Classification of Active Compounds of Type 2 Antidiabetic Medicinal Plants based on Molecular Docking

Siti Arni Wulandya, Farit Mochamad Afendi, Tony Ibnu Sumaryada

Abstract— Jamu is an Indonesian traditional medicine that has more than one pharmacological effect due to various herbal compounds from many types of plants involved in it. This ability cause jamu recommended for the treatment of degenerative metabolic diseases involving protein complex in the human body. In this paper, a computational approach was performed to find the characteristics of compounds from type 2 antidiabeticmedicinal plant that targeting parathyroid hormone (one of the significant protein of type 2 diabetic) using classification model. The characteristics of the compounds were studied from the molecular docking simulation of the herbal compound and the target protein. The result of classification model indicates that the predicted compound can target the parathyroid-hormone mostly come from the ginger plant (*Zingiberofficinale*). The active compounds of ginger plant which has the biggest binding site similarity to the patented anti-diabetes drug (Cinacalcet hydrochloride) areGingerols;[6]-Gingerol,5-Ac and (-)-Zingiberene. Both compounds have binding sites similarities of 60 % (3 out of 5 residues) with Cinacalcet hydrochloride (a synthetic compound) that found in Met-49, Glu-53, and Arg-56.

Index Terms— classification model, discriminant analysis, molecular docking, jamu, type 2 diabetic, binding affinity, binding sites.

1 INTRODUCTION

DISEASE is a condition caused by the malfunction of certain proteins in the human body. Impaired function of the protein can be either deficiency or excess protein function caused by bacterial infection or unhealthy lifestyle. The disease that caused by a complex disorder of protein function isdegenerative metabolic disease. One type of degenerative metabolic disease is type 2 diabetic. This disease is a metabolic disorder disease due to the inability of the human body to use the production of insulin effectively. The number of people with type 2 diabetic almost 90% of all cases of diabetic in the world. This number is expected to continue to increase, especially in developing countries along with increasing of the population, changes in consumption patterns and unhealthy lifestyles.

Treatment of type 2 diabetic and other metabolic degenerativediseasesusually using chemical drugs (synthetic), which only use one compound to target one protein (one drug-one target). But this kind of synthetic drug is inefficient and often cause side effects for the other proteins in the human body. Therefore, drugs with more than one pharmacological effect (multi component-network target) would be more appropriate to deal with these degenerative metabolic diseases. Indonesian traditional medicine that consisting of one or more medicinal plants apply this concept. This concept refers to the involvement of several active compounds of several plants to target one or more proteins that cause disease. Medicinal plants have more than one pharmacological effect and have a lower side effect rather than synthetic drugs, so it is suitable for the treatment of degenerative metabolic diseases (Katno 2008).

Research on the formulation of new antidiabeticmedicinal plants have been done by Nurishmaya (2014) with the conclusion there are four plants that are predicted to lower the blood sugar levels in people with type 2 diabetic. That plantsarepare (*Momordicacharantia*), sembung (*Blumeabalsamifera*), bratawali (*Tinosporacrispa*) and ginger (*Zingiberofficinale*). The search of KNApSAcK family and The Dictionary of Natural Products (DNPdatabase, which has been done by Bakri (2015), Syahrir (2015) and Qomariasih (2015) found that there are 287 unique compounds from all four plants. Meanwhile, Usman (2016) has been successfully identified 21 significant proteins in the human body that associated with type 2 diabetic.

Based on the pubchem database, there are 57 of the 287 compounds of type 2 antidiabetic medicinal plants that have been experimentally tested can targeting significant proteins of type 2 diabetic in the human body. On the network of 21 significant protein of type 2 diabetic, insulin (INS) is an important protein that regulates the interaction between proteins and binding other proteins that interact with it. One of the protein seeds that have interaction with insulin is parathyroid hormone (PTH). Parathyroid hormone is produced by the parathyroid gland that serves to stabilize the concentration of calcium in the blood.

This study used molecular docking approach to obtain interaction information between several compounds and parathyroid hormone. This molecular docking approach has been widely used in bioinformatics to design a new drug candidate that targets a particular disease computationally. On further analysis, a classification model was applied to

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create a model that can clearly distinguish the characteristics of compounds that targeting parathyroid hormone and the compounds that do not target parathyroid hormone. The model was used to predict whether another unaccounted compoundsin the database targeting parathyroid hormone or not.

