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Bioactive Compounds of Insulin Leaves (*Smallanthus sonchifolius*) as DPP4 Enzyme Inhibitors in Insulin Signaling Mechanism for the Treatment of Type 2 Diabetes Mellitus: In Silico Study

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Abstract: Type 2 Diabetes Mellitus (DM) is characterized by a relative insulin deficiency caused by pancreatic cell dysfunction and insulin resistance. Herbal-based traditional medicine can be an alternative, one of which is insulin leaf (*Smallanthus sonchifolius*), which has antidiabetic effects and can lower blood sugar levels by inhibiting glycogenolysis and gluconeogenesis. DPP4 inhibitors are a class of antidiabetic drugs used in the treatment of type 2 DM. This study aims to analyze and predict the binding patterns of flavonoid derivatives from insulin leaf (*Smallanthus sonchifolius*) compounds to the DPP4 enzyme inhibitor, to determine the binding affinity of these compounds to the target protein as an antidiabetic agent. The study was conducted using an in silico method, utilizing the Research Collaboratory for Structural Bioinformatics (RCSB), Avogadro Software, AutoDockTools (version 1.5.6), and Biovia Discovery Studio 2021 for molecular docking and prediction of binding patterns and affinity for the DPP4 N7F protein. The results of this study showed that the binding energy value obtained from the natural ligand N7F was -11.0 kcal/mol. The binding energy value for 1,19-dihydroxy-2,6,10,14-phytateraen-18-oic-acid with the N7F protein was -9.8 kcal/mol. Therefore, 1,19-dihydroxy-2,6,10,14-phytateraen-18-oic-acid has a more stable binding with the DPP4 enzyme N7F target protein. Based on the results obtained from molecular docking of the flavonoid derivative compounds from insulin leaf (*S. sonchifolius*), the compound 1,19-dihydroxy-2,6,10,14-phytateraen-18-oic-acid showed the most potential as a DPP4 enzyme inhibitor among the other compounds.

Keywords: *Smallanthus sonchifolius*, Diabetes Mellitus Type 2, DPP4 Inhibitor

***Abstrak*:** *Diabetes Mellitus (DM) tipe 2 ditandai dengan defisiensi insulin relatif yang disebabkan oleh disfungsi sel pankreas dan resistensi insulin. Pengobatan tradisional dengan menggunakan tanaman herbal dapat menjadi alternatif salah satunya daun insulin (Smallanthus sonchifolius) yang mempunyai efek antidiabetes dan dapat menurunkan kadar gula darah dengan menghambat proses glikogenolisis dan glukoneogenesis. DPP-4 inhibitor merupakan golongan obat antidiabetik dalam pengobatan DM tipe 2. Penelitian ini bertujuan untuk menganalisa dan memprediksi pola pengikatan antara senyawa turunan flavonoid daun insulin (Smallanthus sonchifolius) pada inhibitor enzim DPP-4 untuk mengetahui afinitas pengikatan senyawa tersebut terhadap protein target sebagai antidiabetes. Penelitian ini dilakukan dengan metode Study in Silico menggunakan Research Collaboratory for Structural Bioinformatics (RSCB), Software Avogadro, AutoDockTools (versi 1.5.6), dan Biovia Discovery Studio 2021 untuk penambatan molekuler dan prediksi pola pengikatan dan afinitas protein DPP-4 N7F. Hasil dari penelitian ini adalah nilai energi ikatan yang diperoleh dari ligan alami N7F sebesar -11,0 kcal/mol. Nilai energi ikatan yang diperoleh untuk 1,19-Dihidroxy-2,6,10,14-Phytateraen -18 Oic-Acid dengan protein N7F adalah -9,8 kcal/mol. Oleh karena itu, 1,19-Dihiroxy-2,6,10,14-Phytateraen-18-Oic-Acid dengan protein target enzim DPP-4 N7F memiliki ikatan yang lebih stabil. Berdasarkan hasil yang diperoleh dari penambatan molekul pada senyawa turunan flavonoid daun insulin (Smallanthus sonchifolius) senyawa 1,19-Dihiroxy-2,6,10,14-Phytateraen-18-Oic-Asam mempunyai sifat paling potensial sebagai enzim penghambat DPP-4 di antara senyawa lainnya.*

Kata kunci: *Smallanthus sonchifolius, Diabetes Mellitus Tipe 2, DPP-4 Inhibitor*

