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# Computational insights into shikimate pathway-derived phenolic acids as inhibitors of NorA efflux pump

Microorganisms use efflux pumps to regulate their internal environment by removing toxic substances including antimicrobial agents. Studies have supported drug efflux pumps (EP) as a participant in the emergence of resistance towards antimicrobial drugs. Of the EPs, the NorA remains the most studied druggable target. In this study, the shikimate pathway-derived phenolic acids were evaluated against NorA (PDB ID: 1PW4) in silico subsequent to in vitro evaluations. Of the 22 compounds evaluated, sinapic acid (-9.0 kcal/mol) and p-coumaric acid (-6.3 kcal/mol) had the best and most prominent affinity for NorA relative to the standard ciprofloxacin (-4.9 kcal/mol). A further probe into the structural stability, flexibility and compactness of the resulting NorA-phenolic acids complexes through molecular dynamic simulations over a 100-ns period revealed p-coumaric acid as the best inhibitor of NorA relative to the reference standard. In vitro results further complimented the findings of the in-silico modelling. The antimicrobial screening showed MIC values in the range 31.2 to 62.5 µg/ml against *S. aureus*, *E. coli*, and *P. aeruginosa*, and compounds were bactericidal. Studies further revealed a synergistic effect between the compounds and ciprofloxacin with MIC reductions 4 to 16 times against all three baemphasized textcterial cultures. Hence, molecular insights of receptor-ligand interactions and antimicrobial screening gained from the present investigation will provide a new vision for the development of potent NorA efflux pump inhibitors.*emphasized text*

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