Problems in classification model appear on the imbalance condition of the observations. This imbalance of observations was seen in the presence of more dominant classes (major classes) and very small observations classes (minor class). The condition of this imbalance data will affect the precision of the classification model because the classification model will predominate predicting the major class while the minor class is neglected.That cause the observations on the minor class can not be classified appropriately (Galar et al., 2011). An approach that can be used to solve classification problems in unbalanced data is to pre-process the classification at the data level using the SMOTE method. SMOTE (synthetic minority over-sampling technique) is an over-sampling method by generating artificial data from minor classes based on their k-nearest neighbors.

2 RESEARCH METHOD

2.1 Data

The data used in this research are chemical structures of 287 active compound of four type 2 antidiabetic medicinal plants. The plant consists of pare (*Momordicacharantia*), sembung (*Blumeabalsamifera*), bratawali (*Tinosporacrispa*) and ginger (*ZingiberOfficinale*). Another important component is the chemical structure of parathyroid hormone as protein target. The classification model is built on 57 data compounds that already have target information in the pubchem database. The data was divided into 80% of the training data group to build the model and 20% of the testing data group to evaluate the classification performance of the model. The Table 1 shows the list of variables that use in this study.

TABLE 1
LISTOF VARIABLES

Variables	Explanation	Scale
Y	1: Compounds that have targeting parathyroid hormone 2: Compounds that do not targeting parathyroid hormones	Nominal
$\mathbf{X_1}$	Binding affinity from molecular docking process	Ratio
$\mathbf{X_2}$	The shortest hydrogen bond distance from all the hydrogen bonds in the process	Ratio
$\mathbf{X_3}$	The total number of hydrogen bonds in molecular docking process	Ratio

2.2 Methodsof Data Analysis

The stages of data analysis in this research are as follow:

1. Simulation of molecular docking
   Performed by docking 287 ligand compounds on the parathyroid hormone receptor. The result was scored and obtained the best value (ΔG most negative), then the best docking result was observed in the ligand binding site of the protein receptor. Hydrogen bond interactions, hydrophobic interactions, electrostatic interactions and van der Waalsinteractions are visualized at radius interaction less than 4.5 Å of the docking ligand position.
2. Descriptive Analysis
   Descriptive analysis was performed to explore thegeneral description of data from molecular docking of the ligand compound to the receptor parathyroid hormone.
3. Divide the data group into training data and testing data with a ratio 80% for training and 20% for testing.
4. Generating artificial data with the SMOTE method on the training and testing data in order to obtain a balanced class of observations.
5. Testing the discriminant analysis assumption
   a. Doing the normal multivariate test using chi-square quantile plots.
   b. Testing the homogeneity of variance covariance matrix using the Box-M test.
   c. Testing the correlation between the explanatory variables.
6. Build a discriminant model
   The discriminant model is built based on the results of assumptions test.
7. Calculating the classification performance.
8. Classifying the active compounds of medicinal plants based on the best models that have been obtained.
9. Performing molecular validation using Binding Sites Similarity (BSS) analysis by comparing the similarity of binding sites residues of the ligands compound of medicinal plants to the standard ligand either with synthetic drug or natural ligands that docked to the parathyroid hormone.

3 RESULT AND DISCUSSION

3.1 Descriptive Analysis

The compounds of pare (*Momordicacharantia*),sembung (*Blumeabalsamifera*), bratawali (*Tinosporacrispa*) and ginger (*Zingiberofficinale*) plants are predicted to decrease sugar levels in type 2 diabetic (Nurishmaya 2014).A compound of medicinal plant can be a good drug candidate if it qualifies some characteristics called Lipinski Rules: 1) molecular weight less than 500 grams/mol, 2) the number of donor groups of hydrogen bond protons less than 5, 3) the number of acceptor groups of hydrogen bond protons less than 10 and 4) partitions logarithm in the water and 1-octanol less than 5 (Lipinski et al., 2001).

The molecular weight of the compound should be considered. In order to perform its function, the compound can diffuse into the cell membrane. The number of donor proton hydrogen bonds and the acceptor proton hydrogen bond are related to the stability of the binding conformity. The partition coefficient (P) describes the ratio of drug distribution to the two-phase solvent system that is organic solvent and watertill the compound that used can be absorbed by the body towards the target protein. Figure 2 shows that most compound molecules of type 2 antidiabeticmedicinal plant

have met Lipinski's rules. Compounds that fit the Lipinski rule have a greater indication to be good drug candidates, whereas compounds that not fit the Lipinski's rule can not be ascertained to be good drug candidates as of it set aside in the further analysis process.

