Predicting ADME and Molecular Docking Analysis of Andrographis paniculata and Strobilanthes crispus Chemical Constituents Againts Antidiabetic Molecular Targets

WORD COUNT 4202
TIME SUBMITTED 12-JUN-2020 07:49PM
PAPER ID 60058393

Journal of the Indonesian Chemical Society
J. Idn. Chem. Soc. 2019, 02(2), 106-113 FULL PAPER

Predicting ADME and Molecular Docking Analysis of *Andrographis paniculata* and *Strobilanthes crispus* Chemical Constituens Against Antidiabetic Molecular Targets

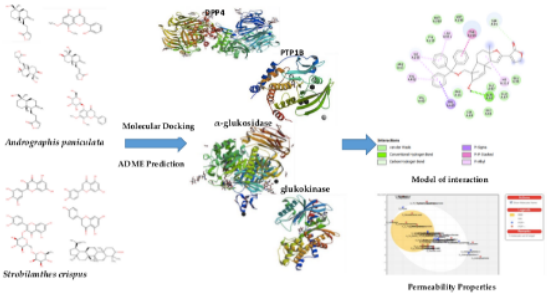
Julaiha, Gunawan P. Widodo and Rina Herowati*

Faculty of Pharmacy, Setia Budi University, Surakarta 57127, Central Java, Indonesia
**Corresponding Authors: rinagunawan53@gmail.com (Tlp. +6281572687689)*

Abstract

Andrographis paniculata and *Strobilanthes crispus* are two medicinal plants from Acanthaceae family, known to have antidiabetic activity. This study aimed to investigate the molecular interaction of *A. paniculata* and *S. crispus* phytochemical constituents with various macromolecular targets of antidiabetic agent through molecular docking. Nineteen *A. paniculata* and twenty *S. crispus* chemical constituents were docked to four macromolecular targets of antidiabetic agent by using AutoDock Vina in PyRx. The results revealed that compounds from *A. paniculata* that have the best binding affinity protein targets was 19-tripenhyl isoandrographolide to glucokinase (-10.4 kcal/mol), Dipeptidyl peptidase 4 (DPP4) (9.3 kcal/mol) and α-glucosidase (-8.8 kcal/mol), and andrographolactone to Protein Tyrosin Phosphatase1B (PTP1B) (-9.5 kcal/mol). Whereas compounds in the *S. crispus* derivatives that have the best binding affinity were stigmasterol to glucokinase (-9.9 kcal/mol), rutin to DPP4 (-9.7 kcal/mol), lupeol to α-glucosidase (-8.8 kcal/mol) and luteolin to PTP1B (-8.8 kcal/mol). The differences between the two plants were due to the differences compounds in each of the plants as well as differences in target proteins. Other than that, profile of absorption, distribution, metabolism, and excretion (ADME) predictions are very important because they play a critical role in assessing the quality of potential clinical candidates for a new drug. Compounds with best binding energy that showed good ADME properties were andrographolactone, stigmasterol, lupeol and luteolin. Deoxyandrographolide was predicted to have the best ADME properties, however its affinity to target proteins was lower than native ligands.

Compounds from *A. paniculata* and *S. crispus* derivate showed the best binding affinity protein targets based on molecular docking. Compounds with best binding energy from good ADME properties were andrographolactone, stigmasterol, lupeol and luteolin. Compound deoxyandrographolide was predicted to have the best ADME properties. However, its affinity to target proteins was lower than native ligands.



Article History:
Received: 1 December 2019, Revised 21 December 2019, Accepted 21 December 2019, Available Online 30 December 2019
http://dx.doi.org/10.34311/jics.2019.02.2.106

Keywords: Antidiabetic, *Andrographis paniculata*, Molecular docking, *Strobilanthes crispus*, Swiss ADME

Acknowledgment
This research was supported by the funding from Ministry of Research, Technology & Higher Education for PDUPT funding year 2019, and fully acknowledged.

Introduction

Diabetes mellitus (DM) is a chronic disease that arises when the pancreas is unable to produce enough insulin or when the body cannot use the insulin being produced effectively. DM is classified into four types: type I DM, type II DM, gestational DM and other types of DM with the most common being type-II DM. This type of DM generally occurs from either reduced body cell response to insulin causing high blood glucose level or β-pancreatic cell is no longer able to produce enough insulin in order to maintain normal glucose level [1].

