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Molecular Docking and Molecular Dynamic Studies of Secondary Metabolites from *Momordica Charantia* as Natural Antidiabetic

(*Studi Penambatan dan Dinamika Molekuler Senyawa Metabolit Sekunder Momordica Charantia sebagai Antidiabetes Alami*)

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ABSTRACT

Background: Diabetes Mellitus is a non-contagious disease characterized by hyperglycemia. Diabetes mellitus occurs when the body cannot receive or use insulin properly. If you already have diabetes, then the patient must take medication continuously because diabetes mellitus is a lifelong disease. Because medicines are quite expensive, alternative ways to cure the disease are needed by consuming traditional medicines, one of which is bitter melon (*Momordica charantia*). **Objectives:** This research aims to predict the secondary metabolite compounds in the bitter melon plant, analyze molecular interactions, and identify compounds that can lower blood sugar levels. **Material and Methods:** 12 compounds from the *Momordica charantia* plant and six proteins (1IR3, 1RHF, 1XU7, 4PNZ, 4YVP, 2NT7) that will be docked using Pyrx and Yasara Dynamics applications. **Results**: From the molecular docking results, three compounds with the highest binding affinity were found in Momordica charantia: momordenol, oleanolic acid, and momordicin. Based on molecular dynamics simulations, these three compounds were stable in their interactions with the six proteins tested, namely 1IR3, 1RHF, 4PNZ, 4YVP, 1XU7, and 2NT7. Momordenol and momordicin showed the most stable interaction profiles. Furthermore, ADMET tests showed that momordenol, oleanolic acid, and momordisin have drug-like characteristics. **Conclusions:** The *Momordica charantia* plant has the potential to act as an antidiabetic agent.

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INTRODUCTION

Diabetes mellitus (DM) is a non-communicable disease that results from metabolic disorders in the body, causing the body to be unable to utilize blood glucose, leading to a buildup of glucose in the bloodstream. DM is characterized by hyperglycemia and disruptions in carbohydrate, protein, and fat metabolism, which are associated with abnormalities in insulin secretion or a lack of insulin secretory action. Common symptoms experienced by people with DM include frequent thirst, frequent urination, polyphagia, significant weight loss, and tingling. DM is classified into four types: type 1, type 2, DM due to other causes, and gestational diabetes.

Traditionally, antidiabetic drugs have been widely used in the treatment of diabetes. However, these drugs have long treatment periods, can be expensive, and may lead to unwanted side effects. As an alternative, traditional medicine can be a safer and more sustainable solution for treating diabetes mellitus. Momordica charantia, commonly known as bitter melon, is one of the plants proven to have antidiabetic properties and can be used as a non-drug therapy for diabetes.

The use of *M. charantia* for antidiabetic treatment is supported by several compounds found in the plant, including polypeptide-P insulin, charantin, lectins, momordin, resinic acid, momordisin, sterols, flavonoids, saponins, polyphenols, and alkaloids. These compounds have been shown to lower blood glucose levels and stimulate insulin production. In order to further understand the activity of these compounds, in silico research is needed to analyze their interactions with target molecules and receptors. In silico testing involves the use of a computer to simulate these interactions

MATERIAL AND METHODS

Materials

The selected proteins are those that play a role in insulin production and enhancing drug effectiveness, including phosphorylated insulin receptor tyrosine kinase (1IR3), human Tyro3-D1D2 (1RHF), human dipeptidyl peptidase IV/CD26 (4PNZ), steroid hormone metabolism enzymes (AKR1Cs), human 11 beta-hydroxysteroid dehydrogenase type I (1XU7), and Tyrosine-protein phosphatase non-receptor type 1 (2NT7). To identify secondary metabolites in *M. charantia*, the KNApSAcK database (knapsackfamily.com) was utilized. The experiments were conducted on a notebook computer with 4 gigabytes of RAM and an Intel (R) Celeron CPU N3350 1.10 GHz (2 CPUs), running Windows 10 (64-bit). Various software programs were used, including PubChem database, Open Babel, String, Pyrx, PyMOL version 2.5, Discovery Studio 2021, PDB (rcsb.org), PDBsum program (ebi.ac.uk), PASS (Prediction of Activity Spectra for Substances) Online (passonline.org), and Yasara Dynamics version 20.14.24.

Methods

Selection of Secondary Metabolites in *M. charantia*

Secondary metabolites in *M. charantia* were searched using the KNApSAcK family website. The compounds were downloaded using their SMILES (Simplified Molecular Input Line Entry System) in 3D format (.sdf format). If 3D format was unavailable, the 2D form could be downloaded and converted to 3D using Open Babel. Geometry optimization was performed using ChemDraw 3D Ultra version 8.0 with MM2 mode.

Prediction of Secondary Metabolite Compound Profiles in *M. charantia*

The selected secondary metabolite was evaluated using the PASS system (way2drug.com) to predict its biological activity, focusing on compounds with a Pa value greater than 0.7, indicating a high probability of activity. The metabolic profile of the compound was then analyzed using the ADMET predictor (simulations-plus.com) to predict its absorption, distribution, metabolism, excretion, and toxicity properties. The pkCSM website (biosig.unimelb.edu.au) was used to predict various pharmacokinetic properties by entering the compound's SMILES and identifying compounds with drug-like properties.

Molecular Docking

The crystal structure (PDB ID: 1IR3, 1RHF, 4PNZ, 4YVP, 1XU7, and 2NT7) was obtained from the Protein Data Bank, with selection criteria including a resolution limit of 1-3, which indicates high-quality structural information with minimal missing residues. The protein is also checked using the Ramachandran plot. This tool evaluates protein structure quality based on phi-psi angles, with proteins having more than 90% of residues in favorable or allowed regions being preferred. PyMol was used to retain polar hydrogen with Kollman charges. Docking was conducted with AutoDock Vina integrated with PyRx 0.9.9, using a grid with the completeness of 8 and sizes of 25, 25, 25, and a center of x = -47.02, y = -32.98, z = -9.92. Docking was considered successful if the RMSD value was less than 2 Å.

Molecular Dynamic

Molecular dynamics simulation was performed on YASARA Structure version 14.12.2 on the Microsoft Windows 10 operating system, using the YAMBER force field. The Coulomb distance interaction was computed through the Ewald particle algorithm, and the Van der Waals force was restricted to 8 Å. The simulation box was shaped like a cube and was placed around the simulated molecules at a distance of 5 nm. It measured 50 × 50 × 50 Å with a value of n = 6, and the boundary was periodically conditioned. The water density was set to 1 g/cc at 298 K, and the simulation lasted for 10 ns with images taken every 100 ps.

RESULTS AND DISCUSSION

Bitter Melon Plant Compounds

Twelve compounds found in *M. charantia* were used in the molecular docking process (Table 1).

Table 1. Compounds of Bitter Melon

No	Compound	Group	Source
1.	*9t,11t,13t conjugated linoleic acid*	*Fatty acid*	(Hsu et al., 2011)
2.	*Arginine*	*Amino Acid*	(Y. Ulung Anggraito, R. Susanti, 2018)
3.	*Benzoic acid*	*Aromatic carboxylic acid*	(Jia et al., 2017)
4.	*Conjugated linoleic acid*	*Fatty acid*	(Hsu et al., 2011)
5.	*Linoleic acid*	*Fatty acid*	(Hsu et al., 2011)
6.	*Momordenol*	*Triterpenoid*	(Torre et al., 2020)
7.	*Momordicin I*	*Triterpenoid*	(Torre et al., 2020)
8.	*Niacin*	*Vitamin B3*	(Rizeki et al., 2012)
9.	*Oleanolic acid*	*Triterpenoid*	(Jia et al., 2017)
10.	*Pectin*	*Polysaccharide*	(Nur Wana, 2013)
11.	*Phenylalanine*	*Amino Acid*	(Y. Ulung Anggraito, R. Susanti, 2018)
12.	*Phenol*	*Phenolic*	(Torre et al., 2020)

Following the selection of the compounds to be used, a SMILES search was conducted to obtain the compounds. The SMILES of the 12 compounds can be found in Table 2.

