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Docking study of secondary metabolites from *Glycyrrhiza glabra* as PPAR-γ agonist

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ABSTRACT

Discovery of potent yet cheap antidiabetic drugs with PPAR-γ agonist activity resulted in the discovery of several partial agonists of PPAR-γ. Glabridin, an isoflavone metabolite found in the root of *Glycyrrhiza glabra* has been associated with a wide range of biological properties, such as antidiabetic and antiobesity properties mediated by PPAR-γ receptors activation. This study aims to determine secondary metabolites of *G. glabra* with the highest affinity as PPAR-γ agonists with molecular docking method. The docking results showed that among other test ligands, the highest affinity was shown by glabrene. However, significant differences occur at amino acid residues from glabrene against the corresponding ligand. Interestingly, besides glabridin with 73% similar amino acid, the similarity of amino acid throughout the test ligands is less than half of glabridin. Glabridin also shows different types of interactions with some thiazolidinediones which are known to have quite dangerous side effects, so that glabridin is predicted not to have similar side effects. Thus, glabridin should be potential to be developed as the PPAR-γ agonist.

Keywords: *antidiabetic, docking, glabridin, Glycyrrhiza glabra, PPAR-γ agonist.*

1. INTRODUCTION

The strategy of diabetes therapy especially for type 2 diabetes involved PPAR-γ have been developed long enough to discover various PPAR-γ agonist including several thiazolidinediones class compounds such as pioglitazone and rosiglitazone [1, 2]. However, this class compounds appeared to have severe side effects including increased risk of myocardial ischemia and congestive heart failure [3 – 5]. The development of PPAR-γ agonist therapy has begun to shift to treatment with compounds derived from natural materials, including various secondary metabolites from medicinal plants [6, 7]. One of the medicinal plants that have the potential to its secondary metabolites as PPAR-γ agonists is *Glycyrrhiza glabra* or also known as licorice [6, 8]. *G. glabra*, better known as a sweetener because of its glycyrrhizin content, also contains some compounds that can act as PPAR-γ agonists [9]. Still, further research is needed to prove the activity of PPAR-γ agonists from secondary metabolites of *G. glabra*. One of the most straightforward but beneficial methods for assessing the potential of secondary metabolites of *G. glabra* as PPAR-γ agonists are the molecular docking [10, 11].

Compared to other *in silico* approaches, molecular docking has several advantages. In addition to a relatively short duration and does not require many resources, molecular docking also provides a visual representation of the interaction between ligands and receptors, which cannot be obtained from other approaches [12, 13]. However, the biggest problem with docking is the result where affinity as the primary parameter of observation from docking results does not always relevant to the *in vitro* results [14]. Therefore, currently, affinity is not the only parameter observed from the results of docking [15, 16].

Another critical parameter to be observed is the similarity of amino acid residues between the test and the corresponding ligands [17]. The similarity of amino acid residues will provide important clues about the types of interactions that occur between several types of ligands. Ligands with similar high amino acid residues tend to have the same kinds of interactions [18]. Information on the type of mechanism of action will be especially useful for receptors that have many members of the same kind as PPAR, where the possibility of cross-interaction between receptors is quite high [19, 20].

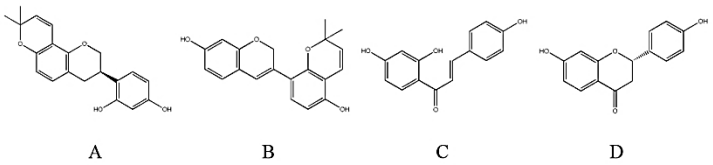
This study aimed to determine secondary metabolites of *G. glabra* with the highest affinity as PPAR-γ agonists, including determining the type of interaction that occurs between ligands. As a comparison, in addition to co-crystal ligands, two corresponding ligands pioglitazone and rosiglitazone are used in the form of known PPAR-γ agonists. The comparison is not only made with the affinity of the ligand but also the degree of similarity of the ligand with corresponding ligands [21, 22]. The comparison results also show essential amino acid residues in PPAR-γ to stimulate agonist activity.

