidates due to their broad-spectrum activity, rapid bactericidal mechanisms, and ability to disrupt biofilms. Unlike conventional antibiotics, AMPs target microbial membranes, reducing the likelihood of resistance development. Their immunomodulatory and anti-inflammatory properties further enhance their therapeutic value, especially in conditions involving persistent infections and inflammation, such as CF. In CF, recurrent lung infections caused by multidrug-resistant bacteria like *Pseudomonas aeruginosa* severely impact patient health and quality of life. AMPs can overcome the limitations of traditional antibiotics by breaking down biofilms and reducing bacterial colonization. Additionally, some AMPs are being explored for their potential to stabilize or modulate host proteins, offering therapeutic benefits beyond antimicrobial action. Thus, AMPs represent a powerful next-generation approach in the treatment of complex infectious diseases (Jouault et al., 2025).

1.4. Mechanism of AMP

AMPs primarily kill microbes by disrupting their cell membranes. Being cationic and amphipathic, AMPs bind to negatively charged microbial membranes, forming pores or disrupting the lipid bilayer, causing cell lysis. Some AMPs act through non-membranolytic mechanisms by targeting intracellular components like DNA, RNA, or enzymes. In addition to their antimicrobial effects, certain AMPs inhibit biofilm formation, modulate immune responses, and aid in wound healing. These combined actions make them highly effective, especially against resistant pathogens and chronic infections seen in Cystic Fibrosis, offering a promising alternative to traditional antibiotics (Miao et al., 2025).

- ❖ Binding to Membrane
- ❖ Membrane Disruption
- ❖ Non-Membranolytic Effects
- ❖ Biofilm Inhibition and distrubtion

1.5. Importance of Computational Drug Discovery

Computational drug discovery has transformed the early stages of therapeutic development by enabling the rapid screening and in-depth analysis of potential drug candidates. In the context of CF, in silico approaches such as network pharmacology, molecular docking, and molecular dynamics (MD) simulations are instrumental in understanding disease mechanisms and predicting drug-target interactions. These tools not only accelerate the discovery process but also provide detailed molecular insights into the stability, binding affinity, and functional impact of compounds like AMPs. By reducing experimental time and cost, computational techniques facilitate the design of more effective and targeted therapies for CF. Such approaches offer a rational framework for the enhancing the precision and efficacy of therapeutic interventions in CF patients (Caputa et al., 2025).

1.6. Role of Network Pharmacology in Target Drug Discovery

Network pharmacology represents a paradigm shift in drug discovery, focusing on multi-target interactions rather than the classical single-target approach. This systems-level strategy is particularly suited to complex diseases like CF, which involve multiple genes, proteins, and signaling pathways. Network pharmacology integrates data from genomics, proteomics, and bioinformatics to identify key nodes and interactions within biological networks, offering a deeper understanding of disease mechanisms and potential therapeutic targets. By constructing interaction networks and identifying central regulatory molecules, it allows researchers to predict drug actions more accurately and design therapies that can modulate multiple components of a disease simultaneously. This approach is especially critical in CF,

where single-drug treatments often fall short due to the involvement of multiple pathogenic factors, including chronic infections, inflammation, and ion transport dysfunction. Network pharmacology helps in discovering candidate drugs that can synergistically target interconnected pathways, enhancing therapeutic efficacy and minimizing resistance or side effects (Al Madhagi and Nassar, 2025).

1.6.1. Concept of Network Pharmacology

Network pharmacology combines systems biology, bioinformatics, and pharmacology concepts to explore how drugs affect complex biological networks. Contrary to classical drug discovery methods that aim at a specific protein or gene, network pharmacology aims to comprehend and take advantage of interconnectedness in molecular interactions within a disease network. It also believes that diseases are generally not due to a single gene mutation, but by disturbances of complex biological networks. Thus, acting on multiple nodes or pathways at once can provide greater therapeutic benefit. In this paradigm, drugs are not just screened for direct binding to a target but also assessed for their impact on the global network behavior. This is especially beneficial for diseases with multifactorial causes, such as cystic fibrosis, cancer, and neurodegenerative disease. By taking into account off-target effects, compensatory mechanisms, and drug repositioning potential, network pharmacology offers a more predictive and integrated strategy for drug development (Yang et al., 2025).

1.6.2. Protein-Protein Interaction Networks

Protein-Protein Interaction (PPI) networks play a central role in network pharmacology, offering a comprehensive view of how proteins interact within a cell to perform biological functions. In these networks, nodes represent proteins, and edges represent physical or functional interactions between them. Constructing PPI networks helps identify key proteins involved in disease pathways and reveals how they influence one another. Tools like STRING, Cytoscape, and BioGRID are

commonly used to generate and analyze these interaction maps. In the context of drug discovery, PPI networks allow for the identification of crucial proteins that, when targeted, can impact multiple downstream processes. These proteins often represent promising drug targets. In diseases like cystic fibrosis, where multiple signaling cascades are disrupted, understanding the PPI network can help pinpoint central regulators of disease progression, such as CFTR and its interacting partners. This knowledge can guide the selection of therapeutics that exert system-wide effects rather than limited, single-pathway actions (Rodrigues, 2025).

1.6.3. Hub Gene Identification in CF

Hub gene identification is a critical step in network pharmacology, as hub genes are highly connected nodes in a PPI network and often play vital regulatory roles in cellular processes. In the context of cystic fibrosis, identifying hub genes helps in understanding which genes contribute most significantly to disease pathology and are most likely to influence multiple biological pathways. Tools like CytoHubba, a Cytoscape plugin, enable the identification of hub genes using various centrality measures (e.g., degree, betweenness, closeness). In CF-related studies, CFTR consistently emerges as a major hub due to its key role in ion transport and epithelial homeostasis. Other associated hub genes may include inflammatory mediators, transcription factors, and immune-related proteins. Targeting such hub genes offers an opportunity to modulate multiple pathological effects with a single therapeutic strategy. Identifying and validating these hub genes lays the groundwork for developing targeted therapies, especially peptide-based drugs or small molecules, tailored for CF treatment (Sahrawat, 2025).

1.7. Screening Approaches for AMP

AMPs are considered promising alternatives for treating chronic infections associated with CF, particularly due to their ability to target biofilm-forming pathogens like *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The screening

of AMPs involves both experimental and computational methods. Experimental approaches typically include high-throughput screening using antimicrobial assays, which allow the identification of peptides with potent antimicrobial activity. Techniques such as liquid chromatography-mass spectrometry (LC-MS) and SPOT synthesis are employed to detect peptides' efficacy and bioactivity. Computational screening, on the other hand, utilizes bioinformatics tools that predict AMP properties such as antimicrobial potency, toxicity, and biofilm disruption ability, helping to filter out peptides with undesirable characteristics. By combining these approaches, researchers can expedite the discovery of effective AMPs, which is crucial for the development of new therapies targeting CF-related pathogens (Wang et al., 2025).

1.8. In-Silico binding affinity assessment of AMPs using Molecular Docking and structure finding

In-silico approaches have become vital tools in the early stages of drug discovery, particularly for evaluating the interaction between therapeutic candidates and biological targets. Among these, AMPs are gaining attention for their broad-spectrum activity and minimal resistance development. Molecular docking and structural modeling play a central role in predicting how well these peptides can bind to their intended targets, thereby offering insights into their therapeutic potential. This section outlines the computational techniques used to assess binding affinity and model 3D structures of AMPs (Bakare et al., 2021).

1.8.1. Principles of Molecular Docking

The primary principle of molecular docking is to predict how a ligand, such as an antimicrobial peptide, interacts with a receptor protein. Scoring functions, which are integral to the docking process, assess the binding affinity by calculating how well the ligand fits into the receptor’s binding site. These functions consider both enthalpic and entropic contributions, providing an overall energy score. Search algorithms help explore different docking poses to identify the most favourable configuration.

Additionally, flexibility considerations are important, as both the peptide and the target protein may undergo conformational changes during the binding process. These principles enable a more accurate prediction of peptide efficacy in targeting proteins associated with cystic fibrosis (Eddhimi et al., 2025).

1.8.2. Binding affinity and docking score interpretation

Binding affinity quantifies the strength of the interaction between AMPs and target proteins, expressed in kcal/mol. Docking software like AutoDock Vina (https://autodock.scripps.edu/) calculates these scores based on empirical scoring functions that simulate molecular interactions. A more negative score generally indicates better binding potential. These values are crucial for prioritizing candidates before deeper analysis (Ayub et al., 2025).

1.8.3. Retrieval of CF-associated protein structure

A critical step in molecular docking is the retrieval of high-quality 3D structures of target proteins associated with CF, such as the CFTR protein. Structures of CF-related proteins can be accessed from databases like the Protein Data Bank (PDB) (https://www.rcsb.org/), which provides experimentally determined protein structures. In cases where no experimentally resolved structure is available, homology modeling techniques can be used to predict the protein structure based on known sequences of similar proteins. Tools such as SWISS-MODEL (https://swissmodel.expasy.org/). These 3D structures are then employed in docking simulations to evaluate the binding interactions between peptides and CF-related targets, enabling the design of targeted therapeutic strategies for CF (Mansour et al., 2025).

