

## Investigating the Mechanism of Action of Pediocin-Plantaricin Antimicrobial Peptide using Atomistic Molecular Dynamics Simulations

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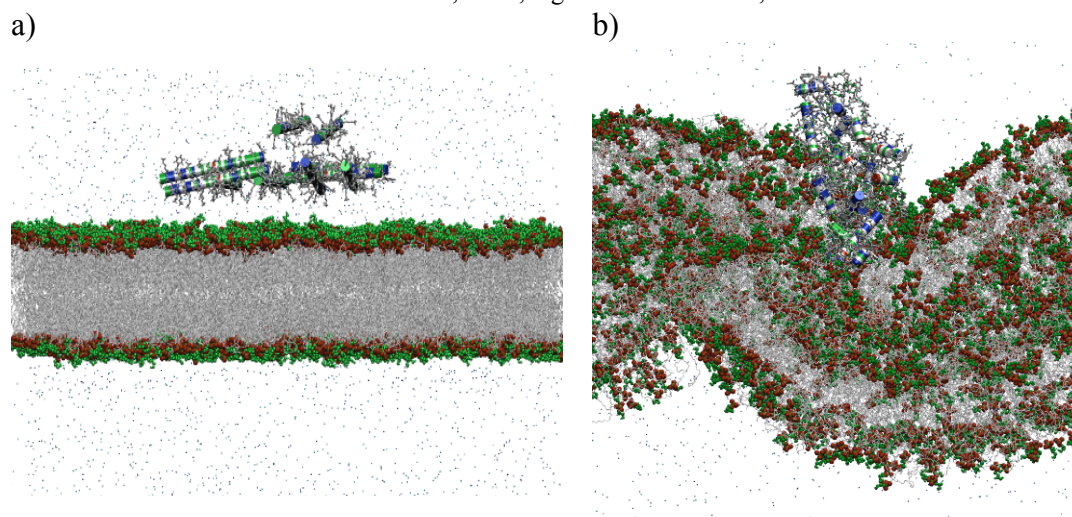
Hybrid antimicrobial peptides (AMPs) are designed for novel or enhanced antimicrobial activity, broad-spectrum targeting, decreased induction of antibiotic resistance, and reduced hemolytic activity and mammalian cytotoxicity.[1] A hybrid peptide sequence has been synthesized from the antimicrobial peptides pediocin A (N-terminal)[2] and plantaricin 149A (C-terminal).[3] Previous studies of circular dichroism and fluorescence spectroscopic studies have shown a disordered to ordered conformational transition of the peptide upon binding to POPG but not to POPC membranes. Optical microscopy measurements have indicated that at low concentrations the peptide causes the disruption of POPG membrane of vesicles and formation of small, heterogeneous complexes of phospholipids and peptides. In order to investigate the molecular mechanism of the hybrid peptide, molecular dynamics (MD) simulations were carried out using the GROMOS parameter set 54A7 at atomistic level and NpT ensemble. The simulated systems were analyzed with respect to time-dependent (peptide secondary structure and lipid tilt angle), and average properties (density profiles and deuterium order parameters). The peptide concentration was also taken into account to investigate the effect over the membranes.

The present simulations show that the peptide adsorbs on both PG and PC membranes via electrostatic interactions. Only upon binding to the PG surface there is an increase of helical content compared to the peptide in solution. Higher helical content is also observed for the single peptide embedded in PG compared to PC membranes, which is in agreement with experimental data. The density of the membrane medium makes conformational transition of the peptide embedded slower than on the surface of the membrane. The results suggest that PA-Pln149 does not form nanopores, but rather promotes the breakdown of membrane integrity through peptide aggregation followed by induction of negative membrane curvatures and membrane transition from a lamellar to a non-lamellar arrangement. Our data points to a mechanism of membrane disruption without deep penetration of the peptide and from a given peptide concentration threshold. Evidence for that comes from increased disorder of the membrane and persistent interactions between the peptide and membrane headgroups throughout the membrane disruption process (Figure 1). Our findings suggest that the hybrid peptide disrupt the membrane via a carpet-like mechanism (in a V-shape) which has also been postulated for the action of Pediocin A and Plantaricin 149A.[4]

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**Figure 1** Structural evolution of the system with ten peptide units interacting with a 100% POPG bilayer. Snapshots were taken from (a) 0 ns and (b) 100 ns of simulation. At the membrane, the glycerol groups are represented in green, the acyl chains are in green, and the oxygen atoms of the phosphate groups are represented in red. Water molecules were hidden to better visualization.

**Key-words:** antimicrobial peptide, mechanism of action, MD simulations, carpet.

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