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Computational investigation of anti-Alzheimer effects of Asiatic acid present in *Centella asiatica* (Gotukola) and its derivatives

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Centella asiatica (Gotukola) is a commonly used medicinal plant that has a wide range of beneficial effects such as antioxidant effects, anti-Alzheimer's disease effects, anti-inflammatory effects, anti-fertility effects, anti-tumor effect and antimicrobial effects. Asiatic acid, pentacyclic triterpenoid is one of the secondary metabolites present in *Centella asiatica* extract that has all the above pharmacological properties. In this study, the Anti- Alzheimer biological activities of Asiatic acid and its derivatives were mainly focused. Alzheimer's disease (AD) is a neurodegenerative disease. It results in loss of cognitive activity and memory and creates impairments in signaling among brain cells. Main proteins involved in Alzheimer's disease are Human amyloid precursor protein (1AAP), Acetylcholine esterase (4PDE), Tau protein (2MZ7), Alzheimer's beta-A (1IYT) and Alzheimer's beta-A fibrils (2BEG). In this study, twenty derivatives of Asiatic acid were considered to investigate the anti-Alzheimer activity and one of cholinesterase inhibitor; Donepezil which is commonly used as a clinical drug in Alzheimer was considered as a reference compound. Initially, energy minimized structures of Asiatic acid and its derivatives were obtained using molecular mechanical calculations. Docking studies were carried out for the reference compound, Asiatic acid and suggested derivatives with Alzheimer's disease related proteins. They were docked using Autodock4.0 to obtain their interactions with target proteins and to determine the amino acid residues in binding pockets. The binding affinities of derivatives with proteins were compared with the binding affinity of parent molecule, Asiatic acid and also with the binding affinity of the reference compound, Donepezil respectively. According to the results, several Asiatic acid derivatives have a higher binding affinity with acetylcholine esterase enzyme and some derivatives showed the high affinity with other proteins. The reasons for their highest binding affinities and further details were obtained by using molecular dynamics (MD) simulations. The parent molecule and several derivatives that have the highest affinity with each protein were then further analyzed using MD simulations. MD simulations were carried out on protein-ligand complexes for 50 ns using CHARMM36 force field. The trajectories obtained from MD simulations were used to calculate the radius of gyration (Rg), root mean square deviation (RMSD), root mean square fluctuation (RMSF), solvent accessible surface areas (SASA), and hydrogen bonding (HB). According to the Rg and RMSD results, the studied protein-ligand complexes were stable throughout simulation time. A significant number of hydrogen bonds were observed between the derivates and protein residues. Further, RMSF and HB results of derivatives were compared with the results of Asiatic acid, in order to investigate the higher binding affinities of the derivatives. The MD analysis results along with docking results indicated that the Asiatic acid derivatives with higher binding affinities according to docking studies have the potential to act as promising anti-Alzheimer agents.

Keywords: Asiatic acid, Alzheimer, Derivatives, Docking, MD