Molecular Docking of Compounds in *Moringa oleifera* Lam with Dipeptidyl Peptidase-4 Receptors as Antidiabetic Candidates

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Abstract
Background*: Diabetes mellitus (DM) type 2 is a metabolic disorder that needs special attention because it can damage several organs if the severity increases. One of the treatments for diabetes mellitus (DM) type 2 is by inhibiting Dipeptidyl peptidase 4 (DPP-IV) with vildagliptin to prolong the hypoglycemic effect of GLP-1 and GIP.* ***Objective****: In the search for candidate compounds as new antidiabetic compounds, an in silico test with molecular docking was carried out to predict the antidiabetic activity of 10 Moringa oleifera Lam (MO) plant compounds at the DPP-IV receptor (PDB ID: 6B1E).* ***Method****: The study was conducted using the molecular docking method.* ***Result****: Validation of the vildagliptin DPP-IV ligand obtained free energy values of -9.27 kcal/mol and RMSD 1.49 Å (RMSD < 2 Å), then tested with 10 test compounds obtained 8 test compounds that have the potential to be antidiabetic.* ***Conclusion****: Serpentine compounds have better potential as an antidiabetic drug than other target compounds because they have the closest Gibbs energy (ΔG) value to the natural ligand of Vidaglibtin, which is -7.90 kcal/mol. This value is still lower than the free energy of vildagliptin, which is -9.37 kcal/mol. Therefore further testing is needed to ensure the potential of the compound as a candidate for antidiabetic drugs.*

Keywords*: diabetes, molecular docking, DPP4, Moringa oleifera* Lam.*, vildagliptin*

Abstrak
Pendahuluan: Diabetes melitus (DM) tipe 2 merupakan penyakit gangguan metabolisme yang perlu mendapatkan perhatian khusus karena dapat merusak beberapa organ jika keparahan meningkat. Salah satu pengobatan DM tipe 2 dengan melakukan penghambatan Dipeptidyl peptidase 4 (DPP-IV) yaitu dengan vildagliptin sehingga dapat memperpanjang efek hipoglikemik GLP-1 dan GIP. **Tujuan**: Dalam pencarian kandidat senyawa sebagai antidiabetes baru, maka dilakukan uji in silico dengan penambatan molekuler untuk memprediksi aktivitas antidiabetes 10 senyawa tanaman *Moringa oleifera* Lam. (MO) pada reseptor DPP-IV (PDB ID: 6B1E). **Metode**: Penelitian dilakukan dengan metode doking molekular. **Hasil**: Validasi ligan vildagliptin DPP-IV didapatkan nilai energi bebas -9,27 kkal/mol dan RMSD 1,49 Å (RMSD < 2 Å), kemudian dilakukan pengujian dengan 10 senyawa uji didapatkan 8 senyawa uji yang berpotensi sebagai antidiabetes. **Kesimpulan**: Senyawa serpentin memiliki potensi lebih baik sebagai kandidat obat antidiabetes dibandingkan senyawa target lainnya karena memiliki nilai energi bebas Gibbs (ΔG) paling mendekati ligan alami Vidaglibtin yaitu sebesar -7,90 kkal/mol. Nilai ini masih lebih rendah dibandingkan energi bebas vildagliptin yaitu -9,37 kkal/mol, oleh karena itu perlu dilakukan pengujian lebih lanjut untuk memastikan potensi senyawa sebagai kandidat obat antidiabetes.

Kata kunci: diabetes, doking molekuler, DPP4, *Moringa oleifera* Lam., vildagliptin

INTRODUCTION

Diabetes Mellitus (DM) is a metabolic disorder characterized by long-term high blood glucose levels. This disease has become one of the main health problems in the world and needs special attention. Over time, DM can damage the heart, kidney, and nervous

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system. DM was divided into two categories (type 1 and 2) based on patients' absolute or relative insulin deficiency. According to International Diabetes Federation (IDF), in 2019, nearly half a million people in the world, approximately 463 million people, were living with diabetes. If this problem persists, it is estimated that the number will continue to increase to 13.7 million in 2030 and 16.9 million in 2045 (IDF, 2019; Yang *et al*., 2020).