Table 2. SMILES of Bitter Melon

No	Compound	SMILES
1.	*9t,11t,13t conjugated linoleic acid*	OC(CCCCCCC/C=C/C=C/C=C/CCCC)=O
2.	*Arginine*	OC([C@H](CCCN=C(N)N)N)=O
3.	*Benzoic acid*	OC(C1=CC=CC=C1)=O
4.	*Conjugated linoleic acid*	C\C=C/C\C=C/CCCCCCCC(=O)O
5.	*Linoleic acid*	OC(CCCCCCC/C=C\C/C=C\CCCCC)=O
6.	*Momordenol*	O=C1[C@H]([C@H](C)CC[C@H](CC)C(C)C)[C@@]2(C)C([C@@H]3[C@@H](CC2)[C@@](CC[C@H]4O)(C)C(C4)=CC3)=C1
7.	*Momordicin I*	O[C@@H]1[C@H]([C@@]([C@H](CC[C@@H]2O)C(C2(C)C)=C1)(C=O)CC3)[C@@]4(C)[C@@]3(C)[C@@H]([C@H](C)C[C@@H](C=C(C)C)O)CC4
8.	*Niacin*	OC(C1=CN=CC=C1)=O
9.	*Oleanolic acid*	O[C@@H]1C(C)(C)[C@H]2[C@@](CC1)(C)[C@@H]3[C@](CC2)(C)[C@@]4(C)C([C@H](CC(C)(C)CC5)[C@@]5(C(O)=O)CC4)=CC3

No	Compound	SMILES
10.	*Pectin*	O[C@H]([C@H]1O)[C@H]([C@@H](C(O)=O)O[C@H]1O)O
11.	*Phenylalanine*	OC([C@H](CC1=CC=CC=C1)N)=O
12.	*Phenol*	OC1=CC=CC=C1

The compounds were subjected to the PASS test, and those with a PA value of > 0.7 were selected. A PA value > 0.7 indicates that the compound has high biological activity and is highly similar to drug compounds.

Table 3. PASS test of Bitter Melon

No	Compound Name	Activity
1.	*9t,11t,13t conjugated linoleic acid*	*Antieczematic, G-protein-coupled receptor kinase inhibitor, Antimutagenic, Antiseborrheic, Antithrombotic*
2.	*Arginine*	*Antiseborrheic, G-protein-coupled receptor kinase inhibitor, CDP-glycerol glycerophosphotransferase inhibitor*
3.	*Benzoic acid*	*Antieczematic, Antiseborrheic, G-protein-coupled receptor kinase inhibitor*
4.	*Conjugated linoleic acid*	*Antieczematic, G-protein-coupled receptor kinase inhibitor, Antimutagenic, Antisecretoric, Antiinflammatory*
5.	*Linoleic acid*	*G-protein-coupled receptor kinase inhibitor, Antimutagenic, Antihypercholesterolemic*
6.	*Momordenol*	*Antihypercholesterolemic, Cholesterol antagonist, Antipruritic, Alkylacetylglycerophosphatase inhibitor*
7.	*Momordicin I*	*Apoptosis agonist, Antineoplastic, Antieczematic, CDP-glycerol glycerophosphotransferase inhibitor*
8.	*Niacin*	*G-protein-coupled receptor kinase inhibitor, Cholesterol antagonist, Insulin promoter*
9.	*Oleanolic acid*	*Protein-tyrosine phosphatase inhibitor, Protein phosphatase inhibitor, antiinflamatory, antineoplastic*
10.	*Pectin*	*G-protein-coupled receptor kinase inhibitor, CDP-glycerol glycerophosphotransferase inhibitor, Antitoxic, Analeptic, Immunostimulant*
11.	*Phenylalanine*	*G-protein-coupled receptor kinase inhibitor, Insulin promoter, Antiseborrheic, Antiviral (Picornavirus)*

No	Compound Name	Activity
12.	*Phenol*	*Antiseborrheic, G-protein-coupled receptor kinase inhibitor, Antimutagenic*

Subsequently, ADMET and druglikeness tests were performed. The druglikeness test included the Lipinski, Ghose, Veber, Egan, and Muegge tests, which are important to predict the pharmacokinetic profile and toxicity of compounds in the body and to assess their similarity to original drug compounds. The ADMET test results can be found in Table 4, while the results of the druglikeness test can be found in Table 5.

Table 4. ADMET Test

Category to Skrining pkCSM	Compound *Momordica Charantia*					
	1	2	3	4	5	6
Absorption						
Water solubility	-6.657	-2.739	-1.506	-6.657	-6.766	-6.765
$CaCO_2$ permeability	1.573	-0.468	1.72	1.573	1.566	1.209
Intestinal absorption	90.917	36.971	98.405	90.917	90.41	95.616
Skin Permeability	-2.704	-2.735	-2.718	-2.704	-2.719	-2.945
P-gp substrate	-	Yes	-	-	-	-
P-gp I inhibitor	-	-	-	-	-	Yes
P-gp II inhibitor	-	-	-	-	-	Yes
Distribution						
VDss	-0.323	-0.681	-1.271	-0.323	-0.293	0.239
FU	0.07	0.701	0.446	0.07	0.068	0
BBB permeability	-0.282	-1.06	-0.181	-0.282	-0.308	-0.104
CNS permeability	-1.563	-4.388	-2.046	-1.563	-1.616	-2.056
Metabolism						
CYP2D6 substrate	-	-	-	-	-	-
CYP3A4 substrate	Yes	-	-	Yes	Yes	Yes
CYP1A2 inhibitior	Yes	-	-	Yes	Yes	-
CYP2C19 inhibitior	-	-	-	-	-	-
CYP2C9 inhibitior	-	-	-	-	-	-
CYP2D6 inhibitior	-	-	-	-	-	-
CYP3A4 inhibitior	-	-	-	-	-	-
Excretion						
CLTOT	1.975	0.127	0.713	1.975	1.932	0.565
OCT2	-	-	-	-	-	-
Toxicity						
AMES toxicity	-	Yes	-	-	-	-
Max. tolerated dose	-0.64	0.595	0.615	-0.64	-0.589	-0.538
hERG I inhibitor	-	-	-	-	-	-
hERG II inhibitor	Yes	-	-	Yes	Yes	Yes
LD50	1.719	2.28	1.994	1.719	1.724	2.193
LOAEL	3.088	2.1	2.634	3.088	3.16	2.26
Hepatotoxicity	-	-	-	-	-	-
Skin Sensitisation	Yes	Yes	-	Yes	Yes	-
T.Pyriformis toxicity	1.386	0.268	-0.069	1.386	1.335	0.608

Category to Skrining pkCSM	Compound *Momordica Charantia*					
	1	2	3	4	5	6
Minnow toxicity	-0.998	3.543	1.836	-0.998	-1.125	-1.621

Description: (1) 9t,11t,13t conjugated linoleic acid, (2) Arginine, (3) Benzoic acid, (4) Conjugated linoleic acid, (5) linoleic acid, (6) Momordenol

Table 5. ADMET Test (Continued)

