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IN-SILICO TEST OF ACTIVITY ANDROGRAPHOLIDE AS A NATURAL COMPOUND IN REDUCING SUGAR LEVELS

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Abstract

The purpose of this study was to determine the bioactivity of these compounds andrographolide on metformin as a blood sugar-lowering drug. The chemical structure of the compound andrographolide found in Metformin was obtained from the literature. The target protein was 3-hydroxy-3-methylglutaryl-coenzyme A reductase, and the control was metformin. PyMol v2.5.2 software was used to remove the water molecules. PyRx-Python Prescription 0.8 software was used to dock the target protein and the compound. When compared to control compounds, the compound andrographolide showed a greater potential for lowering drug sugar levels. The comparative affinity of 3-hydroxy-3-methylglutaryl-coenzyme A reductase for Andrographolide is -8,0, whereas the affinity for metformin is -5,0. Andrographolide toxicity testing revealed that it was not a potential carcinogen and did not cause mutations. The water absorption of andrographolide is greater than that of the control compound.

Keywords: andrographolide, metformin.

1. Introduction

Diabetes mellitus is defined as a metabolic disease caused by various causes of disease characterized by hyperglycemia [1]. In 2005 WHO has noted that 70% of the world's death rate is caused by non-communicable diseases, namely 30% due to heart and blood vessel disease, cancer (13%), other chronic diseases (9%), chronic respiratory tract (7%), accidents. (7%) and 2% due to Diabetes Mellitus. [2]. Obesity is one of the risk factors for DM [3]. The International Diabetes Federation (IDF) in 2017 stated that the prevalence of diabetes mellitus in the world reached 424.9 million people and is expected to reach 628.6 million in 2045. Indonesia is the country with the most DM sufferers in the world with the number of people with diabetes. mellitus reached 10.3 million people. This number is estimated to continue to increase to reach 16.7 million people in 2045 [4].

According to WHO, herbal medicines have been used as a complementary medicine by Latin countries and support the efficacy and safety of herbal medicines [5]. Sambiloto (Andrografis paniculata) is one of the Indonesian plants that is widely used traditionally in the community as a medicine for diabetes mellitus [6]. This herb contains diterpenoids, flavonoids

and polyphenols as the main bioactive components [7]. The active compounds are extracted with ethanol or methanol from whole plants, leaves and stems [8]. Andrographolide (C20H30O5) is a bicyclic diterpenoid lactone group compound in the form of colorless crystals with a very bitter taste [9]. Metformin is a biguanide, a class of drugs of herbal origin that has been widely used to treat diabetes since the 1950s [10]. Metformin is indicated for the treatment of hyperglycemia in type 2 diabetes and improves glycemic control without causing hypoglycemia or weight gain [11]. The use of metformin is supported by randomized clinical trials of intensive vs standard glycemic control among patients with newly diagnosed type 2 diabetes. This trial found a lower rate of myocardial infarction (7% absolute risk reduction; P = 0.01) and mortality (7.1% absolute risk reduction; P = 0.01) in a subgroup of overweight patients randomized to metformin. (n = 342) compared with conventional therapy (diet) (n = 411) [12].

2. Materials and Method

2.1. Ligands Preparation

The chemical structure of Andrographolide was collected from the published literature. The chemical 3D structure and SMILES ligand (andrographolide) were taken from the PubChem compound database (https://pubchem.ncbi.nlm.nih.gov/) with ID numbers: CID 5318517 and Canonical SMILE CC12CCC(C(C1CCC(=C)C2CC= C3C(COC3=O)O)(C)CO)O. The chemical structures of two-dimensional (2D) and three-dimensional (3D) ligands were sketched using Avogadro and saved in PDB format.

2.2. Target Selection

Potential protein target candidates for docking based on published literature. Proteins collected and validated with PDB (Protein Data Bank http://rcsb.org/pdb). The protein used is clean protein. Water molecules from the ligands were removed using PyMOL v.2.5 Software. In this study, the target protein used was Crystal structure of human apo dipeptidyl peptidase IV with the code 5NN4 from PDB.

2.3. Molecular Docking

Molecular docking experiments were carried out using PyRx 0.8 software. The process is carried out using the Vina Wizard feature integrated into the PyRx 0.8 software which reacts to the natural compound Andrographolide, the target protein Crystal structure of human apo dipeptidyl peptidase IV and control compounds.

