ORIGINAL ARTICLE

Molecular docking studies of α-mangostin, γ-mangostin, and xanthone on peroxisome proliferator-activated receptor gamma diphenyl peptidase-4 enzyme, and aldose reductase enzyme as an antidiabetic drug candidate

Rifa'atul Mahmudah[1,2], I Ketut Adnyana[1], Elin Yulinah Sukandar[1]

[1]Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, Institute Technology Bandung, Bandung, West Java, [2]Department of Pharmacy, Mandala Waluya University, Kendari, Southeast Sulawesi, Indonesia

J. Adv. Pharm. Technol. Res.

ABSTRACT

α-mangostin, γ-mangostin, and xanthone are some of the marker compounds found in mangosteen (*Garcinia mangostana* Linn.) whose activity on several treatment targets including toward the peroxisome proliferator-activated receptor gamma (PPAR-γ) receptors, diphenyl peptidase 4 (DPP-4) enzyme, and aldose reductase enzyme is unknown. Although this plant has been predicted to be used as an alternative antidiabetic treatment, it has been proven through several previous studies. This research study used three natural ligands (α-mangostin, γ-mangostin, and xanthone) whose training set was designed using Molecular Operating Environment and then compared them with several drugs on the market that are used in the treatment of diabetes mellitus. The docking molecular results showed that the α-mangostin and γ-mangostin compounds had activity toward PPAR-γ receptor, DPP-4 enzyme, and aldose reductase enzyme by showing almost similar affinity values when compared to the comparison ligands. Meanwhile, xanthone showed unfavorable results. This approach shows that α-mangostin and γ-mangostin are predicted to play a role as antidiabetic mellitus in mangosteen when viewed from these mechanisms.

Key words: Antidiabetic, diphenyl peptidase, peroxisome proliferator-activated receptor gamma-γ, xanthone, α-mangostin, γ-mangostin

INTRODUCTION

One of the plants that are widely used as medicine is mangosteen (*Garcinia mangostana* L.). Part of the mangosteen plant has many benefits including mangosteen peel. Mangosteen peel chemicals include xanthone, α-mangostin, and γ-mangostin, besides there are 160 other aromatic

Address for correspondence:
Mrs. Rifa'atul Mahmudah,
Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, Institute Technology Bandung, Bandung, West Java, Indonesia.
Department of Pharmacy, Mandala Waluya University, Kendari, Southeast Sulawesi, Indonesia.
E-mail: ifamahmudah11@gmail.com

Submitted: 26-Nov-2020 **Revised:** 08-Feb-2021
Accepted: 02-Apr-2021 **Published**: 27-Apr-2021

Access this article online	
Quick Response Code:	Website: www.japtr.org
	DOI: 10.4103/japtr.JAPTR_255_20

How to cite this article: Mahmudah R, Adnyana IK, Sukandar EY. Molecular docking studies of α-mangostin, γ-mangostin, and xanthone on peroxisome proliferator-activated receptor gamma diphenyl peptidase-4 enzyme, and aldose reductase enzyme as an antidiabetic drug candidate. J Adv Pharm Technol Res 2021;12:196-208.

compounds in epicarp and 105 compounds in endocarp.[1,2] Based on the research that has been done, α-mangostin and xanthone compounds found in mangosteen peel can have antidiabetic properties through a protective mechanism against glucose tolerance and also have the potential to increase insulin resistance by increasing GLUT-4 in heart muscle and adipocytes,[3] while gamma-mangostin can show antidiabetic effects through reducing fasting blood glucose, cholesterol, Serum Glutamic Oxaloacetic Transaminase (SGOT), Serum Glutamic Pyruvic Transaminase (SGPT), and repairing damaged hepatocytes.[4] Mangosteen peel extract can also inhibit pancreatic lipase and α-amylase which is suspected by the effect of some of its mangostanaxhantone contents[5,6] which are considered to be closely related to antidiabetic effects. Besides, other mechanisms shown by mangosteen rind extract in dealing with diabetes mellitus (DM) are through lowering blood glucose, improving insulin tolerance, biochemical parameters, improving liver structure, inhibiting glycation, and increasing high-density lipoprotein and total protein levels.[7-9] Mangosteen rind is proven to contain very high antioxidants, i.e., compounds that can react with free radicals thereby reducing the capacity of free radicals where free radicals cause damage to cells, tissues, and organs.[10-12] The results of clinical trials show that the administration of polar fractions from mangosteen rind extract to humans for 24 weeks can act as an antioxidant without any significant side effects.[13] Antioxidants can bind to hydroxyl radicals that damage the β-cells of the pancreas Langerhans so that insulin production will be maximal[14] and is related to the treatment of DM.

DM is a metabolic disorder with a high prevalence and based on the WHO reports showing that in 2015, diabetes was the direct cause of death for 1.6 million people in the world. The number of people with DM in Indonesia occupies the seventh position under China, India, the USA, Brazil, Russia, and Mexico.[15]

DM conditions require long-term treatment. Among the drug regimens that are frequently used are peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists and diphenyl peptidase 4 (DPP-4) enzyme inhibitors. PPAR-γ agonists are used in DM related to insulin resistance. Besides, it also affects slowing the progression of diabetes nephropathy by producing antifibrotic effects on kidney cells when glucose levels increase,[16] whereas DPP-4 is an enzyme that plays an important role in the regulation of the hormone incretins. By inhibiting the DPP-4 enzyme, it increases natural glucagon-like peptide-1 levels and glucose-dependent insulinotropic polypeptides in the blood, which causes a decrease in the storage of glucose levels after meals by increasing insulin secretion and decreasing glucagon.[17,18]

Besides, one of the causes that aggravate type-2 DM (T2DM) is increased oxidative stress. The enzyme that plays a role in this pathway is aldose reductase which reduces glucose to sorbitol using Nicotinamide adenine dinucleotide phosphate (NADPH) as its cofactor.[19] By using a drug that works as an aldose reductase inhibitor (ARI), complications that occur in T2DM can also be overcome, including neuropathy, nephropathy, retinopathy, cataracts, atherosclerotic large vessels, including heart, and brain disease. The ARI class of drugs that have been developed and circulating in the market that can be selected in this situation are zopolrestat, epalrestat, alrestatin, lidorestat, tolrestat, fidarestat, minalrestat, ponalrestat, ranirestat, salfredin B11, sorbinil, zenarestat, and Imirestat.[20]

By paying attention to the opportunity of mangosteen rind as antidiabetic, it is necessary to test its mechanism of action, including PPAR-γ agonist, DPP-4 enzyme inhibitor, and ARI enzyme. This test can be started by using the *in silico* method through molecular docking. This method is an efficient way to predict ligand orientation that is optimized for certain drug targets with the benefit of cost and time savings, limited energy, and shows high similarity with experimental results.[21] Through molecular docking, computer-aided drug design can be predicted with a substantial degree of accuracy, as well as the conformation of ligand-macromolecules in the appropriate target binding location, and has now become a common tool integrated into the drug discovery process. This can give an idea of the condition of the ligand-macromolecular interactions that occur in the body.[22,23]

