Pharmacophore Analysis of *Moringa oleifera* Seeds Constituent as Anti-diabetic Properties

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ABSTRACT Pharmacophore modeling approach is a computer-aided drug design (CADD) method which possessed potential as the most promising candidates to focus on the experimental efforts in modern medicinal chemistry. *M. oleifera,* a well known traditional medicine used for many natural therapeutic such as treatment of inflammation, headache and to combat vitamin deficiency. One of the most important properties that found in *M. oleifera* seeds is anti-diabetic which can prevent from rising of blood sugar level in the body. By using ligand-based pharmacophore Modelling approach, four of established diabetic medicined which is (glibenclamide), (Metformin), (Repaglinide) and (nateglinide) from published literature and database (traning set) used to generate the pharmacophore modelling using Ligandscout 4.1 computer software along with the seeds constituent (test set) to determines the closest proximity.The selected seeds contituent are (4-(-l-rhamnopyranosyloxy)benzyl isothiocyanate), (4-(4¢-o-acetyl-a-l-rhamnopyranosyloxy) benzyl isothio-cyanate), (4-(α-L-rhamnopyranosyloxy) benzyl glucosinolate a), (niazimicin), (pterygospermin), (quecertin) and (kaempferol). Result shown the best constituent which is 4-(α-L-rhamnopyranosyloxy) benzyl glucosinolate and 4-(4-o-acetyl-a-l-rhamnopyranosyloxy) benzyl isothiocyanate show anti diabetic properties.

KEYWORDS: Pharmacophore modelling, *Moringa oleifera*, Ligandbased, Anti-diabetic

INTRODUCTION

Diabetic is a disease in which blood glucose levels are above normal. Most of the food we eat is turned into glucose, or sugar, for our bodies to use for energy. The pancreas, an organ that lies near the stomach, makes a hormone called insulin to help glucose get into the cells of our bodies. According to the Malaysian Diabetes Assosiation (MDA), compared to 2006 where only 8.6 percent adults in Malaysia had diabetes, the most recent study done in 2011 showed 15.2 percent adults were diabetic. Diabetes was a chronic disease that can be prevented and for those affected, diabetes can be managed to delay or prevent its complications. Diabetes disease were divided into 2 types which is **type 1** and **type 2** diabetes. Diabetes Mellitus is one of the commonest chronic non-communicable diseases globally (Ibrahim *et al.*, 2010). The **type 1** diabetes known as insulin-dependent diabetes mellitus (IDDM) , usually occurred for about 5% of all diagnosed cases of diabetes. **Type 2** diabetes, which was previously called non-insulin-dependent diabetes mellitus (NIDDM) and mostly for about 90% to 95% of all diagnosed cases of diabetes.

The basic of antidiabetic medications is stimulating insulin production from the pancreas or increasing the sensitivity of the body cells to insulin and is commonly used along with insulin (Bibi *et al.*, 2013). Different classes secretgogues known as sulfonylureas and meglitinides. Insulin sensitizers are biguanides, thiazolidinedione and metformin, and important inhibitors are α-glycosidase inhibitors include acarbose and miglitol etc. The side-effects of these medications include extreme hypoglycemia, idiosyncratic liver cell injury, lactic acidosis, digestive discomfort, permanent neurological deficit, headache, dizziness and even death. The basic challenge in curing diabetes is to maintain blood glucose level close to normal levels. These therapies are used as

monotherapy or in combination for optimal control of glycaemia. All the drugs nowadays come with good and bad side effect.

Moringa oleifera is a small or middle size tree, about 10m in height cultivated throughout India. A wide range of common names for the tree are documented, including benzolive tree, drumstick tree, horse-radish tree, kelor tree, mother's best friend, never die tree, mlonge, moonga, mulangay and numerous others. All part of tree are consider to possess medicinal properties and used in the treatment of rheumatism and circulatory stimulant (Goyal *et al.*, 2007). A list of possible medical applications conferred by *M. oleifera* plant parts includes, but is not limited to antihypertensive, anticancer, antispasmodic, antitumor, antiulcer, cholesterol lowering, diuretic, hepatoprotective, and hypoglycemic capabilities, as well as treatment of infectious skin and mucosal diseases (Rockwood *et al.*, 2013). Past study reported that methanolic extract of *M. oleifera* seed reduced the blood glucose level in alloxan diabetic rats (Ajibola *et al.*, 2014)

Pharmacophore modeling approach is a computer-aided drug design (CADD) method which possessed potential as the most promising candidates to focus on the experimental efforts in modern medicinal chemistry. It also could provide useful pharmacophoric information for future development of more potent molecules in the series of phenyl pyrazines and determine the structural and molecular properties (Kaur *et al.*, 2012). Computer-Aided Drug Design (CADD) is a specialized discipline that uses computational knowledge-based methods to aid the drug discovery process. In the search for high affinity of anti-diabetes medicine, powerful molecular modelling techniques have been useful in designing lead targets (Kalyaanamoorthy & Chen, 2011). The ligand-based drug design is based on mapping and orientation of certain features of a molecule that could form the basis for its high binding affinity and selectivity and also give information about functional group that bind to target and also type of interactions and atomic distance between functional group and interactions

