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The affinity of the major compounds of bitter melon to receptors for insulin in the PI3K-AKT signaling pathway: computational chemistry insight

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The World Health Organization reports diabetes as the fifth leading global cause of death. Bitter melon (*Momordica charantia*) is an herbaceous plant used for the treatment of diabetes. It includes insulin-like compounds such Charantin, Momordicine II and Cucurbitacine I with anti-diabetic properties. Insulin is widely used to treat type 1 and 2 diabetes, maintaining stable glucose levels in the body. Insulin-like compounds from bitter melon bind to the insulin receptor, regulating glucose absorption and metabolism by activating insulin signaling through the PI3K/AKT pathway. This enhances insulin sensitivity in diabetics by promoting glucose uptake in skeletal muscles via the translocation of glucose transporter type 4 (GLUT4) to the cell surface. AKT (Protein Kinase B) phosphorylates key regulatory proteins like AS160, facilitating the movement of GLUT4 from vesicles, enabling glucose entry into cells for metabolism. AKT also stimulates glycogen synthesis by activating glycogen synthase (GS), converting glucose into glycogen. This combined effect of enhancing glucose uptake and glycogen storage helps lower blood sugar levels effectively. In this research, the aim estimates the binding affinity of major cytochemical in bitter melon by docking analysis. The twenty compounds in bitter melon were selected by literature analysis, and they were downloaded by PubChem in SDF format and translated into PDB through OpenBabel 3.1.1. Then download the 3D structure of insulin receptor protein from the protein data bank (PDB ID: 1IR3). Cleaned the downloaded receptor protein using the Discovery Studio 2021 Client. Molecular docking is performed by Autodock 4.2 and a Lamarckian genetic algorithm. In an in-depth review of 20 compounds that bind to insulin receptor protein (1IR3). Momordicilin has the highest binding affinity (lowest binding energy), and Momordicoside L has the lowest binding affinity (highest binding energy). The ascending order shows the lowest binding affinity to the highest binding affinity, such as Momordicoside L (-2.05 kcal/mol) < Vicine (-3.61 kcal/mol) < Karaviloside XI (-4.15 kcal/mol) < Kuguaglycoside C (-4.38 kcal/mol) < Momordicin II (-4.31 kcal/mol) < Cucurbitacin C (-4.53 kcal/mol) < Momordicoside K (-4.80 kcal/mol) < Momordicoside I (-5.10 kcal/mol) < Cucurbitacin B (-5.19 kcal/mol) < Cucurbitacin E (-5.29 kcal/mol) < Charantin (-5.25 kcal/mol) < Charantoside C (-5.69 kcal/mol) < Karaviloside III (-5.50 kcal/mol) < Momordicin I (-6.22 kcal/mol) < Cucurbitacin I (-6.28 kcal/mol) < Karavilagenin A (-6.44 kcal/mol < Kuguacin H (-6.49 kca/mol) < (-) Momordenol (-6.51 kcal/mol) < Kuguacin J (-6.59 kcal/mol) < Momordicilin (-7.12 kcal/mol). Momordicilin interacts with insulin receptor protein's binding sites, consisting of covalent hydrogen bonds with amino acid residues PRO A1106, PRO A1093, and alkyl and pi alkyl linkages with amino acid residues PRO A1093, PRO A1103. The binding affinity of compounds with binding energy greater than (-7) kcal/mol increases because those compounds bind well with the 1IR3 protein receptor and enhance insulin & also them are suitable for drug development. This computational analysis contributes to the design of new structural molecules, potentially improving the creation of drugs, especially for the production of more effective antidiabetics.

Key words: Auto-docking, Bitter melon, Diabetics mellitus, Insulin receptors, PI3K-AKT signaling pathway