The prevalence of DM patients from year to year continues to increase, especially in developing countries such as Southeast Asia, for example Indonesia. The International Diabetes Federation states that around 415 million people in the world suffer from DM in 2015 and are expected to increase to 642 million cases by 2040 [2]. Increased prevalence of DM can be reduced by simple methods such as diet and regular exercise. In patients who have been exposed to type II DM, they still require conventional therapy, such as oral antidiabetic drugs and insulin injection. Based on its mechanism of action oral antidiabetic drugs are classified into several groups, namely sulfonylurea, biguanide, thiazolidinedione, α-glucosidase inhibitors and inhibitors of glucagon-like peptide 1. However, long-term use of conventional medicines can cause serious side effects for users, such as hypoglycemia, liver toxicity, weight gain, physconia (abdominal enlargement) and lactic acidosis. So, to overcome these problems, herbal medicine is also an option for patients, due to the lack of side effects obtained in herbal medicine and relatively low cost [3]. Some medicinal plants that have been used empirically as efficacious as antidiabetic are *Andrographis paniculata* and *Strobilanthes crispus* (Acanthaceae family).

A. paniculata extract and its isolated compound andrographolide decrease the blood glucose, triglyceride and LDL (Low Density Lipoprotein) level in high fat fructose fed induced diabetic in rats [4,5]. The ethanolic and hot water extract of *A. paniculata* also successfully reduces the blood sugar level in alloxan-induced diabetic [6]. Aqueous extract of *A. paniculata* leaves stimulates glucose uptake in L-6 skeletal muscle cells also show α-amylase and α-glucosidase inhibitory effect [7,8]. The possible mechanism of this hypoglycemic effect may be through controlling glucose uptake and oxidation, restoration of insulin signaling molecules in the liver and decreasing the serum lipid profile [9].

S. crispus leaves extract has been known to have antihyperglycemic and hypolipidemic effects. Aqueous extract of *S. crispus* tea displayed antihyperglycemic activities in hyperglycemic animal models by reduced blood glucose levels and improved lipid profile [10,11]. *S. crispus* juice showed great potential in healing wounds especially for diabetic patients [12]. However, the chemical constituents which reduce the blood glucose levels in both plants are still not well understood.

DM is influenced by several target proteins one of which is Protein Tyrosine Phosphatase1B (PTP1B) as a negative regulator of the insulin signaling pathway considered a potential therapeutic target, especially for type II DM. This is due to the high expression in PTP1B which can induce insulin resistance [13]. Glucagon increases blood sugar levels and Dipeptidyl peptidase 4 (DPP4) inhibitors can reduce glucagon and blood glucose levels by increasing insulin secretion [14]. The conditions of glucokinase deficiency can cause type II DM at an early age. The role of glucokinase as an activator increases liver glucose uptake and pancreatic insulin secretion, so this enzyme is an ideal target for DM therapy [15]. α-glucosidase is a member of the glycoside hydrolase enzyme that breaks the glycosidic bond from the substrate. This enzyme induces glycogen and increases carbohydrate absorption. The inhibition of this enzyme is quite efficient for the treatment of type II DM [13].

However, there is no introduction of targets and mechanisms of active compounds of *A. paniculata* and *S. crispus* that can facilitate optimization of activities. If the work target of a compound in providing a pharmacological effect is known, further optimization of targeted drug activity can be carried out based on the drug-target interaction pattern [16]. The challenge in determining the target of an active compound is a lengthy testing process and costly because it is required to test one compound into many target proteins. One of the approaches to solving the problem is through the silico studies with molecular docking.

With molecular docking, the strongest bonds between compounds and target proteins through various scoring functions can be calculated. Scoring results have a correlation with the ligand affinity for the target protein, which can provide clues about the mechanism of action of the compounds under tests. This is a way to explore molecular interactions such as drug candidates with a target protein that binds to each other. The interaction of ligand complexes with

proteins was identified using the computational method of the docking program and bond affinity evaluated using binding energy simulations [17]. Successful disclosure of antidiabetic agent has been contributed by computer-based drug design approach. Molecular docking and ADME analysis continue as being an extraordinary guarantee in the field of computer-based drug design. This method has advantages such as in terms of shorter time and cheaper cost compared to the in vitro test [18].

Experimental Section

Materials

Hardware that we used in this study was ViewSonic computer with Processor Intel® Core™ i7 3770 CPU @ 3.40GHz, RAM 8.00 Giga Byte Dual-Channel DDR3 @ 665MHz. Installed software that we used were Marvin Sketch (ChemAxon), PyRx 0.8 (Sargis Dallakyan, The Scripps Research Institute, Amerika), VegaZZ, Discovery Studio Visualizer v16.1.0.15350 (Dassault Systems Biovia Corp 2015), PyMOL Educational (Schrodinger) and AutoDock 4.0 (The Scripps Research Institute, Amerika).

Preparation of protein

Protein structure preparation was done using AutoDock Tools. Water molecules and all non-standard residues were removed from initial structure. Then, all missing hydrogens and kollman charges were added to the system, the prepared protein receptor was then saved as pdbqt format and directly placed into PyRx's workspace folders.

