Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol.14 , Issue 33s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Molecular strategies to inhibit ABC Transporters in Prevotella intermedia: Overcoming Periodontal Pathogenesis via Molecular Modelling and docking studies

Snigdha Bharadwaz[1], Dr Jishnu[2]

[1]Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai - 600077, India

[2]Department of Public Health and Dentistry, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical sciences (SIMATS), Saveetha University, Chennai - 600077, India

Email ID: bharadwazsnigdha@gmail.com

Cite this paper as: Snigdha Bharadwaz, Dr Jishnu (2025) Molecular strategies to inhibit ABC Transporters in Prevotella intermedia: Overcoming Periodontal Pathogenesis via Molecular Modelling and docking studies. Journal of Neonatal Surgery, 14, (33s) 1031-1037

ABSTRACT

Periodontal diseases, including gingivitis and periodontitis, are chronic inflammatory conditions driven by complex microbial interactions within the oral cavity. Prevotella intermedia, a Gram-negative anaerobic bacterium, is a key contributor to periodontal pathogenesis due to its virulence factors and ability to thrive in subgingival environments. Among its survival mechanisms, ATP-binding cassette (ABC) transporters play a crucial role in nutrient acquisition, toxin efflux, and antimicrobial resistance. This study aims to explore molecular strategies for inhibiting ABC transporters in P. intermedia using computational approaches such as molecular modelling and docking analysis. The three-dimensional structure of the ABC transporter protein was retrieved from the RCSB Protein Data Bank, while potential inhibitory ligands were selected from the Antimicrobial Peptide Database. Molecular docking was performed using ClusPro to evaluate protein–ligand interactions. The results demonstrated that selected peptides exhibited favorable binding affinities and stable interactions with key functional domains of the transporter. These findings suggest that targeting ABC transporters could impair bacterial survival and reduce pathogenicity. However, further experimental validation is required to confirm these computational predictions. This study highlights the potential of computational drug design in identifying novel therapeutic targets for periodontal diseases and provides a foundation for future translational research..

Keywords: Prevotella intermedia; ABC transporters; Molecular docking; Periodontal disease; Antimicrobial peptides; ClusPro; Computational drug design

INTRODUCTION

Periodontal diseases, encompassing gingivitis and periodontitis, are among the most prevalent chronic inflammatory conditions affecting the oral cavity worldwide. These diseases are characterized by inflammation, progressive destruction of the periodontal ligament, alveolar bone resorption, and eventual tooth loss if left untreated. The pathogenesis of periodontal diseases is multifactorial, involving complex interactions between pathogenic microorganisms and the host immune response. A key initiating factor is the disruption of the normal oral microbial balance, known as dysbiosis, which leads to the overgrowth of pathogenic species within dental plaque biofilms. This dysbiotic state triggers a cascade of host inflammatory responses, resulting in tissue destruction and disease progression.

Among the diverse microbial communities associated with periodontal disease, Prevotella intermedia, a Gram-negative, obligate anaerobic bacterium, plays a significant role in disease etiology. It is commonly isolated from subgingival plaque and periodontal pockets, particularly in cases of chronic periodontitis, necrotizing periodontal diseases, and pregnancy-associated gingivitis. P. intermedia exhibits a strong ability to adhere to host tissues and co-aggregate with other oral pathogens, contributing to the formation and maturation of complex biofilms. These biofilms provide a protective environment that enhances bacterial survival and resistance to antimicrobial agents.

The pathogenicity of *P. intermedia* is attributed to a wide range of virulence factors, including proteolytic enzymes that degrade host proteins, hemolysins that disrupt host cell membranes, and lipopolysaccharides (LPS) that stimulate inflammatory responses. Additionally, this bacterium employs sophisticated immune evasion strategies, such as modulation of host cytokine responses and resistance to phagocytosis, allowing it to persist within the host environment. These mechanisms collectively contribute to sustained inflammation and progressive periodontal tissue destruction. [1–6]

A critical factor underlying the survival, adaptability, and pathogenic potential of *P. intermedia* is the presence of ATP-binding cassette (ABC) transporters. These are highly conserved transmembrane proteins that utilize the energy derived from ATP hydrolysis to transport a wide variety of substrates across cellular membranes. ABC transporters are essential for maintaining cellular homeostasis and play a pivotal role in bacterial physiology.