Category to Skrining pkCSM	Compound *Momordica Charantia*					
	7	8	9	10	11	12
Absorption						
Water solubility	-5.661	-1.16	-3.359	-0.894	-2.127	-0.679
$Caco_2$ permeability	0.945	1.23	1.293	-0.217	0.775	1.638
Intestinal absorption	96.374	86.251	100	17.723	73.888	93.233
Skin Permeability	-3.142	-2.783	-2.721	-2.735	-2.721	-1.795
P-gp substrate	Yes	-	-	-	-	-
P-gp I inhibitor	Yes	-	-	-	-	-
P-gp II inhibitor	Yes	-	-	-	-	-
Distribution						
VDss	-0.329	-1.03	-1.057	-0.922	-0.224	0.068
FU	0	0.697	0	0.776	0.877	0.443
BBB permeability	-0.525	-0.328	-0.127	-1.222	-0.247	0.025
CNS permeability	-1.832	-2.905	-1.124	-4.443	-2.633	-1.853
Metabolism						
CYP2D6 substrate	-	-	-	-	-	-
CYP3A4 substrate	Yes	-	Yes	-	-	-
CYP1A2 inhibitior	-	-	-	-	-	-
CYP2C19 inhibitior	-	-	-	-	-	-
CYP2C9 inhibitior	-	-	-	-	-	-
CYP2D6 inhibitior	-	-	-	-	-	-
CYP3A4 inhibitior	-	-	-	-	-	-
Excretion						
CLTOT	0.453	0.676	-0.081	0.646	0.42	0.218
OCT2	-	-	-	-	-	-
Toxicity						
AMES toxicity	-	-	-	-	-	-
Max. tolerated dose	-1.076	1.071	0.739	1.878	0.474	1.113
hERG I inhibitor	-	-	-	-	-	-
hERG II inhibitor	-	-	-	-	-	-
LD50	4.005	1.965	2.478	1.22	2.764	1.91
LOAEL	1.657	2.757	2.108	3.715	1.871	1.981
Hepatotoxicity	Yes	-	-	-	Yes	-
Skin Sensitisation	-	-	-	-	-	Yes
T. Pyriformis toxicity	0.445	-0.554	0.285	0.285	0.164	-0.721
Minnow toxicity	0.225	2.302	-1.486	4.547	1.997	1.847

Description: (7) Momordicin I, (8) Niacin, (9) Oleanolic acid, (10) Pectin, (11) Phenylalanine, (12) Phenol

The ADMET test results for twelve compounds yielded thirty predictive data, including solubility in water and $CaCO_2$ permeability. Solubility in water, which predicts a compound's solubility at 25°C, is an essential factor in drug efficacy as most drugs on the market have water solubility values between -6 to -2. The smaller the solubility value, the more difficult it is for the compound to be absorbed into the body, as Karyawati (2020) noted. In this study, all twelve compounds fell within the water solubility range for drugs on the market. $CaCO_2$ permeability, which represents the prediction of orally-administered drug absorption, is another essential factor to consider. A compound is deemed to have good permeability if it has a Papp value greater than $8x10^{-6}$ cm/s or a value greater than 0.9 in the pkCSM model, according to Pires et al. (2015). The ADMET test results revealed that compounds (2), (10), and (11) displayed poor $CaCO_2$ permeability. Compounds with poor permeability may have lower oral bioavailability and may require alternative routes of administration to be effective. It is essential to consider these factors when assessing these compounds' potential efficacy and safety as drug candidates. Further testing and analysis may be necessary to evaluate their pharmacokinetic and pharmacodynamic properties fully.

The third factor analyzed in the ADMET test results is the prediction of intestinal absorption in humans, determining the percentage of the administered drug humans will absorb. A good absorption value is >80%, while poor absorption is <30%. Based on the data, almost all compounds had good absorption values, with the percentage absorbed being more significant than 30%, except for compound (10), which had an absorption value of less than 30%. Skin permeability is another crucial factor in drug delivery. According to Pires et al. (2015), a compound has low permeability if it has a log kp value > -2.5 and good permeability if it has a Log kp value < -2.5. The results obtained from the twelve compounds revealed that all compounds, except compound (12), had good permeability to the skin. Compound (12) had a Log kp value of -1.795, indicating poor permeability to the skin. It is important to note that these ADMET test results provide valuable insights into the potential efficacy and safety of these compounds as drug candidates. Further research and analysis, including in vivo testing, are necessary to fully evaluate their pharmacokinetic and pharmacodynamic properties and determine their suitability as drug candidates.

P-glycoprotein (P-gp) is a membrane protein crucial in transporting transmembrane reflux. It is responsible for capturing lipophilic drugs that pass through the lipid bilayer, flipping them from inside to outside, and ultimately expelling the molecule into the extracellular matrix. Based on the data, it was observed that compounds (2), (6), and (7) interact with P-gp. The distribution data include VDSS (volume distribution at steady state), FU (fraction unbound), BBB permeability, CNS permeability, CYP450 inhibitor, and CYP2D/CYP3A4 substrate data. VDSS represents the volume of drug dose required to distribute in the blood plasma. A low VDSS log value is indicated by a value < -0.15, and a

high VDSS log value by a value > 0.45 (Pires, D.E.V., Blundell, T.L and Ascher, 2015). From the table, it can be observed that all compounds have low VDSS values.

P-glycoprotein (p-gp) is a membrane protein that facilitates the transmembrane efflux of compounds. These proteins capture lipophilic drugs as they traverse the lipid bilayer and flip the molecule from the inside to the outside, transporting the drug to the extracellular matrix. The ADMET test results also include information on various distribution parameters, such as VDSS (volume distribution at steady state), FU (fraction unbound), BBB (blood-brain barrier) permeability, CNS (central nervous system) permeability, CYP450 inhibitor data, and CYP2D/CYP3A4 substrate data. VDSS measures the drug dose volume required for blood plasma distribution, and a higher VDSS value indicates greater distribution in non-plasma tissue. A value indicates a low VDSS log value <-0.15, while a value indicates a high VDSS log value>0.45 (Pires, D.E.V., Blundell, T.L and Ascher, 2015). The data shows that all compounds have low VDSS values.

Moreover, the ADMET test results also include information on BBB permeability, which predicts a compound's ability to penetrate the blood-brain barrier. A compound is considered to have BBB permeability if it has a logBB value > 0.3 and difficult to penetrate if it has a logBB value <-1. It can be inferred from the data that all compounds exhibit low BBB permeability. CNS permeability is another essential parameter that measures a drug's ability to cross the central nervous system. A compound can penetrate the CNS if its log PS value is > -2, while a log PS value < -3 suggests that it cannot penetrate the CNS (Pires, D.E.V., Blundell, T.L and Ascher, 2015). The ADMET test results indicate that only compounds (2) and (10) can penetrate the CNS. Lastly, the ADMET test provides information on the metabolic process, which is the breakdown of drugs that form metabolites in the body. The liver is the organ responsible for this metabolism, where Cytochrome P450 plays a crucial role in oxidizing xenobiotics to inactive drug compounds. The ability of compounds to inhibit cytochrome P450 is crucial as it can affect their metabolic activity. Cytochrome P450 has several isoform models, which consist of various substrate compounds such as CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4. Compounds that act as substrates can be metabolized by CYP450, while compounds that act as inhibitors can suppress their metabolic activity. The data in the table show that compounds (1), (4), (5), (6), (7), and (9) inhibit CYP3A4 substrates, which suggests that they inhibit cytochrome P450. Meanwhile, compounds (1), (4), and (5) act as CYP1A2 inhibitors (Krihariyani, Dwi, 2019).

