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Biochemoinformatics Study of Chemical Constituents of *Apium graveolens*, *Aloe vera*, and *Nigella sativa* as Antidiabetic Herbal

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ABSTRACT

Background: Celery (*Apium graveolens*), *Aloe vera*, and black cumin (*Nigella sativa*) are reported to have antidiabetic activity from various studies. The present study aimed to predict the active constituents of *A. graveolens*, *A. vera*, and *N. sativa* that able to interact to macromolecular targets of the antidiabetic agent, i.e. dipeptidyl-peptidase 4 enzyme (DPP4), protein tyrosine phosphatase-1B (PTP1B), glucokinase, as well as α-glucosides through molecular docking analysis, and predict their pharmacokinetic profiles.

Methods: The chemical structures of each plant (from KNApSAcK webserver) had undergone molecular docking simulation using Autodock Vina in PyRx. ADME prediction was conducted by using SwissADME webserver.

Results: The results showed that apiin (*A. graveolens*), rutin (*A. vera*), and quercetin 3-glucosyl-(1→2)-galactosyl-(1→2)-glucoside (*N. sativa*) had the best interaction to DPP4. While 4,8,5'-Trimethylpsoralen (*A. graveolens*), 8-C-Glucosyl-(2'-O-cinnamoyl)-7-O-methylaloediol A (*A. vera*), and nigellidine 4-O-sulfite (*N. sativa*) had the best interaction to PTP1B. Cyanidin 3-[6-(6-p-coumarylglucosyl)-2-xylosylgalactoside] (*A. graveolens*), isoaloeresin D (*A. vera*), and nigellidine 4-O-sulfite (*N. sativa*) had the best interaction to glucokinase. Luteolin (*A. graveolens*), aloeresin E (*Aloe vera*), and quercetin 3-glucosyl-(1→2)-galactosyl-(1→2)-glucoside (*N. sativa*) had the best interaction to α-glucosidase. Additionally, nigellidine 4-O-sulfite and 4,8,5'-trimethylpsoralen were predicted to have good bioavailability score on SwissADME.

Conclusions: *A. graveolens*, *A. vera*, and *N. sativa* contains chemical constituents those were predicted to havo good interaction to molecular target of the antidiabetics therapy, i.e. DPP4, PTP1B, glucokinase, and α-glucosides.

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INTRODUCTION

Diabetes mellitus (DM) has become a major disease that affected at least 415 million people in 2015 and is projected to increase by 2045 to 693 million people (IDF, 2021). The oral drug therapy for DM is still limited and the existing drug possess various side effect (Chaudhury *et al*, 2017; Spiller & Sawyer, 20016). Thus, researchers are keeping explore new antidiabetic drug ether from synthetic based and from medicinal plants (Garg *et al*, 2018; Harvey, 2010; Butler *et al*, 2014). Drugs from medicinal plants are more preferred these days since they are believed to be safe with have no or little side effects.

Studies showed that celery (*Apium graveolens*), *Aloe vera*, and black cumin (*Nigella sativa*) have antidiabetic properties (Bunyapraphatsara *et al*, 1996; Yusni *et al*, 2018; Benhaddou-Andaloussi *et al*, 2008; Widodo *et al*, 2016). However, developing drug medical plants are very challenging because of the diversity of chemical constituents from these plants. Drug developing required a single compound to study its safety, activity, and pharmacokinetics. This makes lead finding from medicinal plant becomes difficult and expensive since a bioactive compound must be isolated from a medicinal plant.

In the era of big data and the completion of the human genome enable utilization of computer prediction model for new drug discovery. This can reduce costs and time to discover a new drug including from natural sources. Based on the knowledge of chemical compounds contained in a medicinal plant, molecular docking analysis can be conducted to elucidate the interaction of the compound with the target molecules. Some target molecules related to DM molecules are α-glucosidase, glucokinase, dipeptidyl-peptidase 4 (DPP4), and protein tyrosine phosphatase-1B (PTP1B) (Al-Zubairi & Eid, 2010). α-glucosidase is a member of the glycoside hydrolase enzyme that cuts the glycosidic bond of carbohydrate leads the elevation of blood glucose level (Patil, 2015). Glucokinase is an enzyme that serves to phosphorylate glucose, the deficiency of this enzyme can cause type 2 DM at an early age (Al- Zubairi & Eid, 2010). DPP-4 is an enzyme that hydrolyses Glucagon-Like Peptide-1 (GLP-1) so that GLP-1 becomes inactive form. GLP-1 plays a role in body metabolism, including insulin secretion, increased β cell mass, glucagon secretion, and reduced gastric discharge (Ekayanti *et al*, 2018). The high expression of PTP1B affects the activity of the substrate of protein tyrosine kinase resulting in insulin failure to join insulin receptors, inducing insulin resistance, and causing DM type 2 (Sun *et al*, 2016).