Preparation of ligand

Nineteen *A. paniculata* and twenty *S. crispus* chemical constituents were reprocessed from Pubchem databases. Ligand preparation for molecular docking was done using Vega ZZ. In this study, we used pdb coordinate with all hydrogens output format. Then the charge is repaired by adding partial gasteiger charges and then force autodock. The compound is minimized by 10.000 steps to obtain the lowest molecular energy with the most stable conformation and saved as pdb format. Then the structures of the compounds were opened on PyRx, by clicking Load Molecule and make ligand.

Docking Validation

Docking validation was performed for all proteins target docking simulation. Native ligand was extracted from pdb complex then prepared in same manner as test ligand using PyRx. Prepared native ligand was then 'redocked' to its receptor. Grid center was placed approximate to center of the ligand, covering all the binding site residues. Validation conformed to be valid if the superimposed RMSD of redocked and crystallography ligand was less than 2 Å.

Molecular docking simulation

Nineteen *A. paniculata* and twenty *S. crispus* chemical constituents were docked to four proteins target using autodock vina in PyRx to study their binding energy and intermolecular interaction. This reverse docking simulation used same grid size, grid center, and exhaustiveness number as was done in validation procedure.

Visualization

PyMOL, Discovery Studio Visualizer were used to visualize the docking result. PyMOL was used for RMSD calculation. Discovery Studio Visualizer was used to analyze intermolecular interaction in two-dimensional space in three-dimensional space.

Predicting ADME

Predict ADME was used to Swiss ADME (www.swissadme.ch) by enter a list SMILES of chemical constituents and click run. Parameters used include Lipinski Rules, bioavaibility, Blood Brain Barrier (BBB) permeant, gastrointestinal absorption, lipophilicity parameter (Log-P), P-gp substrate and inhibitor metabolism enzyme.

Results and Discussion

Docking validation result

Figure 1 presents the structures of macromolecular targets obtained from protein data bank, *i.e.* DPP4 (pdb ID 2QOE), glucokinase (pdb ID 4RCH), α-glucosidase (pdb ID 5NN8) and PTP1B (pdb ID 5T19). Validation method used was done by PyRx. Gridbox settings to determine which ligand bonded space to be docked is shown in Table 1. Docking method validation was done by calculating the deviation of redocking result, which was subsequently compared to 3D crystallographic ligand conformation to the receptor, expressed by the value of Root Mean Square Deviation (RMSD). The

Table 1. Gridbox settings.

Macromolecule	Type	Grid Center (Å)			Grid Size (Å)	Exhaustiviness
		X	Y	Z	X, Y, Z	
PTP1B	Inhibitor	-1.9483	63.0579	1.4067		
α-glucosidase	Inhibitor	-13.9247	-38.0933	95.4026		
Glucokinase	Activator	40.3355	16.1209	64.2028	25.0000	8
4(DPP4)	Inhibitor	41.2666	50.0085	36.6134		

Table 2. $\Delta G_{binding}$ values.

	Test ligand	$\Delta G_{binding}$ (kcal/mol)			
		DPP4	PTP1B	Glucokinase	α-glucosidase
		2QOE	5T19	4RCH	5NN8
	Native ligand	-8.28 ± 0.23	-9.60 ± 1.00	-8.30 ± 0.08	-8.43 ± 0.05
	Positive control	-8.88 ± 0.38 Sitagliptin	-8.60 ± 0.00 C0A	-8.10 ± 0.00 *Cyclopentadeca -4.12-dione*	-
	***Andrographis paniculata* Nees**				
1.	19-Triphenyl isoandrographolide	**-9.33 ± 0.05**	-8.20 ± 0.00	**-10.38 ± 0.05**	**-8.75 ± 0.06**
2.	Andrographiside	**-9.00 ± 0.00**		**-9.10 ± 0.00**	-7.83 ± 0.10
3.	8.17-Epoxy-14-Deoxyandrographolide	-8.78 ± 0.05			-8.03 ± 0.05
4.	Neoandrographolide	-8.60 ± 0.00	-8.30 ± 0.00		**-8.53 ± 0.15**
5.	Deoxyandrographolide		-8.75 ± 0.06		-7.65 ± 0.06
6.	Andrographolactone		-9.45 ± 0.06	**-9.30 ± 0.00**	-7.65 ± 0.08
7.	Isoandrographolide			**-8.88 ± 0.05**	
8.	Apigenin	-8.60 ± 0.00	-8.50 ± 0.00	**-8.90 ± 0.00**	
	Strobilanthes crispus L.				
1.	Rutin	**-9.70 ± 0.00**			-8.00 ± 0.00
2.	Myricetin	**-9.20 ± 0.00**	-8.60 ± 0.80		
3.	Luteolin	-8.70 ± 0.00	-8.83 ± 0.05	**-8.90 ± 0.00**	
4.	Kaempferol			**-9.03 ± 0.05**	
5.	Stigmasterol	-8.28 ± 0.05	-8.30 ± 0.14	**-9.88 ± 0.05**	-8.40 ± 0.12
6.	Beta-sitosterol		-8.25 ± 0.10	**-9.50 ± 0.00**	-8.13 ± 0.05
7.	Verbascoside	-8.43 ± 0.15	-8.38 ± 0.32	**-9.80 ± 0.00**	**-8.60 ± 0.27**
8.	Lupeol				**-8.78 ± 0.05**

