

Selection Of Suitable Drugs Against The Outer Membrane Lipoprotein Omp28 Of Porphyromonas Gingivalis

Soorya Ganesh¹, Abisha², Eswaran Maheswaran¹, Dhanraj Ganapathy^{1,*}

¹Department Of Prosthodontics, Saveetha Dental College And Hospitals, Saveetha Institute Of Medical And Technical Sciences, Saveetha University, Chennai 600077, Tamil Nadu, India.

²Saveetha Medical College, Saveetha Institute Of Medical And Technical Sciences, Saveetha University, Chennai 600077, Tamil Nadu, India.

***Corresponding Author:**

Dhanraj Ganapathy, Department Of Prosthodontics, Saveetha Dental College And Hospitals, Saveetha Institute Of Medical And Technical Sciences, Saveetha University, Chennai 600077, Tamil Nadu, India.

Email: dhanraj@saveetha.com

Abstract

Porphyromonas Gingivalis, A Gram-Negative Anaerobic Bacterium, Is Recognized For Its Significant Role In The Pathogenesis Of Inflammatory Periodontal Disease. Understanding The Outer Membrane Lipoprotein Omp28, A Key Factor In Its Virulence And Pathogenicity, Is Crucial For Developing Effective Control Strategies. Therefore, This In Silico Study Aimed To Investigate The Potential Of Antimicrobial Drug Agents Such As Metronidazole, Amoxicillin, And Clindamycin, For Clinical Applications Targeting Omp28. Molecular Docking Analysis Revealed That Amoxicillin Exhibited The Strongest Binding Affinity (-7.2) For Omp28 Compared To Metronidazole (-5.2) And Clindamycin (-6.8). This Suggests That The Interaction Between Amoxicillin And Omp28 May Be Particularly Relevant For Antimicrobial Activity Against P. Gingivalis. Furthermore, Pharmacokinetic Predictions Using Swissadme Indicated Favorable Water Solubility And Absorption Rates For All Three Drugs, Suggesting Good Drug-Like And Biocompatibility Properties. In Conclusion, These In Silico Findings Support The Potential Of Amoxicillin-Based Therapeutics For The Treatment Of P. Gingivalis Infections.

Keywords: Porphyromonas Gingivalis, Metronidazole, Amoxicillin, Clindamycin.

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Introduction

Porphyromonas gingivalis, a Gram-negative bacterium frequently detected within subgingival biofilms (Bhuyan et al., 2022), is recognized as a significant etiological agent in biofilm-associated infections, notably periodontal diseases such as gingivitis and periodontitis (Gerits, Verstraeten, & Michiels, 2017). These progressive inflammatory conditions, initiated by polymicrobial bacterial communities, result in the degradation of periodontal tissues and alveolar bone resorption. Furthermore, accumulating evidence implicates *P. gingivalis* in the pathogenesis of systemic disorders, including rheumatoid arthritis and orodigestive malignancies (Atanasova & Yilmaz, 2014). The complex interactions between *P. gingivalis* and the host immune system contribute to a dysregulated inflammatory response, thereby exacerbating tissue destruction and promoting disease progression. The biofilm-associated nature of *P. gingivalis* infections

presents a considerable challenge to conventional antimicrobial interventions (Atanasova & Yilmaz, 2014).

Several virulence factors have been produced by the bacterium that promote colonization, immune evasion, and tissue destruction (Aleksijević et al., 2022). Lipopolysaccharide, a cell wall component of anaerobic Gram-negative bacteria, stimulates immune responses in periodontal tissues, resulting in inflammation and the expression of matrix metalloproteinases that degrade connective tissues and bone (Cekici, Kantarci, Hasturk, & Van Dyke, 2014). Among the virulence factors of *P. gingivalis*, the outer membrane protein Omp28 has garnered attention as a potential therapeutic target due to its role in bacterial adhesion, invasion, and biofilm formation, all of which are crucial for establishing and maintaining infection (Aleksijević et al., 2022).

In silico studies have been utilized as a powerful tool to investigate the potential of drug

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compounds such as metronidazole, amoxicillin, and clindamycin. This approach utilizes computational methods to explore interactions between various drugs (metronidazole, amoxicillin, and clindamycin) and outer membrane lipoprotein Omp28 associated with the disease.

Materials and Methods

Study of outer membrane lipoprotein Omp28 of P. gingivalis

Outer membrane lipoprotein Omp28 is a surface protein of *P. gingivalis*, which is responsible for major periodontal diseases. The role of Omp28 in *P. gingivalis* interaction with host cells and its contribution to periodontal disease has been investigated. This protein, present in numerous *P. gingivalis* strains, shows promise as a target for drug-based therapies. Further research into Omp28 could pave the way for novel strategies in the prevention and treatment of this prevalent periodontal disease.