MATERIALS AND METHODS

Protein selection

The two-dimensional (2D) and the 3D crystal structure of which is bound by the Pioglitazone Protein Data Bank (PDB) code 5Y2O, Vildagliptin PDB code 3W2T, and Zopolrestat PDB code 2HV5, homo sapiens obtained from an online database: NCBI website, Research Collaboratory for structural bioinformatics (www.ncbi.nlm.nih.gov), and website PDB (www.pdb.org), while the 3D PPAR-γ structure of the PDB is downloaded via http://www.rscb.org with the 5Y2O code, the 3D DPP-4 enzyme structure with the 3W2T code, and aldose reductase enzyme structure with the 2HV5 code. Furthermore, the molecules that are not needed are removed and stored in the form of PDB (*.pdb) format.[24]

Molecular preparation training set

The derivative training set was downloaded from the PubChem compound with the website address http://pubchem.ncbi.nlm.nih.gov and has been approved by the Food and Drug Administration (FDA). PubChem set compound is a dataset containing compounds that are confirmed to have anti-diabetic activity. The 3D structure of Pioglitazone was extracted from PDB ID 5Y2O, Vildagliptin was extracted from PDB ID 3W2T, and Zopolrestat was

extracted from PDB code 2HV5 kept the conformation for use as a reference in the molecular alignment process.

Making decoy with the test set using the decoy finder

The 3D wall structure of 300 compounds as decoys was taken from Decoy from the Directory of Useful Decoys, Enhanced (DUD-E) database (http://dude.docking.org) using the DecoyFinder application. The selection of compounds that can be used as decoys is molecular weight ≤25 Da, bonds that can rotate ±1, donor hydrogen bonds ±1, hydrogen bond acceptors ±2, LogP ±1, Tanimoto coefficient between candidates decoy and active compound ≤0.75, and the Tanimoto coefficient between the selected decoy and decoy candidate ≤0.9.[25] All training sets and decoy structures are prepared in 3D, then a multi-conformer database construction is carried out.

Molecular docking

Molecular docking is a rigid receptor docking process which means that macromolecules are positioned in rigid conditions. Ligands that will be docking themselves are set inflexible conditions. The procedure used is the re-docking of natural ligands to innate macromolecules and the validation parameter used is the root mean square difference (RMSD) value calculated between docking poses.[26]

The MOE was validated by redocking the natural ligand Pioglitazone on the PPAR-γ receptor, natural ligand Vildagliptin on the DPP-4 enzyme, and natural ligand Zopolrestat on the aldose reductase enzyme. Then, the RMSD value for the best ligand pose was calculated, the result of the method was used to confirm natural ligands. The cutoff value is generally less than 2.0 Å.[26]

The docking of the training set molecule and the feed compound is carried out simultaneously. Some of the validation parameters that are commonly used include the enrichment factor (EF), the area under the curve (AUC), and the value of the receiver operating characteristics (ROC) curve.[27] After the validity was confirmed, the docking method was then applied to the compounds obtained from the previous screening results. To determine the toughness of MOE in distinguishing active and inactive ligands, 3 compounds known as PPAR-γ agonists, 6 compounds known as DPP-4 inhibitors, and 13 compounds known as aldose reductase enzyme inhibitors, and 300 each inactive tethered to PPAR receptor, DPP-4 enzyme, and aldose reductase enzyme using MOE. Then, a ranking list is made based on the scores of each compound. The score is made by the ROC curve by plotting the X-axis as a false-positive fraction and the Y-axis as a true-positive fraction for each compound in an ordered dataset.[27]

RESULTS AND DISUSSION

Selection of molecular training sets, decoys, and target proteins

The 2D and 3D training set on the test compounds found in the mangosteen (α-mangostin, γ-mangostin, and xanthone) was obtained from PubChem compound via the website address http://pubchem.ncbi.nlm.nih.gov, which can be seen in Table 1.

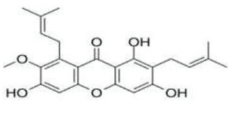
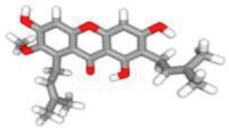
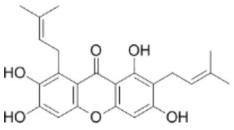
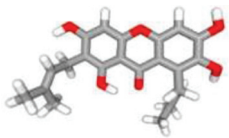
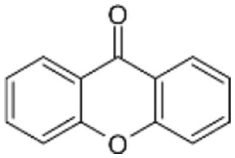
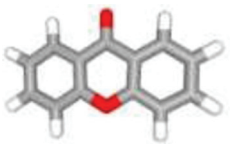
This has also been applied for 2D and 3D training sets of compounds that are confirmed to be antidiabetic drugs [Table 2] that have been downloaded from PubChem via the website address http://pubchem.ncbi.nlm.nih.gov and have been approved by the FDA.

PPAR-gamma receptor molecules, DPP-4 enzyme, and aldose reductase enzyme do not need to be homology modeling because there is already a crystal structure. The selection of receptor structures and enzymes to be used for subsequent simulations is based on several factors, namely resolution of less than 2 Å or smaller.

Molecular docking

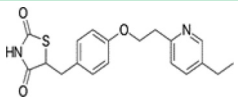
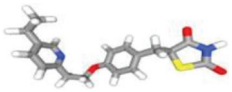
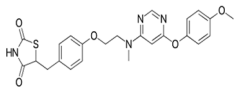
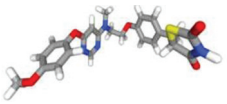
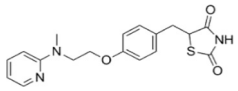
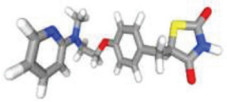
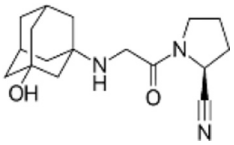
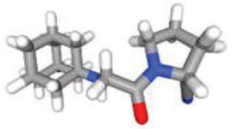
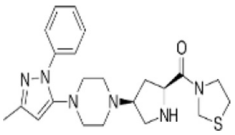
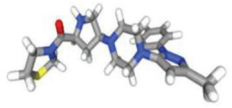
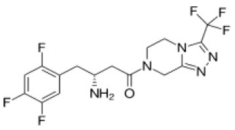
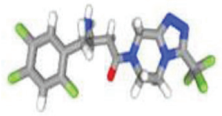
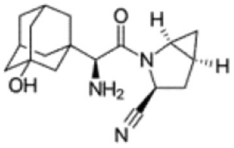
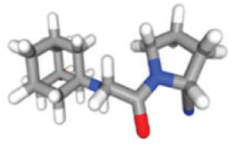
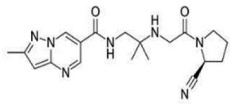
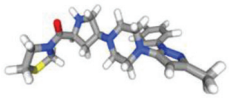
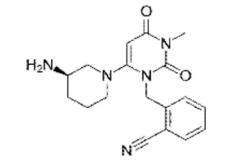
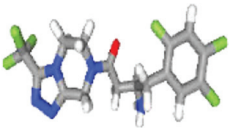
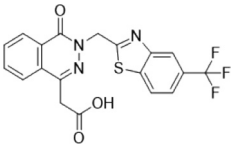
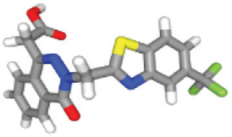
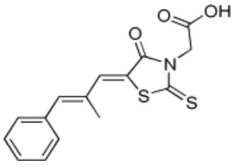
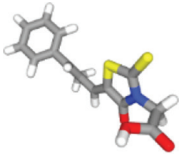
This process begins with the manufacture of complex proteins to be used, i.e., PDB ID: 5Y2O for the PPAR-γ receptor, PDB ID: 3W2T for the DPP-4 enzyme, and 2HV5 for the aldose reductase enzyme. PDB files of structural determination using the X-ray diffraction method generally do not contain complete residual amounts and are unprotected for the intended use of this LigX module. So at this stage, the elimination of water molecules was carried out and the application of the LigX module consists of several processes, namely the Structure Preparation Module (to complete the amino acids sequence information),