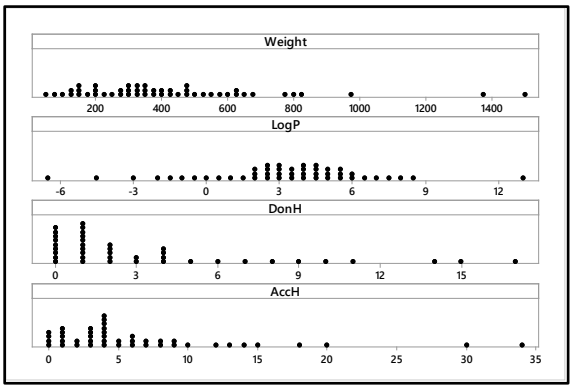


FIGURE 1 THE CHARACTERISTICS DISTRIBUTION OF COMPOUNDS OF TYPE 2 ANTI-DIABETICMEDICINAL PLANT

Figure 1 shows the distribution of compounds characteristics of type 2 antidiabetic medicinal plant. The number of compounds that fit the Lipinski rule were 189 compounds. 57 compounds from them have a record that targeting significant protein type 2 diabetic in the human body.That 57 compounds were used as a training data group and testing data group in model building meanwhile other132 compounds will be predicted whether it has characteristics as a compound that targeting parathyroid hormone. The discriminant model is built using three explanatory variables consist of binding affinity (X_1), H-bond distance (X_2) and total H-bond (X_3). All of the explanatory variables used are the result of molecular docking between molecul compounds and parathyroid hormones.

In therecord ofpubchem database (https://pubchem.ncbi.nlm.nih.gov/assay/assay.cgi), 11% compounds of type 2 antidiabeticmedicinal plants weretargeted parathyroid hormone (category 1) while the remaining majority (89 %) did not targetedthat protein (category 2). This condition indicates a problem of imbalance observation. These seen from the class that havemore dominant observations (major class) while the other class have very little observation (minor class). This imbalance observations will affect the performance of classification model that has obtained.

3.2 Discriminant Model without SMOTE

If P (Y = k | X) is a conditional probability of the k^{th} class of variable X, then the discriminant function for data without the SMOTE process is given as follows.

$$P (Y = k \mid X) = -0.8775X1 + 0.0142X2 - 0.0756X3$$

If the classification performance that obtained with the above discriminant function is good enough, that function can be used to predict the other compounds with unknown class information about its interaction to the parathyroid hormone. Based on the above function the more negative the value of the binding affinity, the farther the hydrogen bond distance and the less number of hydrogen bonds then the discriminant score will be greater.

Table 2 shows the classification performance of discriminant model without SMOTE. Accuracy values describe the overall precision measurement of the classification forboth categories. The accuracy of classification of observations in thediscriminant model without SMOTE up to 91.3%, while the validation rate of the model using testing data up to 81.82%. Values for the accuracy of this model is quite big, it means the ability of this model to classify the observations correctly according to the actual classification up to 81.82%. The value of AUC (Area Under the Curve) is quite large in the training data and testing data up to 50%.

TABLE 2
CLASSIFICATION PERFORMANCE OF MODEL WITHOUT SMOTE (%)

Classification performance	Training	Testing
Accuracy	91.3	81.82
Sensitivity	0	0
Specificity	100	100
AUC	50	50

Sensitivity values describe the precisionof theclassificationin the 1st category (the class of compounds that has targeted parathyroid hormone), whereas the specificity values describe the precision of classification in the2ndcategory (class of compounds that did not targeted parathyroid hormone). Sensitivity value on training data and testing data are 0% while the specificity value in both datasetup to 100%. If we look at the significant differences in the two values, it can be concluded that there is a tendency for prediction differences in 1st category and 2ndcategory classes. The above model is only able to well predict the 2ndcategory classes, while the 1st category that has very small observations unpredicted well. The unbalancevalue of sensitivity and specificity, although the accuracy and AUC are good enough indicates that the above model is not good enough to used to predict compounds oftype 2 antidiabeticmedicinal plants.