Selection of drugs against Omp28

P. gingivalis expresses the outer membrane lipoprotein (Omp28), exhibits a significant role in its virulence and host interactions. Targeting Omp28 represents a promising therapeutic strategy. Omp28 surface localization and involvement in crucial pathogenic processes make it accessible to drug interaction and inhibition. Different classes of antibiotics were commercially used to treat bacterial infections, including periodontal diseases. In this study, we used metronidazole, a nitroimidazole (disrupts bacterial DNA synthesis), amoxicillin (inhibits cell wall synthesis) and clindamycin (inhibits bacterial protein synthesis). The mechanisms of action of drugs could indirectly impact Omp28 expression, localization, or function by disrupting essential bacterial processes. Evaluating their potential interaction with Omp28 can provide insights into existing treatment efficacy and guide future drug development efforts towards this specific virulence factor. This approach combines the strategic targeting of a key virulence factor with the practical consideration of clinically relevant antimicrobial agents.

Molecular Docking and Simulation of Proteins using CB-Dock2

CB-Dock2 is a simple platform for molecular docking simulations for studying the interaction of Omp28 with metronidazole, amoxicillin, and clindamycin. The 3D structure of the Omp28 protein

and the ligand files in SDF format were used for the further process. CB-Dock2 can detect potential binding pockets on the surface of Omp28. Subsequently, it performs docking simulations using AutoDock Vina, predicting the binding poses and affinity scores (Vina scores) for each drug within the pockets.

CB-Dock2 explores the entire protein surface to identify potential interaction regions. The server also incorporates a template-based docking approach, utilizing information from known protein-ligand complexes with similar structures to enhance prediction accuracy, achieving a reported success rate of approximately 85% for binding pose prediction. The output from CB-Dock2 includes the predicted binding poses visualized in 3D, along with their corresponding Vina scores. Lower (more negative) Vina scores are considered as a stronger binding affinity. Moreover, CB-Dock2 uses a fast-docking algorithm to generate multiple binding poses. Particularly, the docking data includes binding scores and binding poses. CB-Dock2 integrated visualization tools have been utilized to analyse hydrogen bonds, and hydrophobic interactions.

Results and Discussion

Molecular docking is a crucial computational technique for predicting the binding affinity and three-dimensional structure of ligand-receptor complexes. It plays a vital role in identifying potential strong-binding ligands and screening compound libraries against a specific target protein (Meng, Zhang, Mezei, & Cui, 2011). *In silico* analysis allows for the comparison of the potential of metronidazole, amoxicillin, and clindamycin to interact with Omp28. The *in silico* analysis can reveal potential off-target interactions or allosteric effects that might influence Omp28 function, providing valuable insights for understanding their efficacy against *P. gingivalis*.

In silico data predicted the binding affinity and mode of interaction between Omp28 and drug targets (metronidazole, amoxicillin, and clindamycin), providing valuable insights into the potential mechanisms underlying antimicrobial activity. The drug compounds metronidazole displayed binding energy including -4.1, -3.8, -5.2, -3.7, -5.0, against Omp28 (2R2C) at the site of C1-C5, respectively. Similarly, amoxicillin showed -5.7, -5.4, -6.6, -5.2, -7.2 the CurPocket value and clindamycin showed -5.1, -5.7, -6.3, -5.1, -6.8 the CurPocket value against Omp28 at the site of C1-C5, respectively. Overall, amoxicillin had the highest binding value with

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Omp28 compared to the other drug compounds like metronidazole, and clindamycin.

Computational analysis reveals that amoxicillin exhibits a superior binding affinity (-7.2) for the *P. gingivalis* Omp28 (PDB: 2R2C) compared to metronidazole (-5.2) and clindamycin (-6.8) (Figure 1-3). Within the context of molecular docking studies, a more negative Gibbs free energy of binding signifies a thermodynamically favorable and stable ligand-receptor complex (Du et al., 2016). The observed lower binding energy for amoxicillin suggests a higher propensity for stable interaction with Omp28 relative to the comparator antibiotics. This strong interaction between amoxicillin and Omp28 posits a potential mechanism for enhanced antimicrobial activity. High-affinity binding of amoxicillin to Omp28 may lead to allosteric modulation or steric hindrance of its native function, thereby compromising bacterial viability and growth. This disruption of a critical protein could potentiate the bacteriostatic or bactericidal effects of amoxicillin.

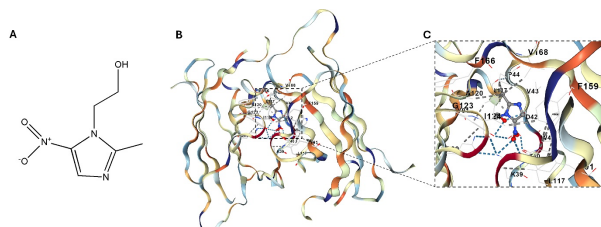


Figure 1. *In silico* analysis of Outer membrane lipoprotein (Omp28) and Metronidazole interactions. (A) Schematic representation of metronidazole generated using ChemDraw Pro 8 software. (B) Interactions and docked 3D structures of Omp28 (2R2C) with Metronidazole. (C) Box indicated the highest interaction between protein and ligand with the Vinascore (-5.2). Dashed lines are illustrated H-bond interactions.