Note: Bolded fonts indicated the values were lowerer than native ligand or positive control

values of RMSD from α-glucosidase, PTP1B, glucokinase, and DPP4 proteins were 1.594 Å, 1.365 Å, 1.317 Å, and 1.626 Å, respectively. Thus, the docking method setting was valid (RMSD < 2 Å). Figure 2 shows the overlay of redocked and X-ray crystallographic conformations of the native ligand for each target protein.

Docking result analysis

The aim of molecular docking is to predict the structure of a ligand within the constraints of a receptor binding site and to correctly estimate the strength of binding. The result of docking analysis of 16 best compounds in two plants is described in Table 2.

The binding free energy (ΔG binding) represents the affinity between ligand-receptors. ΔG binding is the result of the sum of the total intermolecular

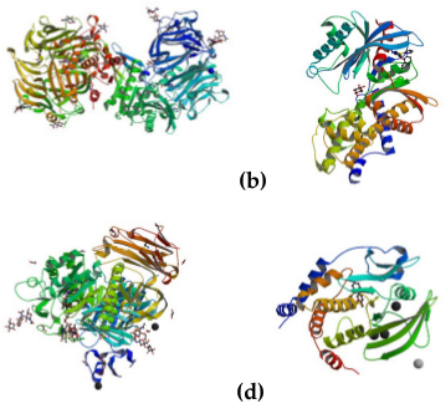


Figure 1. (a) Structures of DPP4, (b) glucokinase, (c) α-glucosidase, and (d) PTP1B.

Table 3. Interaction between ligands and protein.

α-glucosidase (5NN8)	**Amino acid residues involved in interaction of ligand-protein**
Native ligand	Asp282, Met519, Trp481, Arg600, Phe649, Asp616, Trp613, Trp376, Asp518, His674, Asp404, Ile441
19-Triphenyl isoandrographolide	Gly651, **Trp376**, Leu650, **Met519**, Ala284, **Trp481**, Leu283, Ala555, Arg281, **Asp616**, Phe525, **Phe649,** Ser676, Leu678, Leu677, **Arg600**, Asp282
PTP1B (5T19)	**Amino acid residues involved in interaction of ligand-protein**
Native ligand	Asp48, Val49, Tyr46, Gln262, Phe182, Gly220, Arg221, Ser216, Ala217
Andrographolactone	Lys120, Gln262, Asp181, **Gln266, Gly220,** Cys215, **Phe182, Gly218, Ile219, Try46, Val49, Ala217, Ser216, Arg221**
Glucokinase (4RCH)	**Amino acid residues involved in interaction of ligand-protein**
Native Ligand	Try214, Met235, Gln98, Met210, Leu451, Ile211, Val455, Arg63, Val452
19-Triphenyl isoandrographolide	Met210, **Met235**, Tyr214, **Leu451**, Tyr215, Ile211, **Arg63**, Val452, Val62, Val455, Pro66, Ser69, Gly68, Gly97, Glu67, His218, Glu96, Ser64, **Gln98**
DPP4 (2QOE)	**Amino acid residues involved in interaction of ligand-protein**
Native ligand	Tyr585, Tyr5477, His740, Tyr662, Tyr666, Glu205, Asn710, , Arg125, Glu206, Phe357
Rutin	**Glu205**, Phe357, **Tyr666**, **Tyr662**, **Glu206**, Ser209, Tyr547, Ser552, Tyr631, Ser630, Val711, Gln553, Lys554, **Arg125**, **Asn710**, **His740**

Note: Bolded fonts indicated the amino acid residues involved in interaction same as those of native ligand.