Currently, it takes 10 - 15 years to develop new drugs, and this process costs much money (Dimasi *et al*., 2016). Due to the lack of certain drug properties, such as poor pharmacokinetics and toxicity problems that appear in clinical trials, only one drug out of 10,000 candidates can eventually be marketed during the drug development process (Pink *et al*., 2005). With the development of computer technology, structure-based virtual screening such as molecular docking has become one of the methods that can be used for drug discovery (Ma *et al*., 2013). The advantage of this method is that candidate compounds that have low drug ability can be removed, lowering costs and increasing efficiency (Katsuno *et al*., 2015).

Molecular docking analysis is a drug discovery technology based on simulating interactions between ligands and target proteins. The structural libraries of compounds from various sources were screened and analyzed by pharmacophore matching and molecular docking methods, based on the drug-binding site of the target protein (Meng *et al*., 2011). Virtual drug screening based on molecular docking technology has become a popular and effective drug development strategy. Docking was developed to be a tool for drug discovery through an *in silico* approach.

Several medicinal plants have been used as therapeutic agents for various diseases. Moringa oleifera (MO) is a significant medicinal plant because it is traditionally used to treat various health disorders, including diabetes mellitus (DM) type 2 (Farooq *et al*., 2012). MO has long been called the "Tree of Life" and "Magic Tree" in the tropics and subtropics because it can be used as a food and an essential traditional medicine in Asia to treat diabetes and obesity (Moyo *et al*., 2011).

Currently, there are very few studies on the pharmacological activity of the chemical elements contained in MO and these studies this research is limited to the exploration of crude extract bioactivity. Somova *et al*. (2003) found that MO extract had antihypertensive and hypoglycemic activity. Most studies on the hypoglycemic activity of MO extracts have not identified individual components with specific molecular mechanisms. Different parts of MO are enriched with carotenoids, alkaloids, flavonoids, glycosides, anthocyanins, anthraquinones, saponins, steroids, tannins and terpenoids (Patel *et al*., 2014).

Zainab *et al*. (2020) have conducted an in silico study using molecular docking on 10 MO plant compounds, namely Anthraquinone, Laurifolin (flavonoid), Serpentine (alkaloid), 2-Phenylchromenylium anthocyanin, Alpha-Carotene, Sitogluside Glycoside, A-Phenolic Steroid, Saponin, Hemlock Tannins and terpenoids EA-I. The results show that 5 phytochemical compounds screened from MO plants are effective as potential therapeutic drug candidates to treat diabetes mellitus at the Crystal Structure of Insulin kinase receptors.

In this study, molecular docking was carried out to predict the antidiabetic activity of the 10 MO plant compounds with different receptors, namely the DPP-IV receptor. Based on drug-like properties and molecular docking evaluation principles, inhibition of DPP-IV was confirmed by *in vitro* experiments. DPP-IV, also called CD26, is a serine protease. As a treatment for type 2 diabetes, DPP-4 inhibitors inhibit the degradation of incretins, GLP-1 and GIP (Juillerat, 2013). There are DPP-IV inhibitors currently on the market, such as sitagliptin and vildagliptin. The DPP-IV inhibitors currently on the market have significant hypoglycemic effects (Makrilakis, 2019).

MATERIALS AND METHODS

Materials

The materials in this molecular docking are the structure of the compounds contained in MO, namely Anthraquinone, Laurifolin (flavonoids), Serpentine (alkaloids), 2-Phenylchromenylium anthocyanins, Alpha-carotene, Sitogluside glycosides, A-Phenolic Steroids, Saponins, Hemlock tannins, and Terpenoid EA-I. The structures were made in 2D and 3D form using the ChemDraw Ultra 12 application. DPP-IV receptor downloaded from the Protein Data Bank (PDB) database with ID 6B1E.