For the process of excretion of compounds can be done by measuring the total clearance (CLTOT) and the renal constant OCT2 (Organic Cation Transporter 2). CLTOT is a combination of the combination of renal clearance (excretion through the kidneys) and hepatic clearance (metabolism in the liver and bile) related to bioavailability to determine the dose level to achieve steady state concentrations. In the

table, values range from -0.081 to 1.975 ml/minute, while Organic Cation Transporter 2 (OTC2) is a transporter found in the kidneys that has a role in the disposition and clearance of drugs and endogenous compounds. From the data obtained, all compounds do not have potential as OCT2 substrates (Krihariyani, Dwi, 2019).The last is the prediction of the toxicity of the compound. There are predictions of LD50 in mice, AMES toxicity, T. Pyriformis toxicity, Minnow toxicity, MTD, ORCT, hepatotoxicity, skin sensitization, and hERG I and hERG II inhibitors. The first is AMES toxicity, AMES toxicity is used to determine whether the compound has the potential as a compound that causes mutagens and is carcinogenic. In compound (2) it is stated that the compound is a mutagen compound, while in other compounds it is not mutagen (Krihariyani, Dwi, 2019).

For the toxicity of *T. pyriformis*, it was stated that all compounds (8), and (12) were toxic because they had values >-0.5. In Minnow's toxicity, it was also stated that there are 4 compounds that have high toxicity, namely compounds (1), (5), (6), and (9) while the other compounds are not, judging from the log LC50 value <-0.3 which means predicted to have high acute toxicity. For MTD (Maximum Tolerated Dose) is a prediction of the dose that causes toxic. The compound has low toxicity if the maximum dose tolerance is <0.477, while it will be declared high if the maximum dose tolerance value is >0.477. The table states that compounds (1), (4), (5), (6) and (7) have low toxicity, while other compounds do not have high toxicity.

For hepatotoxic data, it is stated to see whether the compound is toxic to the liver. The table states that compounds (7), and (11) are hepatotoxic, while other compounds are not. From the table it is also stated that compounds (1), (2), (4), (5), and (12) are predicted to cause skin sensitization. The last is the potential of the compound as an inhibitor of hERG I and II. If the compound is potent, then this will cause prolonged side effects because compounds that inhibit potassium channels through hERG are the cause of long QT syndrome. In the table, it is predicted that compounds (1), (4), (5), and (6) have potential as hERG II inhibitors. From all the results, it can be concluded that some compounds have potential as medicinal compounds due to their good profile. However, there are some compounds that have an unfavorable profile. However, the pkCSM test has several drawbacks, such as only focusing on the elemental sub-structure of the compound, not the whole compound. Therefore, further testing is needed with molecular docking to see the potential for binding these compounds to antidiabetic receptors.

After the ADMET test the next step is the Drug Likeness test which consists of the Lipinksi test, Ghose test, Veber test, Egan test and Muegge test. This test is carried out to see the similarity of the compound with the original drug. for the results of the Lipinski test can be seen in the table 5 and Ghose test, Veber test, Egan test and Muegge test can be seen in the table 6.

Table 5. Druglikeness Test

No	Lipinski Test	1	2	3	4	5	6
1.	*9t,11t,13t conjugated linoleic acid*	278.43	1	1	5.6605	88.99	5
2.	*Arginine*	174.204	4	3	0.55	44.54	6
3.	*Benzoic acid*	122.12	1	1	1.38	33.4	3
4.	*Conjugated linoleic acid*	278.43	1	1	5.6605	88.99	5
5.	*linoleic acid*	278.43	1	1	5.6605	88.99	5
6.	*Momordenol*	426.67	1	2	5.12	132.96	4
7.	*Momordicin I*	472.7	3	4	5.46	139.57	3
8.	*Niacin*	123.11	1	2	0.78	31.2	5
9.	*Oleanolic Acid*	456.7	2	2	5.23	136.65	4
10.	*Pectin*	194.14	5	6	-3.13	36.35	6
11.	*Phenylalanine*	165.19	2	2	1.34	45.5	5
12.	*Phenol*	94.11	1	1	1.39	28.47	3

Description: (1) Molecular weight, (2) Hydrogen bond donor, (3) Hydrogen bond acceptor, (4) LogP, (5) Molar refractivity, (6) Toxicity Class

Table 5. Druglikeness Test (Continued)

Category		Compound											
Druglikeness		1	2	3	4	5	6	7	8	9	10	11	12
1.	Ghose test	No	No	No	No	No	No	No	No	No	No	Yes	No
2.	Veber tets	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3.	Egan tets	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes
4.	Muegge test	No	No	No	No	No	No	No	No	No	No	No	No
5.	*Bioavailability Score*	0.85	0.55	0.85	0.85	0.85	0.55	0.55	0.85	0.85	0.56	0.55	0.55

From the Lipinski test, the requirements are that the molecular weight must be less than 500, have good lipid solubility characterized by LogP < 5, have less than 5 hydrogen bond donors and less than 10 hydrogen bond acceptors, and have a molar refractivity between 40 and 130. If Lipinski's law is fulfilled, then the membrane of a compound can penetrate a membrane so that the compound can be estimated to have the power to penetrate a good biological membrane. Molecular weights more than 500 Da cannot diffuse through cell membranes (Marillia et al., 2018). From the results that have been carried out, the 12 compounds have met the requirements. The Ghose test has the requirements for atomic number 20-70, molecular weight 160-480, refractivity 40-130, WLogP -0.4 to 5.6. The 12 compounds that have been tested indicate that compound (11) has met these criteria. The Veber test has a requirement, namely the number of bonds that can be rotated. In this test, the criteria are rotatable bonds <10, TPSA value (total polar surface area) <140. In the 12 compounds, only compounds (1), (4) and (5) did not meet these criteria. In Egan's test has a requirement of WLogP <5.88, TPSA value <131.6. Of the compounds tested,

only compounds (5), (6) and (9) did not meet these criteria and the Muegge test has a molecular weight requirement of 200-600, the number of aromatic rings <7, the number of heteroatoms <1, the number of hydrogen bond acceptors <10, the number of hydrogen bond donors <5; XLogP -2-5, rotatable bonds <15, and TPSA value <150 (Ilieva et al., 2018). In the tests that have been carried out, there are no compounds that meet the requirements.

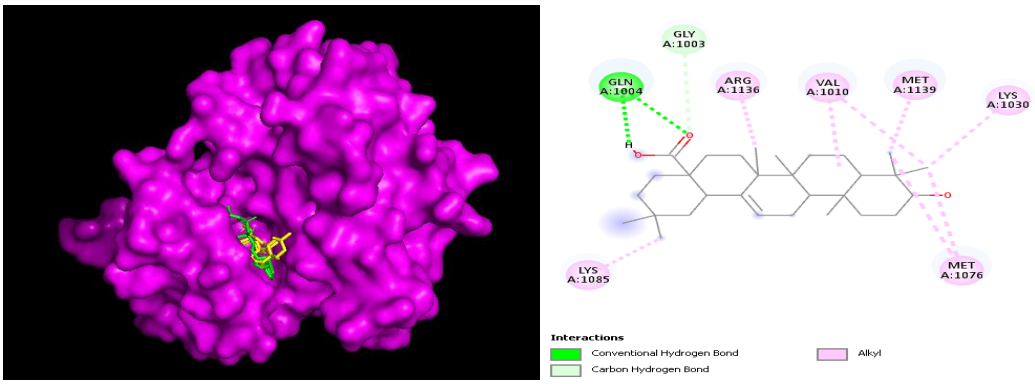
Molecular Docking Results

In this docking was carried out on 6 proteins, namely 1IR3, 1RHF, 4PNZ, 4YVP, 1XU7,2NT7. This protein was chosen because it has a resolution between 1-3 Å, has a Ramanchadra plot >90% and there is no missing residue.

