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Computational investigation of anti-Alzheimer properties of novel Curcumin derivatives

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Curcumin, a naturally- occurring principal curcuminoid of turmeric has been used as a remedy in many Asian countries for the past century. Curcumin has shown remarkable results for the effect of various medical conditions such as cancers, liver diseases, heart diseases, osteoarthritis, and also diabetes. In this study, we discuss the effect of Curcumin and its newly synthesized derivatives as potential anti-Alzheimer compounds. Alzheimer's disease (AD) is a chronic, neurodegenerative disease that can cause dementia that could affect memory, thinking, and behavior. Due to its anti-oxidant, anti-inflammatory, and lipophilic action, Curcumin can improve the cognitive functions in Alzheimer's disease patients. There are satisfactory proofs for the effect of Curcumin on Alzheimer's disease such as decreased Beta-amyloid plaques (the main concern regarding AD) and delayed degradation of neurons. The main proteins that are associated with Alzheimer's disease and highly focused on this article are Amyloid Precursor protein (1AAP), Alzheimer's Beta – A (1IYT), Alzheimer's Beta A fibrils (2BEG), Acetylcholine esterase (4PQE), and Tau protein (2MZ7). In this computational investigation, energy-optimized structures of selected eight derivatives of Curcumin and parent compound, Curcumin were obtained using DFT calculations. To secure a better understanding of binding interactions of the above-mentioned proteins with our selected derivatives and parent compound as ligands, docking studies were performed. To check the validation of docking results, Donepezil, a clinical drug that is currently used for the AD was used as a reference molecule and docking studies were performed. Among the newly synthesized derivatives, which were suggested as potential anti-Alzheimer agents, two derivatives have shown promising results with higher binding affinities for each protein, according to docking studies. The derivatives that showed the highest binding affinities were selected along with the parent compound, Curcumin for each protein for Molecular Dynamics (MD) simulations. MD simulations were performed on protein-ligand complexes for 50 ns using CHARMM36 force field. The mean radius of gyration (Rg), root mean square deviation (RMSD), root mean square fluctuation (RMSF) and solvent accessible surface areas of the binding pockets were calculated and hydrogen bond analysis (HBA) was also performed. Rg and RMSD results indicated the stability of the protein-ligand complex throughout the simulation time. HBA results showed that ligand has significant number of hydrogen bonds with the ligand. RMSF and HBA results of derivatives were compared with the results of Curcumin, in order to explain the higher binding affinities of the derivatives. The MD analysis results along with docking results reveal that the two derivatives with higher binding affinities according to docking studies have the potential to act as promising anti-Alzheimer agents.

Keywords: Alzheimer, Curcumin, Derivatives, Docking, MD