InSilico Drug Repurposing Integrated with Structural Insights to Identify Potent GtfB Targeted Antibiofilm Inhibitors in *Streptococcus mutans*

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Abstract

Background: *Streptococcus mutans* is a predominant cariogenic pathogen whose virulence is strongly driven by glucosyltransferases (GTFs) that synthesize extracellular glucans essential for robust biofilm formation and caries development. Among these enzymes, GtfB is a key determinant of sucrose-dependent biofilm architecture, making it an attractive molecular target for anti-cariogenic and anti-biofilm intervention. This study employed a drug repurposing strategy to identify small molecule GtfB inhibitors at the molecular level using an integrated computational approach.

Methods: A comprehensive structure based computational framework combining high throughput virtual screening, hierarchical molecular docking, and molecular dynamics (MD) simulations was used to characterize protein ligand recognition and complex stability. The crystal structure of GtfB enabled structure based screening of DrugBank approved drugs through a Glide workflow (HTVS → SP → XP), followed by Prime MM GBSA rescoring to refine binding affinity estimates.

Results: Among all screened compounds, the aminoglycoside antibiotic Amikacin showed the highest binding score and followed by Framycetin, Dibekacin, Ribostamycin, and Kanamycin. To validate docking predictions, a 100 ns Desmond MD simulation was performed for the top ranked GtfB Amikacin complex. The protein backbone RMSD stabilized around 2 - 3 Å, and the ligand RMSD remained closely aligned with the protein, with no dissociation from the binding pocket. RMSF analysis indicated limited fluctuations of active-site residues, and Amikacin maintained persistent hydrogen bonds, ionic contacts, and water mediated interactions with key residues such as Asp353, Asn481, Ala512, Lys989, and Glu990.

Conclusion: Overall, these results suggest that Amikacin forms a stable, energetically favourable complex with GtfB and highlight critical interaction features that can guide the rational design of next generation anti cariogenic and anti biofilm agents.

Keywords: *Streptococcus mutans*; Drug repurposing; Amikacin; Biofilm inhibition; Glucosyltransferase B