2. MATERIALS AND METHODS

2.1. Preparation of ligands.

The ligand used in this study were four secondary metabolites from *G. glabra* including glabridin, glabrene, isoliquiritigenin, and liquiritigenin, where the two-dimension structure of all ligands was shown in Figure 1 [23]. Structures of ligands were sketched using GaussView 3.08 Software from Gaussian, Inc. All structures were geometry optimized by Hartree-Fock method basis set 6-311G with Gaussian 03 W software from Gaussian, Inc. Geometry optimization provided an ideal conformation of following compounds that approaching the formation of these compounds in nature [24]. Optimized structures format changed from .log to .pdb using Open Babel 2.4.1 software [25]. Docking program used in

this study was Autodock 4.2.6 from The Scripps Research Institute. All ligands then are given the charge and set torque using software AutoDockTools 1.5.6 [26].



A B C D

Figure 1. Two-dimensional structure of all ligands: A) glabridin; B) glabrene; C) isoliquiritigenin; D) liquiritigenin.

2.2. Preparation of receptor.

The molecular structure of PPAR-γ in complexed with VSP-51, a known PPAR-γ agonist (PDB ID 5TWO) was obtained from the website of the protein data bank (PDB) http://www.rscb.org. The receptors were downloaded in .pdb format and then removed the unused portion, added the non-polar hydrogen group, given the charge, and set the grid box size and coordinate using software AutoDockTools 1.5.6 [27]. The used structure of PPAR-γ is the active site which binds with VSP-51 as the co-crystal ligand. VSP-51 is a partial agonist of PPAR-γ with high affinity to bind with PPAR-γ without stimulating adipocyte differentiation and adipogenesis-related genes expression [19].

2.3. Validation of docking process.

The method used for docking validation was redocking the co-crystal ligand into the active site of the receptor. The parameters observed in validation is root-mean-square deviation (RMSD) of each co-crystal ligands at the selected binding site. RMSD scores describe the average difference in position of the atoms of the redocking ligand with the crystallographic results [28, 29]. Docking programs are preferred to predict outcomes from experimental poses with RMSD no more than 2 Å. Smaller RMSD indicates that the position of redocking results ligand was closer to crystallography results ligand [12].

2.4. Molecular docking.

Molecular docking is done using software AutoDock 4.2.6 from The Scripps Research Institute. Docking for all test ligand performed in the same way as the validation process with similar size and position of a grid box [13]. The primary parameter used in the docking process was the free energy of binding (ΔG), the dissociation constant (K_i), and amino acid residues. ΔG and K_i scores determine ligand affinity to the receptor in the docking method. The more negative ΔG and lower K_i indicated higher ligand affinity towards the active site of the used receptor [16]. Test ligand with the highest affinity was compared with the validation result of co-crystal ligand to determine the potency of test ligand as each receptors inhibitor [14]. The amino acid residues of selected test ligand for each receptor then compared with amino acid residues of co-crystal ligand to assess the similarity of interaction between test and co-crystal ligand. The more similar amino acid residues were indicating a higher probability that the test ligand will have similar activity with the co-crystal ligand [18].

3. RESULTS

Validation results show entirely satisfactory results and can still be accepted with a value of RMSD 1.821 Å. Even though it almost reaches 2 Å, most of the atoms are in a position corresponding to the crystallography results, as shown in Figure 2. A striking difference is only explained in the chloro-fluoro-benzene group in the ligand that is in the opposite position to the result of crystallography. Most likely the difference is due to the presence of water molecules on the binding site which is removed, given the reactive nature of the halogen element itself [30]. Still, the redocking results can yet be said to be valid. Other parameters observed in the validation process was ΔG, K_i, and amino acid residues of the co-crystal ligand.