Insulin Receptor Tyrosine Kinase (PDB ID: 1IR3)

1IR3 is a protein coded for insulin that activates insulin receptor tyrosine kinase which works by promoting insulin signal transduction and plays a role in insulin action. The insulin receptor (IR) itself is an insulin-activated receptor that has a role in glucose hemostasis. The binding of insulin to the alpha subunit of the insulin receptor causes a conformational change of the receptor leading to activation of the beta subunit of tyrosine kinase which in turn activates the insulin signaling pathway associated with K channel closure and Ca channel opening. This protein was chosen because it has the same mechanism of action as the oral antidiabetic drug meglintinide derivatives. Meglintinide-derived oral antidiabetic drugs work by stimulating insulin secretion from pancreatic cells through closing of K channels and opening of Ca channels which will induce insulin secretion (Siswadono, 2016).

The 1IR3 protein shows that the Oleanolic acid compound has the best bond energy, which is -8.9. The control ligand attached to the 1IR3 protein has a binding energy of -8.6. This indicates that the energy required by the oleanolic acid compound to attach to the active site of the 1IR3 protein is less than the energy required by the native ligand and indicates that the compound is more active than the native ligand. The compound binds to the binding site which can be seen in the figure 1.



A B

Figure 1. Result docking 1IR3 (A). The result of the interaction of oleanolic acid compound and protein 1IR3 (B)

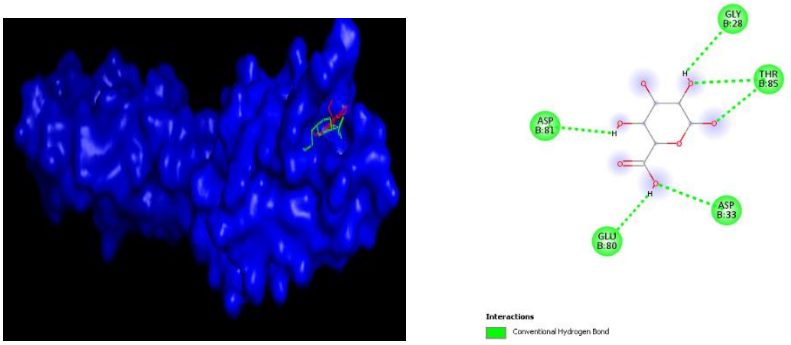
In figure 1B, there is information indicating that the oleanolic acid compound interacts with the binding site of the original ligand. The binding site is the area where the protein binds to the ligand that will affect the function of the protein. Binding sites will show amino acid residues that play an important role in forming interactions between macromolecules. Visualization with biovia discovery studio showed that the compound interacts with the same amino acid residues (GLN1004, GLY1003, VAL1010, MET1139) as the native ligand compounds bind to the binding site at the 1ir3 receptor. This indicates that the oleanolic acid compound has the potential to become an insulin protein that binds to tyrosine kinase by binding to the receptor as native ligands do, so that the insulin receptor can carry out its role as an insulin signaling pathway.

Tyrosine-protein kinase (PDB ID: 1RHF)

IRHF is a protein coding for receptor tyrosine kinases (RTKs) that play a key role in activating insulin signaling which will later provide an antihyperglycemic effect that can reverse or prevent type 1 and 2 diabetes mellitus by improving and reducing insulin resistance and cell dysfunction. Signals through these receptors will induce cell proliferation, differentiation, migration, and cell metabolism. Receptor tyrosine kinase also plays a regulatory role in glucose metabolism. This protein was chosen because it has a mechanism of action like that of oral antidiabetic drugs derived from meglintinide. Meglintinide-derived oral antidiabetic drugs work by stimulating insulin secretion from pancreatic cells through closing of K channels and opening of Ca channels which will induce insulin secretion (Siswadono, 2016).

The docking results obtained 2 results of docking analysis where in the figure 1 is the result of analysis using 3 compounds that have the highest binding affinity using oleanolic acid, momordicin I, and momordenol compounds. From these results, the three compounds did not bind to the original ligand

compound from 1RHF protein so that there was no bond between the three compounds and the original ligand compound from 1RHF. So, from these results it can be said that these compounds do not have the same potential as the 1RHF receptor. As for the figure 1A, of the docking analysis, the pectin compound binds directly to the original ligand compound of 1RHF protein and produces the best bond energy of -6.1. The control ligand attached to the 1RHF protein has a binding energy of -4.1. This indicates that the energy required by the pectin compound to attach to the active site of the 1RHF protein is less than the energy required by the native ligand and indicates that the pectin compound is more active than the native ligand.



A B

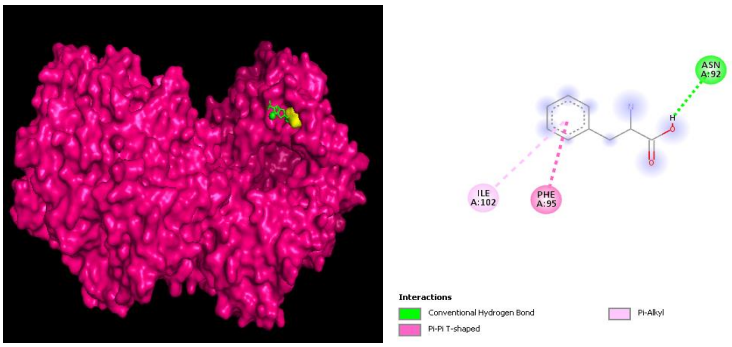
Figure 2. The result of 1RHF protein using the 3 highest compounds (A). The result of 1RHF using pectin compounds (B).

Figure 1B shows that the pectin compound interacts with the binding site of the original ligand. Visualization with Biovia Discovery Studio showed that pectin compounds interact with the same amino acid residues (THR85, GLY28, GLU80) as the native ligand compounds bind to the binding site at the 1RHF receptor. This indicates that the pectin compound has the potential to become a receptor tyrosine kinase by binding to the receptor as native ligands do, so that the receptor tyrosine kinase can perform its role as an insulin signaling pathway.

Dipeptidyl peptidase IV/CD26 (PDB ID: 4PNZ)

4PNZ is a dipeptidyl peptidase IV/CD26 protein that binds to the inhibitor omarigliptin. This protein works by inhibiting the release of glucagon and stimulating insulin secretion. This protein was chosen because it has the same mechanism of action as antidiabetic drugs derived from dipeptidyl peptidase IV (DPP-IV). Antidiabetic drugs derived from dipeptidyl peptidase IV (DPP-IV) work by inhibiting the DPP-IV enzyme, increasing the levels and actions of the endogenous hormone increatin, especially GLP-1 intestine and GIP (Gastric Inhibitory peptide) so that it can reduce the risk of diabetes. increase secretion. insulin from pancreatic cells, and suppresses glucagon secretion from pancreatic cells (Siswadono, 2016).

The docking results obtained 2 results of docking analysis where in the figure 4 is the result of 4PNZ protein docking images using the 3 highest compounds, namely oleanolic acid, momordicin I, and momordenol. From these results the three compounds do not have the same binding site as the original ligand compound from the 4PNZ protein, causing no bonding between the compound and the original ligand. As for the figure 3A, it is an image of the docking result between 4PNZ protein and Phenylalanine compounds. From these results the Phenylalanine compound binds directly to the original ligand compound of the 4PNZ protein and produces the best binding energy of -6.1. The control ligand attached to the 4PNZ protein has a binding energy of -8.3. This indicates that the energy required by the Phenylalanine compound to attach to the active site of the 4PNZ protein is greater than the energy required by the native ligand and indicates that the native ligand is more active than the Phenylalanine compound.



A B

Figure 3. The result of 4PNZ protein using the 3 highest compounds (A). The result of 4PNZ using phenylalanine compounds (B).