3.3 Discriminant Model with SMOTE

If P (Y = k | X) is a conditional probability of the k^{th} class of variable X, then the discriminant function for the data with the SMOTE process is given as follows.

$$P (Y = k \mid X) = -1.0788X1 + 0.0114X2 - 0.0156X3$$

The above discriminant function can be used to predict other compounds with unknown class information about its interaction to the parathyroid hormone. Based on the above function the more negative the value of the binding affinity, the farther the hydrogen bond distance and the less number of hydrogen bonds then the discriminant score will be greater.

TABLE 3
CLASSIFICATION PERFORMANCE OF MODEL WITH SMOTE (%)

Classification performance	Training	Testing
Accuracy	65.85	35.29
Sensitivity	67.50	25
Specificity	64.29	44.44
AUC	65.89	34.72

Table 3 shows the classification performance of discriminant model with SMOTE. There is a significant differences in the classification performance generated by the model with SMOTE process and the model without the SMOTE process.Model with SMOTE process has accuracy value up to 65.85% for training data and 35.29% for testing data. It was smaller compared to the model without SMOTE.Likewise, the larger AUC value is only in the training data. Although the testing data is smaller but the value of sensitivity and specificity in this model has been balanced. The sensitivity value on training data is up to 67.5% while the specificity value is up to 64.29%. In the testing data, sensitivity value up to 25% while the specificity value up to 44.44%. The ability of the model with SMOTE process to classify the observations of the 1st category correctly up to 25%, while the ability of the model to classify the observation of the 2nd categorycorrectly up to 44.44%. The well-balanced values of sensitivity and specificity indicate that models with the SMOTE process have the ability to classify minority observations better than the model without the SMOTE process.

3.4 Distinguish Characteristic of Parameters

The variables that plays an important role as a differentiator of compounds that targeting or not targeting parathyroid hormone is indicated by the correlation value between the explanatory variables and the discriminant functions that has corrected by the information of group membership. Table 4 shows the correlation values of explanatory variables with discriminant functions.

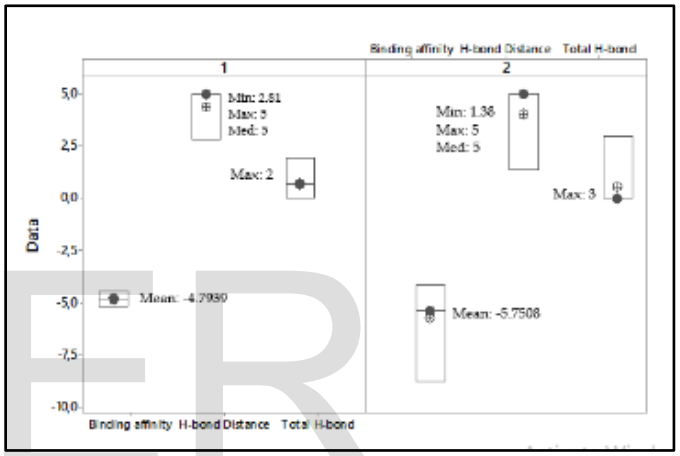
TABLE 4
CORRELATION OF EXPLANATORY VARIABLES WITH DISCRIMINANT FUNCTIONS

Variable	Correlation
Binding affinity (X_1)	-0.8671
H-bond Distance (X_2)	0.3145
Total H-bond (X_3)	-0.1828

The variable with the highest correlation value is the variable that plays an important role as the differentiator for the classification of the compound. The most influential variable in the classification of the compound on its interaction to the parathyroid hormone is binding affinity (X_1). The correlation value of this variable is quite large up to 0.8671, that means the value of binding affinity (X_1) is the main information that indicates the bond strength of the compound interaction with the parathyroid hormone based on molecular docking. The next influential variable is H-bond distance (X_2), with the correlation value amount0.3145. The H-bond distance has a positive effect with the discriminant score, that means the longer the H-bond distance will make the discriminant score greater. The variable that has the least correlation with this function is total H-bond(X_3). The total H-bond has a negative effect, that means this variable contributes to decreasingthe discriminant score although with the small values.

