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In Silico Studies: the Potential of Mangiferin as Antidiabetic Natural Compound

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Abstract.

Mangifera indica is a herbal plant that contains the active compound mangiferin, which has traditionally been used as a diabetes treatment. The goal of this research is to determine the bioactivity of mangiferin as an anti-diabetic substance in silico. Several published papers refer to the chemical structure of mangiferin. The protein Dipeptidyl peptidase IV was used as the study's target protein (DPP-4). PyMOL v2.5.2 software is used to remove water molecules, and PyRx 0.8 software is used to perform molecular docking experiments between the compound and the target protein. Based on its affinity value and intermolecular interactions, the results showed that mangiferin had a higher potential as an antidiabetic. The comparative value of DPP-4 protein binding affinity with mangiferin was -8.2, while the comparative value of DPP-4 protein binding affinity with the control compound saxagliptin was -7.1. The toxicity test revealed that mangiferin is not a carcinogen.

Keyword : In silico, Diabetes mellitus, *Mangifera indica*, Mangiferin, DPP-4

1. Introduction

In 2014, WHO estimated 387 million adults were living with diabetes. A 2017's report from the International Diabetes Federation (IDF) revealed that nearly half a billion adults are estimated to be living with diabetes (1). According to

statistics, about 2.8% of the world's population suffers from this disease and it is expected to increase to more than 5.4% by 2025 (2). Diabetes mellitus is a metabolic disease characterized by chronic hyperglycemia due to defects in insulin secretion, insulin action, or both (3). Diabetes mellitus is classified into two main types: namely insulin-dependent diabetes mellitus (IDDM, Type I) and non-insulin dependent diabetes mellitus (NIDDM, Type II) depending on insulin deficiency or peripheral insulin resistance of tissues respectively (4).

Herbal plants can be used as plant-based medicines which are proven to be better in dealing with a disease, including diabetes mellitus because of fewer side effects, relatively low cost and some plants are very easy to find (5). *Mangifera indica* is a plant that belongs to the Anacardiaceae. The genus Mangifera contains 69 species of which less than half, produce edible fruit (6). *Mangifera indica* has potential as an antidiabetic agent because it contains polyphenols, flavonoids including quercetin, and glycosylated xanthones such as mangiferin (7). In this study, we found the bioactivity of mangiferin compounds in *Mangifera indica* for antidiabetic properties based on the in silico test.

2. Material and Method

2.1. Ligands Preparation

The 3D chemical structure and SMILES of the ligand compound were adopted from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) with ID : CID 5281647 and canonical smile : C1=C2C(=CC(=C1O)O)OC3=C(C2=O)C(=C(C(=C3)O)C4C(C(C(C(O4)CO)O)O)O)O. The chemical structure of the ligands and three-dimensional (3D) were sketched using Avogadro.

2.2. Target Selection

Dipeptidyl peptidase IV (DPP-4) with the code 1PFQ of PDB is used as a targeted protein, which regulate incretins and consequently associated with the pathophysiology of blood glucose (8). The molecular structure was taken from

published literature and validated using Uniport (https://www.uniprot.org), and PDB (Protein Data Bank https:///www.rcsb.org/pdb). Water molecule then removed from the DPP-4 structure using PyMOL v2.5.2.

2.3. Molecular Docking

Molecular docking experiments were carried out using Vina Wizard feature integrated into the PyRx 0.8, which reacts to the natural compound Mangiferin. The control compound used in this study is saxagliptin.

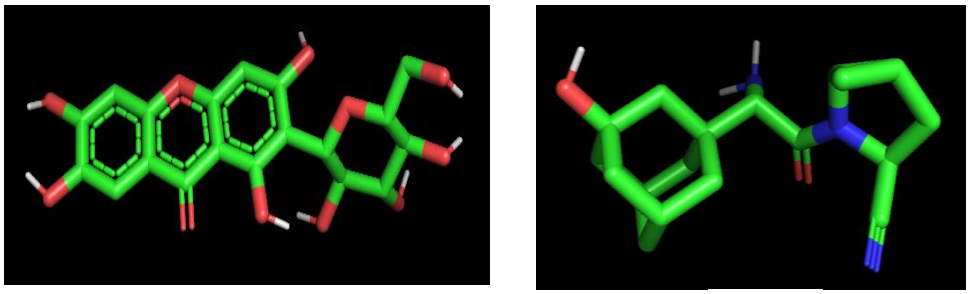
2.4. Visualization of Molecule and Small Molecule Interaction

Interaction between the target protein-ligand (mangiferin - DPP-4), and control ligand (saxagliptin) with known target protein (DPP-4) visualized and analyzed using PyMol v 2.5.2.