Another important step in drug discovery and development is pharmacokinetic parameter prediction. After drug administration, the drug will be distributed throughout the body, based on various factors that can eliminate, damage, or prevent it from reaching the therapeutic target. The influencing factors are absorption, distribution, metabolism, and excretion (ADME), called as pharmacokinetic. Computer approaches have been developed as an alternative to experimental procedures for the prediction of ADME, especially at initial steps. SwissADME is a web tool that gives free access to predict the physicochemical properties, pharmacokinetics, drug-likeness, and medicinal chemistry friendliness of small molecules (Neema and Singh, 2018).

The present study aimed to predict the active constituents of *A. graveolens*, *A. vera*, and *N. sativa* that able to interact to the macromolecular targets of the antidiabetic agents, i.e. DPP4, PTP1B, glucokinase, as well as α-glucosides through molecular docking analysis and predict their pharmacokinetic profiles using SwissADME.

MATERIAL AND METHODS

Material

Hardware that we used in this study was Desktop with Intel I7 @3,6 GHz, 8 Gb RAM. Installed softwares that we used were MarvinSketch 17.8, PyMOL 2.2.3 (education version), PyRx 0.8, Autodock Vina 1.1.2, AutoDock Tools 1.5.6, VegaZZ 3.1.2, and Discovery Studio Visualizer 16.1. KNApSAcK and SwissADME webserver were also used in this study.

Methods

Molecular Docking Analysis

Ligand structures of each plant were obtained from KNApSAcK webserver in form of SMILES and from various studies, then 3d structure of each ligand was generated by using VegaZZ, then charge addition and energy minimization were done under vina force field in VegaZZ and was saved in mol2 format. The prepared ligands then were loaded into PyRx. In total, we obtain 94 ligand structures (32 ligands of *A. graveolens*, 26 of *A. vera* and 36 of *N. sativa*).

Structure of DPP4, PTP1B, glucokinase, and α-glucosidase were obtained from RCSB with PDB id 2QOE, 5T19, 4RCH, and 5NN8, respectively (Kowalchick *et al*, 2007; Punthasee *et al*, 2017; Hinklin *et al*, 2014; Roig-Zamboni *et al*, 2017). Protein structure preparation was done using AutoDock Tools (Trott & Olson, 2019). All non-standard residues and most of the water molecule were removed from the initial structure except those which involved in ligand-protein interaction. 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.

Docking validation was done by means of redocking of native ligand to its respective protein. Grid center was placed approximate to the center of the ligand, covering all the binding site residues. RMSD value of redocked and crystallography ligand must less than 2Å to confirm the validity of the docking method. All prepared ligands then were docked to four proteins target using Autodock Vina in PyRx. Interaction visualization was done by using Discovery Studio Visualizer and PyMol (Seeliger & De Groot, 2010) The binding affinity values were processed by using MS. Excel 365.

Prediction of ADME properties

Prediction of ADME properties was conducted using SwissADME web tool (http//www.swissadme.ch), by input a list SMILES of chemical compounds. The predicted parameters were rules of Lipinski's, bioavailability, BBB permeant, GI absorption, P-gp substrate, and inhibition metabolic enzymes (Daina *et al*, 2017).

RESULTS AND DISCUSSION

We obtain and identified 32 constituents of *A. graveolens*, 26 of *A. vera* and 36 of *N. sativa*. Constituents of *A. graveolens* and *N. sativa* were obtained from KNApSAcK webserver, whereas structures of *A. vera* constituents were obtained from KNApSAcK and various studies (Afendi *et al*, 2012).

Prior to docking simulation, we conducted validation and calculated RMSD. The result of validation showed that the RMSD value less than 2Å (figure 1) for all four redocked ligands. Thus, the docking method was valid.