1.8.4. 3D structure modelling of AMPs

Three-dimensional (3D) structure modeling is crucial for understanding the interaction between AMPs and target proteins. The process typically involves using

computational techniques such as homology modeling or ab initio prediction to generate the 3D structures of peptides. For peptide modeling, online tools like **AlphaFold** (https://alphafold.ebi.ac.uk/) and **I-TASSER** (https://zhanggroup.org/I-TASSER/) are commonly used to generate accurate 3D structures based on deep learning and threading algorithms. These models are then utilized in molecular docking studies to assess the peptides' binding affinity and stability when interacting with target proteins like CFTR. The quality of the 3D model significantly influences the reliability of docking predictions, highlighting the importance of accurate structural representation in the drug discovery process. By incorporating these models into in silico studies, researchers can identify promising AMPs with high therapeutic potential for CF (Anurag Anand et al.).

1.9. Molecular Dynamic Simulation in AMP evaluation

MD simulation provides a time-resolved view of molecular interactions, allowing researchers to study how AMPs behave when bound to their target proteins under conditions that mimic a real biological environment. This technique helps go beyond the static snapshots offered by docking by revealing dynamic features like molecular motion, structural flexibility, and interaction stability. When evaluating AMPs as therapeutic candidates, MD simulations are essential for determining whether the initial binding observed in docking studies remains stable and biologically relevant over time. These insights help in filtering out weak or unstable binders early, thereby streamlining the drug discovery pipeline and increasing confidence in selected AMP candidates for further testing (Dermawan and Alotaiq, 2025).

1.9.1. Principles of Molecular dynamics

MD simulation is a powerful computational method that helps visualize how atoms and molecules move and interact over time. Based on Newton’s laws of motion, this technique shows the natural behavior of biomolecular systems under

near-physiological conditions. In the context of AMP research, MD simulations allow us to explore how peptides interact with their protein targets beyond static snapshots. It provides a dynamic understanding of structural flexibility, conformational shifts, and the stability of complexes. To achieve this, force fields like CHARMM or AMBER are used these are mathematical models that define how atoms attract or repel each other. The system, typically composed of the target protein, peptide, water molecules, and ions, is simulated in a box over nanoseconds to microseconds. This allows researchers to predict how stable or effective a peptide might be when bound to its target, offering deeper insight than docking alone can provide (Blanchet et al., 2025).

1.9.2. Evaluating the stability of Target-AMP complex

MD simulations are vital for understanding how stable and effective an AMP is when bound to a protein target over time. Unlike docking studies that offer only a static prediction, MD simulations provide a dynamic and time-resolved picture of molecular interactions under near-physiological conditions. To evaluate this stability, several key parameters are analyzed—Root Mean Square Deviation (RMSD) helps track how much the structure deviates from its original form, Root Mean Square Fluctuation (RMSF) highlights flexible or unstable regions at the residue level, and Radius of Gyration (Rg) measures the compactness of the overall complex. A consistently stable RMSD and minimal fluctuations in RMSF and Rg typically indicate strong, stable binding between the AMP and its target. This level of detailed assessment supports the therapeutic relevance of the peptide and strengthens confidence in its potential as a drug candidate (Zhao et al., 2024).

1.10. Aim

The primary aim of this research is to computationally identify and evaluate potential AMPs that can interact with and stabilize the target, offering an innovative therapeutic approach to combat chronic infections and underlying molecular

dysfunctions associated with Cystic Fibrosis.

1.11. Objectives

- To analyze CF-associated regulatory genes using UniProt, STRING, and Cytoscape to build PPI networks.
- To select AMPs from the APD3 database based on criteria like hemolytic activity, toxicity, and biofilm disruption.
- To perform molecular docking to evaluate binding affinities and interactions of selected AMPs with CFTR.
- To conduct 100 ns molecular dynamics simulations to examine the stability of AMP-CFTR complexes.

1.12. Research Hypothesis

This study hypothesizes that AMPs can effectively disrupt biofilm formation and modulate CFTR function, offering a novel therapeutic approach for CF. It further posits that the identified AMPs, particularly Scolopendin 2, will demonstrate strong binding affinity and stability with CFTR through computational evaluations, making them viable candidates for treating CF-related infections and improving ion transport dysfunction.

1.13. Significance of the study

This research holds the potential to revolutionize CF treatment by exploring AMPs as alternatives to conventional antibiotics, addressing the growing issue of antibiotic resistance. The in-silico framework developed could expedite the identification of effective CF therapies, offering new hope for patients with chronic bacterial infections and defective CFTR function.

2. LITERATURE REVIEW

2.1. Cause of Cystic Fibrosis

CF is a genetic disease affecting multiple organs caused by mutations in the epithelial chloride channel in CFTR. It is an autosomal recessive genetic disorder caused by mutations in the CFTR gene located on chromosome 7. This gene encodes a protein that functions as a chloride channel on the surface of epithelial cells. Mutations in CFTR disrupt chloride and water transport across cell membranes, leading to the production of thick, sticky mucus that primarily affects the lungs and digestive systems. The most common mutation, F508del, results in a misfolded protein that is degraded before reaching the cell surface (Eldredge et al., 2024).

2.1.1. Morphological and Pathological characteristics

The pathological effect of cystic fibrosis is the accumulation of thick mucus in organs with epithelial linings, particularly the lungs and pancreas. In the lungs, this results in airway obstruction, chronic inflammation, and irreversible bronchiectasis. Histologically, mucus plugging, goblet cell hyperplasia, and neutrophilic infiltration are observed. In the pancreas, fibrosis and atrophy of acinar cells lead to exocrine pancreatic insufficiency. Liver cirrhosis, intestinal obstruction, and infertility in males are also common. Morphological changes vary with disease progression but significantly impact organ function, underscoring the multisystemic nature of CF (Gutiérrez et al., 2025).

2.1.2. Molecular Mechanism in CF

CFTR mutations are classified into six major classes based on their molecular effects, including defective protein production (Class I), misfolding and degradation (Class II), and defective channel gating (Class III). The F508del mutation, a Class II defect, results in misfolded CFTR that is degraded before reaching the cell surface. Other classes involve defective chloride conductance, reduced protein synthesis, or

instability at the cell surface. These mechanistic insights have facilitated the development of mutation-specific therapies. Understanding these pathways is critical for tailoring personalized treatments and advancing CF care (Gryspeert et al., 2025).

2.1.3. CF pathogens and chronic infection

Thickened mucus in CF patients creates a favorable environment for persistent bacterial colonization. *Pseudomonas aeruginosa* is the most prevalent and problematic pathogen, often leading to biofilm formation, chronic lung infection, and progressive decline in lung function. Other common pathogens include *Staphylococcus aureus*, *Burkholderia cepacia*, and *Haemophilus influenzae*. Chronic infections trigger intense inflammatory responses, primarily neutrophilic, contributing to airway damage. Over time, bacterial resistance develops, complicating treatment. Preventing and managing these infections is a major focus of CF care (Massaad and Tal, 2025).

2.1.4. Current treatment strategies for CF

The management of CF has evolved significantly with the advent of CFTR modulators such as ivacaftor, lumacaftor, tezacaftor, and elexacaftor. These drugs target specific classes of CFTR mutations, improving protein function and reducing disease severity. Alongside modulators, therapies include mucolytics, antibiotics, pancreatic enzyme replacements, and airway clearance techniques. Lung transplantation remains a last resort for advanced diseases. Personalized medicine and newborn screening have improved prognosis, allowing earlier intervention and better quality of life. Future approaches aim at gene therapy and advanced RNA-based treatments (Karimulla, 2025).

2.2. Need of Antimicrobial Peptides

The emergence of MDR pathogens, particularly in CF patients, underscores the urgent need for alternative therapeutic strategies. AMPs is a integral components

of the innate immune system, exhibit broad-spectrum antimicrobial activities and possess unique mechanisms that reduce the likelihood of resistance development. Their ability to disrupt microbial membranes and modulate immune responses positions them as promising candidates against MDR infections. Recent studies highlight the potential of AMPs in addressing the limitations of conventional antibiotics, especially in environments like the CF lung, where biofilms and resistant pathogens (Gonçalves et al., 2025).

2.2.1. Properties of AMPs

AMPs are short, typically cationic peptides that play a crucial role in host defense mechanisms. Their amphipathic structures allow them to interact with and disrupt microbial membranes, leading to cell lysis. Beyond their direct antimicrobial activity, AMPs exhibit immunomodulatory properties, influencing cytokine production and inflammatory responses. Their broad-spectrum efficacy, rapid action, and low propensity for inducing resistance make them attractive therapeutic agents. Recent research emphasizes the importance of understanding AMP structures and mechanisms to harness their full therapeutic potential (Erriah et al., 2025).

2.2.2. Role of AMPs in CF treatment

In CF, chronic lung infections caused by pathogens like Pseudomonas aeruginosa pose significant treatment challenges due to biofilm formation and antibiotic resistance. AMPs offer a promising alternative, exhibiting potent antimicrobial and antibiofilm activities. Studies have demonstrated that specific AMPs can effectively disrupt biofilms and kill MDR pathogens in CF models. Moreover, their stability in the protease-rich environment of CF lungs and their ability to modulate immune responses further enhance their therapeutic potential. These properties position AMPs as valuable candidates in developing novel treatments for CF-related infections (Vitiello et al., 2024).

2.3. Computational Approach in Target selection and AMP screening

The integration of computational methodologies has revolutionized the discovery and optimization of AMPs. By leveraging bioinformatics tools, molecular modeling, and machine learning algorithms, researchers can efficiently predict AMP structures, assess their antimicrobial potential, and optimize their properties. These approaches significantly reduce the time and cost associated with traditional experimental methods. Recent advancements have led to the development of sophisticated platforms that facilitate high-throughput screening and rational design of AMPs, accelerating their transition from bench to bedside (Nedyalkova et al., 2024).