Table 1: The two-dimensional and three-dimensional test ligands of α-mangostin, γ-mangostin, and xanthone compounds

Compounds	Training set 2D	Training set 3D
α-mangostin		
γ-mangostin		
Xanthone		

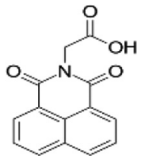
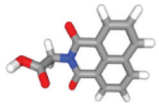
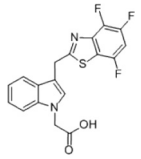
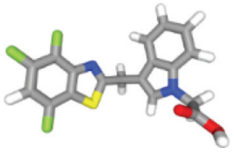
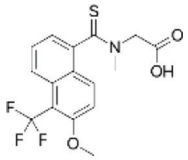
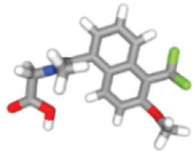
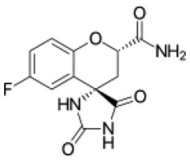
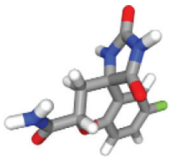
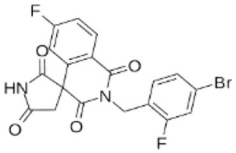
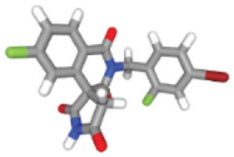
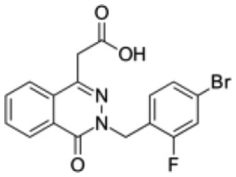
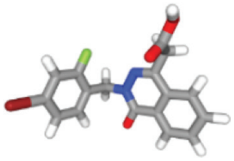
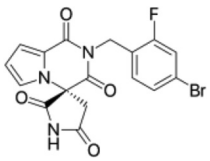
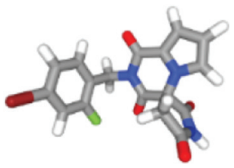
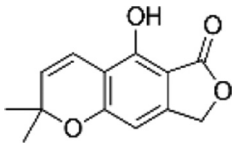
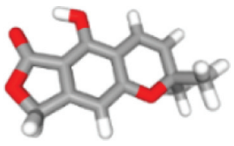
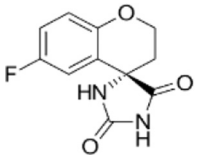
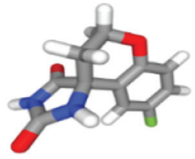
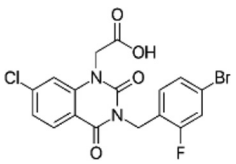
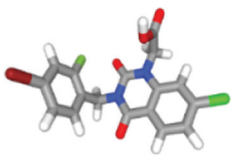
2D: Two-dimensional, 3D: Three-dimensional

Table 2: The two-dimensional and three-dimensional training set of compounds which have activity at peroxisome proliferator-activated receptor gamma, diphenyl peptidase-4 enzyme, and aldose reductase enzyme

Target ligands	Compounds	Training set 2D	Training set 3D
PPAR-γ agonists	*Pioglitazone*		
	Lobeglitazone		
	Rosiglitazone		
DPP-4 enzyme	*Vildagliptin*		
	Teneligliptin		
	Sitagliptin		
	Saxagliptin		
	Anagliptin		
	Alogliptin		
Aldose reductase enzyme	*Zopolrestat*		
	Epalrestat		

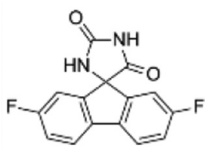
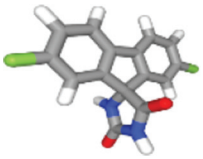
Contd...

Table 2: Contd....

Target ligands	Compounds	Training set 2D	Training set 3D
	Alrestatin		
	Lidorestat		
	Tolrestat		
	Fidarestat		
	Minalrestat		
	Ponalrestat		
	Ranirestat		
	Salfredin B11		
	Sorbinil		
	Zenarestat		

Contd...

Table 2: Contd....

Target ligands	Compounds	Training set 2D	Training set 3D
	Imirestat		

PPAR- γ: Peroxisome proliferator-activated receptor gamma

the Protonate 3D Module (to add hydrogen atoms to complex proteins),[28] and energy minimization and addition of partial charge (Amber12: EHT). Besides, preparations were also made for training sets and helpers. All of these compounds were prepared into a single dataset and given a partial charge based on the MMFF94X force field.

Validation of the docking method was carried out by redocking between natural ligands and each target (PPAR-γ receptor, DPP4 enzyme, and aldose reductase enzyme) to check the validity of the parameters used for the docking test compound. The visible redocking process was visible as RMSD. Docking validation was also performed on training sets and bait compounds. Binding energy test set and decoy values were used as measures for the creation of the ROC curve in which the AUC and EF values were present.[29] This redocking procedure has been applied by trying all the placement and rescoring combinations available in the MOE docking feature. A total of 100 docking poses were generated for each combination, while the evaluation was carried out on 1 docking pose with the lowest score. The parameter evaluated is the lowest RMSD value for each docking pose.

The validation results show that the PPAR-γ receptor combination of proxy triangle placement and alpha *hemoglobin* (HB) score has the lowest RMSD score (0.76 Å), the DPP-4 enzyme shows that the combination of Proxy Triangle and ASE placement results in the lowest RMSD score (0.59 Å), while for the aldose reductase enzyme, the combination of Triangle Matcher placement and GBVI placement resulted in the lowest RMSD score (0.97 Å). Hence, it can be concluded that each of these validations shows an RMSD value <1.5 Å.