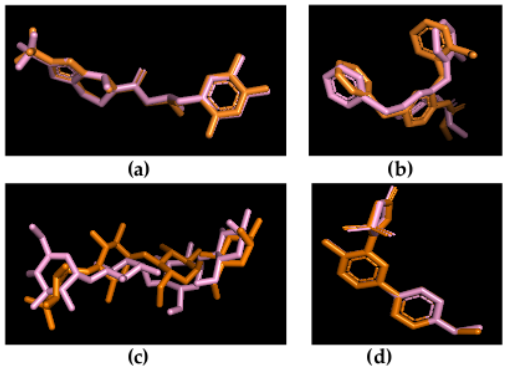


Figure 2. Docking validation result of (a) DPP4 (RMSD 0.172 Å), (b) glucokinase (RMSD 0.978 Å), (c) α-glucosidase (RMSD 1.594 Å), and (d) PTP1B (RMSD 0.114 Å. Pink: native ligand, orange: redocking result.

energy, total internal energy and torsional free energy minus the energy of the unbound system [23]. The conformational with the lowest binding energy value indicates the best interaction pose. Table 2 shows the binding energy values of chemical constituents in A. *paniculata* and S. *crispus*. 19-Triphenyl isoandrographolide (from A. paniculate) showed best affinity to glucokinase, DPP4 and α-glukosidase. Whereas rutin (from S. *crispus*) exhibited best affinity to DPP4.

Docking result visualization

The conformation suitability of the test ligand was compared to the native ligand to confirm the binding free energy value since an active ligand must bind to the particular amino acid residue on the binding site to produce inhibition or induction activities. The amino acid residues that were involved are shown in Table 2. 19-Triphenyl isoandrographolide interacted with 6 amino acid residues of α-glucosid se that were the same as native ligands, *i.e.* Trp376, Met519, Trp481, Asp616, Phe649, Arg600 (Table 3 and Figure 3).

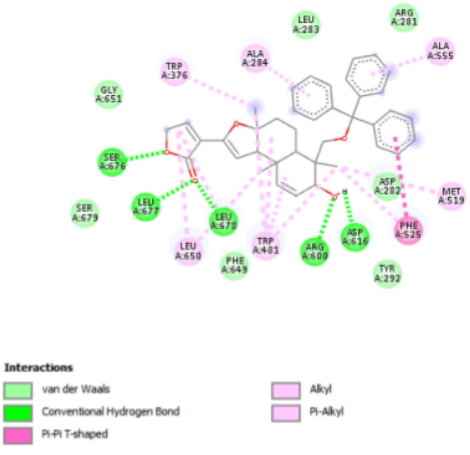


Figure 3. Model interaction of 19-Triphenyl isoandrographolide to α-glucosidase.

Table 4. Lipinski's rule results.

Ligan	Molecular Weight	*H-Bond acceptors*	*H-Bond donors*	Log P	*Druglikeness*
A. paniculata Nees					
19-Triphenyl isoandrographolide	592.72	5	1	6.25	Rejected
Deoxyandrographolide	334.45	4	2	3.12	Accepted
Andrographolactone	296.4	2	0	4.54	Accepted
S. crispus L.					
Rutin	610.52	16	10	-1.51	Rejected
Myricetin	318.24	8	6	0.79	Accepted
Luteolin	286.24	6	4	1.73	Accepted
Verbascoside	624.59	15	9	-0.6	Rejected
Stigmasterol	412.69	5	1	6.98	Accepted
Lupeol	426.72	1	1	7.28	Accepted

Table 5. Pharmacokinetic values of the chemical compounds.

Compounds	GI Absorpsion	BBB Permeant	Pgp Substrate	Inhibitor					Bioavailability Score
				CYP 3A4	CYP A12	CYP2 C19	CYP 2C9	CYP D6	
A. paniculata Nees									
19-Triphenyl isoandrographolide	Low	No	No	No	No	No	No	Yes	0.17
deoxyandrographolide	High	Yes	Yes	No	No	No	No	No	0.55
Andrographolactone	High	Yes	No	No	No	No	Yes	No	0.55
S. crispus L.									
Rutin	Low	No	Yes	No	No	No	No	No	0.17
Myricetin	Low	No	No	Yes	Yes	No	No	No	0.55
Luteolin	High	No	No	Yes	Yes	No	No	Yes	0.55
Verbascoside	Low	No	Yes	No	No	No	No	No	0.17
Stigmasterol	Low	No	No	No	No	No	Yes	No	0.55
Lupeol	Low	No	No	No	Yes	No	No	Yes	0.55

Rutin interacted with 7 amino acid residues of DPP4 that were the same as native ligands, i.e. Glu205, Tyr666, Tyr662, Glu206, Arg125, Asn710, His740 (Figure 4).

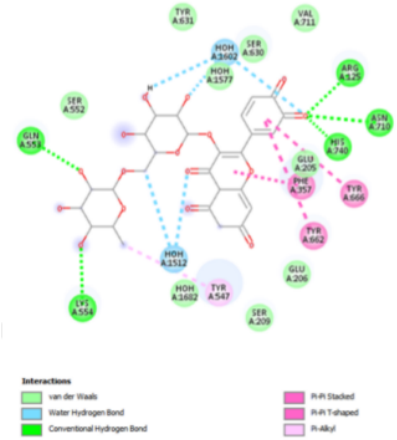


Figure 4. Model interaction of rutin to DPP4.