INTRODUCTION

Diabetes mellitus is a serious chronic metabolic disease, characterized by insulin resistance or impaired insulin secretion, which causes increased blood glucose levels and risks causing damage to the heart, kidneys, nerves, eyes, blood vessels, and other

organs. In the world, currently around 536.6 million people suffer from diabetes, of which 95% are type 2 DM sufferers. This has led to the development of a globally recognized goal to slow the increase in diabetes and obesity rates by 2025 and beyond. The continued development of diabetes can cause various long-term microvascular and macrovascular complications, increasing the risk of premature death, which in this case can cause an economic burden on the global health care system. Maintaining normal blood glucose levels is the most effective treatment to prevent or delay the development and complications of type 2 DM (Prasetiyo *et al*. 2019).

Treatment for type 2 DM patients can be given antidiabetic drugs, namely DPP4 inhibitors and resveratrol with the mechanism of action of DPP4 inhibitors to bind to GLP-1, where inhibition of DPP4 will reactivate insulin signaling in the pancreas and resveratrol works like SIRT6, namely acting as protection from destruction of β-pancreatic cells (Ansari *et al*. 2022). Insulin leaves (*Smallanthus sonchifolius*) have content that can play a role in inducing the cellular defense system contained in flavonoids, saponins and tannins in the field of pharmacology, can fight free radicals. The work of flavonoids in diabetes mellitus can avoid glucose absorption, act as insulin by influencing the mechanism of action of insulin signaling and stimulating glucose uptake in the periphery. Saponins work by inhibiting GLUT-1 so that they can lower glucose. Tannins have hypoglycemic activity by increasing glycogenesis and working by triggering glucose and fat so that they do not cause calorie deposits (Brata & Pratiwi 2019).

Based on the explanation explained above, it is hoped that this research can provide additional information regarding the effectiveness of insulin leaves as an antidiabetic by examining the ability of the compounds contained therein (Dewantoro *et al*. 2023).

MATERIALS AND METHODS

Materials

The macromolecular structure used in this molecular docking was DPP4, downloaded from the RCSB Protein Data Bank (https://www.rcsb.org/) with ID number 4A5S. Ligand structures of diosgenin (CID:99474), enhydrin (CID: 5281441), quercetin (CID: 5280343), fluctuanin (CID: 134692058), smaditerpenic acid B (CID: 00057760), smaditerpenic acid C (CID: 146014779), smaditerpenic acid D (CID: 00057760) and sonchifolol (CID: 00057799) were obtained from PubChem website (https://pubchem.ncbi.nlm.nih.gov/) and the Knapsackfamily (https://www.knapsackfamily.com) as shown in Figure 1-10.

Protein Preparation

The DPP4 structure is contained in a pdb file with ID 4A5S and a resolution of 1.62 Å. The structure was separated from its co-crystallized ligand using BIOVIA Discovery Studio 2021 as saved as individual pdb file. The file was prepared and converted into pdbqt file with AutoDockTools (version 1.5.6).

Ligand Preparation

Compounds derived from insulin leaf plants *(S. sonchifolius*) which come from the flavonoid group were selected as ligands in the study. These compounds include, (diosgenin, fluctuanine, enhydrin,

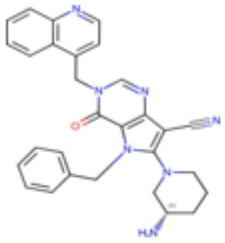

Figure 1. Structure of Natural Ligand N7F

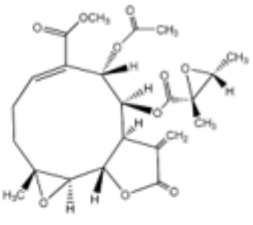

Figure 2. Enhydrin Structure (C00003255)

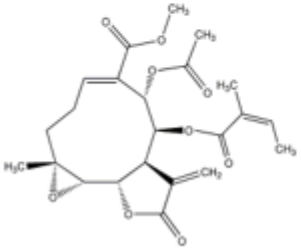

Figure 3. Fluctuanine Structure (C00011880)

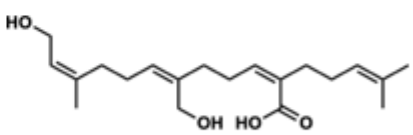

Figure 4. Structure of 1,19-Dihydroxy-2,6, 10,14-phytatraene-18-oic acid (C00056390)

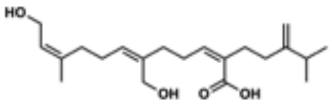

Figure 5. Structure of Smaditerpenic Acid C (C00057749)

