

Title: Identification of Helicobacter pylori-carcinogenic TNF-alpha-inducing protein inhibitors via daidzein derivatives through computational approaches

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Abstract: Gastric cancer is considered a class 1 carcinogen that is closely linked to infection with Helicobacter pylori (H. pylori), which affects over 1 million people each year. However, the major challenge to fight against H. pylori and its associated gastric cancer due to drug resistance. This research gap had led our research team to investigate a potential drug candidate targeting the Helicobacter pylori-carcinogenic TNF-alpha-inducing protein. In this study, a total of 45 daidzein derivatives were investigated and the best 10 molecules were comprehensively investigated using in silico approaches for drug development, namely pass prediction, quantum calculations, molecular docking, molecular dynamics simulations, Lipinski rule evaluation, and prediction of pharmacokinetics. The molecular docking study was performed to evaluate the binding affinity between the target protein and the ligands. In addition, the stability of ligand-protein complexes was investigated by molecular dynamics simulations. Various parameters were analysed, including root-mean-square deviation (RMSD), root-mean-square fluctuation (RMSF), radius of gyration (Rg), hydrogen bond analysis, principal component analysis (PCA) and dynamic cross-correlation matrix (DCCM). The results has confirmed that the ligand-protein complex CID: 129661094 (07) and 129664277 (08) formed stable interactions with the target protein. It was also found that CID: 129661094 (07) has greater hydrogen bond occupancy and stability, while the ligand-protein complex CID 129664277 (08) has greater conformational flexibility. Principal component analysis revealed that the ligand-protein complex CID: 129661094 (07) is more compact and stable. Hydrogen bond analysis revealed favourable interactions with the reported amino acid residues. Overall, this study suggests that daidzein derivatives in particular show promise as potential inhibitors of H. pylori.

Keywords: Helicobacter pylori; ADMET; DFT; computer-aided drug design; gastric cancer; molecular docking; molecular dynamic simulation.

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