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Abstract

The purpose of this research is to ascertain the bioactivity of the anthraquinone compound found in Moringa (Moringa Oleifera) leaves as a naturally occurring antidiabetic substance. The literature was used to determine the anthraquinone compound's chemical structure, which is found in Moringa oleifera leaves. The control substance was metformin, and the target protein was p38 MAPK (Mitogen-Activated Protein Kinase). PyMol v2.5.2 Software was used to eliminate water molecules. Using PyRx-Python Prescription 0.8 Software, docking between the chemical and the target protein was performed. Compared to metformin, a control molecule, the findings indicated that the anthraquinone compound had a stronger potential as an antidiabetic. Anthraquinone has a relative p38 MAPK (Mitogen-Activated Protein Kinase) affinity of -7.3, whereas metformin has a relative p38 MAPK (Mitogen-Activated Protein Kinase) affinity of -5.5.

Keywords: Anthraquinone, Moringa Oleifera, p38 MAPK, Metformin, Antidiabetic

1. Introduction

Diabetes mellitus (DM) is a metabolic disorder disease characterized by increased blood glucose levels in the body with various symptoms such as polydipsia, polyuria, polyphagia, tingling, and weight loss.(Bhatt, Saklani and Upadhayay, 2016). A person is categorized as suffering from diabetes mellitus if his fasting blood glucose level is more or equal to 126 mg/dL and or his blood glucose level is more than or equal to 200

mg/dL.(Lakshita, 2017). High blood glucose levels are caused by impaired insulin secretion or insulin action(Milita, Handayani and Setiaji, 2021). This occurs due to damage to pancreatic gland cells, decreased pancreatic cell glucose receptors, and damage to receptors on target cells.(Bhatt, Saklani and Upadhayay, 2016)

According to The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (2003), there are four (4) types of diabetes mellitus, namely type 1 DM, type 2 DM, other special types of DM and gestational DM, but the most common are found with the most populous population. Most are type 2 diabetes, which is about 90% of all types of diabetes(Milita, Handayani and Setiaji, 2021) (Alethea and Ramadhian, 2015). Type 1 diabetes mellitus is caused by a lack of insulin production by the pancreas while type 2 diabetes is caused by target tissues that are less sensitive to insulin so that it interferes with insulin work.(Riwu, Subarnas and Lestari, 2015)(Sari, 2007). Other types of diabetes mellitus are caused by genetic damage, infection, drug use, or endocrinopathy, while gestational diabetes is diabetes mellitus in pregnancy.(MoH, 2019)

Globally, diabetes cases are doubling every year, in the last 10 years, the cases have increased rapidly in low-income countries(Milita, Handayani and Setiaji, 2021). The World Health Organization (WHO) estimates that the number of people with diabetes in Indonesia will continue to increase to reach 21.3 million in 2030(Lubis, 2020).

Diabetics are very susceptible to complications if they do not receive proper treatment, such as nerve damage, kidney damage, eye damage, heart disease, stroke, and peripheral vascular disease.(Rosyada and Trihandini, 2013). Diabetics usually receive pharmacotherapy in the form of insulin injections or oral drugs such as sulfonyluera agents, biguanides (metformin), thiazolidinedione (TZD), -glucosidase inhibitors, and glucagon-like peptide-1 (GLP-1) inhibitors, however, these drugs have side effects, eg hypoglycemia, liver toxicity, weight gain, abdominal enlargement, and lactic acidosis(Alethea and Ramadhian, 2015). One of the oral drugs most often used as the first line of treatment for type 2 DM is metformin, but this drug also has side effects such as diarrhea, nausea, vomiting, and flatulence.(Princess et al., 2021)

Seeing the side effects of pharmacological therapy in diabetics, it is recommended to use natural ingredients for therapy in diabetics. One of the plants that can be an alternative diabetes treatment is the Moringa leaf (Moringa Oleifera), a plant

that is very easy to find, especially in Indonesia and can grow under various environmental conditions.(Lakshita, 2017).

Moringa leaves (Moringa Oleifera) contain many phytochemicals that can treat various diseases, such as diabetes. These phytochemicals contain carotenoids, alkaloids, flavonoids, glycosides, anthocyanins, anthraquinones, saponins, steroids, tannins and terpenoids. (Zainab et al., 2020). Therefore, this in silico study will look at the potential of anthraquinone as an antidiabetic compound.

2. Materials and Methods

2.1.Ligand Preparation

Anthraquinone's chemical structure was obtained from the PubChem compound database (https://pubchem.ncbi.nlm.nih.gov/) in the form of a 3D chemical structure and SMILES, with the following IDs: CID: 6780 and Canonical Smile: C1=CC=C2C(= C1)C(= O)C3=CC=CC=C3C2=O. Three-dimensional (3D) and the chemical structures of the ligands were drawn using Avogadro and saved in PDB format.

2.2.Target Selection

Using published literature, the target protein for docking was created, and Uniport (https://www.uniprot.org) was used to validate it. Proteins were gathered and verified using PDB (Protein Data Bank; http://www.rcsb.org/pdb), and then the protein was cleaned up for use by eliminating water molecules using PyMOL v2.5.2 software. The target protein in this investigation was p38 MAPK (Mitogen-Activated Protein Kinase), which has the PDB code 1WFC.

2.3.Molecular Docking

Utilizing PyRx 0.8, molecular docking experiments were performed. The target protein responds to the natural substance anthraquinone during the docking process, which is done out using the Vina Wizard tool built into the PyRx 0.8 software. p38 MAPK (Mitogen-Activated Protein Kinase) and metformin served as the control substance. (2010) (O. Trott AJ. Olson).