The combination was then further evaluated in terms of the virtual screening capability of the prepared dataset based on the AUC ROC parameter (>0.5) and the EF value at several points (1%; 5%; 10%; 20%). The effect of adding the rescoring application to the selected method (proxy triangle with Alpha HB forcefield) on the EF value of the PPAR-γ receptor shows that the addition of the Alpha HB assessment function provides a fairly good EF value of 1%. 19.19 was a contribution of the discovery to six compound training sets. Meanwhile, the addition of the GBVI/WSA dG assessment function provides excellent EF scores. A total of 27 training set compounds were found in 20% of the dataset. The results showed that the method with the addition of GBVI/WSA dG docking score was the best.

The effect of rescoring application on the EF value of the DPP-4 enzyme showed that the addition of the London dG scoring function gave a fairly good EF value of 3.75 which was a contribution from the discovery of six training set compounds. Meanwhile, the addition of the London dG scoring function provides an excellent EF score. A total of 27 training set compounds were found in 20% of the dataset. The results showed that the method with the addition of the dG London docking score was the best.

Meanwhile, rescoring the aldose reductase enzyme showed that the addition of the affinity DG scoring function gave an EF value of 1% which was quite good at 8.77 which was the result of the contribution of the discovery of the five training set compounds. A total of 29 training set compounds were found in the 20% dataset. The results show that the method with the addition of the GBVI/WSA dG docking score has a better performance than the random docking score. Thus, a combination of these methods is used in the molecular docking process. In addition, the screening point for compounds at this stage is determined to be 5% of the dataset.

Molecular docking was carried out on each of the 6 compounds for the PPAR-γ receptor, 9 compounds for the DPP-4 enzyme, and 16 compounds for the aldose reductase enzyme with a combination of placement according to the results of the method validation obtained previously. Furthermore, an assessment of the value of the binding affinity of the compound at the PPAR-γ receptor, the DPP4 enzyme, and the aldose reductase enzyme is shown in Table 3.

From the results of the assessment of the binding affinity value, it shows that the α-mangostin and γ-mangostin compounds are predicted to be active in PPAR-γ receptors, DPP-4 enzyme, and aldose reductase enzyme because these two compounds show a binding affinity value that is more negative or almost similar when compared to each other comparative ligands, while xanthone shows a more positive value.

Furthermore, α-mangostin, γ-mangostin, xanthone, and other comparative ligands were analyzed using the

discovery studio visualization software to see the amino acid bonds formed. A description of the specific bonds in the form of hydrogen bonds is shown in Table 4.

Through this picture shown in the Table 4, α-mangostin, γ-mangostin, and xanthone compounds have shown several types of bonds to each of their target ligands as well as the comparative ligands. The difference in the binding affinity value of each compound is influenced by the bonds formed. Hydrogen bonds have an important role in determining the size of the binding value of affinity resulting from the docking process because it has higher energy than hydrophobic bonds.[30] This is as stated by those hydrogen bonds that have higher energy than hydrophobic interactions with values of 1–7 kcal/mol and 1 kcal/mol. Some of the hydrogen bonds have been seen by the bonds between α-mangostin and γ-mangostin compounds with the target ligands.

CONCLUSION

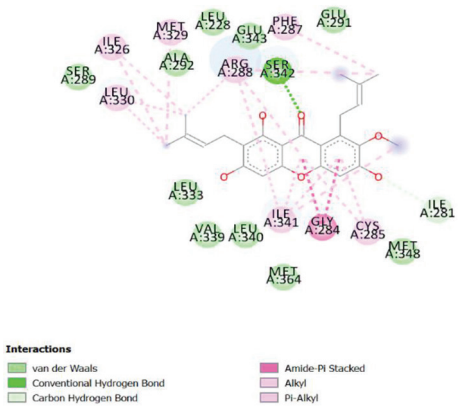
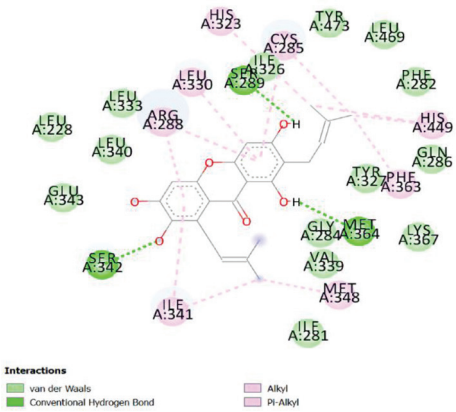
Based on the results of docking using MOE, two candidate compounds were obtained, namely α-mangostin and

Table 3: The value of binding affinity of compounds in peroxisome proliferator-activated receptor gamma, diphenyl peptidase-4 enzyme, and aldose reductase enzyme

The value of binding affinity of compounds					
PPAR-γ receptor		**DPP-4 enzyme**		**Aldose reductase enzyme**	
Compounds	**Binding affinity**	**Compounds**	**Binding affinity**	**Compounds**	**Binding affinity**
α-mangostin	−angost	α-mangostin	−angos	α-mangostin	−8.15
γ-mangostin	−angost	γ-mangostin	−angos	γ-mangostin	−7.24
Xanthone	−antho	Xanthone	−anth	Xanthone	−6.09
Pioglitazone (*native ligand*)	−native	Vildagliptin (*native ligand*)	−nativ	Zopolrestat (*native ligand*)	−12.59
Lobeglitazone	−obegli	Alogliptin	−logli	Epalrestat	−8.33
Rosiglitazone	−osigli	Anagliptin	−nagli	Alrestatin	−6.01
		Saxagliptin	−axagl	Lidorestat	−8.38
		Sitagliptin	−itagl	Tolrestat	−8.78
		Teneligliptin	−eneli	Fidarestat	−4.73
				Minalrestat	−8.05
				Ponalrestat	−8.16
				Ranirestat	−7.60
				Salfredin B11	−5.12
				Sorbinil	−5.35
				Zenarestat	−8.16
				Imirestat	−8.37