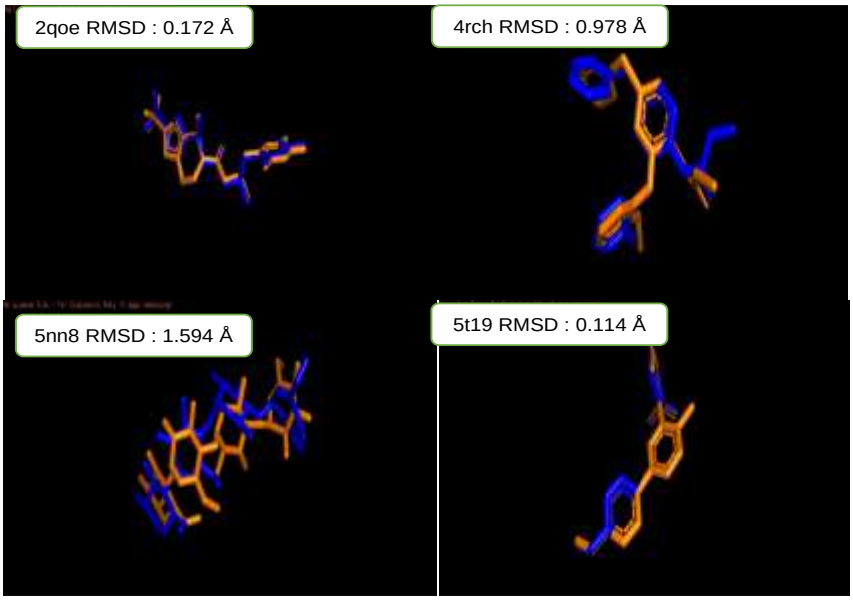

Figure 1. RMSD of superimposed redocked native ligand (blue) and crystallographic conformation (orange)

We choose the best ligand of each plant based on their binding affinity and interaction mode to DPP4, PTP1B, glucokinase, and α-glucosides (Table 1). Figure 2 showed the 3D space of binding pocket and selected ligand.

Table 1. Docking result of best ligand of each plant to the target proteins

Compound	**$\Delta G_{binding}$ (kcal/mol)**	**Amino acid residues involve in interaction**	
		Hydrogen Bond	**Non-hydrogen Bond**
Target: DPP4 (2QOE)			
Native ligand	-8.25 ± 0.29	Tyr585, Glu205, Glu206, Tyr662, Asn710, Arg125	Tyr666, Phe357
Apiin (*A. graviolens*)	-9.6 ± 0.0	**Asn710, Glu205, Glu206**	Trp629, Tyr547
Rutin (*A. vera*)	-8.4 ± 0.0	**Arg125, Glu206**	**Tyr666**, Trp629, **Phe357**
quercetin 3-glucosyl-(1->2)-galactosyl-(1->2)-glucoside (*N. sativa*)	-8.77 ± 0.15	**Arg125, Glu205, Glu206**, Asp545, Trp629, **Tyr662, Asn710**	-
Target: PTP1B (5T19)			
Native ligand	-9.6 ± 0.15	Ala217 Ser216 Arg221, Gly220, Phe182, Gln266	Tyr46, Val49
4,8,5'-Trimethylpsoralen (*A. graviolens*)	-8.9 ± 0.00	Lys120, **Arg221**	Ala217, Ile219, Phe182
8-C-Glucosyl-(2'-O-cinnamoyl)-7-O-methylaloediol A (*A. vera*)	-8.1 ± 0.00	Tyr46, Ser118, **Arg221**	Phe182, **Val49**
Nigellidine 4-O-sulfite (*N. sativa*)	-8.7 ± 0.00	Tyr46, **Phe182**	Lys120, Ala217, **Val49**
Target: Glucokinase (4RCH)			
Native ligand	-8.3 ± 0.08	Arg63	Met210, Met235, Ile211, Val455
Cyanidin 3-[6-(6-p-coumarylglucosyl)-2-xylosylgalactoside (*A. graviolens*)	-9.53 ± 0.05	Ser64, Thr65, Gln98, Glu248	**Met235**, Val62, Val452, **Val455**, Pro66, Ala456, Ile159

Isoaloeresin D (*A. vera*)	-9.63 ± 0.05	-	Arg63, Tyr214, **Val455**, Pro66, Ala456, Ile159
Nigellidine 4-O-sulfite (*N. sativa*)	-9.2 ± 0.00	-	Tyr214, **Val455**, Ieu451, Ile211
Target: α-glucosidase (5NN8)			
Native ligand	-8.43 ± 0.05	Asp404, His674, Asp616, Arg600, Met519, Asp282	Trp376, Trp481, Phe649
Luteolin (*A. graviolens*)	-8.6 ± 0.00	Asp518, **Arg600**, **Asp616**, Leu677	**Trp481**
Aloeresin E (*A. vera*)	-8.43 ± 0.12	Asn524, Leu677	**Trp481**, Phe252, **Trp376, Phe649**, Asp518
Quercetin 3-glucosyl-(1->2)-galactosyl-(1->2)-glucoside (*N. sativa*)	-8.6 ± 0.00	Arg281, **Asp282, Asp404**, Trp481, Asp518	Phe525, Ala555

Bold font means same interaction mode with native ligand.

