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Comparative study of antidiabetic potential of major phytochemicals in bitter melon (*Momordica charantia*): Computational insights

Prasangika F. N.* and Pandithavidana D. R.

Department of Chemistry, Faculty of Science, University of Kelaniya, Kelaniya, Sri Lanka.
naliniprasangika@gmail.com*

Diabetes mellitus is one of the most common diseases that can be found in both developed and developing countries. The fruit of bitter melon, *Momordica charantia* is popular among Asians because of its significant antidiabetic potential. The human GSK-3 protein is known to phosphorylate and inactivate glycogen synthase, which is utilized as a negative regulator in the hormone-regulated maintenance of glucose homeostasis. The antidiabetic substances (Charantin, Vicine, Momordenol, and Momordicilin) which derived from bitter melon activate glycogen synthase by blocking the active site of the GSK-3 protein. These ligands enhance insulin sensitivity and promote glucose uptake into the cell. This research was aimed to investigate and compare the binding affinities of these antidiabetic phytochemicals with the GSK-3 protein. The molecular structures of the ligands were retrieved from the PubChem database. Ligands were optimized geometrically using the density functional theory with B3LYP functional and 6-311G++ (d, p) basis set, employing software of Gaussian-09. The 3D structures of GSK-3 protein molecules were downloaded from the Protein Data Bank (PDB ID: 1Q5K). It contains both isoforms, GSK-3 α and GSK-3 β . The Lamarckian genetic algorithm was used for docking studies using AutoDock 4.2. Molecular interactions between protein-ligand (antidiabetic substances) complexes, bond lengths, and amino acids in binding pockets were analyzed by using the Discovery Studio. Among these four anti-diabetic substances used for this computational study, Momordenol, with the highest binding affinity (-9.91 kcal/mol) for GSK-3 protein, forms a strong and stable complex with the protein. This strong binding enhances its inhibition efficacy by preventing GSK-3 from functioning effectively, leading to greater inhibition potential. In this study, we also compared the binding energies and inhibition constants of N-(4-Methoxybenzyl)-N'-(5-Nitro-1,3-Thiazol-2-Yl) Urea (AR-A014418), a known GSK-3 inhibitor (-7.59 kcal/mol, 2.74 μ M), with Momordenol (-9.91 kcal/mol, 0.05411 μ M), Momordicilin (-9.51 kcal/mol, 0.10359 μ M), Charantin (-8.49 kcal/mol, 0.59355 μ M), and Vicine (-6.71 kcal/mol, 11.99 μ M). The results show that Momordenol has the strongest binding affinity and the lowest inhibition constant, indicating superior inhibitory potential. By using AR-A014418 as a reference, this comparison highlights Momordenol as a promising therapeutic candidate for targeting GSK-3 protein, offering potential advantages in drug development. The comparative study exhibited the anti-diabetic potential of these four major phytochemicals present in the fruit of bitter melon follow the order of Momordenol > Momordicilin > Charantin > Vicine. These computational insights encourage the design of structurally novel antidiabetic substances which will be more economical and beneficial in the pharmaceutical industry.

Keywords: *Momordica charantia*, GSK-3 protein, Optimization, Molecular docking, Momordenol.