Functionally, ABC transporters are involved in several key processes, including:

- **Nutrient uptake:** Facilitating the import of essential molecules such as peptides, sugars, and ions required for bacterial growth and metabolism.
- **Efflux of toxic compounds:** Removing harmful substances, including metabolic by-products and host-derived antimicrobial factors.
- **Antibiotic resistance:** Actively exporting antimicrobial agents out of the cell, thereby reducing intracellular drug concentration and contributing to multidrug resistance.

The role of ABC transporters in mediating antibiotic resistance and enhancing bacterial survival within hostile environments makes them attractive targets for therapeutic intervention. Inhibiting these transport systems can disrupt essential cellular processes, impair nutrient acquisition, and increase bacterial susceptibility to antibiotics, ultimately reducing virulence and pathogenicity.

Recent advancements in computational biology, particularly molecular modelling and docking studies, have provided powerful tools for identifying potential inhibitors of ABC transporters. These in silico approaches enable the prediction of protein–ligand interactions, binding affinities, and structural conformations, facilitating the rational design of targeted therapeutics. Compared to traditional drug discovery methods, computational techniques offer a cost-effective, time-efficient, and high-throughput strategy for screening potential drug candidates. [7-9]

In this context, targeting ABC transporters in *Prevotella intermedia* using molecular modelling and docking approaches represents a promising strategy for the development of novel therapeutic agents aimed at controlling periodontal infections. Such approaches not only enhance our understanding of bacterial pathogenesis at the molecular level but also pave the way for innovative and targeted treatment modalities in periodontal therapy. [10-11]

MATERIALS AND METHODS

Protein Structure Retrieval and Preparation

The three-dimensional structure of the ABC transporter protein was obtained from the RCSB Protein Data Bank. Where experimental structures were unavailable, homology modelling was employed.

Protein preparation involved:

- Removal of water molecules
- Addition of hydrogen atoms
- Energy minimization for structural stability

Ligand Selection and Preparation:

Potential ligands were selected from the Antimicrobial Peptide Database based on their antimicrobial activity.

Ligand preparation included:

- Geometry optimization
- Charge assignment
- Energy minimization

Molecular Docking Using ClusPro:

Docking simulations were conducted using ClusPro to predict binding interactions between the ABC transporter and selected ligands.

The docking process involved:

- Rigid-body docking
- Conformational sampling
- Clustering of low-energy complexes

Scoring and Analysis:

Docked complexes were evaluated based on:

- Binding energy scores
- Hydrogen bonding interactions
- Hydrophobic contacts
- Electrostatic interactions

Top-ranked poses were selected for further structural analysis.

RESULTS

Protein Structure Analysis (Fig 1)

The ABC transporter protein exhibited typical structural features, including nucleotide-binding domains (NBDs) and transmembrane domains (TMDs), essential for ATP hydrolysis and substrate transport.