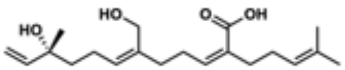

Figure 6. Structure of Smaditerpenic Acid B (C00057759)

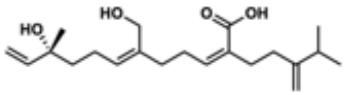

Figure 7. Structure of D-smaditerpenic acid (C00057760)

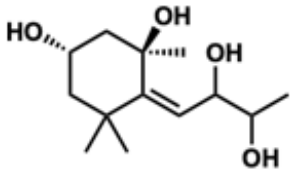

Figure 8. Sonchifolia Structure (C00057799)

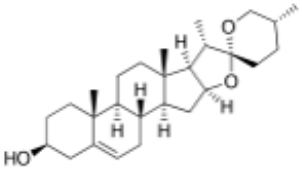

Figure 9. Structure of Active Compound Diosgenin (CID:99474)

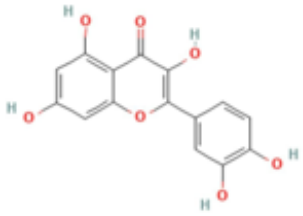

Figure 10. Quercetin Structure (CID : 5280343)

quercetin, sonchifolol, smaditerpenic acid B, C and D) in 3D form obtained from PubChem and Knapsack then underwent a format change from .sdf to pdb via SwissADME (Noviardi & Fachrurrazie 2015). Subsequently, the compounds in the pdb format were prepared and converted into pdbqt with with AutoDockTools (version 1.5.6).

Lipinski Rule of Five

Compounds derived from insulin leaf plants were submitted to the pkCSM webserver (hhttps://biosig.lab.uq.edu.au/pkcsm) for Lipinski Rule of Five evaluation

Molecular Docking against Target Compounds

Ligand molecular docking on 4A5S protein was performed using AutoDockTools (version 1.5.6). The docking process begins by inserting the .pdbqt file into the AutoDock 4.2. The grid box size is adjusted based on the validation results to 40 x 40 x 40 with coordinates X = 23.858, Y = 48.984, Z = 69.796. The results obtained are saved in GPF format through the Grid-Output-Save GPF steps (Syahputra *et al*. 2014). Furthermore, the molecular docking indicators are set by: Docking Macromolecule-Set Rigid Filename-Choose Receptor, selecting the pdbqt file through Docking-Ligand-Choose-Open Ligand-Accept, and docking parameter settings are done by adjusting the energy through Docking-Search Parameter-Genetic Algorithm-Number of GA Runs-Accept. The results are then saved in dock.dpf format. In the final stage, the docking process is carried out by copying the AutoDock4 and AutoGrid4 programs into AutoDockTools (version 1.5.6). After the process is complete, a .dlg format file is generated and can be viewed using Notepad. All molecular docking results are then compared with each other (Asiamah *et al*. 2023).

Interaction Visualization

The interaction between ligand and protein was analyzed and visualized using BIOVIA Discovery Studio 2021. The docking of the molecules formed a complex which was then evaluated using AutoDockTools (version 1.5.6). Furthermore, the interactions in this complex were further analyzed using BIOVIA Discovery Studio 2021 (Manno & Utami 2023).

RESULTS AND DISCUSSION

This experiment is an experimental computational research experiment arranged in the form of in silico research using molecular docking. This computational method is a method used to determine the binding pattern and affinity of proteins (enzymes) and compounds in the form of ligands (Auli *et al*. 2024). Docking allows the identification of new compounds of interest in the field of therapy, predicts the interaction between target proteins and ligands at the molecular level, and explains the structure-activity relationship. Molecular docking studies can be used to make drug discovery more efficient by minimizing costs and maximizing the likelihood of finding the right drug selection (Sutton *et al*. 2012). Molecular docking was carried out on active compounds from *Smallanthus sonchifolius* leaves

against the DPP4 enzyme. The purpose of this molecular docking is to determine the binding affinity of the compound to the target protein (Malikhana *et al*. 2021).