Andrographolactone interacted with 5 amino acid residues of PTP1B that were the same as native ligands, i.e. Gln266, Gly220, Phe182, Gly218, Ile219, Try46, Val49, Ala217, Ser216, Arg221. 19-Triphenyl isoandrographolide also interacted with 4 amino acid residues of glucokinase that were the same as native ligands, *i.e.* Met235, Leu451, Arg63, Gln98. This interaction were similar to the model of interaction of native ligands, so andrographolactone and 19-Triphenyl isoandrographolide were predicted to have similar effect to the protein target.

ADME Prediction

The result of SwissADME prediction results are shown in **Table 4** (Lipinski's rule) and **Table 5** (Pharmacokinetic value). The Lipinski result showed that 19-Triphenyl isoandrographolide violate lipinski's rule by having Log P more than 5 and molecular weight (Mw) exceeded 500. Rutin and verbascoside have Mw more than 500. This could result in poor water solubility which can hindrance

oral bioavailability. Based on the results presented in **Table 5,** these compounds were predicted to having low gastrointestinal absorption and low bioavailability. This indicated that the high doses of this compounds are needed to achieve suitable concentration in plasma and give potential pharmacological effect.

Furthermore, rutin and verbascoside were predicted to be PGP substrate and undergo efflux by PGP which reduced its absorption thus lower bioavailability. However, for drug that intended to be α-glucosidase inhibitor, oral bioavailability must be avoided since it can reduce its effectiveness and give rise to unwanted side effects Boiled egg visualization result showed that several compounds exhibited potential to pass through blood brain barrier (located in yellow part) (Figure 5). For the treatment of diabetes mellitus blood brain barrier penetration is undesirable because it can cause side effects related to the central nervous system, so compounds that are able to penetrate the BBB are not preferred.

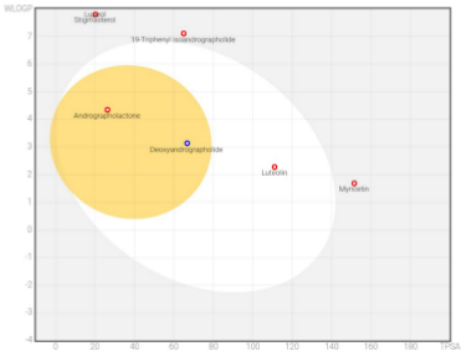


Figure 5. Boiled egg visualization.

Conclusions

Compounds from *A. paniculata* that have the best binding affinity protein targets was 19-tripenhyl isoandrographolide to glucokinase (-10.4 kcal/mol), Dipeptidyl peptidase 4 (DPP4) (9.3 kcal/mol) and α-glucosidase (-8.8 kcal/mol), and andrographolactone to Protein Tyrosin Phosphatase1B (PTP1B) (-9.5 kcal/mol). Whereas compounds in the *S. crispus* derivate that have the best binding affinity were stigmasterol to glucokinase (-9.9 kcal/mol), rutin to DPP4 (-9.7 kcal/mol), lupeol to α-glucosidase (-8.8 kcal/mol) and luteolin to PTP1B (-8.8 kcal/mol). This difference was due to differences in the compounds contained in each plant and differences in target proteins. Compounds with best binding energy that showed good ADME properties were andrographolactone, stigmasterol, lupeol and luteolin, Compound deoxyandrographolide was predicted to have the best ADME properties, however its affinity to target proteins was lower than native ligands.

References

[1] International Diabetes Federation. IDF Diabetes Atlas. *International Diabetes Federation Seven Edition*. 2015.

[2] N. Kerru, A. Sigh-Pillay, P. Awolade, P. Sigh, Current Anti-Diabetic Agents and Their Molecular Targets A Review, *Eur. J. Medicin. Chem.*, **2018**, 152, 436-488, DOI: 10.1016/j.ejmech.2018.04.061.

[3] R. J. Marles, N. R. Fransworth, Antidiabetic Plants and their Active Constituens, *Phytomedicine*, **1995**, 155, 2, 137-189, DOI: 10.1016/S0944-7113(11)80059-0.

[4] A. E. Nugroho, M. Andrie, N. K., Warditiani, E. Siswanto, S. Pramono, E. Lukitaningsih, Antidiabetic and Antihiperlipidemic Effect of *Andrographis paniculata* (Burm. f.) Nees and Andrographolide in High-fructose-fat-fed Rats. *Indian J. Pharmacol*., **2012**, 44(3), 377-381, DOI: 10.4103/0253-7613.96343.