Tools

This study was performed using ASUS Windows 10 equipped with Intel® Core™ i3-4030U CPU @ 1.90 GHz, 64-bit operating system, 84.7 GB hard drive capacity, and 2.00 GB RAM memory. The software includes (1) Chemdraw® Ultra 12.0 free trial (Cambridge Soft Corporation, downloaded at www.cambridgesoft.com) used to draw ligand structures in 2D and 3D; (2) Autodock 4.2 (downloaded from http://autodock.scrips.edu); (3) BIOVIA

Discovery Studio 2016, used for visualization of protein data bank (PDB) complexes.

Methods

This study was performed to find new antidiabetic potential drugs in MO plant compounds using the in silico method, namely molecular docking including preparation of target receptors, ligand preparation, molecular docking validation, and molecular docking (Muchtaridi *et al.*, 2017).

Preparation of target receptor

DPP-IV receptor was obtained from Protein Data Bank (PDB ID: 6B1E) with a resolution of 1.77 A. The receptor was separated (using Discovery Studio) by removing the water molecules and the ligand molecules. The obtained protein molecule was saved in the receptor.pdb file format. The receptor that will be tested was prepared using the AutoDockTools application by adding a hydrogen group and increasing the Kollman charge. The receptor was saved in the receptor.pdbqt file format.

Ligand preparation

The ligands were separated (using Discovery Studio) by removing water molecules and protein molecules. The obtained ligand molecules were saved in the ligand.pdb file format. The ligands that will be tested were prepared using the AutoDockTools application by adding a hydrogen group, merging the non-polar group, and increasing the Gasteiger charge. Then, detect and select the root. After that, choose torsion and set the number of torsions. The ligands were saved in the ligand.pdbqt file format.

Validation of molecular docking

Grid parameters are used to define region boundaries in the molecular docking process, and the receptor's active site will be covered to improve docking efficiency. These parameters were created in the grid menu of AutoDockTools, and the file was saved in .gpf file format. The AutoGrid process ran these parameters, and the file was saved in glg format.

Docking parameters were created through the docking menu. Then, the receptor and ligand file were selected in pdbqt format. The Lamarckian parameter was added and the file was saved in dpf format.

The receptor.pdbqt file and ligand.pdbqt was inserted. Select the ligand, prepare the grid box (x: 36.602; y: 50.275; z: 35.416) and save in gpf format. Sets the receptor's rigid filename. The ligand and the parameters of the Genetic Algorithm were chosen. Make the number of GA runs 50. After choosing the docking parameters, the file was saved in dpf format using Lamarckian GA. The validation result of molecular docking was interpreted as the Root Mean Square Deviation (RMSD) value.

Molecular docking

After obtaining the grid box parameters and RMSD values, molecular docking of the test ligands and target receptors was carried out in the same steps. The molecular docking results are the ligand's Gibbs energy (ΔG), the number of clusters, the inhibition constant (KI), and the interactions involved in the 2D and 3D forms by opening BIOVIA to see the bonds in the receptor and ligand.

RESULT AND DISCUSSION

A total of 10 compounds are contained in the MO plant, namely, Anthraquinone, Laurifolin (flavonoid), Serpentine (alkaloid), 2-Phenylchromenylium anthocyanin, Alpha-carotene, Sitogluside glycoside, A-Phenolic Steroid, Saponin, Hemlock tannin, and Terpenoid EA-I were selected to in silico study its activity at the DPP-IV receptor. The DPP-IV receptor in complex with vildagliptin (PDB ID: 6B1E) was selected in the present study based on the already in the organism *Homo sapiens* and the method used is the x-ray diffraction method. The structure that has been made with this method has a resolution of 1.77Å, which is a good value. The free R-value that is owned is 0.186, and the working R-value is 0.161. This value itself can be used as a factor in evaluating the quality of molecular crystals. The working R-value can also be used to measure the deviation between the intensity of the observed diffraction pattern and the intensity of the calculated model prediction. The R-value of good working is smaller than 0.20, and the DPP-IV receptor in the complex with vildagliptin has a smaller value than the requirement, so it can be said to be ideal.