2.4. Visualization of Small Molecules and Small Molecules

Interaction between ligands (anthraquinone) of target proteins p38 MAPK (Mitogen-Activated Protein Kinase), and control ligand (metformin) with target

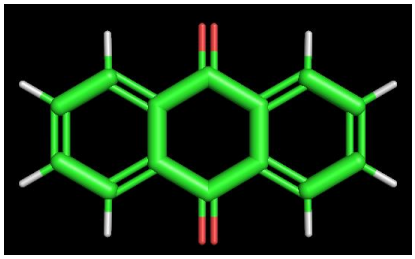
proteinp38 MAPK (Mitogen Activated Protein Kinase)known were visualized and analyzed using PyMol Software v 2.5.2.

2.4.Compound Properties and Prediction of ADMET

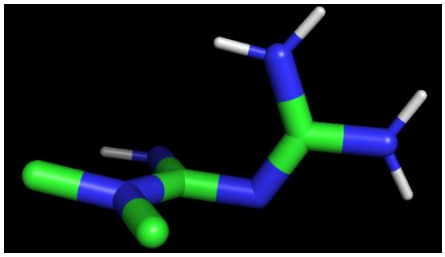
It was utilized to forecast and was a major descriptor of the compounds' physicochemical qualities, lipophilicity, pharmacokinetics, and drug-likeness properties (http://lmmd.ecust.edu.cn/admetsar2/).

3. Results

Using the PyMol program, the structure of the herbal compounds, the control compounds, and the target proteins were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/) (Fig. 1). The PyRx application's docking results revealed that anthraquinone can interact with the p38 MAPK (Mitogen-Activated Protein Kinase) target protein, demonstrating that it can be employed as an antidiabetic. The binding affinity determined by the docking results indicated a lower value for the anthraquinone compound compared to metformin as a control compound, indicating that the anthraquinone required less energy to bind to the target protein than did metformin.

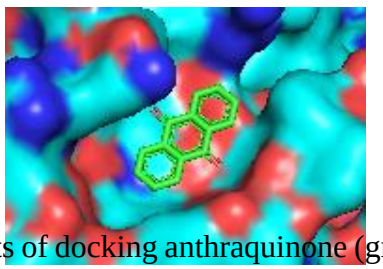


(a)



(b)

Figure 1. (a) 3D image of Anthraquinone (b) 3D image of Metformin. control



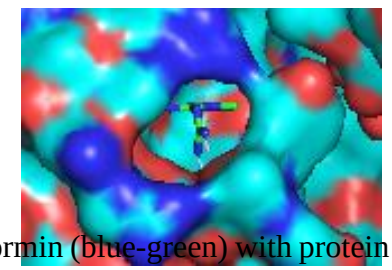


Fig.2. results of docking anthraquinone (green) and metformin (blue-green) with protein p38 MAPK (Mitogen-Activated Protein Kinase)

Table.1. Docking results between Anthraquinone & Metformin compounds with target proteins

Origin of Compound	Ligand	Binding Affinity (kcal/mol)
Moringa Oleifera	**Anthraquinone**	**-7.3**
Control	**Metformin**	**-5.5**

4. Discussion

There are several active compounds in Moringa leaves (Moringa Oliefera) that function as antidiabetic substances, including anthraquinone.(Zainab et al., 2020). This compound can reduce blood glucose levels in the body through several mechanisms, namely p38 MAPK inhibitors, DPP4 inhibitors, PTP 1B inhibitors, suppressing cortisol hormone activity, increasing AMPK, and inhibiting -Glucosidase enzyme activity.(Mohammed et al., 2020).

p38 MAPK is the main isoform of inflammation and proinflammatory activity which is generally active in diabetics(Du et al., 2010). Anthraquinone functions as a p38 MAPK inhibitor that can suppress p38 MAPK activity thereby reducing and preventing the formation of ROS.(Mohammed et al., 2020)(Chien et al., 2015). Thus insulin sensitivity and secretion increase, resulting in a decrease in blood sugar levels in the body(Mohammed et al., 2020)

Anthraquinone also functions as a DPP4 inhibitor that can increase incretin hormone secretion and suppress glucagon hormone secretion. Both of these increase insulin sensitivity and secretion and increase glucose uptake in muscles. Thus, blood glucose levels in the body will be reduced.(Mohammed et al., 2020)

The next mechanism is that anthraquinone triggers AMPK by inhibiting ATP synthesis and increasing AMP levels thereby increasing GLUT1/4 levels and mediating glucose uptake, causing a decrease in blood glucose levels.(Martorell et al., 2021). Anthraquinone is known to reduce the activity of the enzyme -Glucosidase in the small intestine so that glucose absorption in the intestine is reduced. This will eventually cause blood sugar levels in the body to decrease.(Mohammed et al., 2020)

The last mechanism in lowering blood sugar levels is a PTP 1B inhibitor which increases the activity of insulin receptors and the P13 K enzyme. This triggers an increase

in GLUT4 and then increases insulin sensitivity so that glucose uptake increases and blood glucose levels decrease.(Mohammed et al., 2020)

Although anthraquinone compounds have not been found to be potentially carcinogenic in toxicity studies based on ADMET predictions, it is not advised to extract this molecule directly because it is potentially hazardous. Consuming dried and then powdered moringa leaves (Moringa Oleifera) will boost its nutritional value (Lakshita, 2017).

5. Conclusion

Anthraquinone chemicals in Moringa (Moringa Oleifera) leaves can be employed as anti-diabetic therapy, according to the results of intermolecular interactions and their level of affinity.

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