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Computational assessment of novel derivatives of epigallocatechin gallate as potential anti-Alzheimer agents

R. P. G. A. P. Rajapaksha[1] and J. N. Dahanayake[1*]

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

Alzheimer's disease (AD) is a chronic, neurodegenerative disease that affects memory, thinking, and behaviour problems. The neuroprotective effects of natural products against AD have been studied in preclinical and clinical studies using in vitro and in vivo models. This computational chemistry study explores the effects of epigallocatechin gallate (EGCG) and its novel derivatives as potential anti-Alzheimer agents using computational chemistry. Among natural products that are tested against AD in clinical studies, catechins are a very commonly found constituent of green tea. Catechins are a bioactive ingredient of green tea and potential anti-oxidative and anti-inflammatory agents. In addition, various putative features associated with AD prevention and modification have been discovered in preclinical in vitro and in vivo studies of catechins. Due to its anti-inflammatory and antioxidant properties, EGCG has neuroprotective effects on AD patients' brains. EGCG inhibits the formation of neurotoxic beta-amyloid and regulates the formation of a soluble form of amyloid protein (sAPP) and prevents AD progression. Effects of EGCG and its derivatives on Amyloid precursor protein (APP), Amyloid β-protein (Aβ), Alzheimer's Beta A fibrils (Aβ - fibrils), Acetylcholine esterase (AChE), Butyryl choline esterase (BChE), and Tau protein were investigated in this study. Those proteins are highly associated with AD. The Density Functional Theory (DFT) calculations were used to get energy-optimised structures of EGCG and derivative EGCG-G1, EGCG-G2, PEGCG, EGCG-EPA, 5,3,4,3,4,5-O-ethyl-EGCG, and (-)/ (+)-epicatechin-3-O-gallate. The binding interaction of those ligands with each protein can be understood by molecular docking studies. To compare protein-ligand interactions, the protein-donepezil complex was used as a reference in molecular docking. Donepezil is a clinically approved drug for AD. Among considered ligands, EGCG, PEGCG, and (-)/ (+)-epicatechin-3-O-gallate showed better docking scores with AChE, BChE, and APP proteins. Those protein-ligand complexes that showed the best docking scores and protein-donepezil complexes were taken to further analysis of Molecular Dynamics simulations (MD). MD simulations were done for a 50 ns period on protein-ligand complexes which are selected according to docking scores. In MD simulations, CHARMM36 forcefield was used for protein. For ligands, external sources were used for generating topology. The parameters that were used for MD analysis to determine the stability of protein-ligand complexes were Radius of gyration (Rg), Root Mean Square Deviation (RMSD), and Root Mean Square Fluctuation (RMSF). The MD analysis, along with docking studies, revealed that the EGCG and derivative PEGCG can act as anti-Alzheimer agents due to their effects on important AD-related proteins.

Keywords: Molecular docking, Molecular dynamics MD, Radius of gyration, RMSD, RMSF