2.3.1. Network Pharmacology in Target selection

Network pharmacology offers a holistic perspective in identifying therapeutic targets by analyzing the complex interactions within biological systems. In the context of AMP research, this approach facilitates the identification of key molecular targets and pathways involved in microbial infections. By constructing and analyzing interaction networks, researchers can pinpoint critical nodes that, when modulated by AMPs, could disrupt pathogenic processes. This system-level understanding enhances the precision of target selection, paving the way for the development of more effective and specific AMP-based therapies (Zhang et al., 2024).

2.3.2. Tools involved in AMP collection and screening

The discovery and development of antimicrobial peptides (AMPs) have been significantly enhanced by various computational tools and databases. Resources such as CAMPR4, APD3, and dBAASP provide comprehensive repositories of AMP sequences and their properties. Advanced tools like PyAMPA enable high-throughput prediction and optimization of AMPs, while machine learning algorithms facilitate the identification of novel peptides with desired antimicrobial activities. These computational platforms streamline the screening process, allowing for

efficient selection and design of potent AMPs against specific pathogens (Yang et al., 2024).

2.4. Molecular Docking

Molecular docking is a computational technique that predicts the preferred orientation of one molecule to a second when bound to each other, forming a stable complex. This method is pivotal in drug discovery, allowing researchers to model the interaction between drugs and their targets. By simulating these interactions, molecular docking helps in understanding binding affinities and specificities, facilitating the design of more effective therapeutics. Recent advancements have enhanced the accuracy of docking simulations, integrating machine learning algorithms to predict binding modes more reliably (Muhammed and Aki-Yalcin, 2024).

2.4.1. Docking in Protein-Peptide Interactions

Protein-peptide interactions are fundamental to numerous biological processes, and understanding these interactions is crucial for therapeutic development. Molecular docking serves as a valuable tool in modeling these interactions, predicting how peptides bind to protein targets. This approach aids in identifying potential binding sites and understanding the structural basis of protein-peptide recognition. Recent studies have utilized docking to design peptide-based inhibitors, demonstrating its effectiveness in therapeutic development (Zalewski et al., 2025).

2.4.2. Applications in Drug Discovery

Molecular docking has become an indispensable tool in drug discovery, enabling the virtual screening of vast chemical libraries against target proteins. This approach accelerates the identification of potential drug candidates by predicting their binding affinities and modes. Docking facilitates the optimization of lead compounds,

reducing the need for extensive experimental testing. Recent advancements have improved docking algorithms and scoring functions, enhancing the reliability of predictions and streamlining the drug development process (Zhang et al., 2025).

2.5. Molecular Dynamics Simulation

MD simulations are pivotal in understanding the dynamic behavior of biomolecules at the atomic level. By simulating the physical movements of atoms and molecules over time, MD provides insights into structural conformations, stability, and interactions, which are crucial for drug design and understanding disease mechanisms. Recent advancements have enhanced the accuracy and efficiency of MD simulations, enabling the study of complex biological systems with greater precision (Von Domaros and Tobias, 2025).

2.5.1. MD in Protein-Peptide complex studies using GROMACS

GROMACS is one of the most widely used molecular dynamics simulation software packages, particularly in protein-peptide complex studies. It is renowned for its efficiency in simulating large biomolecular systems and its capability to handle high-performance computing environments. In protein-peptide complex studies, GROMACS allows researchers to perform simulations that observe the binding interactions between peptides and target proteins in detail. It can model the dynamic behavior of protein-peptide complexes, including binding events, conformational changes, and the stability of the complex over time. The software provides various tools for analyzing binding affinities, the stability of protein-peptide interactions, and the effects of different conditions (such as temperature, pressure, or ion concentration) on these complexes. GROMACS also facilitates the visualization of the structural evolution of protein-peptide interactions through trajectory analysis, enabling the identification of critical residues involved in binding and the potential influence of peptide sequence variations on complex stability. Additionally, GROMACS is equipped with tools for performing free energy calculations, which

help assess the strength of peptide binding to its protein target. This makes it a valuable tool in the rational design of peptide-based therapeutics, where detailed molecular insights are essential for optimizing peptide sequences for better efficacy and specificity. Overall, GROMACS enhances the understanding of protein-peptide interactions, making it indispensable in the study of molecular dynamics related to drug development, including the design of AMPs (Munna et al., 2024).

2.5.2. Applications of MD in CF and AMPs Research

In CF research, MD simulations have been utilized to study the structural dynamics of the CFTR protein and its mutants, providing insights into disease pathology and potential therapeutic targets. Similarly, in the study of AMPs, MD helps in understanding their interaction with microbial membranes, aiding in the design of more effective AMPs. Recent studies have highlighted the role of MD in exploring the conformational behavior of AMPs and their mechanisms of action (Huang et al., 2024).

2.5.3. Post-MD Analysis Techniques

Post-MD analysis is crucial for interpreting simulation data and extracting meaningful insights. Techniques such as RMSD, RMSF, hbond, angle, Rg are commonly employed to assess the stability and conformational changes of biomolecules. Advanced visualization tools and trajectory analysis methods have been developed to facilitate the interpretation of complex MD data, enhancing our understanding of molecular behaviour (Pandey et al., 2025).

3. MATERIALS AND METHODS

3.1. Protein Data Collection

UniProt (Universal Protein Resource; https://www.uniprot.org/) is the most comprehensive and reliable database for protein sequences and their functional annotations globally. Protein data relevant to CF in humans were retrieved using the search term "Cystic fibrosis", "Homo sapiens". Human proteins that play a role in cystic fibrosis pathogenesis and underlying biological mechanisms were downloaded from the UniProt database (Burley et al., 2025).

3.2. Network formation and key regulatory gene identification

3.2.1. PPI Network Construction

STRING version 12.0 (Search Tool for the Retrieval of Interacting Genes/Proteins; https://string-db.org/) is a bioinformatics database that is used to construct and analyse PPI network based on various evidence scores (Ye et al., 2025). The proteins were then uploaded into the STRING search bar to build a PPI network. The minimum interaction score was 0.4 (medium confidence), and the network clustering was performed using the k-means algorithm integrated to define groups that are functionally related and similarities in the interaction profiles (Alruily et al., 2025).

3.2.2. Hub Gene identification

Cytoscape is open-source software mostly applied for visualization and analysis of PPI networks, gene regulatory networks, and other biological data types. The constructed PPI network was exported to Cytoscape (version 3.8.0) for visualization shown in Fig 2. Different layout approaches were used to increase visual clarity and representation. The CytoHubba plugin was used to analyse the network

topology of the PPI interactions. To assess the relevance of individual nodes, the Maximum Neighbourhood Component (MNC) was chosen from numerous centrality measures. Based on MNC scores, the top 10 hub genes were identified, in which emerging as the most significant and chosen as the key therapeutic target for further exploration (Cai et al., 2025).

3.3. Collection of AMPs data

The APD3 (Antimicrobial Peptide Database 3; https://aps.unmc.edu/) is an online resource that contains information on AMPs in the fields of microbiology, pharmacology, and drug development, particularly in the context of antimicrobial resistance. It contains a total of 3,306 natural antimicrobial peptides, which were downloaded along with their corresponding sequences and accession numbers. It also provides the important physicochemical features of antimicrobial peptides, such as peptide length, Boman index (protein-binding capacity), GRAVY index (hydrophobicity), and net charge, which are essential parameters to assess the therapeutic potential of AMPs (Jha et al., 2025).

3.4. Screening and identification of Potential AMPs

3.4.1. Based on Hemolytic Activity

To ensure therapeutic safety, an initial screening of AMPs ranging from 5 to 30 amino acids in length was performed, resulting in a primary dataset of 1,776 peptides. The HemoPI tool (http://crdd.osdd.net/raghava/hemopi/) was used to predict hemolytic activity, allowing the exclusion of peptides that could potentially lyse red blood cells. Only non-hemolytic AMPs were retained for further analysis, reducing the number of candidates to 665. This step was essential to avoid peptides that could cause hemotoxicity when administered (Carpenter and Van Hoek, 2024).

3.4.2. Based on Toxicity

To further validate the safety of the shortlisted peptides, toxicity prediction

was carried out using the ToxinPred tool (http://crdd.osdd.net/raghava/toxinpred/). This analysis assessed amino acid composition, motif patterns, and physicochemical properties to predict peptide toxicity. From this evaluation, 650 peptides were classified as non-toxic, suggesting their suitability for human application (Rathore et al., 2024).

3.4.3. Based on Biofilm activity

The biofilm inhibition potential of the non-toxic peptides was evaluated using the dPABBs (Design Peptides Against Bacterial Biofilms) database (https://webs.iiitd.edu.in/raghava/dpabbs/). This database predicts the anti-biofilm capability of AMPs based on machine learning algorithms. As biofilm-forming bacteria play a critical role in chronic infections such as cystic fibrosis, peptides with strong biofilm-disruptive properties are highly desirable. This step refined the dataset to 369 peptides with effective anti-biofilm potential (Qi et al., 2025).

3.4.4. Based on Pathogenicity

To enhance pathogen-specific targeting, the peptides were screened using the dBAASP database (https://dbaasp.org/), which provides experimentally validated activity profiles of AMPs against specific pathogens. Peptides exhibiting confirmed antimicrobial activity against Pseudomonas aeruginosa and Staphylococcus aureus two major pathogens in CF were selected. This pathogen-specific refinement resulted in 39 candidate peptides (Marczak et al., 2025).

