

ABSTRACT

Treatment of diseases that attack the brain becomes difficult because of the barrier between the blood and the brain in the paracellular pathway, namely the blood brain barrier (BBB). This barrier is formed from interactions between proteins, namely Epithelial cadherin (EC), so that efforts to deliver drugs into the brain can be increased by inhibiting this interaction. Peptide ADTC5 (Ac-CDTPVC-NH₂) is one of the E-cadherin derivative peptides that can inhibit the intercellular barrier. Chitosan (Cs) is used in the drug delivery system as a carrier and vitamin C is a strong antioxidant because of its ability to neutralize free radicals. This study aims to determine the interaction between Cs, ADTC5 and vitamin C with E-cadherin using modeling, so that the hypothesis is obtained that the interaction causes conformational changes in the E-cadherin protein and increases BBB permeability and predicts the combination with the right sequence in delivery to the brain.

The intermolecular interactions of Cs 5 monomer, ADTC5 and vitamin C with the EC1 and EC2 domains of E-cadherin were studied *in silico* using molecular mechanics methods through three stages, namely: 1) Molecular docking using AutoDock Vina software to determine the interactions in the EC1-EC2 complex with Cs, EC1-EC2 with ADTC5 and EC1-EC2 with Vitamin C. 2) Molecular dynamics simulation or molecular dynamics (MD) using YASARA software to determine the conformational changes from the results of molecular docking for 50 ns. 3) Sequential docking to determine the effect of the order of ligand addition on the interaction energy. The analysis of the results in this study were the value of interaction energy, binding site, interaction distance, total potential energy, Root Mean Square Deviation (RMSD) and binding free energy.

The results of the study showed that the increase in BBB porosity using ADTC5 peptide interacting with the EC1 domain produced an interaction energy of -25.10 kJ/mol, chitosan can carry ADTC5 and vitamin C to the target cells by interacting with the EC2 domain producing an interaction energy of -30.12 kJ/mol, while vitamin C can interact with the EC1 domain producing an interaction energy of -21.34 kJ/mol. MD simulations showed that the conformational changes in the EC1-EC2 complex with ADTC5 were quite significant with an average total energy potential of -1638979.77 kJ/mol, the average difference in atomic position from the initial structure was 11.44 Å with a variation of ± 3.82 and a free binding energy of -17.79 kJ/mol. Sequential docking showed that the predicted combination with the correct sequence was the EC1-EC2...ADTC5...Vitamin C...Cs complex with an interaction energy of -30.12 kJ/mol.

Keywords : Blood brain barrier, Chitosan, Vitamin C, Molecular docking, Molecular dynamic