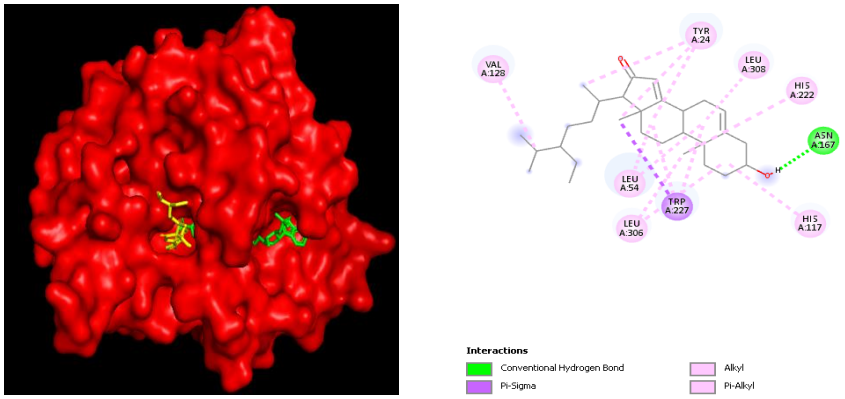
Figure 3B showing that the phenylalanine compound interacts with the binding site of the native ligand. Visualization with Biovia Discovery studio showed that the compound interacts with the same amino acid residues (ASN92, ILE102) as the original ligand compounds bind to the binding site at the 4PNZ receptor. This indicates that phenylalanine compounds have the potential to become DPP-1V receptors that bind to omarigliptin inhibitors by binding to receptors as native ligands do, so that the DPP-1V receptor can play its role in stimulating insulin secretion and inhibiting glucagon release.

Aldo-keto reductase family 1 (PDB ID: 4YVP)

4YVP is the code for a protein that binds to glibenclamide. This protein works by stimulating insulin secretion from pancreatic cells, reducing endogenous insulin intake to the liver and directly suppressing glucagon secretion. This protein was chosen because of the same mechanism of action as oral antidiabetic drugs of sulfonylurea derivatives, where glibenclamide is an antidiabetic drug of sulfonylurea class, so it is hoped that this protein can give a reaction like using antidiabetic drugs derived

from sulfonylureas. Antidiabetic drugs belonging to the sulfonylurea group work by stimulating insulin secretion from pancreatic cells, reducing endogenous insulin entry to the liver and directly suppressing glucagon production (Siswadono, 2016).

The 4YVP protein showed that momordenol had the best bond energy of -9.8. The control ligand attached to the 4YVP protein has a binding energy of -11.6. This indicates that the energy required by the momordenol compound to attach to the active site of the 4YVP protein is greater than the energy required by the native ligand and indicates that the native ligand is more active than the momordenol compound. The docking results can be seen in figure 4.



A B

Figure 4. Result docking 4YVP (A). The result of the interaction of momordenol compound and protein 4YVP (B)

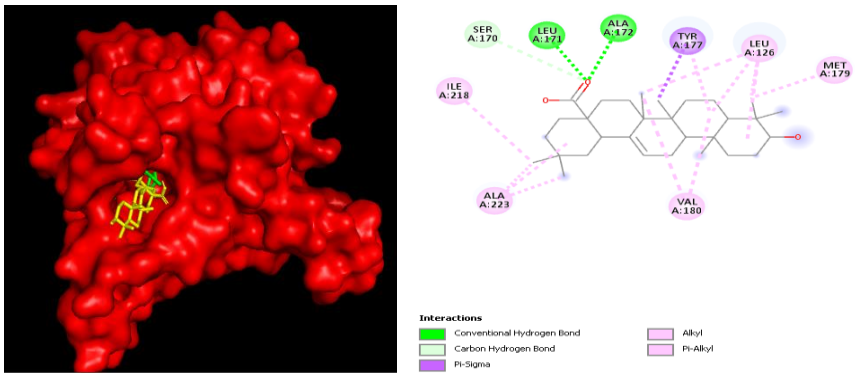
In the figure 4B, there is information showing that the momordenol compound interacts with the binding site of the native ligand. Visualization with Biovia Discovery studio showed that momordenol interacts with the same amino acid residues (ASN167, TYR24, HIS222) as the native ligand compounds bind to the binding site at the 4YVP receptor. This indicates that the momordenol compound has the potential to become a glibenclamide protein by binding to the receptor as native ligands do, so that the glibenclamide protein can perform its role by stimulating insulin secretion.

Protein dehydrogenase (PDB ID: 1XU7)

1XU7 is a protein dehydrogenase (Tetrametric 11b-HSD1) that can be used as a drug in type II diabetes patients. This protein works by catalyzing and converting cortisone into cortisol which is available in the liver, brain, and adipose tissue. Cortisol is an active glucocortisoid that has a key role in diabetes. The hormone cortisol is responsible for controlling and maintaining blood sugar. Many studies have shown that high circulating levels of the active glucocorticoid cortisol cause central obesity, insulin resistance, hypertension, and dyslipidemia. This protein was chosen because it has a relationship with thiazolindione class of diabetes drugs because these drugs work by reducing insulin resistance through

the activation of the nuclear receptor PPAR-γ (peroxisome Proliferator Activated receptor gamma) which can increase the expression of genes involved in glucose and fat metabolism. PPAR-γ has three isoforms of ribonucleic acid (mRNA) namely PPAR-γ1, PPAR-γ2 and PPAR-γ3. In addition, PPAR-γ is also regulated by necrosis, insulin, and glucocorticoids (Doan, Nguyen and Le, 2012).

In Figure 5 it is found that the Oleanolic Acid compound has the best bond energy, which is -11.9. The control ligand attached to the 1XU7 protein has a binding energy of -12.4. This indicates that the energy required by the oleanolic acid compound to attach to the active site of the 1XU7 protein is greater than the energy required by the native ligand and indicates that the native ligand compound is more active than Oleanolic Acid.



A B

Figure 5. Result docking 1XU7 (A). The result of the interaction of oleanolic acid compound and protein 1XU7 (B)

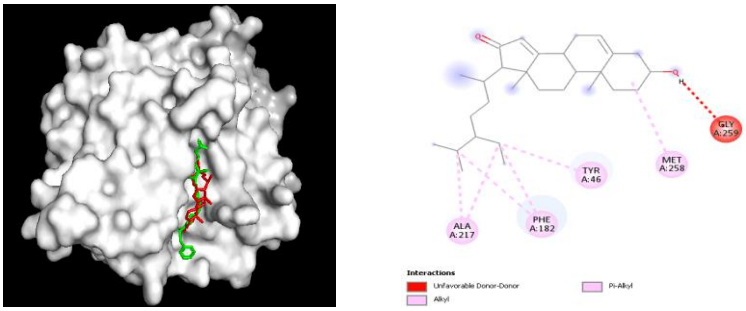
In Figure 5B there is information showing that the Oleanolic Acid compound interacts with the binding site of the original ligand. Visualization with Biovia Discovery studio shows that the Oleanolic Acid compound interacts with the same amino acid residues (SER170, ILE218) as the original ligand compounds bind to the binding site at the 1XU7 receptor. This indicates that oleanolic acid compounds have the potential to become protein dehydrogenases by binding to receptors like native ligands do, so that protein dehydrogenase can perform its role by reducing insulin resistance.