3.4.5. Based on Peptide Ranking

Finally, the shortlisted 39 peptides were subjected to activity scoring using PeptideRanker(http://bioware.ucd.ie/~compass/biowareweb/Server_pages/peptideranker.php), which predicts the biological activity probability of peptides based on their sequence features. Peptides scoring above 0.8 were considered highly bioactive. From this evaluation, the top 10 peptides were selected as the most promising therapeutic candidates for subsequent molecular docking studies to assess their binding affinity with the target protein (Xiao et al., 2025).

3.5. 3D structure retrieval

3.5.1. Target Structure

The three-dimensional structure of the CFTR protein, identified as the primary therapeutic target, was retrieved from the RCSB PDB (https://www.rcsb.org/) using the PDB ID: 1XMI. The structure was downloaded in .pdb format, containing high-resolution atomic details essential for accurate interaction and binding studies. The structural information served as a basis for subsequent molecular docking and molecular dynamics simulations (Berman and Burley, 2025).

3.5.2. AMPs structure

The 3D conformations of the shortlisted AMPs were predicted using the AlphaFold Protein Structure Database (https://deepmind.google/technologies/alphafold/), an advanced deep learning-based prediction tool developed by DeepMind. AlphaFold has demonstrated high accuracy in predicting peptide and protein structures directly from amino acid sequences, especially beneficial for peptides lacking experimentally resolved structures. The predicted peptide structures were downloaded in .pdb format and prepared for downstream computational analysis, including molecular docking and dynamic simulation with the CFTR protein to evaluate binding affinity and complex stability (Gai et al., 2025).

3.6. Active site Prediction and Target-AMPs binding affinity

The target protein's active site was predicted using the Supercomputing Facility for Bioinformatics and Computational Biology (SCFBio) online Active Site Prediction Tool (https://www.scfbio-iitd.res.in/dock/ActiveSite.jsp). This program evaluates the geometric and physicochemical features of the protein's 3D structure to

identify probable binding pockets. The anticipated active site residues were used in further peptide docking and interaction analyses. Molecular docking was performed using AutoDock Vina to study the interaction of target AMPs with the target protein (PDB ID: 1XMI).The SCFBio Active Site Prediction Tool was utilized for the identification of the protein active site and was located at central coordinates of X = 17.077, Y = 56.583, and Z = 119.771. A grid box of size 35Å around the coordinates utilized to limit the docking simulations near the active site. AMPs and the target protein were prepared and optimized using OpenBabel and docking performed using in-house Python and shell scripts on the High-Performance Computing (HPC) system. The docking result was analysed in order to obtain the most appropriate binding poses as well as the binding affinities (Pitarch and Pazos, 2025).

3.7. Dynamic Modelling of Target-AMP

3.7.1. System Preparation

The CFTR protein and antimicrobial peptide 7 (Scolopendin 2) were prepared for molecular dynamics simulations using **GROMACS 2021.5** and the **AMBER95ILDN (**AMBER95 force field with Isoleucine, Leucine, DAspartate, and NAsparagine**) force field**, chosen for its accurate side-chain torsion potentials and realistic hydrogen bonding and electrostatics. The ACPYPE tool was used to generate compatible topology files, ensuring consistent parameterization of both the protein and peptide for simulation. This setup aimed to explore long-term interaction dynamics while balancing computational efficiency with biophysical accuracy, crucial for large systems like CFTR (Guru and Ramadevi, 2025).

3.7.2. Solvation

To mimic a realistic biological environment, the peptide–protein complex was placed inside a triclinic simulation box, ensuring a minimum distance buffer between

the protein and the box edges to avoid boundary artifacts. The system was then solvated using explicit **TIP3P water molecules**, a model chosen for its computational efficiency and well-documented ability to replicate hydrogen-bonding networks in aqueous environments. This step was crucial to emulate the native epithelial cellular fluid conditions that CFTR typically resides in, ensuring the hydration shell around the complex was well-represented (Ramos and Martínez, 2025).

3.7.3. Ion Addition

To further approximate physiological conditions, the system's net charge was neutralized by adding counterions specifically, sodium **(Na^+) and chloride (Cl^-) ions**. These were added to a final ionic strength of 0.15 M, reflecting the typical salt concentration in human epithelial tissues. This not only stabilized electrostatic interactions within the system but also prevented potential artifacts that might arise from unbalanced charges, thereby enhancing simulation stability and biological relevance (Le Nguyen et al., 2025).

3.7.4. Energy Minimization

Before initiating dynamics, energy minimization was conducted using the steepest descent algorithm to relieve any steric clashes or geometric strain within the solvated system. This process was essential to guide the system into a low-energy conformation that closely resembles a stable starting point. Without this step, high-energy contacts could have led to numerical instabilities or unrealistic conformational shifts during the early stages of simulation. The minimization ensured all atoms were properly positioned with minimal interatomic repulsion, laying a strong foundation for the subsequent equilibration (Panday et al., 2025).

3.7.5. Equilibration

Equilibration was carried out in two key phases to gradually bring the system

to thermodynamic stability. First, the **NVT ensemble** (constant volume and temperature) was run for 10 nanoseconds using the V-rescale thermostat to maintain a physiological temperature of 310 K. This allowed the system to stabilize its kinetic energy distribution. Next, the **NPT ensemble** (constant pressure and temperature) was employed for another 10 nanoseconds, using the **Parrinello–Rahman barostat** to adjust system density and maintain 1 bar pressure. These steps were crucial in recreating a biologically accurate environment where the peptide–protein complex could equilibrate properly before launching the production run (Stanton et al., 2025).

3.7.6. Production MD

The main simulation was executed over **100 ns** with a **2-femtosecond timestep**, allowing us to capture fine-grained interaction dynamics between CFTR and Scolopendin 2. The LINCS algorithm was applied throughout to constrain high-frequency bonds involving hydrogen atoms, improving computational performance without sacrificing accuracy. For long-range electrostatic calculations, the Particle Mesh Ewald (PME) method was employed, which is considered the gold standard for simulating charged biomolecular systems. Given the large size and complexity of the CFTR protein, the simulation focused on the strongest binding pose determined from prior docking studies, optimizing resource utilization while preserving the scientific depth. This high-resolution approach provided rich insights into conformational behavior, binding stability, and potential allosteric effects induced by the peptide (Do and Gnanakaran, 2025).

4. RESULTS AND DISCUSSION

4.1. Protein Network Analysis

4.1.1. STRING Network

The Protein-Protein Interaction (PPI) network was successfully constructed using the STRING database (version 12.0), which integrates various evidence sources including experimental data, co-expression patterns, and curated biological pathways. A total of 142 nodes and 1,669 edges were identified in the constructed network, reflecting a rich interaction landscape among the input proteins shown in Fig 4.1. The network demonstrated a relatively high average node degree of 23.5, indicating a densely connected system, and an average local clustering coefficient of 0.69, which suggests that many of the proteins interact within tightly knit groups or modules. Using a medium confidence threshold of 0.4, functionally related protein clusters were generated through the k-means clustering algorithm, facilitating the identification of biologically meaningful groups and potential regulatory patterns within the cystic fibrosis context. These results offer a foundational view of the molecular interaction network and help guide downstream hub gene analysis (Szklarczyk et al., 2025).