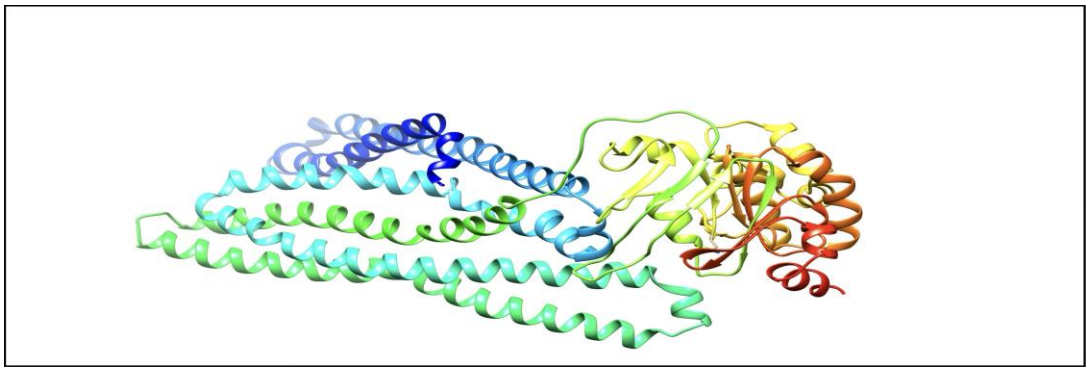
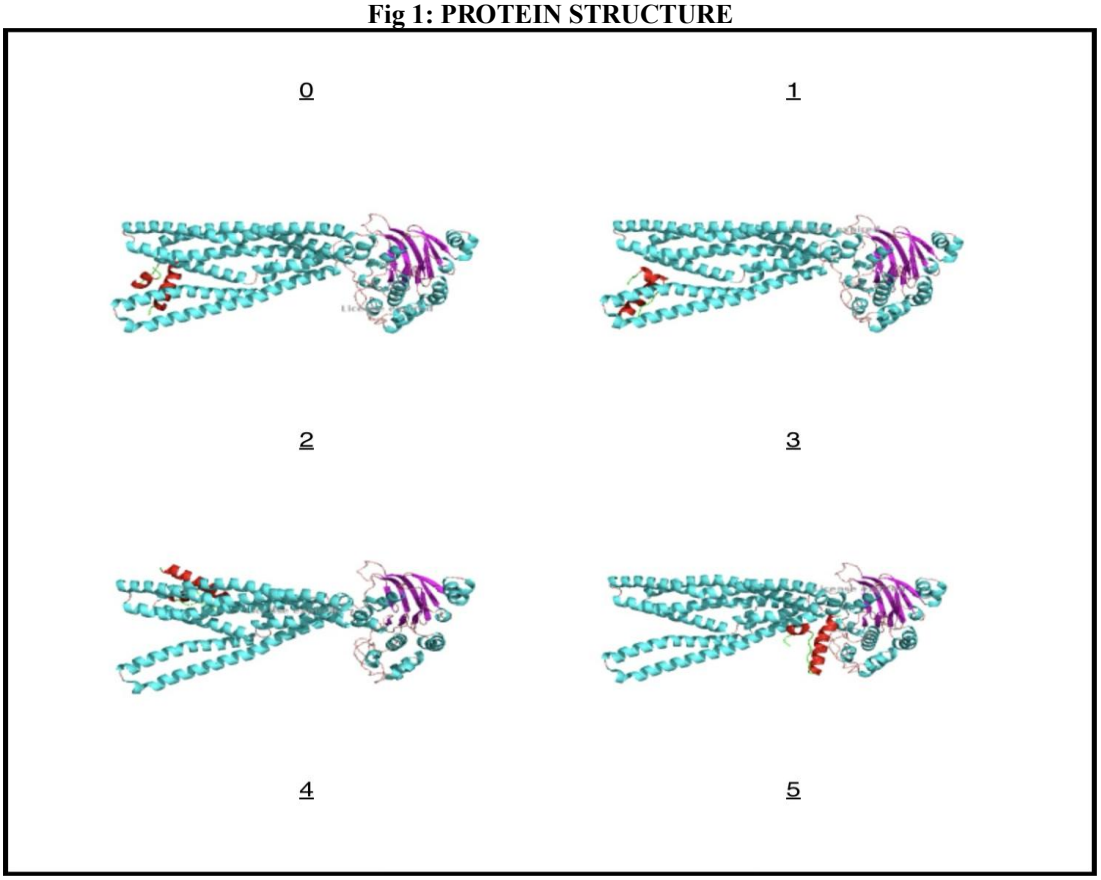


Fig 1: PROTEIN STRUCTURE



Peptide Structure Modelling (Fig 2 & Fig 3)

The selected peptides displayed stable secondary structures, including α-helices and β-sheets, facilitating effective interaction with membrane proteins.

