ABSTRAK

Alzheimer merupakan penyakit neurodegeneratif progresif yang ditandai oleh penurunan kadar asetilkolin (ACh) akibat hidrolisis ACh oleh enzim asetilkolinesterase (AChE) yang meningkat aktivitasnya. Uleine menunjukkan potensi tinggi sebagai inhibitor AChE dengan aktivitas penghambatan yang mendekati Fisostigmin dan sebanding dengan galantamine, serta memiliki nilai IC_{50} sebesar 0,450 μM. Penelitian ini bertujuan untuk mengevaluasi stabilitas kompleks uleine terhadap sisi aktif AChE melalui pendekatan penambatan molekul dan simulasi dinamika molekul selama 15 ns pada kondisi fisiologis menggunakan perangkat lunak YASARA-*Structure*. Parameter yang diamati meliputi nilai *Root Mean Square Deviation* (RMSD) penambatan ulang, energi ikatan uleine, serta RMSD *backbone* AChE dan *ligand movement* selama simulasi. Hasil penambatan uleine sebanyak 100 kali menghasilkan satu klaster konformasi terbaik. Simulasi dinamika molekul menunjukkan bahwa uleine berada dalam konformasi yang stabil dengan nilai ΔRMSD ≤ 2,000 Å baik pada *backbone* AChE maupun *ligan movement*. Interaksi dominan yang menstabilkan kompleks uleine–AChE meliputi interaksi ionik, aromatik, ikatan hidrogen karbon, dan *van der Waals* yang melibatkan residu Trp 84, Glu 199, dan Phe 330. Temuan ini mendukung potensi uleine sebagai kandidat inhibitor AChE serta memberikan wawasan terkait stabilitas interaksinya pada sisi aktif AChE untuk pengembangan terapi Alzheimer berbasis bahan alam.

Kata Kunci: Alzheimer, Asetilkolinesterase, Uleine, Dinamika Molekul.

ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by reduced levels of acetylcholine (ACh), resulting from its hydrolysis by the enzyme acetylcholinesterase (AChE), whose activity is elevated in the disease. Uleine has strong potential as an AChE inhibitor and has value inhibitory activity comparable to galanthamine and approaching that of physostigmine, with an IC_{50} value of 0.450 µM. This study aimed to evaluate the stability of the uleine–AChE complex at the enzyme's active site through molecular docking and 15-nanosecond molecular dynamic simulations under physiology conditions, using the YASARA-Structure software. The parameters assessed included the redocking root mean square deviation (RMSD), uleine binding energy, and the RMSD of both the AChE backbone and ligand movement throughout the simulation. Docking of uleine was repeated 100 times, yielding a single cluster of optimal binding conformations. Molecular dynamics simulations revealed that uleine maintained a stable conformation, with ΔRMSD values ≤ 2.000 Å for both the AChE backbone and ligand movement. The primary interactions stabilizing the uleine–AChE complex included ionic interactions, aromatic interactions, carbon–hydrogen bonds, and van der Waals forces, predominantly involving residues Trp 84, Glu 199, and Phe 330. These findings support the potential of uleine as a candidate AChE inhibitor and provide valuable insights into the stability of its binding at the enzyme's active site, thereby contributing to the development of natural product-based therapeutic approaches for Alzheimer's disease.

Keyword: Alzheimer, Acetylcholinesterase, Uleine, Molecular Dynamic.