In silico determination, peptide engineering demonstration, and preliminary docking studies of potential antimicrobial peptides from cocosin-1 against methicillin-resistant *Staphylococcus Aureus* muramyl E (MurE) ligase

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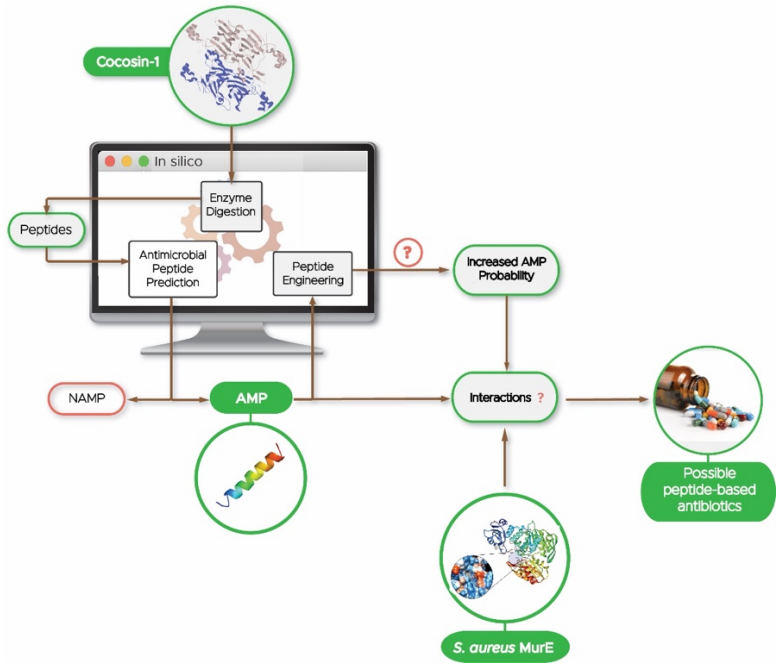
Abstract: alarming rise of antibiotic resistance triggered the search for antimicrobial alternatives such as plant-based antimicrobial peptides (AMPs) as they possess a wide range of bioactivities. The main objective of the study is to determine the in silico antimicrobial probability of peptides from enzyme-digested cocosin-1, improve the antimicrobial probability of selected peptides through engineering, and perform docking to analyze possible peptide-enzyme interactions. Cocosin-1 was separately digested using pepsin, trypsin, and chymotrypsin. The top three peptides with the highest antimicrobial probabilities produced per enzyme were subjected to site-specific amino acid (X) substitution while maintaining the conserved amino acids intact. Then, the top five engineered peptides with the highest antimicrobial probabilities and probability improvements were selected and their physicochemical properties were assessed. Finally, the original and engineered AMPs with the highest antimicrobial probabilities were modelled using PEP-FOLD3 and docked to Staphylococcus aureus muramyl E (MurE) ligase, our sample bacterial enzyme, using ClusPro 2.0 and visualize any significant binding interactions using PyMol and Visual Molecular Dynamics. In silico enzymatic digestion and AMP prediction yielded 9 AMPs (CAMPR3) and 25 AMPs (DeepAmPEP30). Upon performing location-specific triple amino acid substitution, the peptide 129QRSEREEGERHRW141 possessed the highest antimicrobial probability (82.45%) while 33QSPRRSVSSRNECRIERL50 exhibited the highest antimicrobial probability improvement (31.70%). Findings from the *in silico* peptide-MurE docking studies show salt bridge and hydrogen bonding interactions are present which could be essential during AMP-based enzyme inhibition. This study highlights those site-specific changes in the amino acid composition may possibly render antimicrobial property improvements of selected peptides.

Graphical abstract:



Keywords: antimicrobial resistance; antimicrobial peptides; cocosin-1, peptide engineering; amino acid substitution; muramyl E ligase (murE); docking studies

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