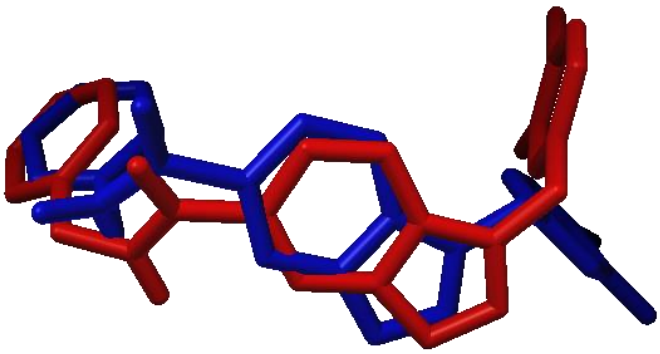


Figure 2. Validation results of the PPAR-γ receptor with RMSD = 1.821 Å (blue: redocking result; red: crystallography results).

All test ligands were sketched then performed geometry optimization with Hartree-Fock basis set 6-311G, an ab initio approximation with a high confidence rate for *in silico* analysis. From each test ligand, one pose with the most negative ΔG and the smallest K_i was chosen as representative [24]. That ligand pose shows the pose with the highest affinity for the binding site used [31]. The docking results of all test and corresponding ligands were compared to each other as shown in Table 1.

Compared to other test ligands, the highest affinity is shown by glabrene, which is even higher than pioglitazone and rosiglitazone as corresponding ligands although lower than VSP-51 as a co-crystal ligand. At first glance, the results seem to indicate that glabrene is a secondary metabolite of *G. glabra* which is the most potential as a PPAR-γ agonist. However, the comparison of amino acid residues from each ligand shows something interesting.

Amino acid residues are an important parameter that must be considered, mainly because of the high level of uncertainty in *in silico* approach [32]. A significant difference in affinity will have no meaning if amino acid residues from the test ligand are very different from corresponding ligands. Therefore, it is wise to consider how the similarity level between amino acid residues from the test and corresponding ligands to determine ligands with the highest affinity [12, 33].

In fact, in addition to glabridin, all test ligands showed significant differences in amino acid residues both with the co-crystal and corresponding ligand. These results imply that although the

highest affinity is shown by glabrene, most likely the interaction between glabrene and PPAR-γ receptor will be different from corresponding ligands [34]. In the end, the different types of interaction will raise doubts that glabrene and test ligands other than glabridin will have activity as PPAR-γ agonists [35].

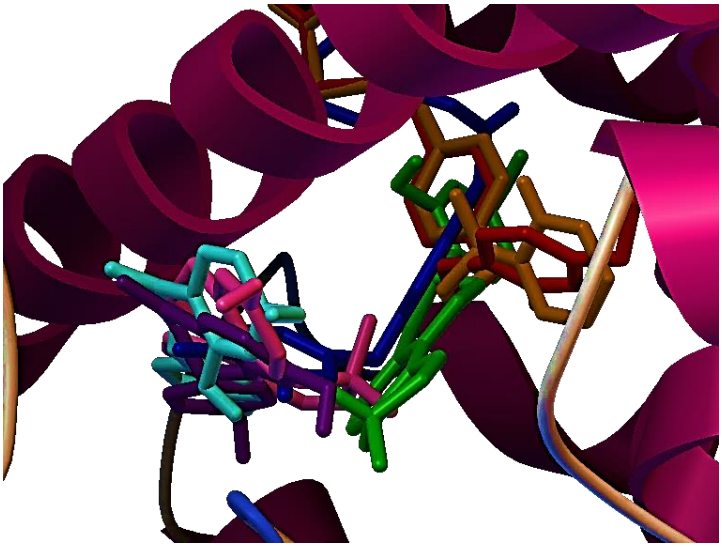


Figure 3. Comparison of docking results position at PPAR-γ receptor (blue: VSP-51; red: pioglitazone; orange: rosiglitazone; green: glabridin; pink: glabrene; cyan; isoliquiritigenin; magenta: liquiritigenin).

On the other hand, the highest similarity of amino acid residues is shown by glabridin. The similarities shown are even quite large, where eight of the eleven amino acid in the co-crystal ligand also interacts with glabridin as shown in Table 1. This amount is quite a lot, considering the significant difference between the structure between glabridin and VSP-51, including molecular weights, functional groups, and log P [36]. The affinity of glabridin is relatively large among pioglitazone and rosiglitazone, although it is still lower than VSP-51. This indeed shows the enormous potential of glabridin to be developed as a PPAR-γ agonist.