[5] A. E. Nugroho, N. Y. Lindawati, K. Herlyanti, L. Widyastuti, and S. Pramono, Antidiabetic Effect of a Combination of Andrographolide Enriched Extract of *Andrographis paniculata* (Burm f.) and Asiaticoside Enriched Extract of *Centella asiatia L.* in High Fructose Fat Fed Rats, *Indian. J. Exp. Biol*., **2013**, 51, 1101-1108.

[6] A. Chowdhury, and S. K. Biswas, Comparative Study of Hypoglicemic Effect of Ethanolic and Hot Water Extracts of *Andrographis paniculata* in Alloxan Induced Rat, *Intern. J. Pharma. Sci. Res*., **2012**, 3(3), 771-773, DOI: 10.13040/IJPSR.0975-8232.3(3).815-17.

[7] A. W. Augustine, A. Narashimhan, M. Vishwanathan, and B. Karundevi, Evaluation of Antidiabetic Property of *Andrographis paniculata* Powder in High Fat and Sucrose-induced Type-2 Diabetic Adult Male Rat, *Asian Pac. J. Trop. Dis*., **2014**, 4(1), S140-S147, DOI: 10.1016/S2222-1808(14)60429-1.

[8] N. Prem Kumar, S. K. Vijayan, J. N. Dharsana, K. X. Seena, and A. K. Anjana, Comparing the Effect of Antidiabetic Activity of *Andrographis paniculata, Salacia reticulata* and *Ocimum sanctum* by Invitro Screening, *Asian J. Pharma. Clin. Res*., **2012**, 5(4), 146-149.

[9] S. M. Rammohan, A. Zaini, and S. Amirin, In

Vitro α-Glucosidase and α-Amylase Inhibitory Effects of *Andrographis paniculata* Extract and Andrographolactone, *Acta Biochimica Polonica*, **2008**, 55(2), 391-398.

[10] B. M. F. Abu, A. H. Teg, A. Rahmat, and F. Osman, Effects of *Strobilanthes crispus* Tea Aqueous Extracts on Glucose and Lipid Profile in Normal and Streptozotocin-induced Hyperglycemic Rat., *Plant Foods Human Nutrion*, **2006**, 61, 7-12.

[11] A. B. Mohd Fadzelly, and R. O. F. Asmah, Effects of *Strobilantes crispus* Tea Aqueous Extracts on Glucose and Lipid Profile in Normal and Streptozotocin-induced Hyperglycemic Rats, *Plant Foods Human Nutrition*, **2010**, 1(2), 7-12, DOI: 10.1007/s11130-006-0002-z.

[12] N. A. Norfarizan-Hannon, R. Asmah, M. Y. Rokiah, Fauziah, and H. Faridah, Effects of *Strobilanthes crispus* Juice on Wound Healing and Antioxidant Enzymes in Normal and Streptozotocin-induced Diabetic Rats, *J. Bio. Sci*., **2009**, 9 (7), 662-668, DOI: 10.3923/jbs.2009.662.668.

[13] H. Sun, D. Wang, X. Song, Y. Zhang, W. Ding, X. Peng, X. Zhang, Y. Li, Y. Ma, R. Wang, and P. Yu, Natural Phenylcalconaringenins and Phenylnaringenins as Antidiabetic Agents; α-Glucosidase an α-Amilase Inhibition an In vivo Anthyperglycemic and Anthyperlipidemic Effects, *J.Agric. Food Chem*., **2017**, 65, 1574-1581, DOI: 10.1021/acs.jafc.6b05445.

[14] D. J. Drucker, Enhancing Incretin Action for the Treatment of Type 2 Diabetes, *Diabetes Care*., ***2003***, 26(10), 2929-40, DOI: 10.2337/diacare.26.10.2929.

[15] A. S. Al-Zubari, and E. E. M. Eid, Molecular Targets in Development of Antidiabetic Drugs, *Inter. J. Pharmacol*., **2010**, 6(6), 784-795, DOI: 10.3923/ijp.2010.784.795.

[16] D. W. Young, A. Bender, J. Hoyt, E. McWhinnie, G. W. Chirn, C. Y. Tao, J. A. Tallarico, M. Labow, J. L. Jenkins, T. J. Mitchison, and Y. Feng, Integrating High-content Screening and Ligand-Target Prediction to Identify Mechanism of Action, *Nature Chem. Bio*., **2007**, 4, 59-68, DOI: 10.1038/nchembio.2007.53.

[17] Z. Y. Meng, H. X. Zhang, Meizai, and M. Cui, Molecular Docking: A Powerfull Approach for Structure-based Drug Discovery, *Curr. Comput. Aided Drug Des*., **2011**, 7, 146-157, DOI: 10.2174/157340911795677602.