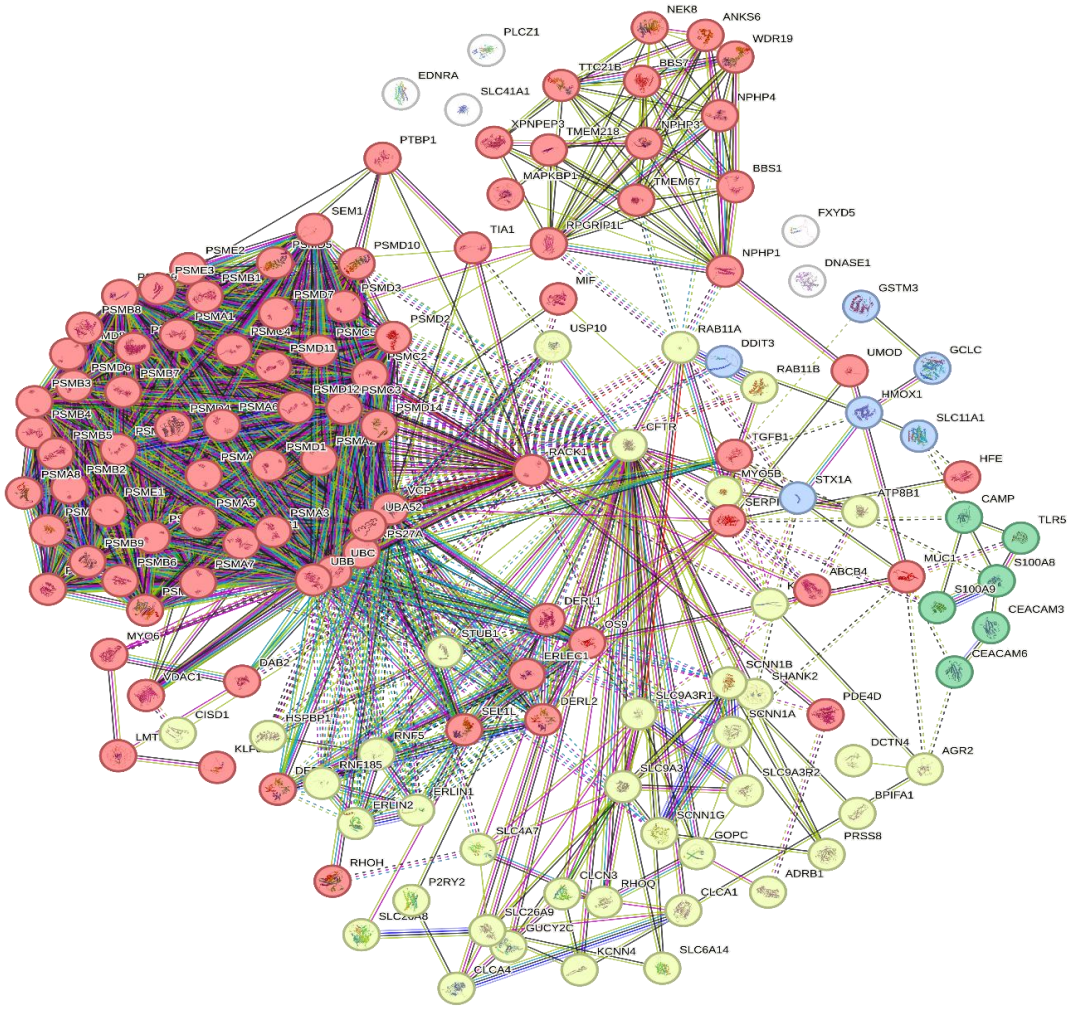


Figure 4.1 PPI Network formation in STRING

4.1.2. Cytosacpe Network Analysis

The PPI network imported into Cytoscape and visualized (shown in Fig 4.2) that revealed distinct interaction patterns upon applying various layout algorithms. Centrality analysis using the MNC algorithm identified the top 10 hub genes, among which CFTR was ranked the highest which is shown in Table 4.1 and the network is shown in Fig 4.3. This gene exhibited the most significant connectivity within the network, indicating its key regulatory role. The identification of CFTR as a major hub supports its potential as a core therapeutic target in cystic fibrosis (Buzzao et al., 2025).

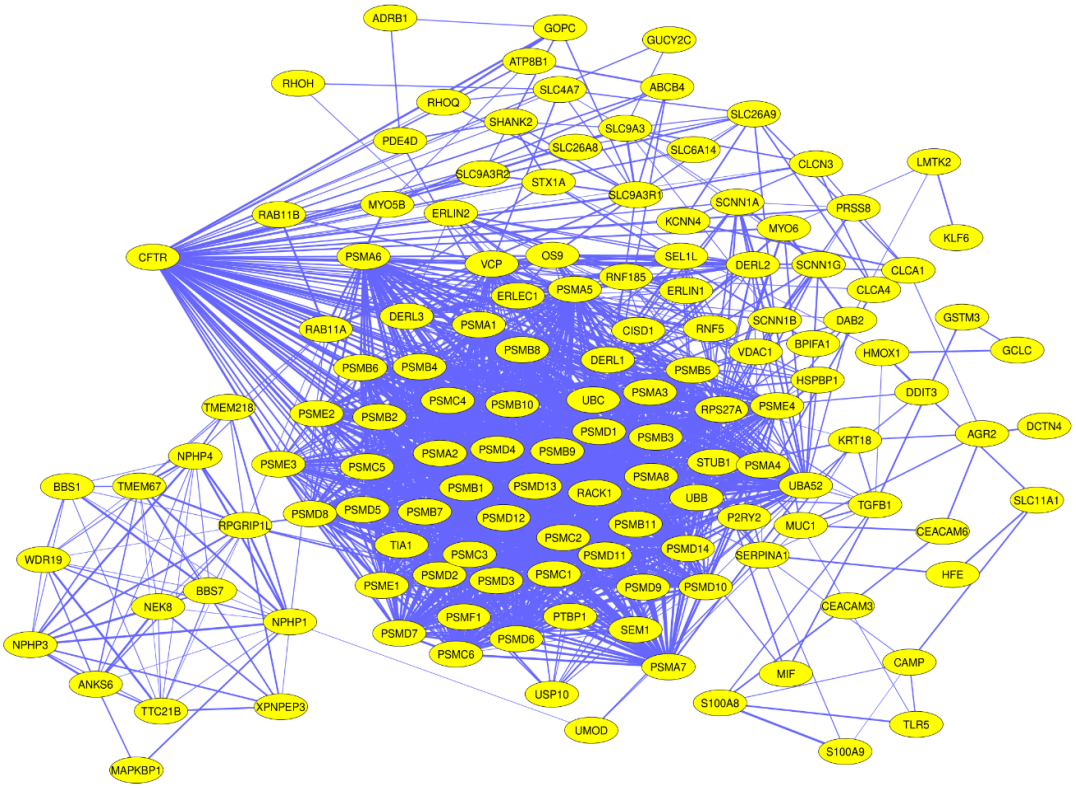


Figure 4.2 Network Visualization in Cystoscape

Table 4.1 Top 10 Hub genes based on MNC Scores

Rank	Name	Score
1	CFTR	93
2	UBA52	72
3	UBC	71
3	RPS27A	71
3	VCP	71
6	UBB	70
7	PSMD14	54
8	PSMA3	53
8	PSMA2	53
8	PSMA7	53

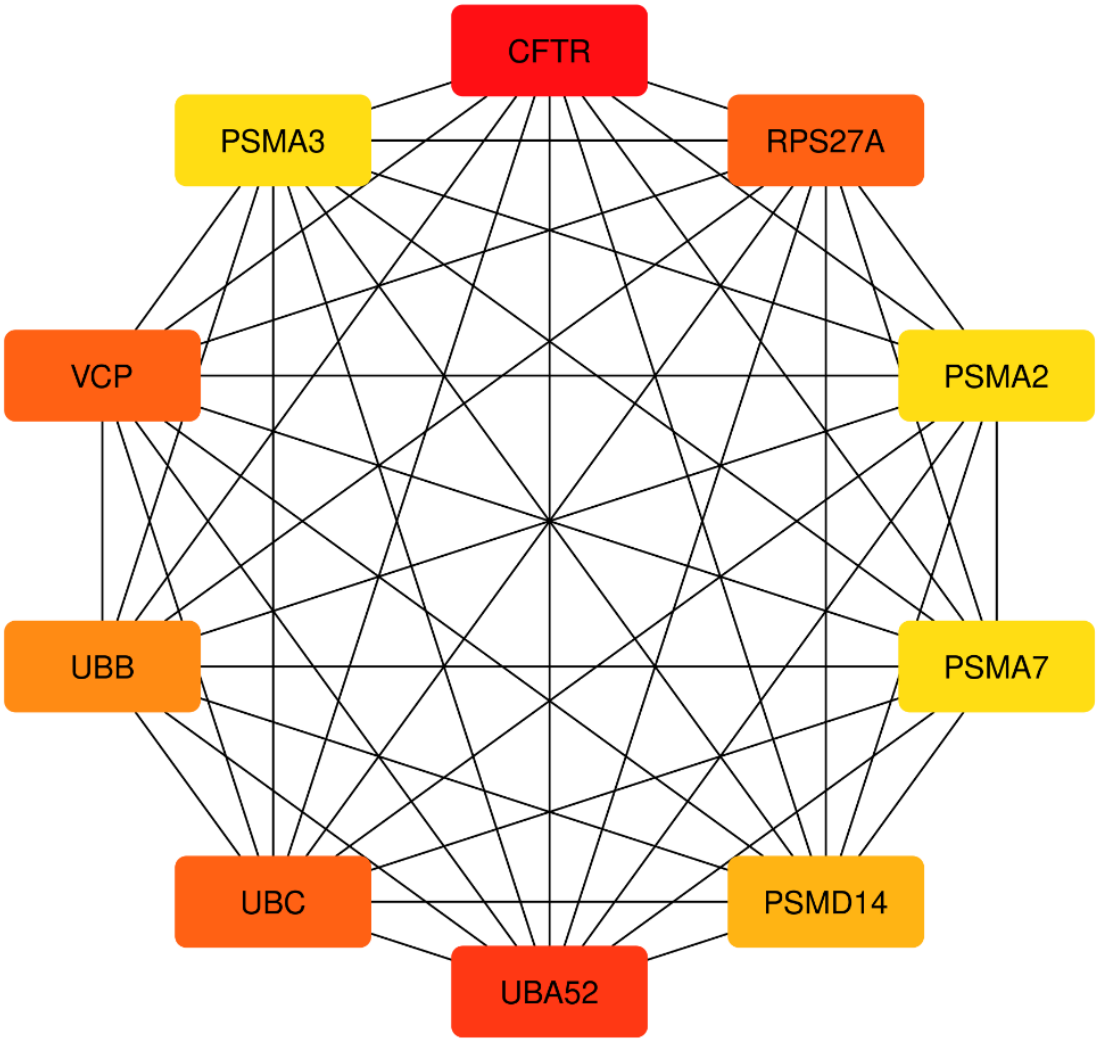


Figure 4.3 PPI network of top 10 hub gene

4.2. Screened AMPs

From the initial dataset of 3,336 AMPs, 1,776 contains 5-30 amino acids 665 non-hemolytic peptides were identified. Further toxicity filtering yielded 650 non-toxic peptides. Screening for biofilm inhibition refined the list to 369 peptides with anti-biofilm potential. Pathogen-specific analysis targeting *Pseudomonas aeruginosa* and *Staphylococcus aureus* resulted in 39 active peptides. Final scoring using PeptideRanker led to the selection of the top 10 highly bioactive AMPs which is shown in Table 4.2 and they are ready for downstream docking studies (Zhang et al.,

2025).

