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In Silico Elucidation of A Novel Peptide's Inhibitory Mechanism Against KPC-2-Beta-Lactamase

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Structured Abstract

Background: Antimicrobial resistance is a condition where antibiotics fail to treat pathogen-caused infections. *Klebsiella pneumoniae* carbapenemase-2 (KPC-2), a beta-lactamase enzyme produced by *Klebsiella pneumoniae*, is one of the five most harmful bacteria. It hydrolyzes strong antibiotics like imipenem and carbapenem. Antimicrobial peptides are naturally occurring compounds produced by numerous organisms. It can kill microbes due to their extensive antimicrobial action. This study aims to explain peptide 6B, which originated from frogs. The peptide sequence was modified to yield a 16-amino-acid peptide. In silico techniques were used to characterize the synthetic peptide and evaluate its inhibitory action against KPC-2.

Methods: The original 6B peptide sequence contained an unidentified amino acid residue, X, substituted with positively charged amino acids to generate multiple peptide variants. Physicochemical properties of the modified peptides were analyzed and compared with known amphibian-based antimicrobial peptides, resulting in the selection of a 16 amino acid variant, ALADDLQCRKRKFIDL. Structural prediction was performed using AlphaFold Colab to predict the modified 6B peptide's secondary structure. Molecular docking analysis was conducted using two docking platforms with different algorithms, ClusPro and HPEPDOCK, to analyze the peptide-protein interactions with KPC-2.

Results: Physicochemical properties and structural prediction showed that the modified 6B peptide with 16 amino acids is similar to known amphibian-based peptides and formed a stable alpha-helical structure. Docking results from using different docking platforms, ClusPro and HPEPDOCK consistently demonstrated the modified 6B peptide binding near the entrance of the KPC-2 "pocket" binding active sites. Distance analysis revealed the proximity of the peptide to 16 amino acid residues of KPC-2. This involves contact with Ser70, the residue at the catalytic site of KPC-2, suggesting a potential disruption of enzymatic activity via steric hindrance or obstruction of substrate access to the enzyme.

Conclusion: This study showed that the modified 6B peptide with 16 amino acids could potentially be an antimicrobial peptide due to the similarity in physicochemical properties with known amphibian-based peptide. Molecular docking results show the potential of the 6B peptide to bind on the KPC-2 "pocket" binding site. Distance measurements between residues of the peptide and the KPC-2 active sites increase the confidence level of the potential interactions.

Keywords: Antimicrobial peptide, KPC-2-beta-lactamase, antibiotic resistance, *in silico*, molecular docking

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