METHODOLOGY

Data Set Collection

Training Set was selected from the established diabetic medicine which used treating the type 2 diabetic patient. The selection is essential for generating the pharmacophore model. Test set were selected from the chemical constituent of *M.oleifera* seed which had been isolated and characterized from previously reported. The 2D chemical structures of the compounds were drawn using ChemDraw. Optimizied training set were shown in Figure 1.
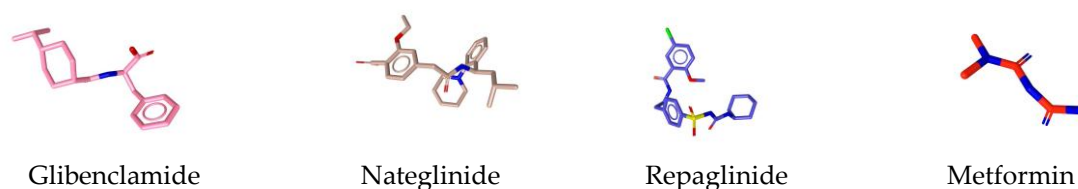

Glibenclamide   Nateglinide   Repaglinide   Metformin

Figure 1. 2D Chemical Structre of Training Set

Pharmacophore Model Generation

Ligand-Based pharmacophore modeling approach was selected to evaluate the potential compound isolated from *M.oleifera* seed by analysis using pharmacophore Fit-Value and screening

based on the chemical features. By using computer software, Ligandscout 4.1 will be used to create the pharmacophore model. LigandScout software efficiently allows rapidly and transparently generation of 2D and 3D pharmacophore of data set. Ligand-Based pharmacophore model was created by alignment of all training set forming a set of model of antidiabetic drug. This model will exhibit all the features from all of training set. The expected chemical features derived from the model using Ligandscout 4.1 software are H-bond acceptors, H-bond donors, hydrophobic regions, aromatic rings, negative ionizable groups and positive ionizable groups.

Validation

Validation process was done by aligning test sets with the pharmacophore model. Pharmacophore Fit-values and chemical features of interactions were obtained when test set and pharmacophore model were aligned and overlap together.

RESULT AND DISCUSSION

Figure 2 shows the pharmacophore model that resulted from the aligning of all training set. From the model created, there are 3 chemical features were obtained which is Hydrogen-Bond Acceptor (HBA), Hydrophobics (Hyp) and Hydrogen-Bond Donor (HBD). Ligand-Based virtual screening were done on the test set that were superimposed and overlapping with the pharmacophore model. This model possessed as anti-diabetic reference and all of the seeds constitutent were fitted into this model to check the similarity exhibiting the anti-diabetic properties based on the reference drug.
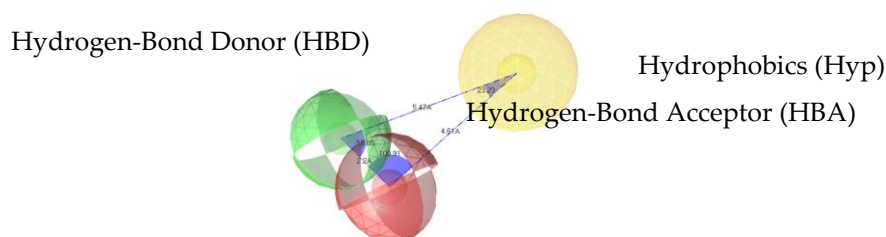

Figure 2. Pharmacophore Model

Figure **3,4,5,6,7,8** and **9** shows the align and interactions of test set with the pharmacophore model. From the Table 1, test set from Figure **3** and **4** ranked among the highest based on it pharmacophore fit-values. All compound possessed same interactions with the pharmacophore model which is (HBA),(HBD) and (H). The only that makes them different in fit values is because the different of interactions between the functional group in each compound. Compound from Figure **3** and **4** show the interactions of features HBA towards the (C-O-C), HBD towards (O-H) and the Hydrophobics towards the (CH$_3$). Compound from Figures **5** are slightly different because the interactions of Hydrophobics are towards the benzene ring (C$_6$H$_6$). As a result, compound from Figure **3** and **4** shows the same fit value (38.20) and compound from Figure **5** (38.09) which is lesser because of the different in interactions. Compound from Figure **6**, **7** and **8** shows the intermediate fit value. Their interactions are mostly same with the functional group OH interacts towards the (HBD) and the benzene ring interacts towards the (Hydrophobics). The least fit value of compound from Figure **9** which is the value is (0.00). This compound does not show any interactions with the pharmacophore model.

