Chromenone-based GSK-3ß inhibitors as potential therapeutic targets for cardiovascular diseases: In silico study, molecular dynamics, and ADMET profiles

ABSTRACT

Glycogen synthase kinase-3 beta (GSK-3ß) regulates glycogen metabolism and many different cellulars, including apoptosis, signaling, and neural. It is a crucial therapeutic receptor in heart disease, type 2 diabetes, and Alzheimer's. In this study, using computational methods, flavonoid compounds were investigated for potential inhibitors against GSK-3ß. Virtual screening was utilized to investigate flavonoid compounds obtained from the PubChem database. Structure of human heart mitochondria of GSK-3ß receptor constructed by homology modeling. Best binding poses were discovered via in silico molecular docking simulation. We surveyed noncovalent interactions among amino acid residues involved in the active site of the modeled Protein and compounds via molecular docking and molecular dynamics (MD). Moreover, ADMET characteristics of best docking conformers have been investigated. The obtained results revealed that compound 1 containing chromenone moiety with binding energy H-bond -11.4 kcal/mol inhibited effectively binding pocket of the GSK-3ß receptor. Moreover, MD simulation analysis (RMSD and radius of gyration indicated complex of the compound and GSK-3b receptor remained stable throughout 100 ns MD simulation, and also analysis of ADMET profiles revealed that selected compounds had good drug-likeness and pharmacokinetic properties. Hence, it was suggested that compounds with chromenone scaffold could potentially inhibit GSK3ß. Structural modification of the chromenone derivatives may result in the discovery of promising candidates for identifying novel drugs as GSK-3ß inhibitors.