Figure 2 shows the distribution of the variables in each category. The average value of binding affinity in 1st category is -4.7939, while in the 2nd category is -5.7508. This means that the average of binding affinity in the category of compounds that have not targeted parathyroid hormone is more negative than compounds that have targeted parathyroid hormone. In other words, the bond between the compound and the parathyroid hormone in 2nd category is more stable than in the 1st category. The H-bond distance above 4.5 Å indicates that no hydrogen bond in the interaction between compounds and the parathyroid hormone. The distance of hydrogen bonds above 4.5 Å are dominates in most observations in both categories. The minimum hydrogen bond distance in the 1st category is 2.81Å, while in the 2nd category is 1.38Å. In the 2nd category, there is an observation that has a shorter H-bond distance than the observation in the 1st category. The maximum number of hydrogen bonds in 2nd category is greater than in 1th category. This indicates the characteristic number of hydrogen bonds in 2nd category is greater than 1st category.

FIGURE 2



DISTINGUISH CHARACTERISTIC OF PARAMETERS

3.5 Candidate Compounds that Targeting Parathyroid Hormones

The SMOTE classification model was used to predict the type 2 anti-diabetes compound candidates that have potential in targeting the parathyroid hormone. Based on the classification model, the compounds of ginger plant include Methylglyoxal, 2-Nonanone, alpha-Linalool, Shogaols;[10]-Shogaol,6ξ-Hydroxy, Shogaols;[8]-Shogaol,6ξ-Hydroxy, Gingerols;[6]-Gingerol,4'-Me ether, Gingerols;[6]-Gingerol,5-Ac, Gingerols;[8]-Gingerol,5-Me ether, 4(10)-Thujene, Methyl allyl sulfide, Teresantanane, (-)-Zingiberene, (+)-Cyclosativene and Copaene. There is also one compound from the sembung,that is 9-Hydroxy-4-eudesmene-1,6-dione-9β-form and one compound from pare, that is Kuguacin M.

3.6 Hydrogen Bond

Interactions that occur in the binding process of compounds with targeted proteins include hydrogen bond interactions, hydrophobic interactions, electrostatic interactions and van der Waals interactions in the bindingsite area less than 4.5Å. The hydrogen bond involves the interaction of hydrogen atoms that bonded covalently with electronegative atoms such as flour(F), nitrogen(N) and oxygen(O) (Glowacki et al., 2013).

As comparators (control ligand) of predicted compounds that targeting the parathyroid hormoneCinacalcet Hydrochloride, a commercial drugthat acts as anhyperparathyroidism inhibitor, was used. In this study, the hydrogen bond distance exceeds 4.5Å is classified as a weak bond and it is not included in the discussion. Table 5 shows the analysis of hydrogen bonds of predicted compounds that targeting paratiroid hormone.

Generally, all compounds that are predicted to target the parathyroid hormone have strong hydrogen bonds and can be used as candidates for parathyroid hormone inhibitor. The control ligand, Cinacalcet hydrochloride shows one strong hydrogen bond between Glu-53 and H-696. Methylglyoxal compounds, Alpha-Linalool, Shogaols, [10] -Shogaol, 6ξ-Hydroxy, and Gingerols; [6] -Gingerol, 4'-Me ether from ginger plants have more hydrogen bonds than the Cinacalcet hydrochloride. This found indicates that these compounds may have a better ability to bind to parathyroid hormones as compared to the Cinacalcet hydrochloride.

TABLE 5
ANALYSIS OF HYDROGEN BOND

No	Compound	Total H-bond	Amino Acid Residues	Ligands groups	Amino acid interacting groups	Bond distance
1	Cinacalcet Hydrochloride	1	Glu-53	H-693	OE-35	1,71
2	Methylglyoxal (J222)	2	Arg-56	O-646	NE-414	2,52
			Arg-56	O-646	NH-417	1,45
3	2-Nonanone (J235)	1	Arg-56	O-645	NH-417	1,93
4	alpha-Linalool (J254)	2	Arg-56	O-645	NE-414	2,56
			Arg-56	O-645	NH-417	1,83
5	Shogaols; [10]-Shogaol, 6ξ-Hydroxy (J105)	2	Trp-54	H-698	O-361	1.85
			Lys-58	O-647	NZ-463	1.82
6	Shogaols; [8]-Shogaol, 6ξ-Hydroxy (J098)	3	Arg-56	O-647	NH-417	2,91
			Arg-56	O-647	NH-420	3,06
			Arg-56	O-648	NH-414	2.73
7	Gingerols;[6]-Gingerol, 4'-Me ether (J038)	2	Glu-53	H-682	OE-355	2,52
			Arg-56	O-646	NH-417	2,62
8	9-Hydroxy-4-eudesmene-1,6-dione; 9β-form (S010)	1	Glu-50	H-681	O-291	2,57
9	Gingerols; [6]-Gingerol, 5-Ac (J039)	1	Arg-56	O-646	NH-417	2,05
10	Gingerols; [8]-Gingerol, 5-Me ether (J047)	1	Arg-56	O-646	NH-417	1,67

3.7 Binding Sites Similarity

In the molecular docking, the functional groups of ligands will have tendency to bind with the residues in specific sites (pockets) which play important roles in the complex stability. (Arwansyah 2014). Thebinding sites similarity (BSS) of the test ligands to the control ligand's indicates the potential of such ligands to act or inhibit the target in the same way (biochemistry pathway) as control ligand.

