Title

From Proteome to Potential Drugs: Integration of Subtractive Proteomics and Ensemble Docking for Drug Repurposing against Pseudomonas aeruginosa RND Superfamily Proteins

Abstract

Pseudomonas aeruginosa (P. aeruginosa) poses a significant threat as a nosocomial pathogen due to its robust resistance mechanisms and virulence factors. This study integrates subtractive proteomics and ensemble docking to identify and characterize essential proteins in P. aeruginosa, aiming to discover therapeutic targets and repurpose commercial existing drugs. Using subtractive proteomics, we refined the dataset to discard redundant proteins and minimize potential cross-interactions with human proteins and the microbiome proteins. We identified 12 key proteins, including a histidine kinase and members of the RND efflux pump family, known for their roles in antibiotic resistance, virulence, and antigenicity. Predictive modeling of the three-dimensional structures of these RND proteins and subsequent molecular ensemble-docking simulations led to the identification of MK-3207, R-428, and Suramin as promising inhibitor candidates. These compounds demonstrated high binding affinities and effective inhibition across multiple metrics. Further refinement using non-covalent interaction index methods provided deeper insights into the electronic effects in protein–ligand interactions, with Suramin exhibiting superior binding energies, suggesting its broad-spectrum inhibitory potential. Our findings confirm the critical role of RND efflux pumps in antibiotic resistance and suggest that MK-3207, R-428, and Suramin could be effectively repurposed to target these proteins. This approach highlights the potential of drug repurposing as a viable strategy to combat P. aeruginosa infections.

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Anti-Bacterial Agents; Bacterial Proteins; Drug Repositioning; Humans; Molecular Docking Simulation; Proteome; Proteomics; Pseudomonas aeruginosa; Suramin; bemcentinib; protein histidine kinase; proteome; suramin; virulence factor; antiinfective agent; bacterial protein; proteome; suramin; antibiotic resistance; antigenicity; Article; benchmarking; binding affinity; drug repositioning; human; nonhuman; predictive model; proteomics; Pseudomonas aeruginosa; chemistry; drug effect; metabolism; molecular docking; procedures

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