Before conducting further studies on molecular docking, a search for pharmacokinetic data on natural ligands, drugs, ligands from plants and their derivatives was carried out. This prediction was carried out by following the rules of Lipinski Rule of Five which has requirements for a molecule, namely the maximum number of hydrogen bond donors is 5, the number of hydrogen bond acceptors is less than 10, the molecular weight is less than 500 g/mol, and the log P value is less than 5. The function of Lipinski's rule itself is to determine the physicochemical properties of a ligand, to determine the hydrophobic or hydrophilic properties of a compound so that it can pass through the cell membrane by passive diffusion. Based on the results of the prediction of the molecular properties of ligands using pkCSM, all ligands meet the requirements according to Lipinski's rules, the data can be seen in Table 1.

This in silico study study involves method validation and molecular docking of target compounds. Method validation is the initial process of simulation that binds the target enzyme DPP4 with its natural ligand, deazahypoxanthine. This compound is known by several other names such as 6-[(3s)-3-aminopiperidin-1- yl]-5-benzylzyl-4-oxo-3-(quinolin-4-ylmethyl)-4,5-dihydro-3h-pyrrolo[3,2-d]pyrimidine-7-carbonitrile. Deazahypoxanthine is formed through the hexosamine biosynthesis pathway and plays a key role in the pathological development of diabetes and diabetic complications (Nursanti *et al*. 2023).

Then the molecular docking process of target compounds was carried out, namely diosgenin, enhydrin, quercetin, fluctuanin, 1,19-dihydroxy-2,6,10,14-phytatetraen-18-oic-acid, Sonchifolol, smaditerpenic C, and smaditerpenic D against the DPP4 enzyme. The binding energy results obtained from this process can be seen in Table 2.

Based on the results obtained, the natural ligand deazahypoxanthine has a binding energy of -11.0. Deazahypoxanthine is a natural ligand of the DPP4 enzyme with PDB code 4A5S. From the results that have been obtained through the molecular docking stage, the binding energy of eight ligands was obtained, namely diosgenin, enhydrin, quercetin, fluctuanin, 1,19-dihydroxy-2,6,10,14-phytatetraen-18-oic acid, smaditerpenic C, smaditerpenic D, and sonchifolol. So it can be concluded that the weakest binding energy obtained is from the smaditerpenic C ligand with an energy of -5.9 kcal/mol, and the strongest binding energy is obtained from the ligand 1,19-dihydroxy-2,6,10,14-phytatetraen-18-oic acid which is -9.8 kcal/mol. Based on these results, it can be seen that the ligand 1,19-dihydroxy-2,6,10,14-phytatetraen-18-oic-acid was considered as the most

Table 1. Results of prediction of physicochemical properties of compounds based on Lipinski's rules

Compound	BM	Log P	HBA	HBD	Inf
Deazahypoxanthine	489.6	3.1	6	1	v
Diosgenin	414.63	5.7139	3	1	v
Enhydrin	464.46	1.1558	10	0	v
Quercetin	302.238	1.988	7	5	v
Fluctuanin	448.46	1.9446	9	0	v
1,19-Dihidroxy-2,6,10,14-Phytatetraen-18-Oic-Acid	350.499	4.4059	3	3	v
SmaditerpenC	322.445	3.7714	3	3	v
SmaditerpenD	350.499	4.4059	3	3	v
Sonchifolol	244.33	0.5864	4	4	v

Table 2. Docking results between ligand and DPP4 enzyme

Target Proteins	Ligand	*Binding Energy (kcal/mol)*
DPP4 (PDB ID:4A5S)	Deazahypoxanthine	-11.0
	Diosgenin	-6.8
	Enhydrin	-6.9
	Quercetin	-7.7
	Fluctuanin	-6.9
	1,19-Dihidroxy-2,6,10,14-Phytatetraen-18-Oic-Acid	-9.8
	SmaditerpenC	-5.9
	SmaditerpenD	-7.9
	Sonchifolol	-7.6

potential properties among the other seven ligands.

Validation of the docking method was carried out to determine the parameters of molecular docking. This validation was carried out using AutoDockTools software. Validation of the docking method was carried out by reattaching the test compound to the DPP4 enzyme with position parameters (Xiao *et al*. 2018). The grid box positions used were center_x = 23.858, center_y = 48.984, and center_z = 69.796, while the grid sizes at size_x = 40, size_y = 40, and size_z = 40 were centered on the active position enzyme action. Validation of the docking method is said to be valid if the resulting RMSD value is less than or equal to 2.00 Å. The validation results in this study showed an RMSD value <2.00 Å, which was 0.37 Å. The validation results obtained indicate that the shift in the binding position of the inhibitor compound is not significantly shifted from the position before validation. The RMSD value obtained also states that the grid box parameters used are valid (Pantaleão *et al*. 2018). The results of the 3D structure visualization of the DPP4 enzyme receptor with (PDB ID: 4A5S) are presented using Discovery Studio software (Figure 11). The results obtained from the visualization of the DPP4 enzyme with an active site on the amino acid residue. The active site functions as a substrate and inhibitor binding site. The active site of the DPP4 enzyme is also divided into 3 types, namely the catalytic triad, the oxytocin space, and the salt bridge area (Wan *et al*. 2023).

