Computational insights into phenolics as leads against bacterial penicillin-binding protein 3

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Introduction: Antibacterial resistance to β-lactams has been attributed to alterations in penicillin binding proteins (PBPs) coupled with β-lactams' inactivation by β-lactamase (Palacios *et al.*, 2020). Consequently, identification of novel class of therapeutics with improved modulatory action on the PBPs is imperative and plant secondary metabolites including the phenolics have found relevance in this regard (Al-Orphaly *et al.*, 2021; Alhadrami *et al.*, 2020; Zhao *et al.*, 2002). In this study, phenolics were computationally evaluated against PBP3 of *Pseudomonas aeruginosa*, a superbug implicated in several nosocomial infections.

Methodology: A library of phenolics with affinity for PBP3 of *Pseudomonas aeruginosa* was screened using structure-activity relationship-based pharmacophore and molecular docking approaches. Subsequent screening of the top 5 phenolics with more drug-likeness attributes, feasible synthetic accessibility and less toxicity characteristics was achieved through molecular dynamic (MD) simulation to understand their flexibility, compactness and stability upon binding to PBP3 over a 120 ns evaluation period.

Result: Except for epicatechin gallate, all the hit phenolics had significantly higher negative free binding energy than cefotaxime (-18.72 kcal/mol), with catechin 3-rhamside having the highest affinity (-28.99 kcal/mol) for PBP3. All the hits were stable at the active site of the protein with catechin 3-rhamside being the most stable (2.14 Å) and established important interactions with Thr487 and Arg489, implicated in the catalytic activity of PBP3. Furthermore, following binding of the test compounds, PBP3 became more compact (bound: 29.90 Å Vs unbound: 30.39 Å) with less fluctuation (bound: 0.95 Å Vs unbound: 1.23 Å) of the active site amino acid residues.

Discussion and conclusion: These observations are indicative of the potential of the test compounds as PBP3 inhibitor, with catechin 3-rhamside being the most prominent of the compounds that could be further improved for enhanced druggability against PBP3 *in vitro and in vivo*.

References:
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