Title: Docking and Molecular Dynamics Simulation Studies of Interactions between Cyclooxygenases Enzymes and Celecoxib Drug

Introduction: The major enzymes responsible for the synthesis of Prostaglandins (PGs) are cyclooxygenases (COXs) which have been identified into two isoforms, known as COX-1 and COX-2. COX-1, the pre-dominantly form of the enzyme, is expressed throughout the body and performs a number of homeostatic functions, while COX-2 expression is associated with inflammation, pain and other pathologies such as cancer proliferation. Both enzymes are sensitive to inhibition by conventional Nonsteroidal Anti-Inflammatory Drugs (NSAIDs). Efforts have been done to develop COX-2 selective inhibitors in order to reduce the classical side-effects. In this study, we have employed homology modeling, molecular dynamics (MD) simulation, and molecular docking to analyze the interactions of Celecoxib (selective COX-2 inhibitor) with both COX enzymes and specify their effective binding sites.

Method: The amino acid sequences of COXs, taken from the NCBI Web site were loaded to the SWISS-MODEL server (A fully automated protein structure homology-modeling server) to obtain 3D structures of the receptors. The crystal structures of 1Q4G and 3NT1 were obtained as templates for COX-1 and COX-2, with sequence identities of 93.85% and 88.2% respectively.
Resulting 3D structures of COX-1 and COX-2 were submitted to Gromacs simulation package for energy minimization and molecular dynamics simulation. Two separate simulations, each for 10 ns were carried out on COX-1 and COX-2 at 310 K. Both enzymes were first dissolved in water and the systems were neutralized by adding suitable ions. Analysis of RMSD plots and Gyration radiuses confirmed that final structures are equilibrated. On the other hand, the Celecoxib structure was drawn by GaussView and optimized by Gaussian 03. We used HF method and 3-21G basis set for optimizing this drug. Finally, the molecular docking of Celecoxib to COX enzymes were carried out by Molegro Virtual Docker package in order to analyze the interactions of studied enzymes with Celecoxib.

Results: The main purpose in drug-receptor docking is to specify the effective interactions of drug with various aminoacids of the receptor. In this study the main enzyme residues (responsible for interactions between COX enzymes and Celecoxib drug) and their respective total interaction energies, were obtained and tabulated using the Molegro Virtual Docker. These results can be used in designing new derivatives of Celecoxib as potent and selective COX-2 inhibitors.

Keywords: Cyclooxygenase, Molecular Dynamics Simulation, Molecular Docking Simulation, Celecoxib, NSAIDs.