Table 4.2 Top 10 Bioactive AMPs

Peptide	Sequence	Seq length	Name	Prediction	Toxicity	Prediction	*P.aeruginosa* & *S.aureus*	Peptide Ranking
1	KIKFLKVLT	9	PEP1	Non-Hemolytic	Non-Toxin	Biofilm Active	Active	0.997067
2	INWKGIAAMAKKLL	14	Mastoparan-X	Non-Hemolytic	Non-Toxin	Biofilm Active	Active	0.994509
3	NLKAIAALAKKLL	13	Mastoparam-VT2	Non-Hemolytic	Non-Toxin	Biofilm Active	Active	0.991304
4	INLKAITALAKKLL	14	Mastoparam-VT3	Non-Hemolytic	Non-Toxin	Biofilm Active	Active	0.990002
5	INLKAIAPLAKKLL	14	Mastoparam-VT4	Non-Hemolytic	Non-Toxin	Biofilm Active	Active	0.977801
6	RLFRHAFKAVLRL	13	Pep39	Non-Hemolytic	Non-Toxin	Biofilm Active	Active	0.975108
7	AGLQFPVGRIGRLLRK	16	Scolopendin 2	Non-Hemolytic	Non-Toxin	Biofilm Active	Active	0.947293
8	LRLKSIVSYAKKVL	14	Mastoparan-S	Non-Hemolytic	Non-Toxin	Biofilm Active	Active	0.940122
9	GLLSALRKMIPHILSHIKK	19	Antapin	Non-Hemolytic	Non-Toxin	Biofilm Active	Active	0.879878
10	INLKAIAALAKKLF	14	Mastoparan-AF	Non-Hemolytic	Non-Toxin	Biofilm Active	Active	0.814254

4.3. 3D structure

4.3.1. Target structure

The 3D structure of the CFTR protein (PDB ID: 1XMI) was successfully retrieved from the Protein Data Bank in .pdb format and shown in Fig 4.4. The structure provided high-resolution details suitable for downstream molecular docking and simulation studies (Choudhary et al., 2025).

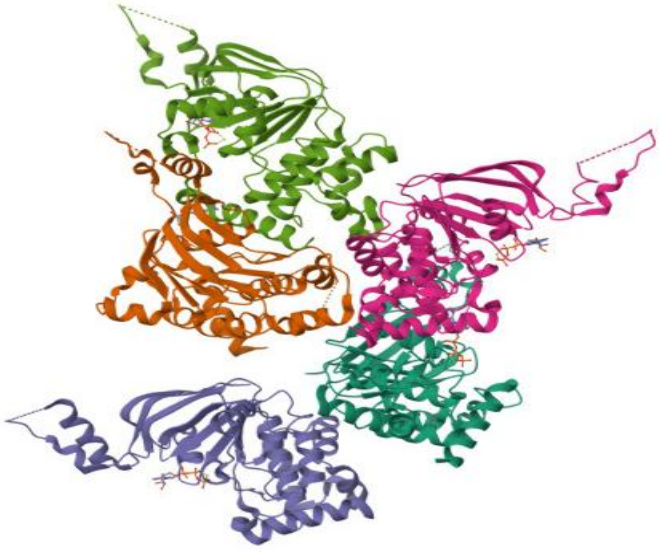
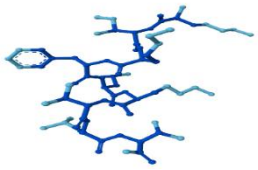


Figure 4.4 CFTR protein structure (PDB ID: 1XMI)

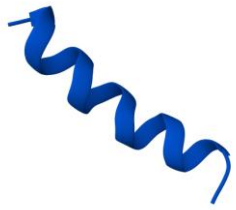
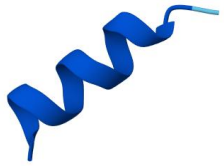
4.3.2. AMPs structure

The 3D structures of the 10 shortlisted AMPs were predicted and downloaded from the AlphaFold server were shown in Table 4.3. All peptides were obtained in .pdb format with structurally stable conformations, enabling their integration into binding and dynamics analyses with the CFTR protein (Iglesias et al., 2025).

Table 4.3 AMPs Structure retrieved from AlphaFold Server

Peptide ID	Name/Class	AMP Structure
Peptide_1	PE1	
Peptide_2	Mastoparan-X	

Peptide ID	Name/Class	AMP Structure
Peptide_3	Mastoparan-VT2	
Peptide_4	Mastoparan-VT3	
Peptide_5	Mastoparan-VT4	
Peptide_6	Pep39	
Peptide_7	Scolopendin 2	

Peptide ID	Name/Class	AMP Structure
Peptide_8	Mastoparan-S	
Peptide_9	Antapin	
Peptide_10	Mastoparan-AF	

4.4. Binding of Target-AMP Analysis

Molecular docking shown in Fig 4.5 results revealed strong binding interactions between the CFTR protein and the shortlisted AMPs. Among them, **Peptide 7 – Scolopendin 2 (AP02447) (Fig 4.5. (g))** with 16 amino acid sequence exhibited the highest binding affinity with a docking score of –7.6 kcal/mol. This peptide demonstrated stable interactions within the predicted active site region, suggesting it as a promising candidate for further molecular dynamics simulations and therapeutic evaluation (Çungur et al., 2025).

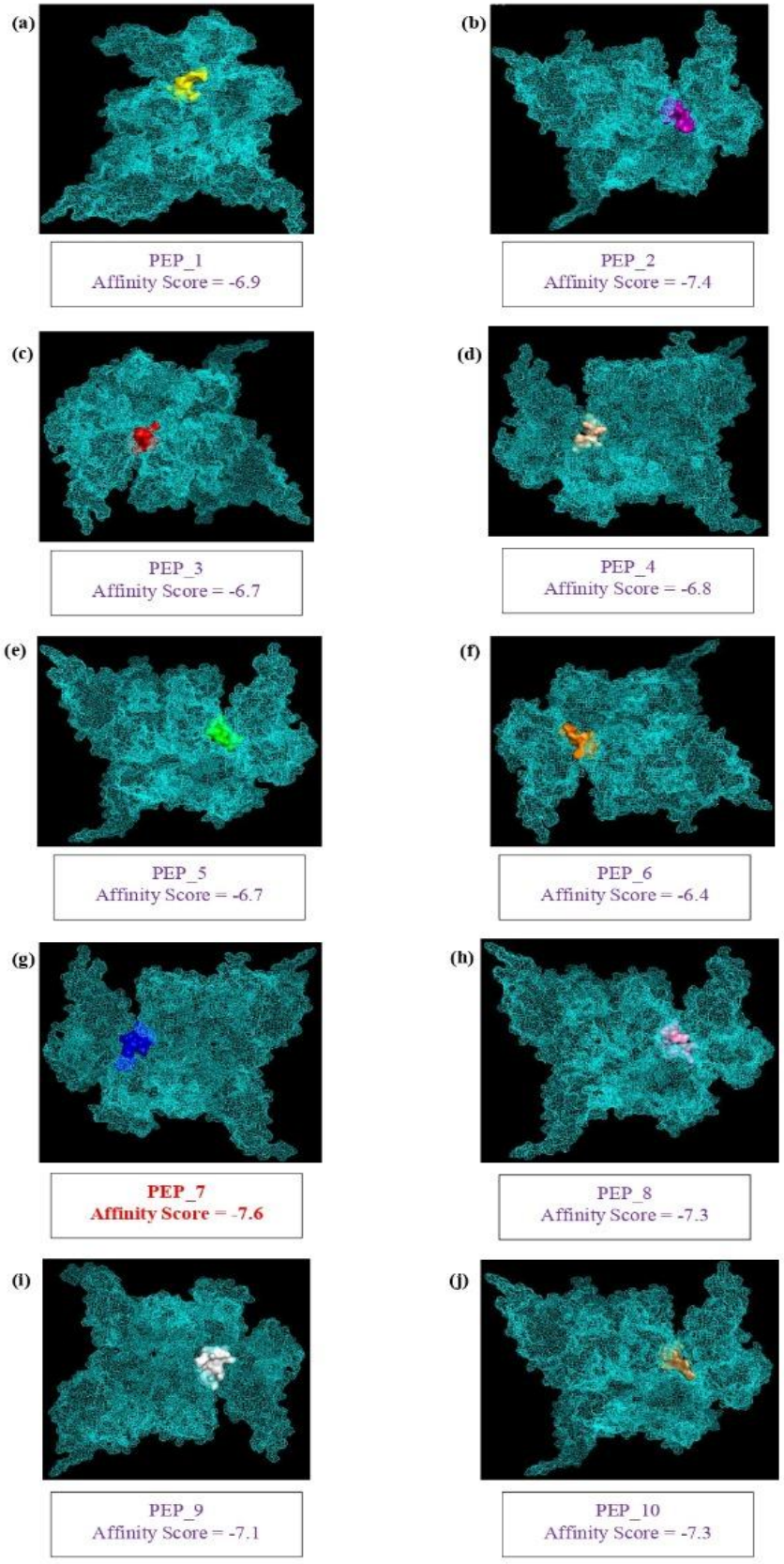


Figure 4.5 Binding Affinity Scores of Target-AMPs

4.5. Post-Simulation Analysis

4.5.1. RMSD

The RMSD plot (Fig 4.6) shows the structural deviation of the CFTR–Scolopendin 2 complex over time. The RMSD ranges between 1.5 Å and 3.5 Å, indicating that the complex undergoes initial structural adjustment, likely due to peptide binding or membrane reorganization. After this phase, the system reaches a relatively stable conformation, suggesting that Scolopendin 2 forms a consistent interaction with the CFTR protein. The absence of sharp fluctuations implies stable peptide association and no significant unfolding of CFTR, which is essential for maintaining its function as a membrane channel (Da Fonseca et al., 2024).

