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Computational assessment of novel derivatives of gingerol as potential anti Alzheimer agents

D. M. I. M. Disanayaka[1] and J. N. Dahanayake[1*]

[1]Department of Chemistry, Faculty of Science, University of Kelaniya, Sri Lanka
jayangikadh@kln.ac.lk *

Ginger (*Zingiber officinale*) is commonly used as a spice and folk medicine, which helps to prevent heart diseases, high blood pressure and lung diseases. Gingerols, zingiberene, shogaols and monoterpenes are the principal components of the extract of ginger. Gingerol is known to provide protective effects against Alzheimer's disease (AD). AD is a neurodegenerative disease, resulting in loss of cognitive activity and memory and impaired signalling among brain cells. There are only a few approved drugs available for AD. Since developing synthetic chemicals as drugs is a challenging task, many pharmaceutical companies are now focused on the development of plant-derived drugs. Therefore, discovering natural products with medicinal properties for AD as lead compounds can be considered as an important task. There are five main proteins involved in AD: Amyloid precursor protein (APP), Tau protein, Amyloid β-protein (Aβ), Alzheimer's Beta A fibrils (Aβ - fibrils) and Acetylcholine esterase (AChE). In this study, the effects of 6-gingerol eight gingerol derivatives on those five main proteins highly associated with AD were considered to investigate anti-Alzheimer activities. Donepezil which is commonly used as a clinical drug in Alzheimer was considered as a reference compound. Initially, energy minimized structures of 6-gingerol, and its derivatives were obtained using molecular mechanical calculations. Docking studies were carried out for the 6-gingerol and suggested derivatives with AD related proteins. Through docking studies, secondary interactions with target proteins and amino acid residues in binding pockets were identified. The binding affinities of derivatives with proteins were compared with the binding affinity of the parent molecule (6-gingerol). According to the results, the parent molecule and studied derivatives have good binding affinities with Acetylcholinesterase. Therefore, further studies of molecular dynamic (MD) simulation studies were performed for the Acetylcholinesterase-ligand complexes for 50 ns using the CHARMM36 force field. The trajectories obtained from MD simulations were used to calculate the radius of gyration (Rg), root mean square deviation (RMSD) and root mean square fluctuation (RMSF). According to the Rg and RMSD results, the studied protein-ligand complexes were stable throughout the simulation time. Further, RMSF results of derivatives were compared with the results of 6-gingerol parent molecule, in order to investigate the higher binding affinities of the derivatives. The stability of the complexes is an essential feature which can provide information about the lifetime of the complex. Therefore, the ligand bound to the proteins can act as an inhibitor and inhibit the specific function of that protein. Since Rg and RMSD results showed the stability of the protein-ligand complexes, it can be stated that the studied gingerol derivatives have the ability to inhibit AChE. Therefore, the MD analysis results, along with docking results, indicated that the studied gingerol derivatives have the potential to act as promising anti-Alzheimer agents.

Keywords: Alzheimer's disease, Derivatives, Gingerol, Molecular docking, Molecular dynamics