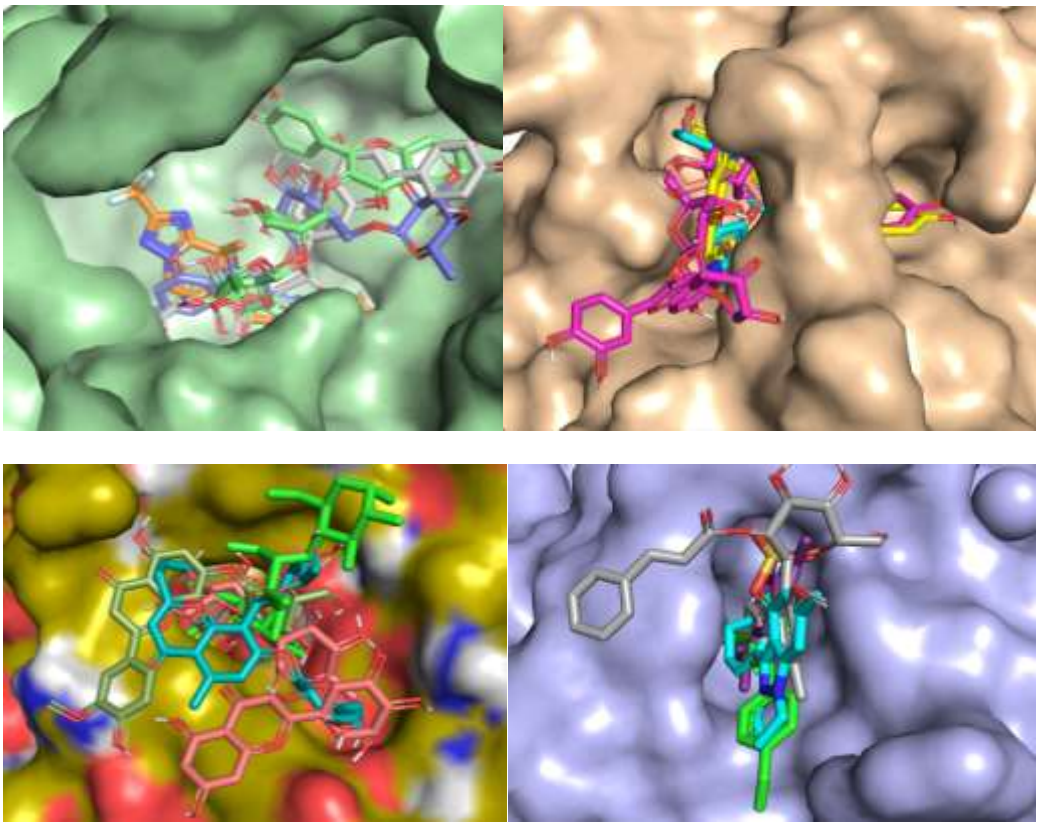

Figure 2. 3D space of binding pocket and selected ligand. a) DPP4, b) glucokinase, c) α-glucosidase, d) PTP1B

A. graveolens, *A. vera*, *N. sativa* were known to have antidiabetic activity from various study however the active constituent that attributed to this activity is still unknown. In this present study, we aimed to predict which constituent that responsible for the antidiabetic activity of each plant by using molecular docking simulation as well as its ADME (Absorption, Distribution, Metabolism, and Excretion) by using a web-based prediction tool.

DPP4 degrade glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide, reduce insulin secretion in beta pancreas cells (Mentlein *et al*, 1993). Thus, inhibition of DPP4 can increase insulin secretion in diabetic type 2 people. DPP4 active site contains S1, S2, S'1, S2, and S2 extensive subsites (Arulmozhiraja, 2016).