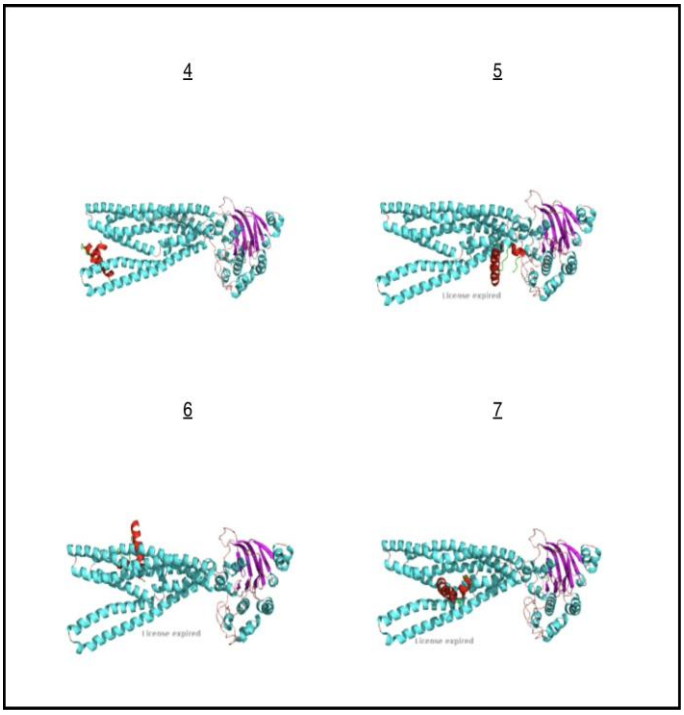


Fig 2 and 3: PEPTIDE MODELS

Binding Energy Analysis (Fig 3 Table)

Docking results revealed significant variation in binding energies among the peptides. Certain ligands demonstrated lower binding energy values, indicating stronger and more stable binding affinity toward the ABC transporter.

Cluster	Members	Representative	Weighted Score
0	100	Center	-775.2
		Lowest Energy	-862.9
1	76	Center	-777.1
		Lowest Energy	-892.0
2	76	Center	-872.4
		Lowest Energy	-872.4
3	69	Center	-810.6
		Lowest Energy	-885.3
4	59	Center	-746.9
		Lowest Energy	-820.2
5	58	Center	-900.4
		Lowest Energy	-900.4
6	55	Center	-755.5
		Lowest Energy	-870.3
7	45	Center	-833.1
		Lowest Energy	-833.1
8	42	Center	-764.0
		Lowest Energy	-854.1
9	37	Center	-772.3
		Lowest Energy	-855.2
10	36	Center	-799.3
		Lowest Energy	-833.8
11	33	Center	-761.3
		Lowest Energy	-846.9
12	31	Center	-751.0
		Lowest Energy	-814.9
13	27	Center	-763.7
		Lowest Energy	-833.5
14	24	Center	-799.0
		Lowest Energy	-808.6
15	22	Center	-759.3
		Lowest Energy	-818.5

Fig 3: TABLE DEPICTING DIFFERENT ENERGIES OF PEPTIDES

Docked Complex Visualization (Fig 4)

Visualization of docked complexes showed that peptides occupied critical binding pockets within the transporter, forming hydrogen bonds and hydrophobic interactions with key amino acid residues.

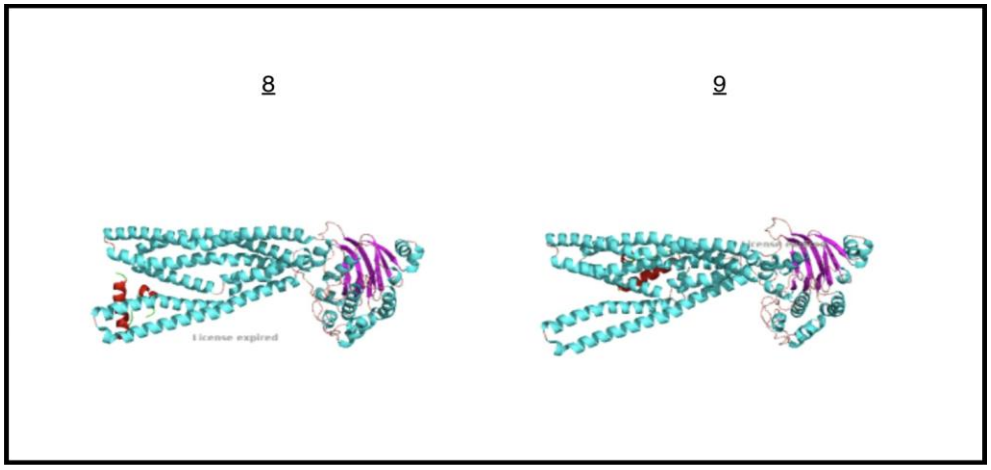


Fig 4: PEPTIDE MODELS

DISCUSSION

The inhibition of ATP-binding cassette (ABC) transporters in *Prevotella intermedia* represents a highly promising molecular strategy for the management of periodontal diseases. These transporters are essential for bacterial survival and adaptability, as they regulate the uptake of vital nutrients and the efflux of toxic substances, including antimicrobial agents. By facilitating these processes, ABC transporters contribute significantly to bacterial persistence within the hostile microenvironment of periodontal pockets.

