ABSTRACT

Type 2 diabetes mellitus is a chronic metabolic disorder characterized by prolonged hyperglycemia, which can lead to complications in organs such as the retina, kidneys, and peripheral nerves. Under hyperglycemic conditions, glucose continues to be passively absorbed through insulin-independent GLUT transporters, resulting in glycolytic saturation and activation of the polyol pathway. Activation of this pathway then causes sorbitol accumulation, which induces osmotic and oxidative stress. Aldose reductase is the key catalytic enzyme of the polyol pathway and thus represents a potential target for preventing these complications. Triterpenoid compounds such as ursolic acid and ganoderic acid have been reported to inhibit aldose reductase in vitro, with ursolic acid also previously evaluated in silico through molecular docking. This study aimed to predict the molecular mechanisms of both compounds in inhibiting aldose reductase using molecular dynamics simulations. Aldose reductase (PDB ID: 2HV5) was employed together with ursolic acid and ganoderic acid, as well as zopolrestat serving as a control. Simulations were carried out at 300 K and 1 bar, followed by analyses of conformational stability using RMSD and interaction strength through electrostatic and van der Waals energies. The results showed that ursolic acid exhibited lower interaction energy and formed more stable interactions with catalytic residues such as His-110 and Trp-111 compared to ganoderic acid. The relatively smaller structure of ursolic acid further supported optimal interactions within the active site. These findings suggest that ursolic acid has greater potential as an effective aldose reductase inhibitor compared to ganoderic acid.

Keywords: *molecular dynamics, aldose reductase, diabetes complications, ursolic acid, ganoderic aci*