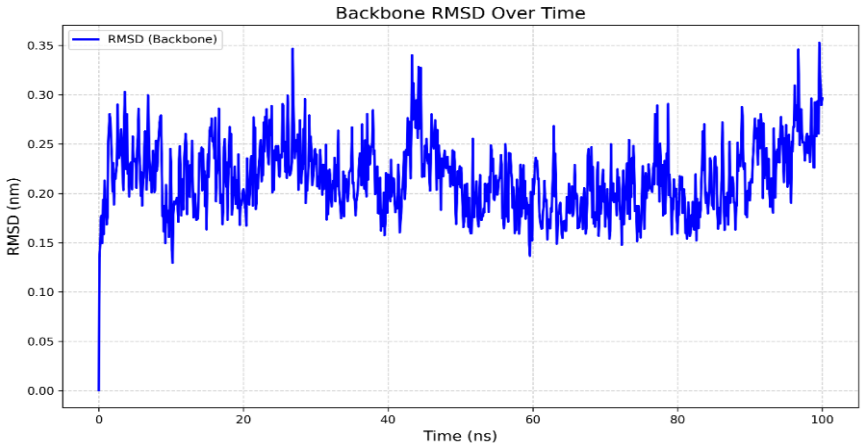


Figure 4.6 RMSD Plot

4.5.2. RMSF

The RMSF plot (Fig 4.7) provides insight into the local flexibility of residues in the complex. Terminal and loop regions of CFTR show higher fluctuations (up to ~0.3 nm), which is common and reflects their dynamic nature. However, the core transmembrane and nucleotide-binding domains exhibit lower fluctuations, indicating they remain structurally intact during peptide binding. Notably, regions with elevated RMSF might correspond to the peptide-binding interface, where Scolopendin 2 induces local flexibility, possibly enhancing interaction adaptability without compromising CFTR's structural core (Sokolov and Cui, 2025).

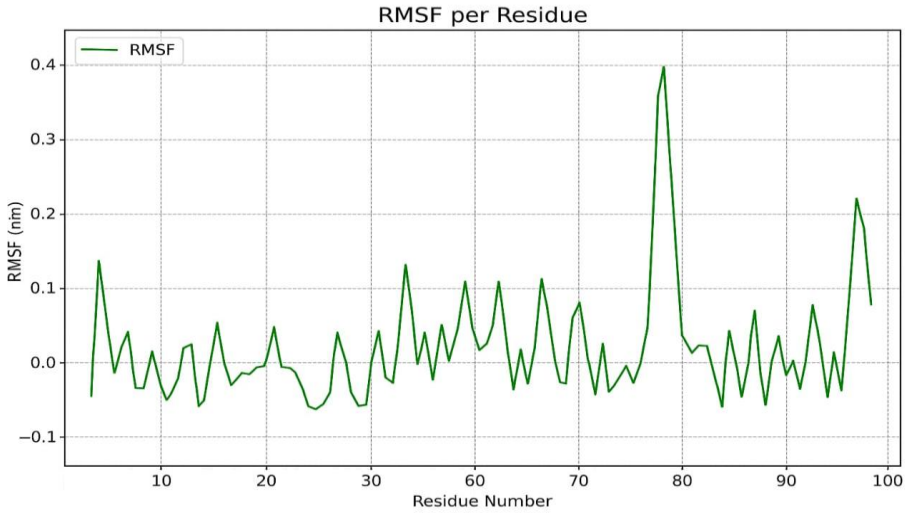


Figure 4.7 RMSF Plot

4.5.3. Radius of Gyration (Rg)

The Rg plot(Fig4.8)provides information about the compactness and structural stability of the CFTR–Peptide 7 complex during the simulation. The Rg values remain relatively stable, fluctuating between 2.15–2.33 nm, indicating no major unfolding or destabilization of CFTR. A slight dip around 60 ns suggests a moment of tighter peptide-protein interaction, but overall, the structure retains its native-like conformation. This highlights the structural compatibility of Peptide 7 with CFTR, reinforcing its potential as a non-disruptive therapeutic agent (Logan et al., 2025).

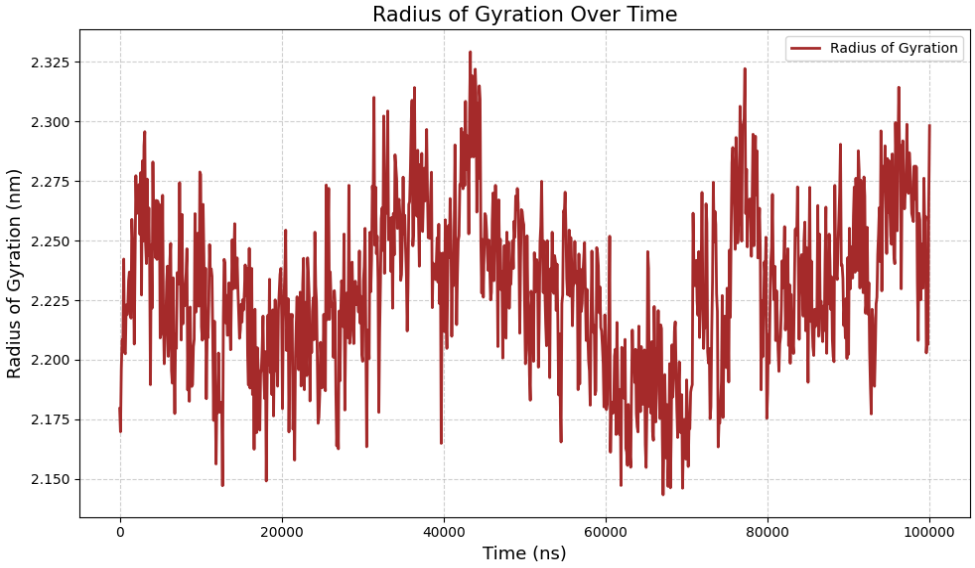


Figure 4.8 Rg Plot

4.5.4. Hydrogen Bond

Hydrogen bonding plot (Fig 4.9) reflects specific, transient interactions between CFTR and Peptide 7. While the number of H-bonds is low, peaks between 55–62 ns show up to 2 stable hydrogen bonds, coinciding with the Rg dip. This points to a period of enhanced binding stability. Outside this window, the interactions are sporadic, suggesting a reversible, surface-level binding mode—desirable for modulating protein function without permanent alteration (Bakó et al., 2025).

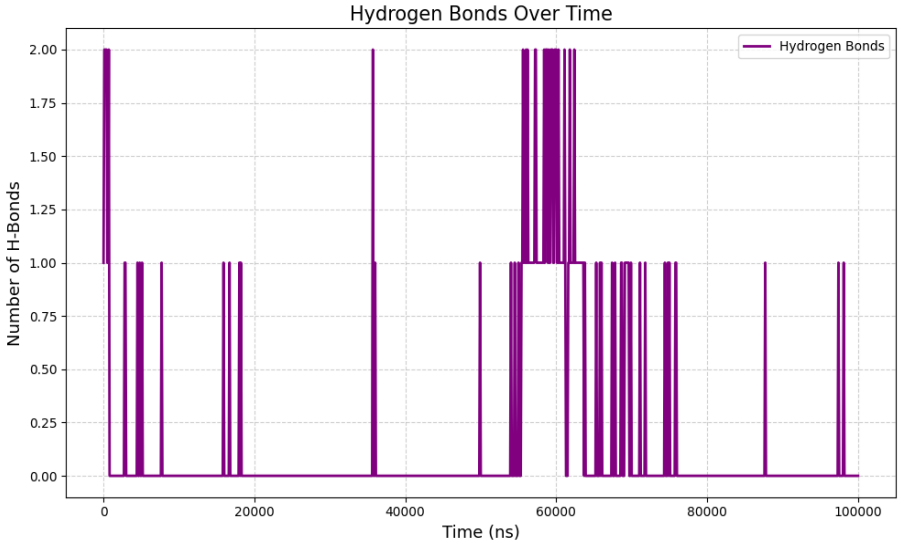


Figure 4.9 Hydrogen Bond Plot

4.5.5. Angle

The angular variation depicted in this plot indicates how a specific angle, possibly a dihedral or inter-residue angle fluctuates during the simulation. The values remain largely between 60° and 130°, with relatively smooth transitions and a lack of abrupt jumps (Fig 4.10). This suggests that the structural elements being monitored remain flexible yet within a controlled range, likely representing a hinge or binding angle that undergoes moderate motion. The consistency of the angle values implies a dynamic but stable interaction or domain movement within the molecular system (Liu et al., 2024).