Protein tyrosine phosphatase 1B (PDB ID: 2NT7)

2NT7 is the code for Protein tyrosine phosphatase 1B (PTP1B) which is an enzyme that plays a role in treating diabetes. In this protein there will be a process of tyrosine phosphorylation. Tyrosine phosphorylation is often said to be the process of adding a phosphate group (PO4) to a molecule that has a role in inhibiting the mechanism of many diseases such as type 2 diabetes (Salinas-moreno and Milenkovic, 2020). The PTP1B protein plays an important role in the process of insulin signal transduction and the leptin pathway in insulin activation. PTP1B showed greater insulin sensitivity

reactions and maintained lower levels of glucose and insulin. This protein will also control glucose levels and increase insulin sensitivity (Doan et al., 2012). This protein was chosen because it has the same mechanism of action as oral antidiabetic drugs with biguanide derivatives. Biguanide antidiabetic drugs work by increasing hepatic gluconeogenesis, decreasing glucose absorption in the intestine, increasing receptor sensitivity to insulin, and increasing anaerobic glucolysis thereby increasing glucose utilization.

From the results of the docking that has been done, Figure 6 is obtained which can be seen that the momordenol compound has the best bond energy, which is -7.1. The control ligand attached to the 2NT7 protein has a binding energy of -9.8. This indicates that the energy required by the momordenol compound to attach to the active site of the 2NT7 protein is greater than the energy required by the native ligand and indicates that the native ligand is more active than the momordenol compound.



A B

Figure 6. Result docking 2NT7 (A). The result of the interaction of momordenol compound and protein 2NT7 (B)

In Figure 6B there is information showing that momordenol interacts with the binding site of the original ligand. Visualization with Biovia Discovery studio showed that momordenol interacts with the same amino acid residues (TYR46, ALA217) as the native ligand binds to the binding site at the 2NT7 receptor. This indicates that the momordenol compound has the potential to become a protein tyrosine phosphatase 1B (PTP1B) by binding to the receptor as native ligands do, so that the protein tyrosine phosphatase 1B (PTP1B) can play its role in the phosphorylation process so as to increase insulin sensitivity.

Molecular Dynamic Result

YASARA is an application of molecular dynamics. Molecular dynamics is a computer simulation technique that is carried out by observing the movements of interacting molecules and simulating molecules attracting and pushing and hitting each other. Molecular dynamics was carried out with the aim of obtaining information about protein-ligand complex interactions more clearly and in a flexible manner. In these molecular dynamics, it is possible to analyze the stability and interaction mechanism of protein-ligand complex through RMSD (Root Mean Square Deviation). RMSD is the deviation distance from the binding position of the native ligand to the protein after docking to the actual position of the native ligand. This RMSD plays an important role in protein stability and is usually used to measure accuracy to compare a molecular model with a molecular model at equilibrium. Stable RMSD indicates that the maximum conformation (arrangement) of the protein bound to the ligand has begun to be reached so that the protein is able to maintain its position. In addition, the interaction between residues makes proteins tend to maintain their structure (Tita Karyawati, 2020). While the unstable RMSD value indicates the occurrence of the search for binding sites or the appropriate coordinates in the protein. The ligand will start its action to find the binding site or the appropriate coordinates in the protein. The value of the best RMSD is 2Å because from the validation results it can be said that the results are valid, and the docking parameters used are in a flexible ligand state. The smaller the RMSD value obtained, the better the method used (Tita Karyawati, 2020).

Protein 1IR3

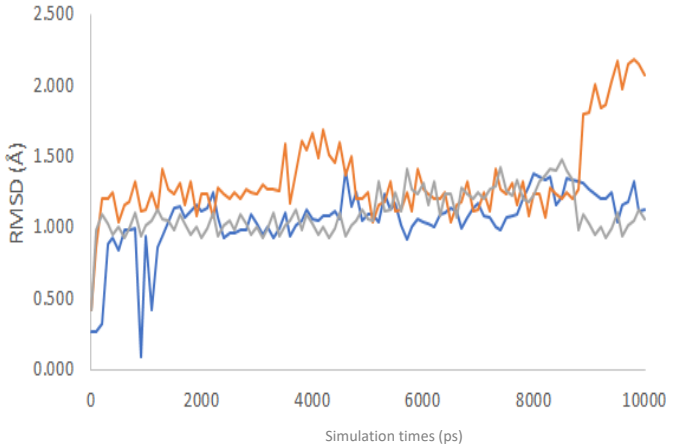


Figure 7. Momordenol compound (blue), oleanolic acid compound (orange) and momordicin compound (grey)

From the graph, it can be seen that the three compounds fluctuated (up and down) at 0-10000ps. For momordenol, it can be seen that the compound fluctuated at 0-2000ps and started to stabilize at 2100ps-4000ps then fluctuated again at 4100ps-10000ps. The compound is stabilized with a constant RMSD which is at 1.2Å. Meanwhile, the oleanolic acid compound experienced stability at 0-3700ps and fluctuated at 3800ps-5000ps and stabilized again at 5100ps-9000ps and experienced the highest fluctuation at 9000ps-10000ps. The oleanolic acid compound was stabilized with a RMSD of 1.2 Å. For

the last one, momordicin 1, it can be seen that the compound is stable at 0-5000ps and fluctuates at 5100ps-8700ps and stabilizes again at 8800-10000ps. The momordicin 1 compound was stabilized at RMSD of 1.2 Å (Figure 7).

Protein 1RHF

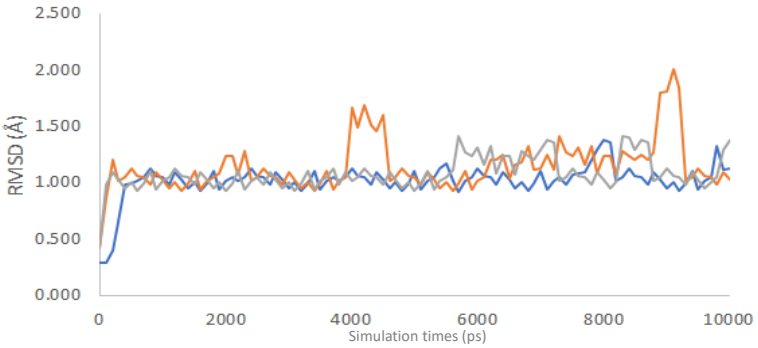


Figure 8. Momordenol compound (blue), oleanolic acid compound (orange) and momordicin compound (grey)

From the results that have been carried out, it was found that the momordenol compound experienced stability at 0-7900ps and fluctuated at 8000-8500ps and stabilized again at 8600-10000ps. The momordenol compound was stabilized with an RMSD of 1Å. While the oleanolic acid compound experienced stability at 0-3900ps and fluctuated at 4000-4900ps and stabilized again at 5000ps-6000ps then fluctuated at 6100-10000ps. This oleanolic acid compound was stabilized with an RMSD of 1.25. The last compound is momordicin I which is stable at 0-7800ps and fluctuates at 7900-8400ps and stabilizes again at 8500-9700ps then fluctuates again at 9800-10000ps. The momordicin I compound was stabilized with an RMSD of 1Å (Figure 8)

Protein 4PNZ

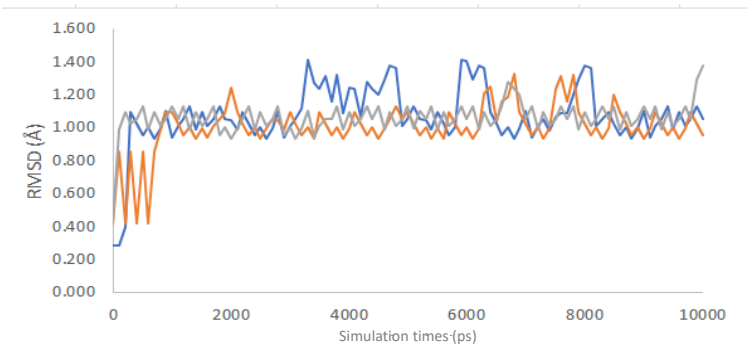


Figure 9. Momordenol compound (blue), oleanolic acid compound (orange) and momordicin compound (grey)