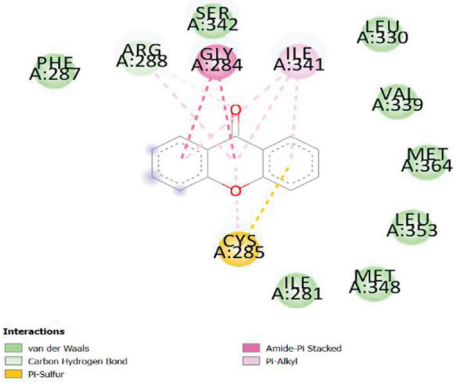
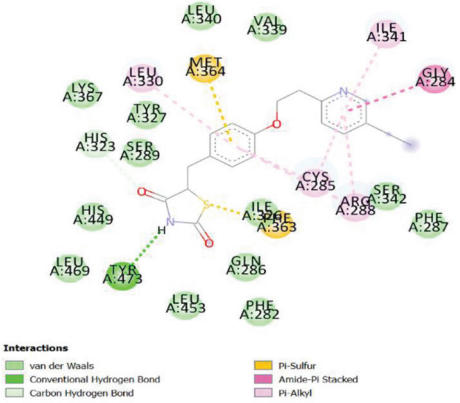
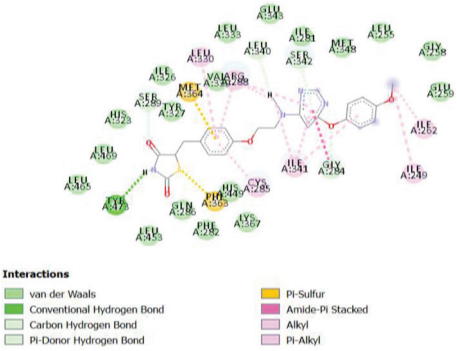
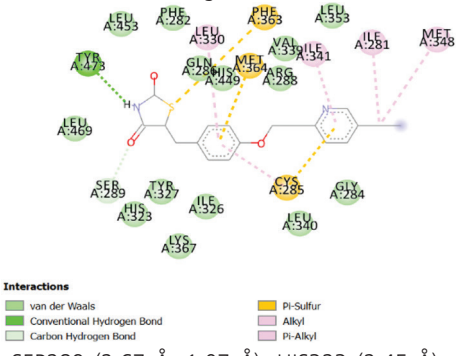
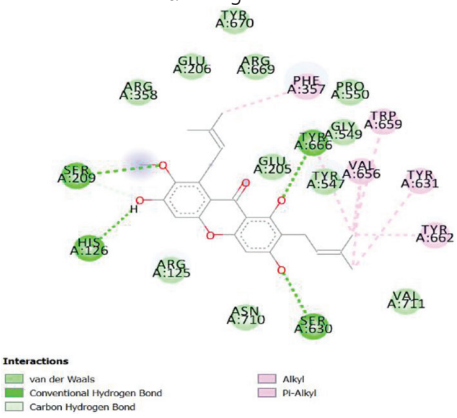
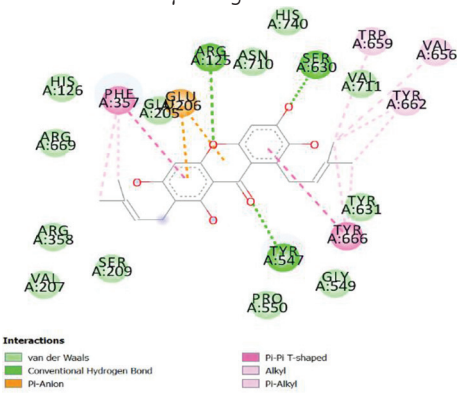
PPAR-γ: Peroxisome proliferator-activated receptor gamma, DPP-4: Diphenyl peptidase 4

Table 4: Interaction of amino acids of test compounds and other comparative ligands

Target ligands	Interaction of amino acids	
PPAR-γ receptors	α-mangostin	γ-mangostin
		
	ILE281 (2,78 Å); SER342 (2,18 Å)	SER289 (1,88 Å); SER342 (2,05 Å); MET364 (2,72 Å)

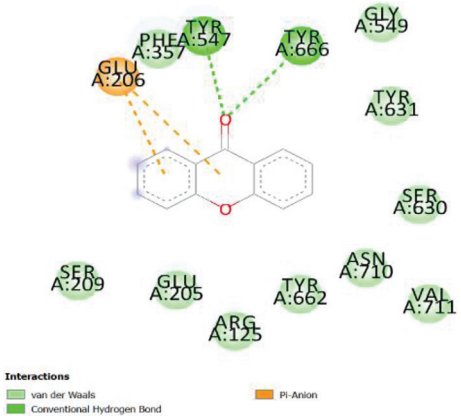
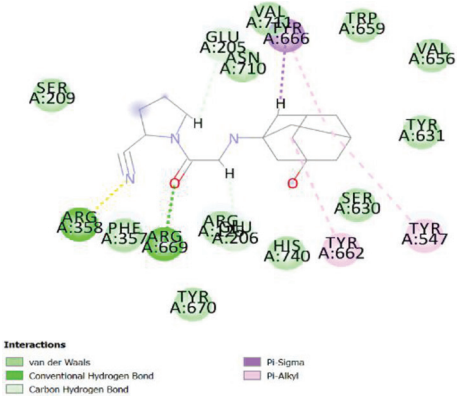
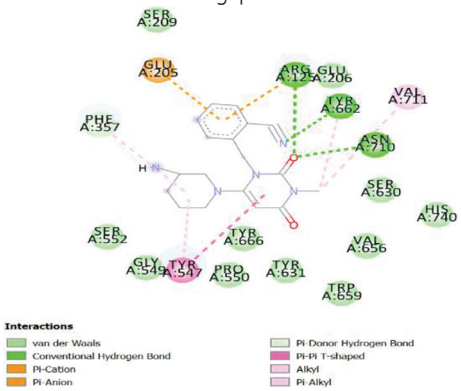
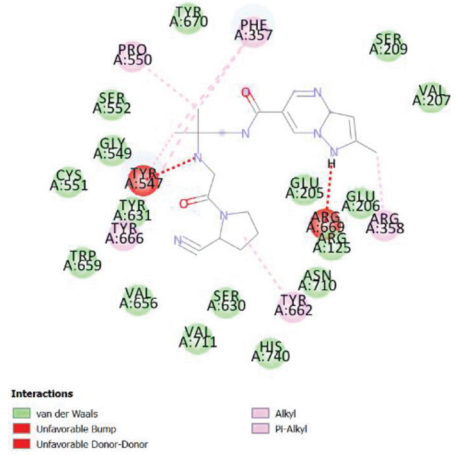
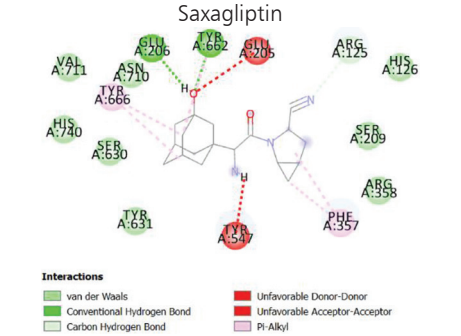
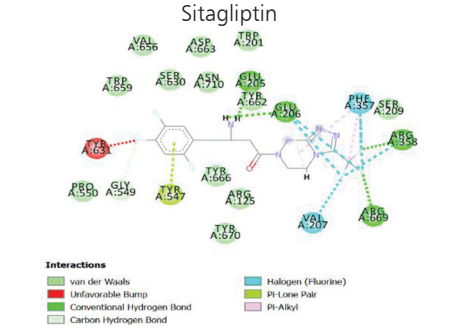
Contd...

Table 4: Contd...