[18] S. Cosconati, S. Forli, A. L. Perryman, R. Harris, D. S. Goodsell, and A. J. Olson, Virtual Screening with AutoDock: Theory and Practice, *Expert. Opin. Drug Discovery*, **2011**, 5, 597–607, DOI: 10.1517/17460441.2010.484460.

[19] O. Rabal, P. Fernando, V. Helena, M. S. Mario, H. Sandra, and O. Julen, In silico Aptamer Docking Studies: from a Retrospective Validation to a Prospective Case Study-TIM3 Aptamers Binding, *Molecular Therapy—Nucleic Acids*, **2016**, 5, e376, DOI: 10.1038/mtna.2016.84.

[20] M. Kontoyianni, L. M. McClellan, and G. S. Sokol, Evaluation of Docking Performance: Comparative Data on Docking Algorithms, *J. Med. Chem*., **2004**, 47(3), 558-65.

Predicting ADME and Molecular Docking Analysis of Andrographis paniculata and Strobilanthes crispus Chemical Constituents Againts Antidiabetic Molecular Targets

ORIGINALITY REPORT

11%

SIMILARITY INDEX

PRIMARY SOURCES

1	globalresearchonline.net Internet	92 words — 3%
2	www.imedpub.com Internet	31 words — 1%
3	onlinelibrary.wiley.com Internet	28 words — 1%
4	repository.setiabudi.ac.id Internet	26 words — 1%
5	diaclin.co.uk Internet	22 words — 1%
6	scialert.net Internet	21 words — 1%
7	www.omicsonline.org Internet	18 words — 1%
8	Heli Siti Halimatul Munawaroh, Gun Gun Gumilar, Fina Nurjanah, Galuh Yuliani et al. "In-vitro molecular docking analysis of microalgae extracted phycocyanin as an anti-diabetic candidate", Biochemical Engineering Journal, 2020 Crossref	17 words — < 1%
9	www.pubmedcentral.nih.gov Internet	16 words — < 1%

10	A. B. Mohd Fadzelly, R. Asmah, O. Fauziah. "Effects of Strobilanthes crispus Tea Aqueous Extracts on Glucose and Lipid Profile in Normal and Streptozotocin-Induced Hyperglycemic Rats", Plant Foods for Human Nutrition, 2006 Crossref	15 words — < 1%
11	"Minutes of the 44th Genral Assembly of the European Association for the Study of Diabetes", Diabetologia, 2009 Crossref	15 words — < 1%
12	Eric Yuk Fai Wan, Daniel Yee Tak Fong, Colman Siu Cheung Fung, Esther Yee Tak Yu et al. "Classification Rule for 5-year Cardiovascular Diseases Risk using decision tree in Primary Care Chinese Patients with Type 2 Diabetes Mellitus", Scientific Reports, 2017 Crossref	14 words — < 1%
13	www.jove.com Internet	12 words — < 1%
14	craftblock.me Internet	11 words — < 1%
15	linknovate.com Internet	10 words — < 1%
16	Xu, Feifei, Yan. Ding, Yingying Guo, Baoyue Liu, Zinong Kou, Wei Xiao, and Jingbo Zhu. "Anti-osteoporosis effect of Epimedium via an estrogen-like mechanism based on a system-level approach", Journal of Ethnopharmacology, 2016. Crossref	9 words — < 1%
17	Jianzhong Zhu, Bin Zhang, Chinping Tan, Qiang Huang. " α-Glucosidase inhibitors: consistency of docking data with inhibitory data and inhibitory effect prediction of quercetin derivatives ", Food & Function, 2019 Crossref	9 words — < 1%

18	worldwidescience.org Internet	9 words — < 1%
19	Miao Liu, Jian Luo, Jun Zhou, Xiaomin Zhu. "Intervention effect of neuromuscular electrical stimulation on ICU acquired weakness: A meta-analysis", International Journal of Nursing Sciences, 2020 Crossref	7 words — < 1%
20	Hanan S El-Abhar, Mona F Schaalan. "Phytotherapy in diabetes: Review on potential mechanistic perspectives", World Journal of Diabetes, 2014 Crossref	7 words — < 1%
21	G. Reshmi, M. Pillai. "In Silico Screening of Novel Inhibitors for HPV: A Rational Structure Based Approach (Docking Versus Pharmacophore Model Generation)", Letters in Drug Design & Discovery, 2009 Crossref	6 words — < 1%
22	"Translational Bioinformatics and Its Application", Springer Science and Business Media LLC, 2017 Crossref	6 words — < 1%

EXCLUDE QUOTES	OFF	EXCLUDE MATCHES	OFF
EXCLUDE BIBLIOGRAPHY	ON		