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COMPUTATIONAL STUDIES ON ANTIBACTERIAL ACTIVITIES OF 6*β*-HYDROXYBETUNOLIC ACID AND ITS DERIVATIVES

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Antibiotic resistance is a major global health threat. Developing novel antibacterial agents with enhanced mechanisms against specific strains, supported by computational drug design, offers a promising solution to this challenge. Previous studies have shown that 6*β*-hydroxy betulinic acid (6*β*-HBA) possessed strong antibiotic activity (16 mg L^{-1}) against methicillin-resistant *Staphylococcus aureus* (MRSA) which has limited antibiotic activity. However, its synthetically modified derivatives demonstrated reduced antibacterial activity. Therefore, in this study, *in-silico* investigations were conducted to elucidate the mechanism underlying the antibacterial effects of 6*β*-HBA. Lupane-type triterpenoids feature a hydroxyl group at the C-6 position. The synthesised derivatives involved modifications at the C3-OH to C3-OAc, C6-OH to C6-C=O, and C17-COOH group to C17-COOR. Preliminary computational investigation on ligand interactions with penicillin binding protein 2a (PBP2a) from MRSA was carried out, using molecular docking and molecular dynamics (MD) simulations. Molecular docking analyses revealed strong binding affinities (–8.3 kcal mol^{-1}) for 6*β*-HBA and the derivatives which had free C17-COOH group, with PBP2a. Further validation through MD simulations confirms the stability of the ligand-protein complexes of 6*β*-HBA and identified key interactions with active site residues, such as ASP665, TYR664, and ASN624, of PBP2a, which are essential for inhibiting bacterial cell wall synthesis. However, no such interactions were observed for the synthetic derivatives without free COOH at C17. These *in-silico* results directly support and explain previous findings, where modification of the C17-COOH group led to a dramatic increase in MIC values and a complete loss of antibacterial activity against Gram-positive bacteria, including MRSA. Moreover, C3-OAC protected compound showed promising interactions with the acetate group and protein residues, which is again corroborated with the strong antibacterial activity obtained in *in-vitro* studies. Thus, this study provides molecular-level evidence that C17-COOH and the C3-OAc groups are essential for effective protein binding and highlights their critical role in designing potent antibacterial agents.

Keywords: Antibiotic resistance, 6*β*-hydroxybetulinic acid, Molecular docking, MRSA, Penicillin-binding protein 2a