Furthermore, *in silico* pharmacokinetic analysis using SwissADME indicates that amoxicillin possesses favorable physicochemical properties, namely high aqueous solubility and high gastrointestinal absorption (Bakchi et al., 2022; Bitew et al., 2021; Bojarska et al., 2020). Adequate aqueous solubility is crucial for drug dissolution and subsequent absorption into the systemic circulation. High GI absorption suggests efficient uptake of orally administered amoxicillin, leading to sufficient plasma concentrations required for therapeutic efficacy at the site of infection (Solli et al., 2023). These pharmacokinetic attributes support the potential for oral administration of amoxicillin in treating *P. gingivalis* infections.

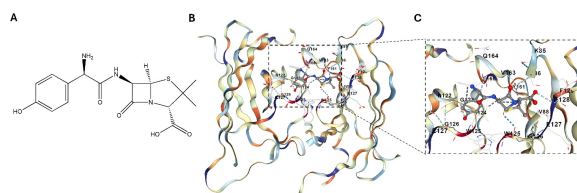


Figure 2. *In silico* analysis of Outer membrane lipoprotein (Omp28) and Amoxicillin interactions. (A) Schematic representation of amoxicillin generated using ChemDraw Pro 8 software. (B) Interactions and docked 3D structures of Omp28 (2R2C) with Amoxicillin. (C) Box indicated the highest interaction between protein and ligand with the Vinascore (-7.2). Dashed lines are illustrated H-bond interactions.

In silico study underscores the utility of computational methodologies in the rational design and optimization of antimicrobial agents targeting *P. gingivalis* similar like previous study (Satish et al., 2023). The identified high binding affinity of amoxicillin for Omp28, coupled with its predicted favorable pharmacokinetic profile, provides a compelling rationale for further investigation into amoxicillin-based therapeutics. Future research could explore structure-activity relationship studies involving amoxicillin analogs with potentially enhanced Omp28 binding, as well as the development of targeted drug delivery systems to improve local drug concentration within the periodontal environment, potentially enhancing therapeutic outcomes and mitigating systemic exposure or the selection of antibiotic-resistant strains (Varshan & Sankar, 2024). This study exemplifies the power of computational approaches in identifying promising drug candidates and guiding the development of more effective antimicrobial strategies.

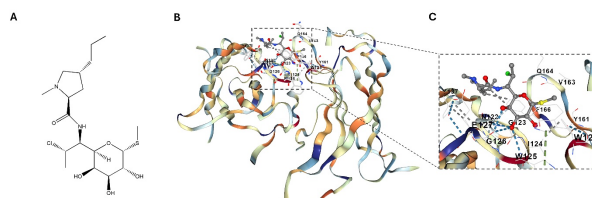


Figure 3. *In silico* analysis of Outer membrane lipoprotein (Omp28) and Clindamycin interactions. (A) Schematic representation of clindamycin generated using ChemDraw Pro 8 software. (B) Interactions and docked 3D structures of Omp28 (2R2C) with clindamycin. (C) Box indicated the highest interaction between protein and ligand with the Vinascore (-6.8). Dashed lines are illustrated H-bond interactions.

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Table 1. Study of interaction of commercially available drugs (metronidazole, amoxicillin, and clindamycin) with the outer membrane (Omp28) of *P. gingivalis*.

Protein/Ligand	C1	C2	C3	C4	C5
Metronidazole	-	-3.8	-5.2	-3.7	-5.0
	4.1				
Amoxicillin	-	-5.4	-6.6	-5.2	-7.2
	5.7				
Clindamycin	-	-5.7	-6.3	-5.1	-6.8
	5.1				

Conclusions

In silico investigation provides valuable insights into the potential of repurposing existing antimicrobial agents to target Omp28, a key virulence factor of *P. gingivalis*, the primary etiological agent of inflammatory periodontal disease. Molecular docking studies demonstrably identified amoxicillin as the highest binding affinity for Omp28 (-7.2) when compared to metronidazole and clindamycin. This strong predicted interaction suggests a possible mechanism by which amoxicillin could interfere with Omp28, potentially attenuating *P. gingivalis* pathogenicity and inhibiting bacterial growth.

Furthermore, the pharmacokinetic profiling of the tested drugs using SwissADME revealed favorable drug-like properties, including acceptable water solubility and absorption rates for all three compounds. This indicates their potential for effective delivery and bioavailability within the host. However, the superior binding affinity of amoxicillin for Omp28 positions it as a particularly promising candidate for further exploration. These computational findings lay the groundwork for future *in vitro* and *in vivo* studies to validate the observed interactions and assess the efficacy of amoxicillin, and its potential derivatives, in controlling *P. gingivalis* infections. The results underscore the utility of structure-based drug design in identifying potential therapeutic agents and provide a rationale for prioritizing amoxicillin in the development of targeted treatments against periodontal disease.

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