The protein was downloaded using PDB as a database for data on the three-dimensional structure of large biological molecules, such as proteins and nucleic acids. DPP-IV is a proteolytic enzyme or protease found on the cell surface. DPP-IV inhibitor enzymes play a role in maintaining glucose balance by proteolytic inactivation of incretins so that this enzyme will improve glucose tolerance and pancreatic islet cell function in diabetic patients. One of the pathogeneses of DM is an increase in the activity of the DPP-IV enzyme, which results in impaired glucose metabolism in the body. Therefore, several drugs are designed with the mechanism of the DPP-IV inhibitory pathway to increase the signal on insulin secretion and restore normal glucose metabolism.

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The initial step of receptor preparation was carried out using the software *BIOVIA Discovery Studio* to separate ligand and water molecules with receptors because water molecules can cause the molecular docking process to become more complex and allow hydrogen bonds to occur with compounds other than ligand. The results of this process are saved in the receptor .pdb file format. The next step is the preparation of the ligand with vildagliptin as the standard ligand. The ligands to be tested are Anthraquinone, Laurifolin (flavonoid), Serpentine, which belongs to the alkaloid group, 2-Phenylchromenylium anthocyanin, Alpha-carotene, Cytogluside glycoside, A-Phenolic Steroids, Saponins, Hemlock tannins, and Terpenoids EA-I. 2D structure modelled with software *Chemdraw Ultra* and optimized geometric design into 3D using software *Chem3D* then saved as a .pdb file. Ligand optimization is done by adding the charge *Gasteiger* using the software *Autodock Tools* and then merging nonpolar so that only the polar hydrogen atoms appear. Before the ligand is docked to the receptor, it is necessary to identify the active pocket binding to the receptor using the parameter *grid.*

Then, the validation process of the molecular docking method was carried out. Validation of computational methods is carried out to ensure that the method used has met the validity requirement so that it can be used for another molecular testing. In the docking process, the standard ligand separated from the receptor is redocking, namely vildagliptin and the test ligand with the DPP-IV receptor. The grid box (bond area) is determined to limit the search space for the ligand conformation in the docking process. The resulting grid box is x = 36.602; y = 50.275; z = 35.416. The results of the validation follow the requirements of 1.49 Å (RMSD requirements < 2 Å) so that it can be said that the system is valid and ready for the next process.

Parameters used to see the interaction of the test compound with the receptor include Gibbs free energy, inhibition constant, and the interaction between the ligand and receptor complex. The test results are used as a standard to determine which compounds have similar activity at the DPP IV receptor.

Molecular docking between the standard ligand vildagliptin and the DPP-IV receptor resulted in a Gibbs free energy of -9.37 kcal/mol with an inhibition constant of 135.65 uM (Table 1). Based on the test results on ten compounds in the MO plant, the serpentine compound (Figure 1) has a Gibbs energy value of -7.90 kcal/mol with a constant inhibition value of 1.61 uM. This value is indeed not more damaging than vildagliptin but better than other compounds. It is known that the more negative the Gibbs free energy value (ΔG) indicates a good level of stability between the ligand and the receptor so that it will form a stronger bond (Du *et al.*, 2016). In addition, the value of the inhibition constant is also directly proportional to the Gibbs energy; the smaller the case, the smaller the inhibition constant, which indicates the bond interaction between the ligand and receptor is getting stronger (Du *et al.*, 2016; Brooks *et al.*, 2009). The value of the inhibition constant shows the concentration required for a ligand to affect the receptor (Cortés *et al*., 2001; dos Reis *et al*., 2013).