From the results that have been carried out, it was found that the momordenol compound experienced stability at 300-2500ps and fluctuated at 2600-4500ps, stabilized again at 4600-5000ps and fluctuated again at 5100-6000ps and had experienced stability at 6100-6900ps and experienced fluctuates back at 7900-8100ps and stabilizes Back at 8200-10000ps. The momordenol compound was stabilized with an

RMSD of 1.1Å while the oleanolic acid compound fluctuated at 0-1000ps and stabilized at 1100ps-1800ps and fluctuated again at 1900-2100ps. The compound stabilized again at 2200-5800ps and fluctuated at 5900-10000ps. This oleanolic acid compound was stabilized with a RMSD of 1.2Å and the last one was momordicin I, where the compound was stable at 0-3000ps and fluctuated at 3100ps-4900ps and stabilized again at 5000-5700ps then fluctuated again at 5800ps-6800ps and experienced stability again at 6900-7200ps and fluctuated at 7300-8500ps and stabilized again at 8600ps-10000ps. This momordicin I compound was stabilized with a RMSD of 1.4Å (Figure 9)

Protein 4YVP

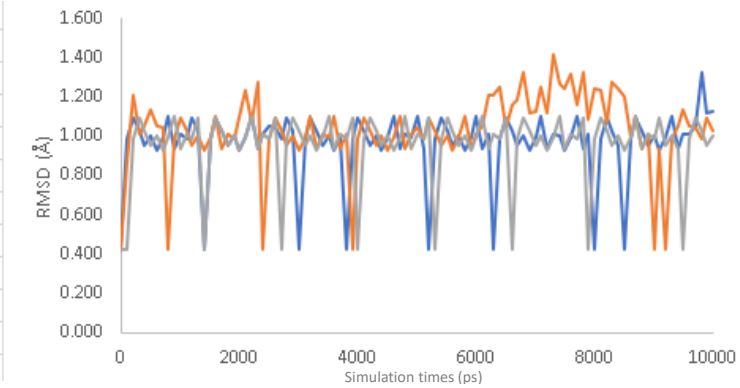


Figure 10. Momordenol compound (blue), oleanolic acid compound (orange) and momordicin compound (grey)

From the results that have been carried out, it was found that the momordenol compound experienced stability at 0-3000ps and fluctuated at 3100-6500ps and stabilized again at 6600-7800ps then fluctuated again at 7900-10000ps. This momordenol compound was stabilized with an RMSD of 1.1Å. While the oleanolic acid compound fluctuated at 0-2800ps and experienced stability at 2900-5800ps then fluctuated again at 5900-10000ps. This oleanolic acid compound was stabilized with an RMSD of 1.1Å. The third compound, momordicin I, experienced stability at 0-1700ps and fluctuated at 1800-2000ps, then stabilized again at 2100-2800ps and fluctuated again at 2900-3000ps and stabilized again at 3100-4000ps. However, it stabilized again at 4100-5000ps and fluctuated again at 5100-5300ps then stabilized again at 5400-6800ps and again fluctuated at 6900-7100ps and stabilized again at 7200-9800ps then fluctuated again at 9900-10000ps. The momordicin I compound was stabilized with an RMSD of 1.1 Å (Figure 10).

Protein 1XU7

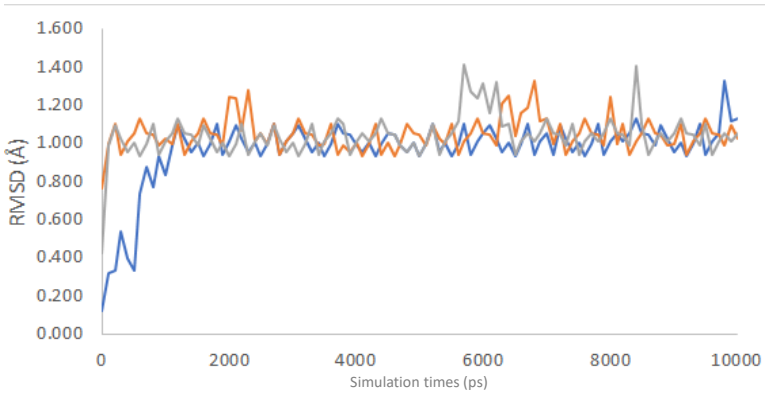


Figure 11. Momordenol compound (blue), oleanolic acid compound (orange) and momordicin compound (grey)

From the results that have been carried out, it is found that momordenol compounds fluctuated at 0-1000ps and experienced stability at 1100-9800ps and fluctuated again at 9900-10000ps. This momordenol compound was stabilized with an RMSD of 1.1Å. Meanwhile, the oleanolic acid compound experienced stability at 0-1900ps and fluctuated at 2000-2500ps then fluctuated again at 2600-6200ps and fluctuated again at 6300-10000ps. This oleanolic acid compound was stabilized with an RMSD of 1.1Å. The third compound, momordicin I, was stable at 0-5700ps and fluctuated at 5800-6500ps, then stabilized at 6600-8500ps and fluctuated at 8600-8900ps and stabilized at 9000-10000ps. This momordicin I compound was stabilized with an RMSD of 1.1Å (Figure 11).

Protein 2NT7

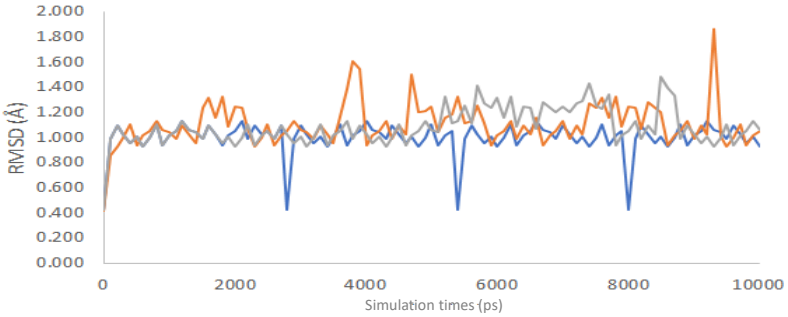


Figure 12. Momordenol compound (blue), oleanolic acid compound (orange) and momordicin compound (grey)

From the results that have been carried out, it is found that the momordenol compound experienced stability at 0-2800ps and fluctuated at 2900-3100ps then stabilized again at 3200-5400ps and again fluctuated at 5500-5800ps and stabilized again at 5900-7900ps and fluctuated. at 8000-8300ps then stabilized again at 8400-10000ps. This momordenol compound was stabilized with an RMSD of 1.1Å. Meanwhile, the oleanolic acid compound was stable at 0-1000ps and fluctuated at 1100-2300ps then stabilized again at 2400-3700ps and fluctuated at 3800-6000ps and stabilized again at 6100ps-7600ps then fluctuated again from 7700-10000ps. The oleanolic acid compound was stabilized with an RMSD

of 1.3Å. For the third compound, momordicin I was stable at 0-5700ps and fluctuated at 5800ps-8900ps and stabilized again at 9000-10000ps. The momordicin I compound was stabilized with an RMSD of 1.4Å (Figure 12).

CONCLUSION

The research findings indicate that 3 compounds, namely oleanolic acid, momordicin I, and momordenol, demonstrated the highest binding affinity among the 12 compounds used in both the docking and the ADMET study, which involved 6 proteins. The YASARA test showed that all 3 compounds had an RMSD value of less than 2Å, indicating that the compounds was stable during 10000ps molecular dynamics simulation.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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