2.5. Compound's Properties and ADMET Predictions

AdmetSAR (http://lmmd.ecust.edu.cn/admetsar2/) is used to predict significant descriptors of the Physicochemical Properties, Lipophilicity, Pharmacokinetics, and Druglikeness properties of the compounds.

3. Results and Disscussion



(a) (b)

Figure 1. (a) 3D structure of mangiferin compound, (b) 3D structure of saxagliptin control compound

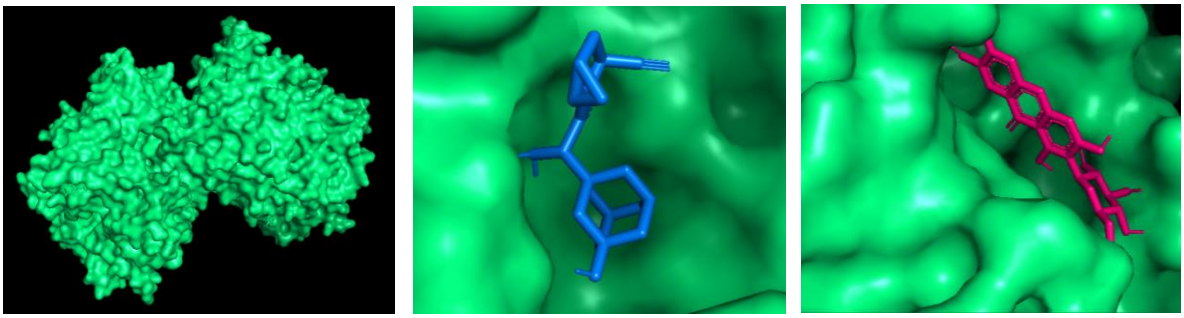


Figure. 2. Results of docking saxagliptin (blue) and mangiferin (pink) with DPP-4 protein

Table 1. The result of docking between mangiferin and saxagliptin compounds with target proteins

Origin of Compound	Ligand	Binding Affinity (kkal/mol)
Mangifera indica L	**Mangiferin**	**-8.2**
Control	**Saxagliptin**	**-7.1**

One of the plants used as herbal medicine for the disease treatment is the mango plant (*Mangifera indica*). The main compound contained in *Mangifera indica* is mangiferin which is an active antidiabetic compound. Mangiferin reduces changes in blood glucose levels and restores pancreatic function. In addition, mangiferin can reduce DDP-4 protein levels by inhibiting DPP-4 protein activity in the setting of diabetes. Mangiferin significantly reduces the level of MDA, a marker of lipid peroxidation in different organs, i.e., heart, liver, and kidney by ameliorating changes in antioxidant enzymes in the treatment of diabetic complications (9). The compound used in controlling diabetes mellitus is saxagliptin. The compound saxagliptin is responsible for the DPP-4 inhibitor that improves glycemic control by preventing the

inactivation of the incretin hormone GLP-1 and glucose-dependent insulinotropic polypeptide (10).

The structure of herbal compounds and control compounds as well as target proteins were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/) and then visualized in 3D through the PyMol application (Figure 1). Based on the results of docking using the PyRx application, it was found that the herbal compound, mangiferin, has potential as an antidiabetic. It is because herbal compounds can interact with target proteins. The binding affinity value of the mangiferin with the target protein obtained based on the docking results, shown lower value than the binding of the control compound, saxagliptin with the target protein. If the binding affinity value of the ligand is lower, then the energy required by the mangiferin to bind with target protein is smaller than the energy required by the saxagliptin with the target protein.

The main substrate for the DPP-4 protein is incretin hormone, which is a major regulator of post-prandial insulin release. Inhibition of DPP-4 leads to greater bioavailability thereby prolonging the half-life of insulin. The majority of the effect seen in DPP-4 inhibition was an increase in GLP-1 levels. GLP-1 slows down intestinal motility thereby reducing the absorption of carbohydrates and glucose. Therefore, DPP4 becomes the main target for diabetes treatment (11). DDP-4 protein has interactions with natural compounds from mangiferin which been visualized in 3D using PyMol software. The binding affinity for mangiferin with DPP-4 protein is -8.2, while saxagliptin is -7.1, shown that mangiferin has the ability to bind to DPP-4 protein. Toxicity tests have been carried out through ADMET predictions which show that mangiferin compounds are not potentially carcinogenic. However, it is not recommended to extract this compound because it is potentially toxic.

4. Conclussion

Based on the results of an intermolecular interaction and its affinity level, which is -8.2, the mangiferin compound in the Mangifera indica plant has potential as an antidiabetic.

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