2.4. Visualization of Molecule and ADMEt Predictions

The interactions between natural ligands, target proteins and known control compounds were visualized and analyzed using PyMOL v.2.5 Software.

2.5. Compound's Properties and ADMET Predictions

Swissadme (http://swissadme.ch) and admetSAR (lmmd.ecust.edu) were used to predict and significant descriptors of the Physicochemical Properties, Lipophilicity, Pharmacokinetic and Druglikeness properties of the compounds.

3. Results and Discussion

The main compound found in Andrografis paniculata is Andrographolide. Labpen which is a diterpenoid (andrographolide). The preparation process for HMG-CoA Reductase protein is carried out using chain B. The preparation process will obtain a protein structure without native ligand and a native ligand structure, so that there will be space (pocket/cavity) in the protein. The protein structure obtained is a protein that has lost its native ligand, other molecules such as water (H2O) and other single atoms, so that during the docking process only the test compound interacts with the protein [13].

The structure of natural compounds and control compounds as well as target proteins were visualized in three dimensions (3D) using PyMol (Figure 1). Through the reverse docking technique, the potential of andrographolide as an antihyperlipidemic can be determined. The interaction of andrographolide with Crystal structure of human apo dipeptidyl peptidase IV compared to the control compound Metformin showed that Metformin was more bound to Crystal structure of human apo dipeptidyl peptidase IV compared to Metformin. When the affinity of the ligand is low, it will inherit the target protein more strongly. Therefore, the lower the binding affinity, the lower the energy required for the ligand to interact with the target protein [14]. The binding affinity of Andrographilide with Crystal structure of human apo dipeptidyl peptidase IV was -8.0 while the binding affinity of Metformin with Crystal structure of human apo dipeptidyl peptidase IV was -5.0. Based on the research results, Andrographolide and Metformin on Crystal structure of human apo dipeptidyl peptidase IV showed that andrographolide has the ability to bind to target proteins.

(A) (B)

Figure 1. (a) Chemical 3D Structure of Andrographolide and **(b)** Beta Metformin were showed by *software* PyMol

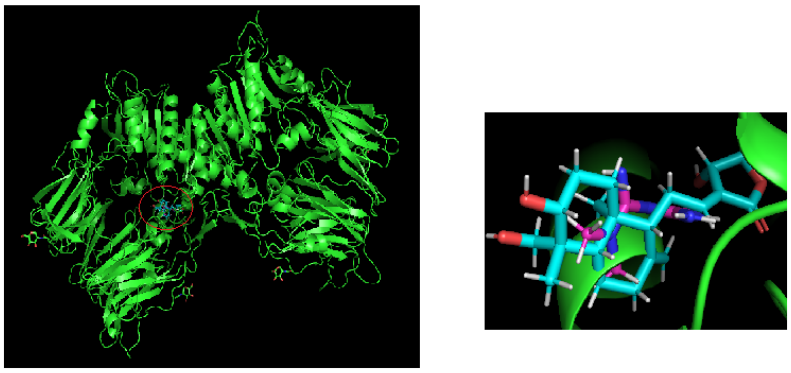

Figure 2. Binding Site of Andrographolide (blue, red), Metformin (purple, blue) and Crystal structure of human apo dipeptidyl peptidase IV (ribbon).

Tabel 1. The result of Crystal structure of human apo dipeptidyl peptidase IV with ligand and control

Ligand	**Binding Affinity**
Crystal structure of human apo dipeptidyl peptidase IV and andrographolide	-8.0
Crystal structure of human apo dipeptidyl peptidase IV and metformin	-5.0

Drugs are aimed mostly at treating chronic diseases [14]. The side effects of andrographolide compounds with ADMET observations and predictions were evaluated and associated with cell permeation, metabolic processes and bioavailability, the results showed Andographolide is not a carcinogen. This compound should not be extracted because it is potentially toxic. The search results showed that apigenin complied with the rules of Lipinski, Ghose, Veber, Egan, Muegge and Bioavailability score 0.55. Meanwhile, the control compound Metformin did not meet the Ghose and Muegge rules.

4. Conclussion

This study proves that andrographolide has potential as an antidiabetic based on its binding affinity with -8.0 and intermolecular interactions. Andrografis paniculata contains andrographolide which is a potential antihyperlipidemic drug according to the rules of Lipinski, Ghose, Veber, Egan and Muegge and a Bioavailability Score of 0.55.

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