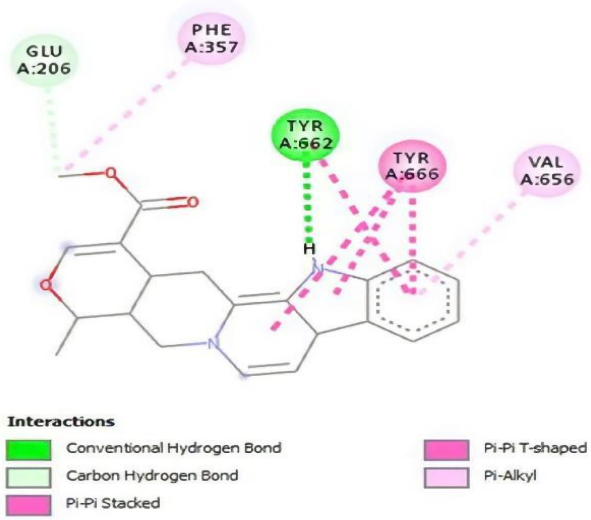

Figure 1. Interaction between serpentin and DPP4

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Table 1. Parameters of molecular docking of the test compound with the DPP4 enzyme

No.	Compound	Free energy (kcal/mol)	Inhibition constant (uM)	Interaction with Amino Acid	
				Hydrogen bond	Hydrophobic bond
1.	Vildagliptin	-9.37	135.65	Tyr547	Glu205, Glu206, Asp663, Tyr666, Tyr662
2.	Serpentine	-7,90	1,61	Tyr662	Tyr666, Glu206, Val656, Phe357
3.	A-phenolic steroid	-6,67	12,97	Ser630	Phe 357, Tyr666
4.	2-Phenylchromenylium Anthocyanin	-6,44	19,12	Ser 630, Tyr547	His740, Trp629
5.	Antraquinone	-6,35	22,12	Tyr666, Tyr 662, Asn 710	Glu206
6.	Hemlock tannin	-6,31	23,89	Glu205, Tyr662	Phe357, His740, Arg125
7.	Terpenoid EA-I	-6,12	32,91		Tyr666, Val711, Phe357, Val656, Tyr631, Tyr662, Phe357
8.	Laurifolin	-5,56	84,15	Ser630	Glu206, Phe357, Tyr547
9.	Sitogluside glycoside	-5,18	159,26	Arg125, Glu205, His126	Glu 206, His740, Tyr666, Tyr662
10.	Saponin	+1178.77	unavailable	-	-
11.	Alpha-carotene	+214551.80	unavailable	-	-

Then, the visualisation results to see the presence of residues that bind between the standard ligand vildagliptin and the DPP-IV receptor, hydrogen bond interactions occur in Tyr547 and hydrophobic bonds interactions Glu205, Glu206, Asp663, Tyr666, and Tyr662 (Figure 2). Based on the hydrogen bonds formed in the 10 test compounds, 2-Phenylchromenylium Anthocyanin has a good affinity for the DPP-IV receptor on the amino acid residue Tyr547. This result is consistent with the hydrogen bonding interaction with the standard ligand vildagliptin on the amino acid residue Tyr547 (Figure 3). An interaction occurs at the same amino acid residue so that 2-Phenylchromenylium Anthocyanin is predicted to have similar biological activity to vildagliptin (Muttaqin, 2019).