Table 6 shows the binding sites similarity of the predicted compounds of tipe 2 antidiabetic medicinal plants compared to the standard ligand. The type 2 antidiabeticcompound from the medicinal plants which have the biggest BSS percentage are the natural compound of Gingerols compound;[6]-Gingerol,5-Ac and (-)-Zingiberene from ginger plants. Both of them have a BSS level up to 60% (3 of 5 sites). Gingerols;[6] -Gingerol,5-Ac has a binding affinity score of -5,5448 kcal/mol with one H-bond distance 2.05Å from the binding site. Meanwhile, (-)-Zingiberene has binding affinityscore of -4.7797 kcal/mol without H-bond at all. Methylglyoxal, Alpha-Linalool, Shogaols, [10]-Shogaol, 6ξ-Hydroxy and Gingerols;[6]-Gingerol,4'-Me ether from ginger plants with more than one hydrogen bond has only 40% (2 of 5 residues) percentage of similarity. The interactions that formed between the compound and the target protein usually consist of hydrogen bonding interactions, hydrophobic interactions, electrostatic interaction and van der Waals interactions. Not all protein-ligand interactions has H-bond, eventhough they have a strong binding affinity. This property realy depend on the nature of the compounds. Natural compounds usually have a more distinct hydrophobic property as a compared to the synthetic one, this emphasize that the hydrophobic interactions play an important roles in the complexes binding. Sometimes the strongest binding occurred with limited number of H-bond but many hydrophobic interactions. This might come from the fact that hydrophobic interaction push the ligand away from the solution (water) which results in ligand buried deeply in the interior of the pocket.

TABLE 6
BINDING SITES SIMILARITY TO STANDARD LIGAND

No	Ligand	Binding Sites	Binding sites similarity	Binding Affinity (kcal/mol)
1	Cinacalcet Hydrochloride	Glu-53, Leu-42, Met-49, Val-52, Arg-56	100%	-8,7752
2	Methylglyoxal	Arg-56, Glu-53, Gln-60	40%	-4,7584
3	2-Nonanone	Arg-56, Glu-53	40%	-4,7829
4	alpha-Linalool	Arg-56, Glu-53, Gln-60	40%	-5,2648
5	Shogaols; [10]-Shogaol, 6ξ-Hydroxy	Trp-54, Lys-58, Met-49, Glu-53, Trp-54, Lys-57, Asp-61	40%	-5,6342
6	Gingerols; [6]-Gingerol, 5-Ac	Arg-56, Met-49, Glu-50, Glu-53	60%	-5,5448
7	Gingerols; [8]-Gingerol, 5-Me ether	Arg-56, Glu-53, Trp-54, Lys-57	40%	-5,0441
8	(-)-Zingiberene	Met-49, Glu-53, Arg-56	60%	-4,7797
9	(+)-Cyclosativene	Glu-53, Arg-56	40%	-4,3812
10	Kuguacin M	Met-49, Glu-53, Trp-54, Lys-57	40%	-4,4877

4 CONCLUSION

The classification of model using SMOTE shows better results in classifying the minority observations. The most important variable in this classification model is the binding affinity. The main characteristic of these differentiating variables is having more negative value in the not targeting parathyroid hormone category. Most of the predicted compounds thattargeting parathyroid hormoneare from ginger plants. The Ginger plant compounds that have the biggest BSS are Gingerols compounds;[6]-Gingerol,5-Ac and (-

)-Zingiberene. Both of them have the binding sites similarity to the synthetic compounds of Cinacalcet Hydrochloride at MET-49, GLU-53, ARG-56 residues. More investigation must be done in the future to explain pharmacological effects of those compounds in combating the type 2 diabetic via in vitro and in vivo studies. The next studies are expected to use variouscompounds of medicinal plant and various target proteinsto obtain better classification models.

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