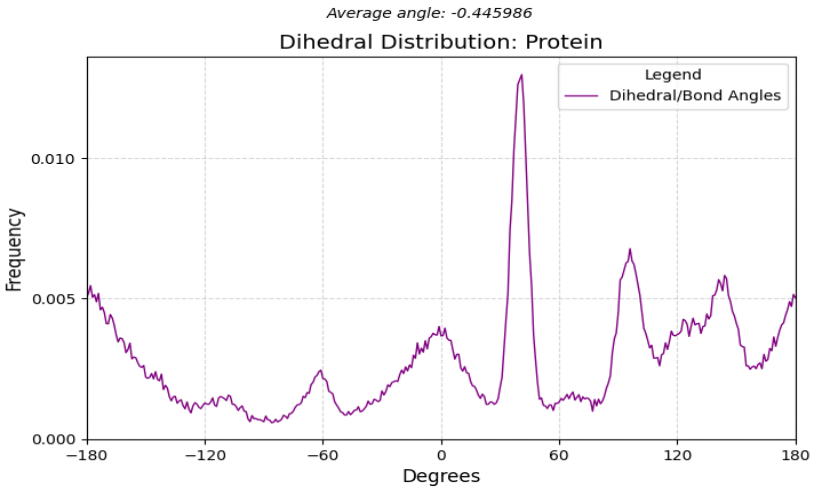


Figure 4.10 Angle Plot

4.5.6. Potential Energy

The potential energy profile of the CFTR–Scolopendin 2 complex shows a sharp decline from approximately –500,000 kJ/mol to –750,000 kJ/mol within the first 5 picoseconds, followed by a gradual stabilization over the remaining simulation period (Fig 4.11). This rapid energy drop signifies the system undergoing initial relaxation, likely due to electrostatic and van der Waals adjustments as Scolopendin 2 interacts with CFTR, finding an energetically favorable binding conformation. The subsequent plateauing trend reflects the system reaching a thermodynamically stable state, essential for meaningful molecular dynamics analysis. The absence of significant energy spikes further supports the idea that Scolopendin 2 binds stably without disrupting CFTR's structural integrity. Overall, the progressive minimization of potential energy confirms a successful equilibration, and highlights Scolopendin 2's potential as a stable therapeutic binder in cystic fibrosis-related studies (Bertani et al., 2024).

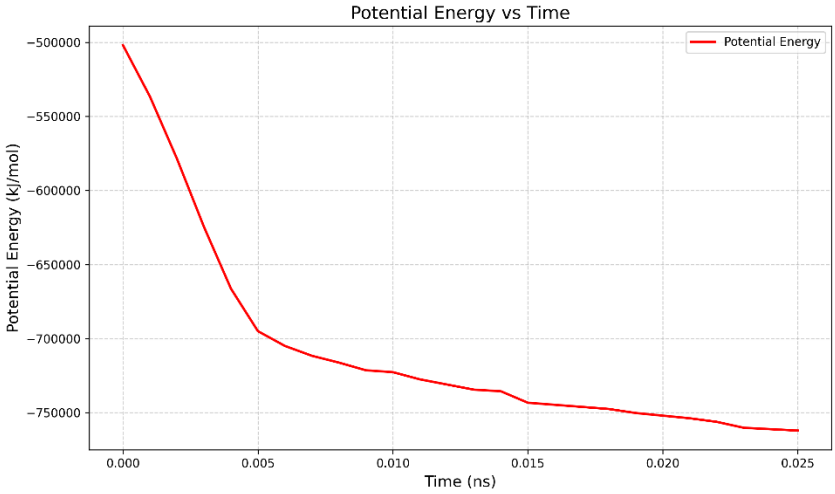


Figure 4.11 Potential Energy Plot

4.5.7. SASA

The SASA plot (Fig 4.12) reveals fluctuations in the solvent-exposed surface area of the biomolecule during the simulation. The values generally range between 120 nm² and 165 nm², indicating minor changes in the degree of solvent exposure. These fluctuations could reflect breathing motions or subtle conformational adjustments, but no drastic changes are observed, implying the absence of major unfolding or collapse events. The relatively steady pattern of the SASA suggests that the molecular complex maintains a consistent global shape and solvation profile throughout the simulation (Cao et al., 2024).

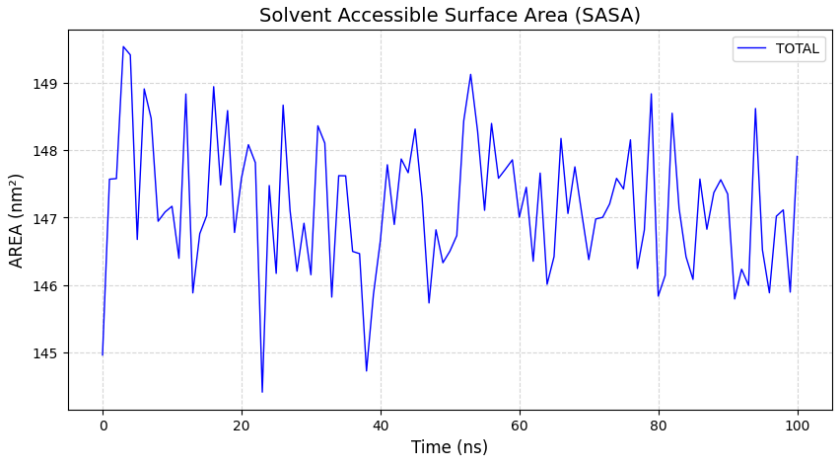


Figure 4.12 SASA Plot

5. CONCLUSION

This study presents a comprehensive computational approach to identify potential antimicrobial peptides (AMPs) for cystic fibrosis (CF) therapy, targeting the CFTR protein. By integrating network pharmacology, peptide screening, molecular docking, and molecular dynamics simulations, Scolopendin 2 was identified as a promising candidate. The peptide demonstrated favorable binding interactions with CFTR and maintained complex stability throughout 100 ns of MD simulation, supported by RMSD, RMSF, Rg, hydrogen bonding, potential energy and angle. These findings suggest that Scolopendin 2 not only possesses antimicrobial and biofilm-disrupting properties but may also directly interact with and stabilize CFTR, potentially modulating its function. The use of AMP-based strategies could thus offer a dual benefit managing persistent infections and addressing protein-level dysfunctions in CF. This study contributes a valuable in silico framework for AMP discovery and prioritization in CF, providing a foundation for further experimental exploration.

6. FUTURE PROSPECTS

The promising results of this study mark an exciting step forward in the search for novel cystic fibrosis (CF) therapeutics. The identification of Scolopendin 2 as a potential antimicrobial peptide (AMP) capable of both biofilm disruption and CFTR modulation opens up a new frontier in CF treatment strategies. Building upon these strong in silico findings, the next logical step is experimental validation to confirm the peptide's functional efficacy. Techniques such as patch-clamp assays, epithelial chloride efflux measurements, and bacterial biofilm inhibition assays can provide robust insights into its biological activity under physiological conditions.

To ensure clinical applicability, further studies must assess the immunogenicity, stability, and pharmacokinetic properties of Scolopendin 2. Chemical modifications such as PEGylation, cyclization, or incorporation of non-natural amino acids may enhance its in vivo stability and therapeutic potential. Moreover, innovative delivery systems such as inhalable nanoparticles or hydrogels could optimize targeted lung delivery, enhance retention time, and reduce systemic exposure.

This computational pipeline demonstrates great adaptability and can be applied to discover AMPs targeting other biofilm-associated diseases or genetic disorders. The integration of artificial intelligence and machine learning models could further streamline AMP screening and predict off-target effects with greater accuracy. Incorporating patient-specific genomic and proteomic data can also pave the way for personalized peptide therapeutics, aligning with the goals of precision medicine.

Overall, this study provides a solid foundation for AMP-based drug discovery and development in CF. With continued research and translational efforts, peptides like Scolopendin 2 hold the potential to revolutionize current treatment paradigms offering a dual-function approach that addresses both the genetic mutation and persistent infections characteristic of cystic fibrosis.

7. CO/PO ATTAINMENT

The present work entitled "Screening of Potential Antimicrobial Peptides for Cystic Fibrosis Using Network and Dynamic Studies", attains the following Cos, that aligns with the work's objectives and methodologies

Course Outcomes:

- **CO1**: Understand the molecular basis and pathophysiology of cystic fibrosis, including the role of CFTR and biofilm-forming pathogens.
- **CO2**: Apply bioinformatics tools to identify and analyze protein-protein interaction (PPI) networks relevant to disease targets.
- **CO3**: Screen and evaluate antimicrobial peptides (AMPs) using various computational tools based on hemolytic activity, toxicity, and pathogen-specific activity.
- **CO4**: Perform molecular docking to assess the binding affinity between AMPs and CFTR.
- **CO5**: Conduct molecular dynamics simulations to evaluate the stability and behavior of AMP–CFTR complexes.
- **CO6**: Develop a comprehensive in-silico pipeline to identify and validate potential peptide therapeutics for cystic fibrosis.

COs	PO1	PO2	PO3	PO4	PO5	PO6	PO7	PO8	PO9	PO10	PO11	PO12	PSO I	PSO II	PSO III
CO1	3	3	0	0	0	2	2	0	0	0	0	2	3	1	2
CO2	3	3	0	3	3	0	0	0	0	0	0	2	3	3	2
CO3	0	3	0	2	3	0	0	0	0	0	0	2	2	3	2
CO4	0	0	2	3	3	0	0	0	0	2	0	2	2	3	2
CO5	0	0	2	3	3	0	0	0	0	2	0	2	2	3	3
CO6	2	2	3	3	3	2	2	2	2	3	2	3	3	3	3

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