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In Vitro and *In Silico* Studies of Peptide Inhibitors of Antibiotic Resistance Enzymes

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Antibiotic drugs have had an extensive use in recent medical history for their ability to fight infectious diseases. Aminoglycoside antibiotics target gram positive and negative bacteria and are beneficial for several varying medical diseases. However, misuse or overuse of these drugs has resulted in creation and over expression of aminoglycoside modifying enzymes (AMEs), which alter the drugs chemical structure, preventing the antibiotic from reaching the host RNA. The primary focus of this research is the mechanism of chemical alteration of the aminoglycoside antibiotic paromomycin-I by the 3',5" phosphotransferase-IIIa AME and the inhibitory effect of a group of antimicrobial peptides on this enzyme.

Molecular docking and Molecular Dynamics (MD) simulations were employed to study the binding mode of selected antibiotics and antibacterial peptides against the phosphotransferase-IIIa enzyme. The analyses of both the conformational changes of the antibiotics ternary complexes and the peptide with the best binding affinity to the enzyme in the presence of ATP were performed using GROMOS 53a6 force field parameters with SPC water model.

An antibacterial peptide, chosen among a small library of selected peptides, yielded a greater binding affinity to the antibiotic binding site than the chosen antibiotics. As well, this peptide contained residues that were determined to occupy the similar space as the antibiotic, yielding an inhibition capability. The different and unique confirmations of the AME were also determined when bound with the either the antibiotic or peptide. The results from this research provide a novel insight into the structure of the enzyme and was able to address questions that were not possible to answer based solely on the available data from the enzymes solved crystal structure. There is currently little information regarding these complexes and the potential antibacterial peptide inhibitors. These analyses will help bind the gap between the available data for future pharmaceutical research and the overall goal of antibiotic resistance prevention.

Biography

Laleh Alisaraie is an Assistant Professor with the School of Pharmacy, Memorial University of Newfoundland, St. John's, Canada.

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