The molecular docking analysis performed in this study identified several peptide candidates exhibiting strong binding affinity toward the ABC transporter protein. These findings suggest that such peptides may act as effective inhibitors by interacting with key functional domains of the transporter, thereby interfering with its normal activity. The inhibition of ABC transporters can have multiple downstream effects on bacterial physiology, including:

- **Reduction in bacterial virulence:** By limiting nutrient acquisition and disrupting essential cellular processes, bacterial growth and pathogenic potential may be significantly reduced.
- **Disruption of metabolic homeostasis:** Blocking transporter activity may impair the transport of metabolites, leading to metabolic imbalance and reduced bacterial viability.
- **Enhanced antibiotic susceptibility:** Inhibition of efflux mechanisms can increase intracellular concentrations of antimicrobial agents, thereby restoring or enhancing their efficacy against resistant strains.

These findings highlight the potential of targeting ABC transporters as a novel therapeutic approach in periodontal disease management. Such strategies may complement existing treatments, including mechanical debridement and antibiotic therapy, by addressing the underlying molecular mechanisms of bacterial resistance and persistence.

Understanding the molecular basis of bacterial pathogenicity is crucial for the development of targeted and effective therapies. ABC transporters play a pivotal role not only in bacterial survival but also in the transition from a commensal to a pathogenic state. In dysbiotic environments such as periodontal pockets, where microbial balance is disrupted, these transport systems enable bacteria like *P. intermedia* to adapt, proliferate, and evade host immune responses. Therefore, targeting these systems offers a strategic point of intervention to control disease progression.

Despite the promising findings, several challenges must be addressed before translating these results into clinical applications:

- **Specificity:** Achieving selective inhibition of bacterial ABC transporters without affecting homologous transporters in host cells is critical to avoid adverse effects.
- **Toxicity:** The safety profile of potential inhibitors must be thoroughly evaluated to ensure minimal cytotoxicity to host tissues.
- **Resistance development:** Long-term use of inhibitors may lead to adaptive resistance mechanisms, necessitating the development of combination therapies or multi-target approaches.

Nevertheless, computational approaches such as molecular modelling and docking provide valuable preliminary insights into protein–ligand interactions and significantly accelerate the drug discovery process. These techniques allow for high-throughput screening of potential inhibitors, reducing both time and cost associated with experimental studies.

LIMITATIONS AND FUTURE SCOPE

Limitations

- **Structural Availability:** One of the primary limitations of this study is the limited availability of high-resolution three-dimensional structures of ABC transporters specific to *Prevotella intermedia*. In the absence of experimentally determined structures, homology modelling may introduce inaccuracies, thereby affecting docking reliability.
- **Binding Site Prediction:** Accurate identification of ligand binding sites remains challenging, particularly when experimental validation data are lacking. Incorrect or approximate binding site predictions may influence docking outcomes and reduce the precision of interaction analysis.
- **In Silico Constraints:** Molecular docking studies are predictive in nature and may not fully replicate the complexity of biological systems. Factors such as protein flexibility, solvent effects, and dynamic interactions are not always fully accounted for.
- **Lack of Experimental Validation:** The absence of in vitro and in vivo validation limits the ability to confirm the biological efficacy and safety of the identified inhibitors.

