Machine learning and Cheminformatics Approach for Screening Lichen-Derived Inhibitors Targeting Mutant PBP4R200L in *Staphylococcus aureus*

Romita Guchhait[1,2], Shalini Mathpal[1,2], Tushar Joshi[1,3], P. Priyamvada[1,2], Sudha Ramaiah[1,2] and Anand Anbarasu[1,3]

1. Medical and Biological Computing Laboratory, School of Biosciences and Technology, Vellore Institute of Technology (VIT), Vellore, Tamil Nadu 632014, India

2. Department of Biosciences, School of Biosciences and Technology, Vellore Institute of Technology (VIT), Vellore, Tamil Nadu 632014, India

3. Department of Biotechnology, School of Biosciences and Technology, Vellore Institute of Technology (VIT), Vellore, Tamil Nadu 632014, India

(Corresponding author Email: sudhaanand@vit.ac.in)

Abstract

Penicillin-binding protein 4 (PBP4) plays a key role in β-lactam resistance in *Staphylococcus aureus*. The R200L mutation further enhances non-susceptibility, complicating therapeutic options. Therefore, the search for new therapeutics against mutant PBP4 is crucial. Lichen-derived natural compounds offer valuable prospects in this regard. Our study employed a machine learning approach to identify novel inhibitors targeting the R200L mutation. Predictive models, using six machine learning (ML) algorithms, were developed and evaluated through ROC curves, confusion matrices, and statistical metrics to classify lichen-derived compounds as active or inactive. The Extra Trees algorithm exhibited highest predictive accuracy of 81%, identifying 115 active lichen-derived compounds that were further subjected to drug-likeness and resemblance to β-lactam antibiotics. The top 23 compounds with structural similarity to β-lactam drug were further analyzed through molecular docking. Among the top 10 compounds, Barbatolic acid and Orcinyl lecanorate demonstrated better docking scores and stability in 200 ns molecular dynamics (MD) simulations and MM-PBSA analysis, in comparison with the reference compound. Moreover, DFT analysis revealed narrower smaller HOMO–LUMO gaps for both compound, highlighting their chemical stability and favorable reactivity. The findings underscores the utility of ML in identifying active natural compounds, paving the way for developing novel antimicrobial therapeutics in future.

Keywords: *Staphylococcus aureus*, PBP4, Lichen, Machine learning, Molecular docking, MD simulations