Another exciting feature is visualized in Figure 3., were compared to pioglitazone and rosiglitazone, the binding position of glabridin is very similar to VSP-51. This is interesting because it is different from pioglitazone and rosiglitazone which are pure PPAR-γ agonists, VSP-51 is a dual PPAR-α and γ agonists [19, 37]. As is known, pioglitazone and rosiglitazone have quite dangerous side effects and are not allowed to use them in some countries [3 – 5]. The nature of the side effects has not been seen in VSP-51, and the possible cause is the different types of interaction with pioglitazone and rosiglitazone [38]. This is very beneficial for glabridin because the position of glabridin which is very similar to VSP-51 shows the possibility that glabridin interaction with PPAR-γ will resemble VSP-51. These results suggest that glabridin is not expected to cause side effects such as pioglitazone and rosiglitazone. Of course, this will be very beneficial because glabridin is a compound that is directly isolated from medicinal plants so that the production costs will be cheaper than synthetic compounds [39]. Overall, with further development glabridin will provide cheaper but no less effective options as a PPAR-γ agonist.

Table 1. Docking results of the test and corresponding ligands at the PPAR-γ receptor.

Parameters	VSP	PIO	ROS	GRD	GRN	ILR	LRG
ΔG (kcal/mol)	-10.91	-9.23	-8.78	-9.01	-9.74	-7.73	-8.06
K_i (μM)	0.01003	0.17297	0.36494	0.24837	0.07258	2.14	1.23
Amino Acid Residues	-	-	-	228-Leu	-	-	-
	-	-	-	-	262-Ile	262-Ile	262-Ile
	-	-	-	-	263-Lys	263-Lys	263-Lys
	-	-	-	-	281-Ile	281-Ile	281-Ile
	282-Phe	282-Phe	282-Phe	-	-	-	-
	284-Gly	-	-	-	284-Gly	284-Gly	284-Gly
	285-Cys	285-Cys	285-Cys	285-Cys	285-Cys	285-Cys	285-Cys
	-	286-Gln	286-Gln	-	-	-	-
	-	-	-	-	-	287-Phe	-
	288-Arg	288-Arg	288-Arg	288-Arg	288-Arg	288-Arg	288-Arg
	289-Ser	289-Ser	289-Ser	289-Ser	-	-	-
	-	292-Ala	292-Ala	-	-	-	-
	-	326-Ile	326-Ile	-	-	-	-
	327-Tyr	327-Tyr	327-Tyr	327-Tyr	-	-	-
	-	329-Met	329-Met	-	-	-	-
	-	330-Leu	330-Leu	330-Leu	-	-	-
	-	-	-	333-Leu	-	-	-
	-	-	-	340-Leu	-	-	-
	-	-	-	341-Ile	341-Ile	341-Ile	341-Ile
	342-Ser	-	-	-	342-Ser	342-Ser	342-Ser
	-	-	-	-	343-Glu	343-Glu	343-Glu
	-	-	-	-	-	-	348-Met
	363-Phe	363-Phe	-	363-Phe	-	-	-
	364-Met	-	-	364-Met	-	-	-
	367-Lys	-	-	367-Lys	-	-	-
	449-His	449-His	449-His	449-His	-	-	-
	-	465-Leu	465-Leu	-	-	-	-
	-	469-Leu	469-Leu	-	-	-	-

4. CONCLUSIONS

Eventually, the present study was successfully showed that although it doesn't show the highest affinity, glabridin has the enormous potential as a PPAR-γ agonist. The interesting point is that the type of glabridin interaction tends to be different from that shown by thiazolidinediones, so it is likely that glabridin does not have similar side effects. However, the affinity of glabridin is still lower than the corresponding compounds. Of course, the affinity of glabridin can yet be optimized. One way that can be done is to maximize pharmacophore in functional groups of glabridin, especially in the aromatic group constituents. Thus, optimization of glabridin will further increase its potential as a PPAR-γ agonist, so that it can be used for type 2 diabetes therapy effectively.

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