Target ligands	Interaction of amino acids	
	Xanthone	Pioglitazone *(native ligand)*
		
	ARG288 (2,70 Å)	HIS323 (2,50 Å); TYR473 (2,32 Å)
	Lobeglitazone	Rosiglitazone
		
	SER289 (2,74 Å); LEU340 (2,61Å); TYR473 (2,71 Å); GLY284 (2,51 Å); SER342 (3,13 Å)	SER289 (2,67 Å; 1,07 Å); HIS323 (2,45 Å); LEU340 (2,85 Å; 3,00 Å); TRY473 (2,31 Å)
DPP-4 enzyme	α-mangostin	γ-mangostin
		
	HIS126 (2,47 Å); SER209 (2,31 Å; 2,78 Å); SER630 (2,73 Å); TYR666 (2,99 Å)	ARG125 (3,08 Å); SER630 (1,52 Å); TYR547 (2,52 Å)

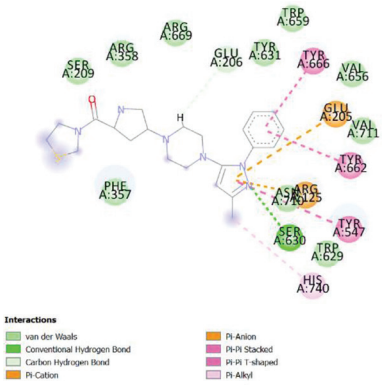
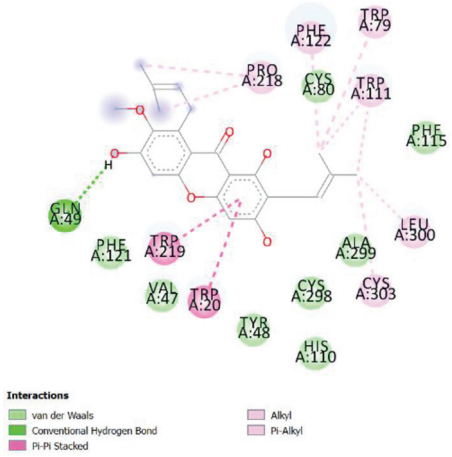
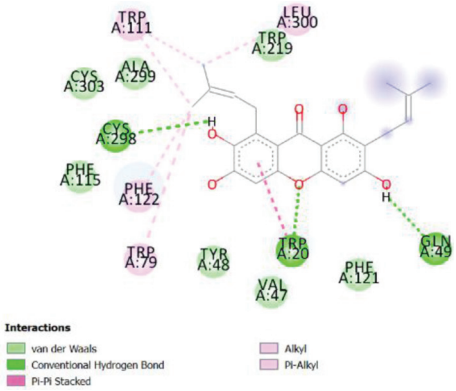
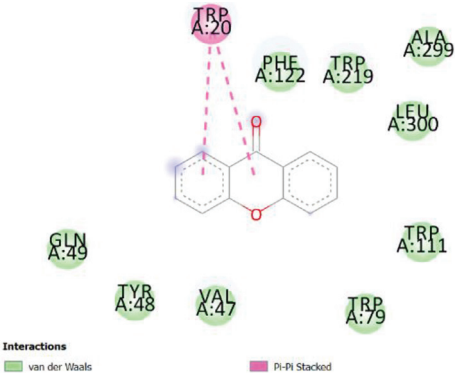
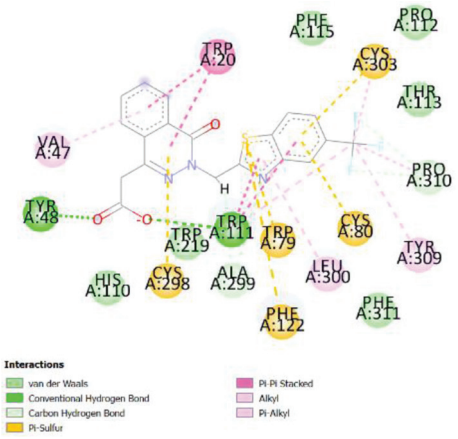
Contd...

Table 4: Contd...

Target ligands	Interaction of amino acids
Xanthone	Vildagliptin (*native ligand*)
	
TYR547 (2,40 Å); TYR666 (2,84 Å)	GLU205 (2,91 Å); GLU206 (2,12 Å); ARG358 (2,04 Å); ARG669 (2,67 Å)
Alogliptin	Anagliptin
	
ARG125 (3,10 Å); PHE357 (2,90 Å); TYR662 (2,51 Å); ASN710 (2,84 Å)	-
Saxagliptin	Sitagliptin
	
ARG125 (2,80 Å); GLU206 (1,09 Å); TYR662 (1,81 Å)	GLU205 (1,68 Å); GLU206 (1,56 Å; 2,49 Å); ARG358 (1,94 Å); GLY549 (2,75 Å); ARG669 (2,52 Å)

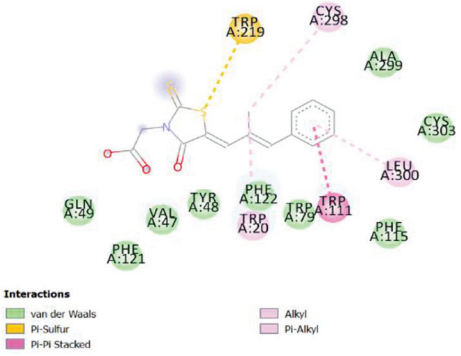
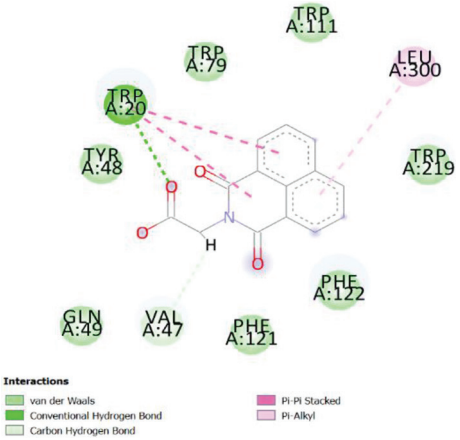
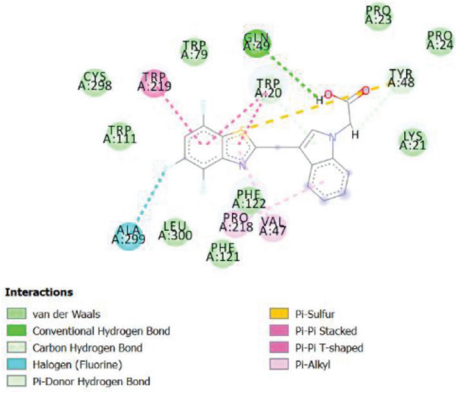
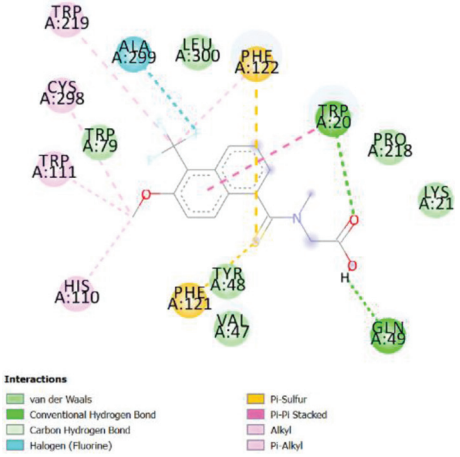
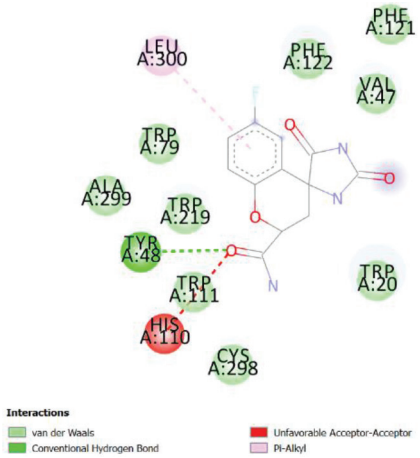
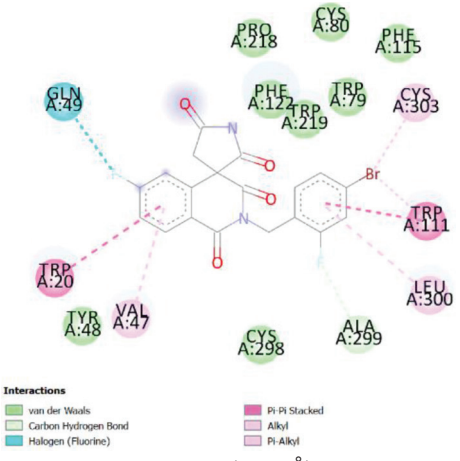
Contd...