Figure 3. 4-(α-L-rhamnopyranosyloxy) benzyl glucosinolate align with the phamacophore model
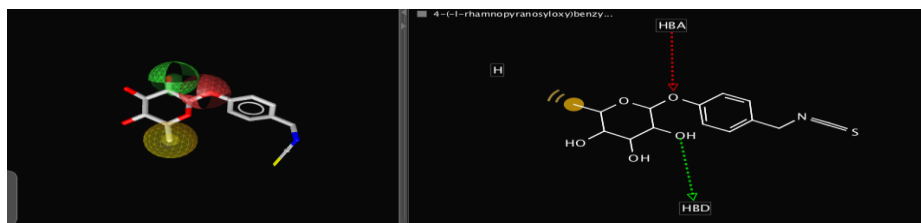

Figure 4. 4-(-l-rhamnopyranosyloxy) benzyl isothiocyanate align with the pharmacophore model

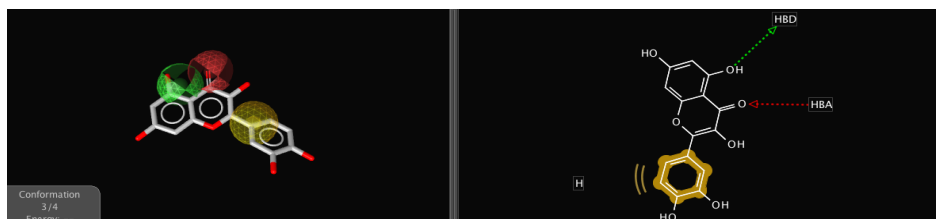**Figure 5.** 4-(4-o-acetyl-a-l-rhamnopyranosyloxy) benzyl isothiocyanate align with the pharmacophore model

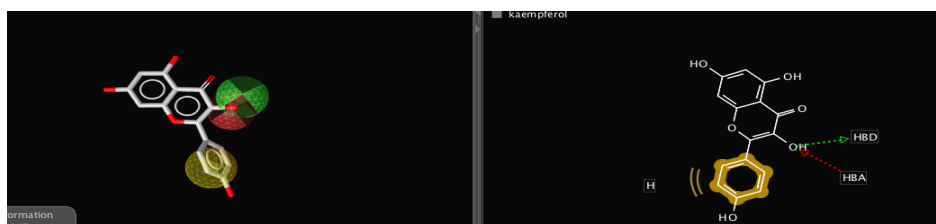
Figure 6. Quecertin align with the pharmacophore model

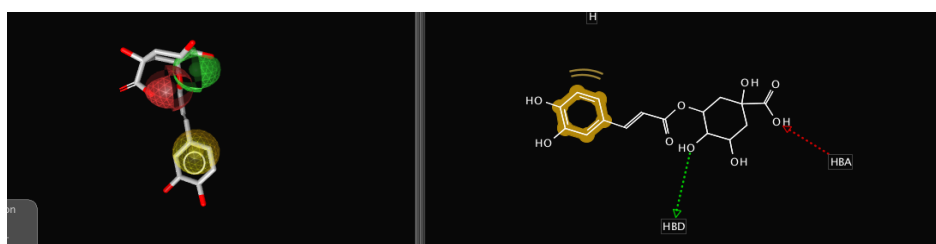**Figure 7.** Kaempferol align with the pharmacophore model

Figure 8. 3-caffeoylquinic align with the pharmacophore mode

Figure 9. Ptygospermin align with the pharmacophore model

Table 1. Summary of Pharmacophore Features And Pharmacophore Fit-Values

Name/Compound	Type	Pharmacophore Features			Pharmacophore Fit-Value
		HBD	HBA	H	
Metformin	Training	C-(NH$_2$)	C=N-H	N-(CH$_3$)	38.46
4-(α-L-rhamnopyranosyloxy) benzyl glucosinolate	Test	C-O-C	C-CH$_3$	C-OH	38.20
4-(-l-rhamnopyranosyloxy)benzyl isothiocyanate	Test	C-O-C	C-CH$_3$	C-OH	38.20
Nateglinide	Training	N-H	C=O	C-CH$_3$	38.16
4-(4¢-o-acetyl-a-l-rhamnopyranosyloxy) benzyl isothiocyanate	Test	C-OH	C-O-C	C$_6$H$_6$	38.09
Glibenclamide	Training	N-H	C=O	C$_6$H$_6$	38.09
Quecertin	Test	C-OH	C=O	C$_6$H$_6$	36.13
Kaempferol	Test	C-OH	C-OH	C$_6$H$_6$	35.98
3-caffeoylquinic	Test	C-OH	C-OH	C$_6$H$_6$	35.82
Ptygospermin	Test	No Interactions			0.00

CONCLUSION

Proposed pharmacophore model had showed one HBD, HBA and Hydropobics interactions. Each chemical constituent have different functional group. From this study, the best constituent which is 4-(α-L-rhamnopyranosyloxy) benzyl glucosinolate and 4-(4-o-acetyl-a-l-rhamnopyranosyloxy) benzyl isothiocyanate show anti diabetic properties. Previous studies had proved that *M.oleifera* seeds shows the best anti-diabtic properties but there no studies that have been made on identifiying which compound from this seed exhibit the anti-diabetic properties. This study also improves the development of new drugs from the natural resource. Further studies on isolation and assay on this compound should be conducted for developing of new sources of diabetic medicine.

TRANSACTIONS ON SCIENCE AND TECHNOLOGY

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