Future Scope

- **Experimental Validation:** Future studies should include in vitro assays and in vivo models to validate the inhibitory effects of identified peptides on ABC transporters and assess their therapeutic potential.
- **Development of Selective Inhibitors:** Designing highly specific inhibitors targeting bacterial ABC transporters while minimizing off-target effects on host cells remains a key area of research.
- **Integration with Nanotechnology:** Nanoparticle-based drug delivery systems can be explored to enhance the targeted delivery, bioavailability, and controlled release of ABC transporter inhibitors.
- **Personalized Therapeutic Approaches:** Advances in microbial profiling and molecular diagnostics can enable personalized treatment strategies tailored to individual patient microbiota and disease severity.
- **Structure-Based Drug Design:** Improved structural elucidation using techniques such as cryo-electron microscopy and X-ray crystallography will enhance the accuracy of computational modelling and facilitate rational drug design.
- **Combination Therapies:** Combining ABC transporter inhibitors with conventional antibiotics or antimicrobial peptides may provide synergistic effects and reduce the risk of resistance development.

CONCLUSION

Molecular strategies targeting ABC transporters in *Prevotella intermedia* hold significant promise for advancing periodontal therapy. By disrupting key mechanisms involved in nutrient transport, toxin efflux, and antibiotic resistance, these approaches have the potential to reduce bacterial virulence and enhance treatment outcomes.

Molecular modelling and docking studies provide a powerful and efficient platform for identifying potential inhibitors and understanding protein–ligand interactions at the molecular level. Although challenges such as structural variability, specificity, and resistance mechanisms persist, ongoing advancements in computational biology, structural biology, and drug design are expected to address these limitations.

Ultimately, the integration of computational approaches with experimental validation and clinical research may lead to the development of targeted, effective, and personalized therapeutic strategies for the management of periodontal diseases

REFERENCES

1. Wu T, Jiang W. Computational-aided drug design strategies for drug discovery and development against oral diseases. Frontiers in Pharmacology. 2025 Nov 7;16:1678652.
2. Li Y, He X, Luo G, Zhao J, Bai G, Xu D. Innovative strategies targeting oral microbial dysbiosis: unraveling mechanisms and advancing therapies for periodontitis. Frontiers in cellular and infection microbiology. 2025 Apr 30;15:1556688.
3. Anika A. Targeting Porphyromonas gingivalis in Oral and Esophageal Cancer: A Bioinformatic and Medicinal Plant-Based Approach (Doctoral dissertation, AUW).
4. Alqarni, A., Hosmani, J., Alassiri, S.A., Al Qahtani, A.F.A., Al Magbol, M., Almubarak, H. and Patil, S., 2025. Periodontal Implications of Porphyromonas gingivalis-Derived Metabolites in Host Antioxidant and Anti-Inflammatory Mechanisms: A Computational Analysis. Medical science monitor: international medical journal of experimental and clinical research, 31, p.e949167.
5. Hashim NT, Babiker R, Chaitanya NC, Mohammed R, Priya SP, Padmanabhan V, Ahmed A, Dasnadi SP, Islam MS, Gismalla BG, Rahman MM. New insights in natural bioactive compounds for periodontal disease: advanced molecular mechanisms and therapeutic potential. Molecules. 2025 Feb 10;30(4):807.
6. Alam M, Gulzar M, Akhtar MS, Rashid S, Zulfareen, Tanuja, Shamsi A, Hassan MI. Epigallocatechin-3-gallate therapeutic potential in human diseases: molecular mechanisms and clinical studies. Molecular biomedicine. 2024 Dec

27;5(1):73.
7. Zarzosa-Moreno D, Avalos-Gómez C, Ramírez-Texcalco LS, Torres-López E, Ramírez-Mondragón R, Hernández-Ramírez JO, Serrano-Luna J, de la Garza M. Lactoferrin and its derived peptides: an alternative for combating virulence mechanisms developed by pathogens. Molecules. 2020 Dec 8;25(24):5763.
8. Malešević M, Jovčić B. Targeting Gram-Negative bacterial biofilm with innovative therapies: communication Silencing strategies. Future Pharmacology. 2025 Jul 3;5(3):35.
9. Gogeneni H. Porphyromonas gingivalis infection in gestational diabetes mellitus and survival in tobacco smokers.
10. Barros CH, Casey E. A review of nanomaterials and technologies for enhancing the antibiofilm activity of natural products and phytochemicals. ACS Applied Nano Materials. 2020 Aug 4;3(9):8537-56.
11. Chan NA. Discovery of\emph {Klebsiella aerogenes} CDI Receptor and Investigation of the Binding in the Receptor (Doctoral dissertation, UC Santa Barbara).