The interaction between the ligand and the target enzyme can be seen using the BIOVIA Discovery Studio 2021 software. The visualization results can be seen in Figure 12.

In the 2D visualization of the natural ligand deazahypoxanthin bound to the amino acid of the DPP4 enzyme. Several interactions were obtained, namely van der waals bonds, conventional hydrogen bonds, carbon hydrogen bonds, Pi-Donor hydrogen bonds, Pi-Pi Stacked, and Pi-Pi T-shaped. In the van der waals bonds of amino acids involved are GLU A:205; GLU A:206; TRP A: 659; VAL A: 711; VAL A: 656; TRP A: 659. In conventional hydrogen bonds, the amino acids involved are TYR A: 631. Then in the carbon hydrogen bonds, the amino acids involved are SER A: 630. The Pi-Donor hydrogen bond for the bound amino acids is PHE A: 357.

In the 2D visualization of diosgenin ligands, several interactions were formed, namely van der Waals bonds, conventional hydrogen bonds, Alkyl bonds, and Pi-Alkyl bonds. In the van der waals bonds, the amino acids involved are LYS A: 554, VAL A: 546; TRP A: 629, GLY A: 632. The conventional hydrogen bonds of the amino acids involved are TYR A: 631. The Alkyl bonds of the amino acids involved are VAL A: 711; VALA: 656;

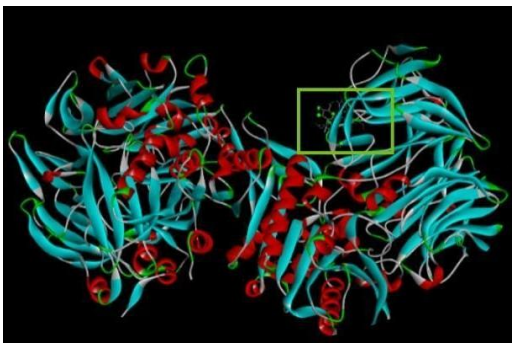

Figure 11. Visualization of the 3D structure of the receptor (DPP4 enzyme) (PDB ID: 4A5S)

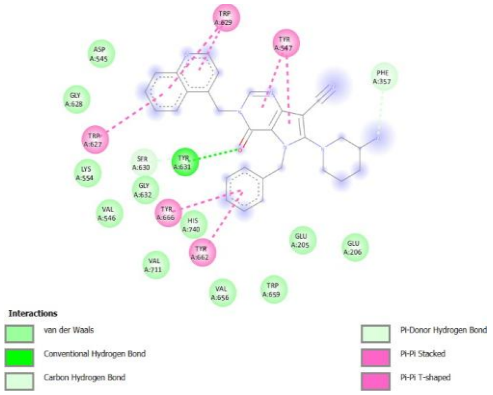

Figure 12. 2D visualization of natural ligand interaction complex on DPP4 enzyme amino acids

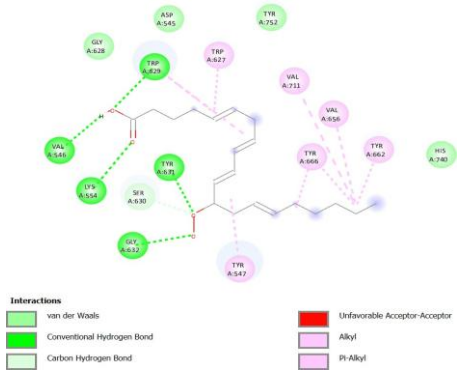

Figure 13. 2D visualization of the interaction complex of 1,19-Dihydroxy-2,6,10,14-Phytatetraen-18-Oic-Acid ligand on DPP4 enzyme amino acids

TRP A:627; and TYR A: 666. As well as the Pi-Alkyl bonds of the amino acids involved are TYR A: 547 and TYR A: 662.