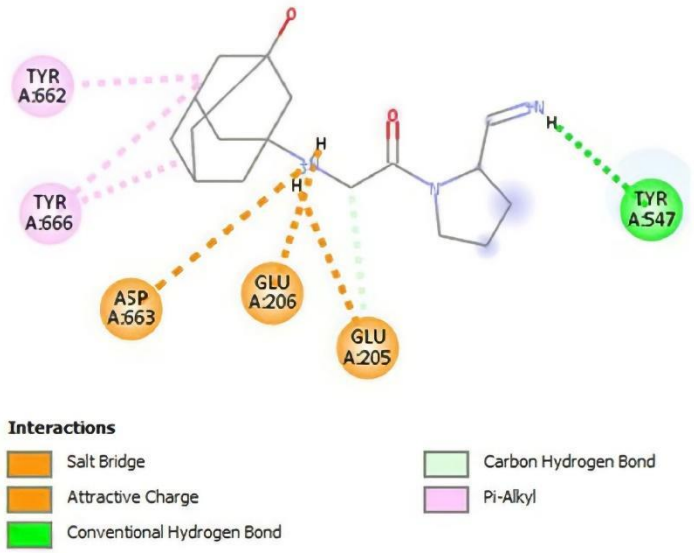

Figure 2. Interaction between vildagliptin and DPP4

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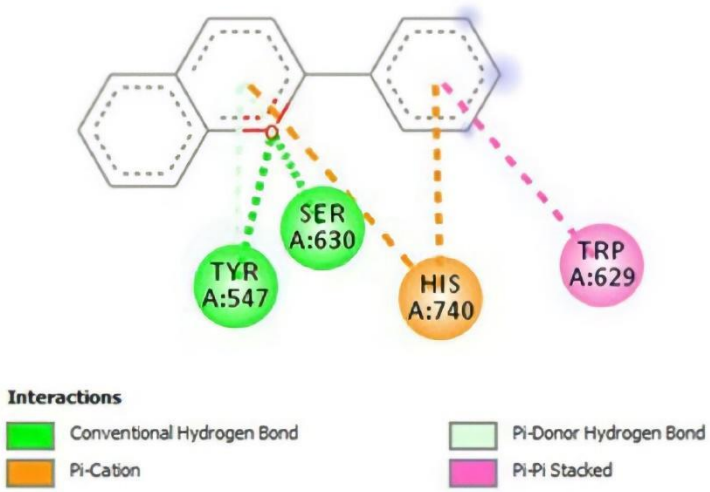

Figure 3. Interaction between 2-phenylchromenylium anthocyanin and DPP4

Hydrogen bonding contributes to the affinity of a molecule for the target protein, thereby forming electrostatic interaction (hydrogen donor and acceptor) (Murray, 2003; Bissantz *et al*., 2010). The number of hydrogen bond donors and acceptors indicates that the higher the hydrogen bonding capacity, the higher the energy required for the absorption process to occur (Syahputra *et al*., 2011).

The value of Gibbs free energy between the ligand-receptors is not only influenced by the presence of hydrogen bonds but is also influenced by several factors such as hydrophobic and electrostatic interactions. Hydrophobic interactions are interactions that occur between nonpolar groups. This bond is an essential bond in the process of combining the nonpolar region of the drug molecule with the nonpolar region of the biologic receptor, where the nonpolar part of the drug molecule that is unable to dissolve in water will combine with the surrounding water molecules through hydrophobic bonds form a quasi-crystalline structure. This hydrophobic bond also has a significant role in determining the binding strength between protein and ligand (Bharathi *et al*., 2014; Chakraborty *et al*., 2014).

It is known from the results of molecular docking that serpentine compounds have Gibbs free energy (ΔG), which is closest to natural ligand compounds of vildagliptin. This condition can be influenced because there are two residues in the hydrophobic interaction between serpentine and vildagliptin, namely Tyr666 and Glu206 residues, while the 2-Phenylchromenylium Anthocyanin compound does not have the same residue as vildagliptin in hydrophobic interactions. The interaction of the amino acid residues involved can allow for contact between the ligand and the DPP-IV receptor to have inhibitory activity.

By comparing the results of the interactions that occur and the Gibbs free energy value (ΔG) of vildagliptin with 10 test compounds, serpentine compounds have the greatest potential as antidiabetic drug candidates compared to other test compounds because they have the Gibbs free energy (ΔG) which is closest to the energy free of Gibbs (ΔG) vildagliptin. However, further tests are needed to ensure that these compounds have the most potential candidates for antidiabetic drugs, such as *in vitro, in vivo*, and clinical trials.

CONCLUSION

The compound contained in Moringa oleifera (MO), namely serpentine has better potential as an antidiabetic drug candidate when compared to other target compounds because it has a Gibbs free energy value (ΔG) which is closest to the natural ligand of Vidaglibtin, which is -7.90 kcal/mol. This value is still lower than vildagliptin, which is -9.37 kcal/mol. Therefore, it is necessary to conduct further experiments to ensure that these compounds have the most potential as candidates for antidiabetic drugs, such as *in vitro, in vivo*, and clinical trials.

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