Kowalchick *et al*. (2007) reported that 2,4,5-trifluorophenyl moiety of triazolopiperazine occupied the hydrophobic pocket in the DPP-4 enzyme, while the (R)-b-amino group interacts with glutamate residues (Glu205 and Glu206) through four hydrogen-bonding interactions. A water molecule connected the nitrogen atoms of the triazolopiperazine and the carboxylic oxygen and the hydroxyl of Tyr547. The interaction also occurred between

the molecule of triazolopiperazine and amino acid residues (Phe357 and Arg125). Figure 3 presented that triazolopiperazine as the native ligand from DPP4 makes hydrogen interaction with Tyr585, Glu205, Glu206, Tyr662, Asn710 and Arg125. π-π interaction was present with Tyr666 and Phe357. Quercetin 3-glucosyl-(1→2)-galactosyl-(1→2)-glucoside from *N. sativa* had interaction resembles to the native ligand as shown in table 1 and figure 3. *N. sativa* seed extract was proved to have insulinotropic properties[9]. This agrees with the result that Quercetin 3-glucosyl-(1→2)-galactosyl-(1→2)-glucoside from *N. sativa* can inhibit DPP4 which could result in elevated insulin secretion by β-pancreatic cell.

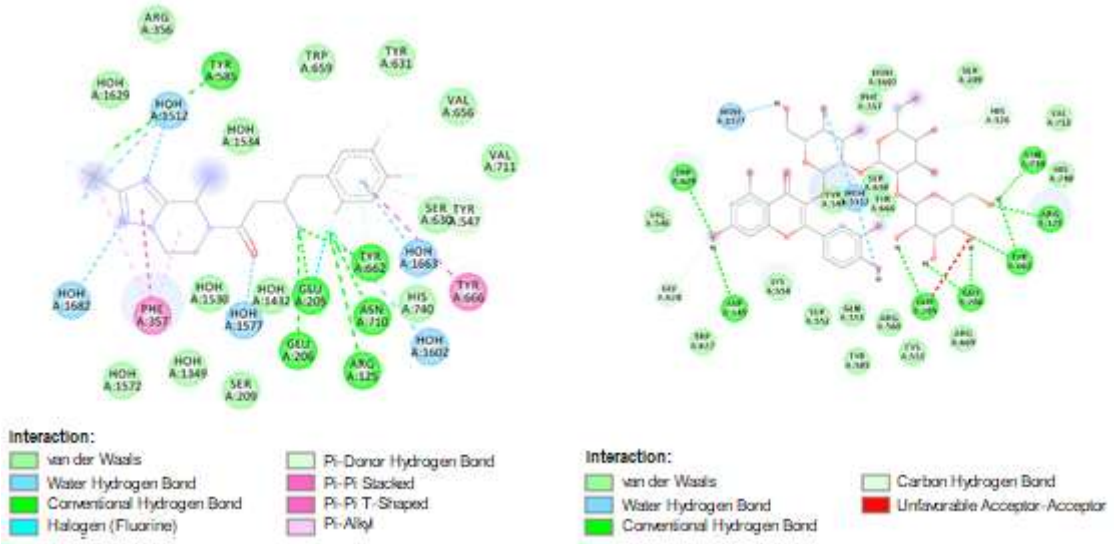

Figure 3. DPP4 interaction (a) native , (b) Quercetin

PTP1B is a negative regulator of the insulin-signaling pathway, inhibition can increase insulin activity (Zhang and Zhang, 2007). Punthasee *et al*. (2017) reported that a hydrogen bond was occurred between sulfone oxygens and Arg221, while the 1,2,5-thiadiazolidin-3-one 1,1-dioxide ring fully occupied the loop consisted of residues 216-220. The carbonyl oxygen of this ring was hydrogen-bonded to Phe182 and Gln266. The methylene residue of the heterocycle and the aromatic rings of the biphenyl group interact with the aromatic and nonpolar residues Tyr46, Val49, Ala217, Ile219, and Phe182. PTP1B native ligand interacts active site by hydrogen interaction with Ala217 Ser216 Arg221, Gly220, Phe182, Gln266. Nigellidine 4-O-sulfite from *N. sativa* had the most similar interaction with native ligand (figure 4).