1,19-Dihydroxy-2,6,10,14-Phytatetraen-18-Oic-Acid Hydrolyzed diosin, is a natural steroidal saponin found in a number of plants, including *Smallanthus sonchifolius*, *Trigonella foenum graecum*, *Solanum incanum*, *Solanum xanthocarpum*, *Smilax china* Linn, and *Dioscorea nipponoca Makino*. As a physiologically active phytochemical, 1,19-Dihydroxy-2,6,10,14-Phytate traen-18-Oic-Acid has a variety of effects on plants. It is used as a medicine to treat conditions such as diabetes, hypercholesterolemia, climacteric syndrome, leukemia and cancer, as well as in the production of steroids.

1,19-Dihydroxy-2,6,10,14-Phytatetraen-18-Oic-Acid is a compound that has good affinity with the ER-a receptor and can bind to various amino acids, showing potential as an effective ligand in the treatment of diabetes mellitus. In several journals, 1,19-Dihydroxy-2,6,10,14-Phytatetraen -18-Oic Acid was found to have potential as a ligand that can bind to receptors, including in the treatment of diabetes mellitus (Wan *et al*. 2023). The compound 1,19-Dihy droxy-2,6,10,14-Phytatetraen-18-Oic-Acid has been shown to increase insulin sensitivity and glucose absorption in the body, which can help regulate blood sugar levels and relieve diabetes symptoms (Röhrborn *et al*. 2016). Natural ligands, such as those found in plants, have been traditionally used to treat diabetes and these compounds often interact with specific receptors in the body, affecting metabolic processes and glucose regulation (Bharti *et al*. 2018). 1,19-Dihydroxy-2,6,10,14-Phytatetraen-18 -Oic-Acid and natural ligands both compounds can improve insulin sensitivity and glucose uptake, thereby helping to regulate blood sugar levels. However, the specific receptor interactions and metabolic pathways affected by these compounds may differ.

The energy bond value obtained from the natural ligand deazahypoxanthine (N7F) is -11.0 kcal/mol. The energy bond value obtained in 1,19-Dihydroxy-2,6,10,14-Phytatetraen-18-Oic-Acid with N7F protein is -9.8 kcal/mol. Based on these results, it can be seen that 1,19-Dihydroxy-2,6,10,14-Phytatetraen-18-Oic-Acid with the DPP4 N7F enzyme target protein has a more stable bond than other ligands with the DPP4 N7F enzyme target protein. Thus, the results of the study can predict that 1,19-Dihydroxy-2,6,10,14-Phytate traen-18-Oic-Acid has an affinity for the Dipeptidyl peptidase-4 (DPP4) protein. The interaction between 1,19-Dihydroxy-2,6,10,14-Phy tatetraen-18-Oic-Acid and the protein Dipeptidyl Peptidase-4 (DPP4) can occur by inhibiting the DPP4 enzyme, because the interaction occurs at the active site of the target protein, which causes inhibitory activity (Munhoz & Frode 2018).

It is known that the DPP4 inhibitor interacts strongly with the amino acid TYR A: 631, forming a salt hydrogen bond. Based on the data in Figure 13 regarding the interaction of natural ligands on the amino acid DPP4, it is known that the free energy of interaction (IFIE) calculated from the residue with all inhibitors is significant, with TYR A: 631 in particular showing the highest IFIE among all inhibitors considered. A closer look at the complex structure shows that the inhibitor not only interacts with the amino acid TYR A: 631 forming a salt bridge, but also effectively forms a hydrogen bond with it. Then besides that, besides the amino acid TYR A: 631 which has similarities with amino acids such as TRP A: 627; TYR A: 547; and TYR A: 662. So that most of the deazahypo xanthine analogs have very good selectivity (Arulmozhiraja *et al*. 2016).

CONCLUSION

Based on the results obtained from molecular docking on flavonoid derivative compounds of Insulin Leaves (*Smallanthus sonchifolius*), it was found that all ligands met the requirements according to Lipinski's rules, so that all of these derivative compounds were estimated to have antidiabetic activity. In the docking results for the binding energy obtained, namely the largest binding energy in the Smaditerpenic C compound (-5.9 kcal/mol), the

smallest binding energy in the compound 1,19-Dihydroxy-2,6,10,14 -Phytatetraen-18-Oic-Acid (-9.8 kcal / mol). So it can be concluded that the compound 1,19-Dihydroxy-2,6,10,14 -Phytatetraen-18-Oic-Acid has the most potential properties as a DPP4 Inhibitor enzyme among other compounds.

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