Table 4: Contd...

Target ligands	Interaction of amino acids
	Teneligliptin  GLU206 (2,62 Å); SER630 (2,33 Å)
Aldose reductase enzyme	α-mangostin  GLN 49 (2,39 Å) γ-mangostin  TRP 20 (3,08 Å); GLN 49 (2,63 Å); CYS298 (3,08 Å)
	Xanthone  - Zopolrestat *(native ligand)*  TRY48 (1,71 Å); TRP111 (1,91 Å); ALA299 (3,08 Å; 2,64 Å); PRO310 (2,54 Å; 2,54 Å)

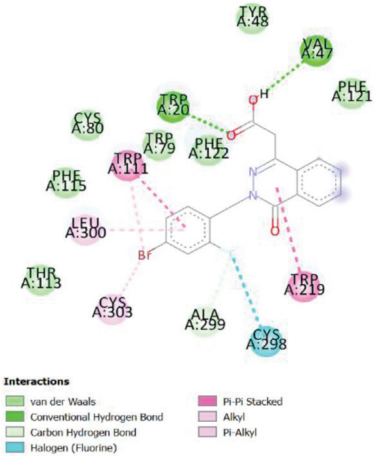
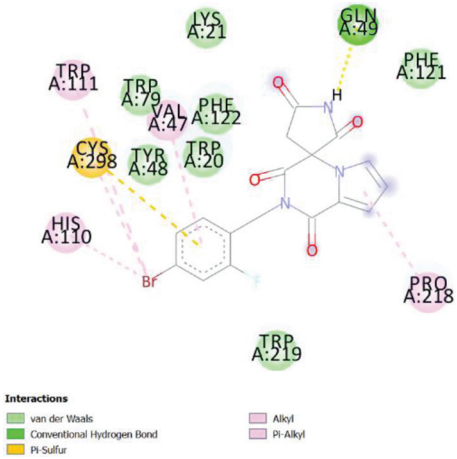
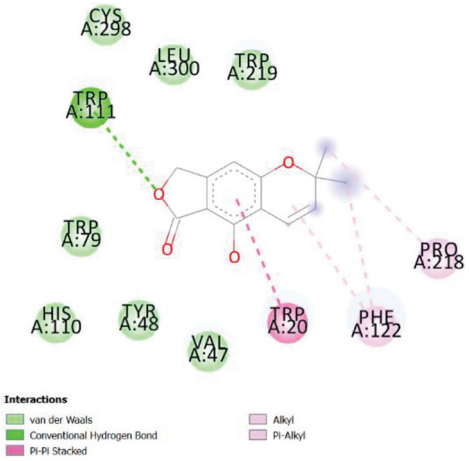
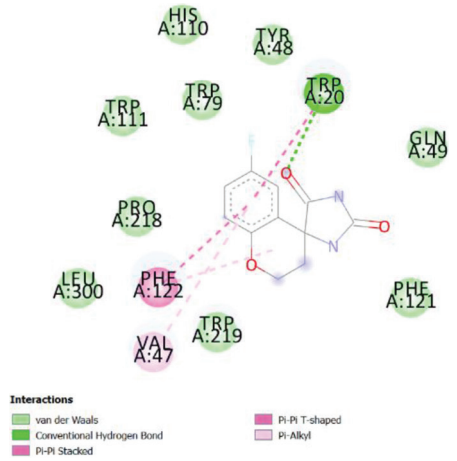
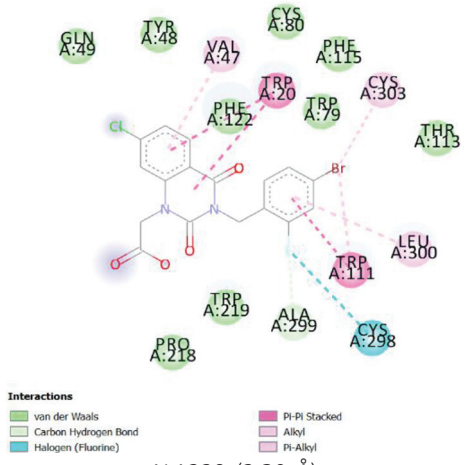
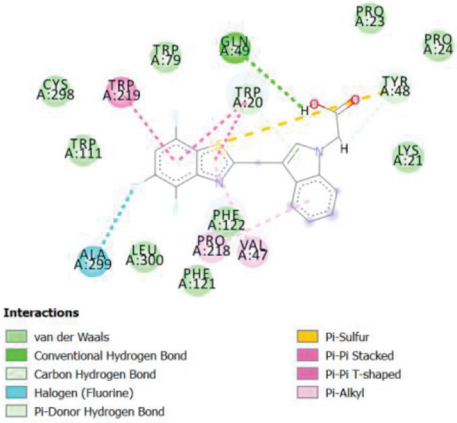
Contd...

Table 4: Contd...

Target ligands	Interaction of amino acids
Epalrestat	
-	
Alrestatin	
	TRP 20 (2,50 Å); VAL47 (2,68 Å)
Lidorestat	
	TRP20 (3,18 Å); TRY48 (2,74 Å); GLN 49 (3,00 Å)
Tolrestat	
	TRP20 (2,83 Å; 3,05 Å); GLN49 (2,24 Å)
Fidarestat	
	TYR48 (2,58 Å)
Minalrestat	
	ALA299 (2,70 Å)

Contd...

Table 4: Contd...

Target ligands	Interaction of amino acids
Ponalrestat	 TRP20 (2,17 Å); VAL47 (2,35 Å); ALA299 (2,50 Å)
Ranirestat	 GLN49 (1,70 Å)
Salfredin B11	 TRP111 (2,97 Å)
Sorbinil	 TRP20 (2,31 Å)
Zenarestat	 ALA229 (2,30 Å)
Imirestat	 TRP20 (3,18 Å); TRY48 (2,74 Å); GLN49 (3.00 Å)

PPAR-γ: Peroxisome proliferator-activated receptor gamma, DPP-4: Diphenyl peptidase 4

γ-mangostin which are thought to be active at PPAR-γ receptor, DPP-4 enzyme, and aldose reductase enzyme because each of these compounds shows more negative or almost similar affinity binding values when compared to the ligands of several drugs on the market and shows several models of protein-bound bonds, including hydrogen

bonding, so that these compounds can be predicted in the treatment of DM. Meanwhile, xanthone showed unfavorable results.