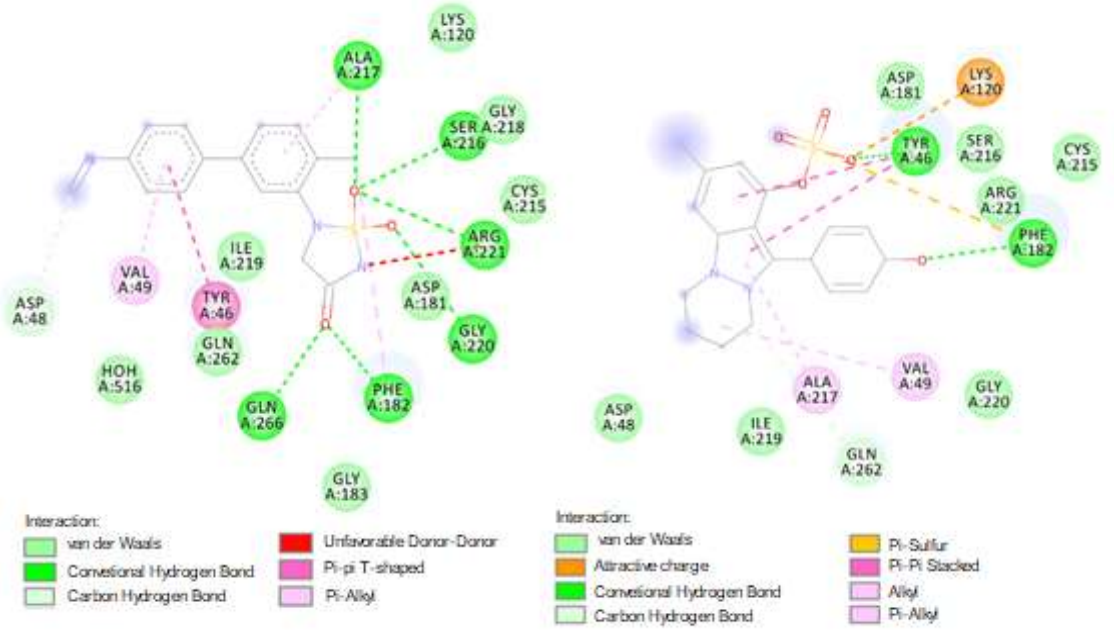

Figure 4. PTP1B interaction (a) native , (b) Nigellidine

Hinklin *et al*. (2014) reported that a hydrogen bond was occurred between the urea group and Arg63, while ethyl pyridyl ether on the 3-position of the pyridyl core formed hydrophobic interaction with some hydrophobic residues (including Ser64). Thiopyridyl group in 5-position also fully occupied the hydrophobic cavity by interacted to Ile211 and Tyr214. Docking simulation to glucokinase showed no promising result since there was no ligand interacted with Arg63 which very important for inductor activity. However, cyanidin 3-[6-(6-p-coumarylglucosyl)-2-xylosylgalactoside had very good binding affinity although no interaction that identical to native ligand was observed.

Roig-Zamboni *et al*. (2017) reported that stable interaction occurred through hydrogen bonds with side chains Asp282, Asp404, Asp518, Arg600, Asp616, and His674. Acarbose as native ligand covering the catalytic site of α-glucosidase with hydrogen interaction to Asp404, His674, Asp616, Arg600, Met519, and Asp282. Luteolin from *A. graviolens* had the best interaction model with α-glucosidase and covering its catalytic site and interact with Asp518, Arg600, Asp616, and Leu677 via hydrogen bond which increases inhibitory activity. This result was relevant to the previous report that luteolin showed the α-glucosidase inhibitory activity (IC_{50} value of 1.72 $x10^{-4}$ mol L^{-1}) (Yan *et al*., 2014).

CONCLUSION

Apiin (*A. graveolens*), rutin (*A. vera*), and quercetin 3-glucosyl-(1->2)-galactosyl-(1->2)-glucoside (*N. sativa*) had the best interaction to DPP4. 4,8,5'-Trimethylpsoralen (*A. graveolens*), 8-C-Glucosyl-(2'-O-cinnamoyl)-7-O-methylaloediol A (*A. vera*), and Nigellidine 4-O-sulfite (*N. sativa*) had the best interaction to PTP1B. Cyanidin 3-[6-(6-p-coumarylglucosyl)-2-xylosylgalactoside] (*A. graveolens*), isoaloeresin D (*A. vera*), and nigellidine 4-O-sulfite (*N. sativa*) had the best interaction to glucokinase. Luteolin (*A. graveolens*), Aloeresin E (*A. vera*), and quercetin 3-glucosyl-(1->2)-galactosyl-(1->2)-glucoside (*N. sativa*) had the best interaction to α-glucosidase. Additionally, nigellidine 4-O-sulfite and 4,8,5'-trimethylpsoralen were predicted to have good bioavailability score on SwissADME. Further studies are required to investigate the interaction of each ligand through in vitro test and molecular dynamic simulation.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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