Acknowledgment

We would like to thank the Higher Education Research Consortium from The Indonesian Ministry of Research, Technology, and Higher Education (Ristekdikti), for funding this research.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Manimekalai I, Sivakumari K, Ashok K, Rajesh S. Phytochemical profiling of mangosteen fruit, *Garcinia mangostana.* World J Pharm Pharm Sci 2016;5:221-52.
2. Ovalle-Magallanes B, Eugenio-Pérez D, Pedraza-Chaverri J. Medicinal properties of mangosteen (*Garcinia mangostana* L.): A comprehensive update. Food Chem Toxicol 2017;109:102-22.
3. Ratwita W, Sukandar EY, Adnyana IK. Alpha mangostin and xanthone from mangosteen (*Garcinia mangostana* L.) role on glucose tolerance and glucose transporter-4 in diabetes mellitus. Int J Pharm Phytochem Res 2017;9:1206-12.
4. Ghosh AK, Palit S, Samajdar S. *In silico* molecular docking study of dihydroisoquinolinium derivatives as DPP IV inhibitors in Type II diabetes mellitus. Pharmatutor 2017;5:22-8.
5. Adnyana IK, Abuzaid AS, Iskandar EY, Kurniati NF. Pancreatic lipase and α-amylase inhibitory potential of mangosteen (*Garcinia mangostana* Linn.) pericarp extract. Int J Med Res Health Sci 2016;5:23-8.
6. Ibrahim SR, Mohamed GA, Khayat MT, Ahmed S, Abo-Haded H, Alshali KZ. Mangostanaxanthone VIIII, a new xanthone from *Garcinia mangostana* pericarps, α-amylase inhibitory activity, and molecular docking studies. Revista Brasileira de Farmacognosia 2019;29:206-12.
7. Taher M, Tg Zakaria TM, Susanti D, Zakaria ZA. Hypoglycaemic activity of ethanolic extract of *Garcinia mangostana* Linn. in normoglycaemic and streptozotocin-induced diabetic rats. BMC Complement Altern Med 2016;16:135.
8. Kumar V, Bhatt PC, Kaithwas G, Rashid M, Al-Abbasi FA, Khan JA, *et al*. α-Mangostin mediated pharmacological modulation of hepatic carbohydrate metabolism in diabetes induced Wistar rat. Beni Suef Univ J Basic Appl Sci 2016;5:255-76.
9. Husen SA, Kalqutny SH, Ansori AN, Susilo RJ, Alymahdy AD, Winarni D. Antioxidant and antidiabetic activity of *Garcinia mangostana* L. pericarp extract in streptozotocin-induced diabetic mice. Biosci Res 2017;14:1238-45.
10. Indrajati V. Herbal Expert to Overcome Disease. Jakarta: Penebar Swadaya; 2013.
11. Ohno R, Moroishi N, Sugawa H, Maejima K, Saigusa M, Yamanaka M, *et al*. Mangosteen pericarp extract inhibits the formation of pentosidine and ameliorates skin elasticity. J Clin Biochem Nutr 2015;57:27-32.
12. Pal PB, Sinha K, Sil PC. Mangiferin, a natural xanthone, protects murine liver in Pb (II) induced hepatic damage and cell death via MAP kinase, NF-κB and mitochondria dependent pathways. PLoS One 2013;8:E56894.
13. Suthammarak W, Numpraphrut P, Charoensakdi R, Neungton N, Tunrungruangtavee V, Jaisupa N, *et al*. Antioxidant-enhancing property of the polar fraction of mangosteen pericarp extract and evaluation of its safety in humans. Oxid Med Cell Longev 2016;2016:1-10.
14. Dewi YF, Anthara MS, Dharmayudha AA. The effectiveness of red betel leaf extract (*Piper crocatum*) on reducing blood glucose levels of male white rats (*Rattus novergicus*) induced by alloxan. Udayana Veterinary Bulletin 2014;6:73-9.
15. Federation, Internasional Diabetes. IDF Diabetes Atlas. Vol. 128. Brussels: International Diabetes Federation; 2013. p. 40-50.
16. Muralidaran S, Roy A. The role of PPAR agonists in diabetes mellitus. J Pharm Sci Res 2016;8:864.
17. Gosh AK, Palit S, Samajdar S. Insilco molecular docking study of dihydroisoquinolinium derivatives as DPP IV inhibitors in type II diabetes mellitus. Pharmatutor 2017;5:22-8.
18. Katzung BG, Masters SB, Trevor AJ. Basic Clinical Pharmacology. A Large Medical Book. New York; McGraw-Hill Medical; 2012.
19. Decroli E. Diabetes Mellitus Type 2. 1st ed. Padang: Publishing Center for Internal Medicine Section, Faculty of Medicine, Andalas University; 2019.
20. Zhu C. Aldose Reductase Inhibitors as Potential Therapeutic Drugs of Diabetic Complications. Vol. 2. Intech open publisher. London; 2013.
21. Shah K, Mujwar S, Gupta JK, Shrivastava SK, Mishra P. Molecular docking and *in silico* cogitation validate mefenamic acid prodrugs as human cyclooxygenase-2 inhibitor. Assay Drug Dev Technol 2019;17:285-91.
22. Meng XY, Zhang HX, Mezei M, Cui M. Molecular docking: A powerful approach for structure-based drug discovery. Curr Comput Aided Drug Des 2011;7:146-57.
23. Sliwoski G, Kothiwale S, Meiler J, Lowe EW Jr. Computational methods in drug discovery. Pharmacol Rev 2014;66:334-95.
24. Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. In: Chemical Biology. New York, NY: Humana Press; 2015. p. 243-50.
25. Cereto-Massagué A, Guasch L, Valls C, Mulero M, Pujadas G, Garcia-Vallvé S. DecoyFinder: An easy-to-use python GUI application for building target-specific decoy sets. Bioinformatics 2012;28:1661-2.
26. Peng X, He J, Niemi AJ. Clustering and percolation in protein loop structures. BMC Struct Biol 2015;15:22.
27. Empereur-Mot C, Zagury JF, Montes M. Screening explorer-an interactive tool for the analysis of screening results. J Chem Inf Model 2016;56:2281-6.
28. Labute P. Protonate3D: Assignment of ionization states and hydrogen coordinates to macromolecular structures. Proteins 2009;75:187-205.
29. Bendix F, Wolber G, Seidel T. Strategies for 3D pharmacophore-based virtual screening. Drug Discov Today Technol 2010;7:e203-70.
30. Hernandez MA, Rathinavelu A. Basic Pharmacology: Understanding Drug Actions and Reactions. England: CRC Press; 2006.