International Journal of Pharmacy
Journal Homepage: http://www.pharmascholars.com

Original Article **CODEN: IJPNL6**

Molecular Docking of Macarangin isolated from *Macaranga denticulata* with two targets related to diabetes

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Received on: 12-02-2017; Revised on: 24-04-2017; Accepted on: 09-05-2017

ABSTRACT

To investigation Macarangin, an isolated compound of *Macaranga denticulata*, can be considered for developing into a potent antidiabetic drug by docking analysis. The plant has used for carminative, emetic, haemoptysis and healing wounds by the tribal in Khagrachari, Bangladesh. Macarangin isolated from *Macaranga tanarius* was taken as ligand for molecular docking. The molecular targets Alpha amylase and Glucokinase whose crystallographic structures are available on the PDB database as 1PPI, 1V4S respectively, were used for the docking analysis using the Schrödinger-Maestro v10.1. The docking studies of the ligand Macarangin with three different target proteins showed -5.238 and -4.534 respectively Alpha amylase and Glucokinase. According, to the molecular docking it is proved that Macarangin is a potent antidiabetic compound. So, it is need to *in vivo* investigation in future to identify appropriate antidiabetic activity of Macarangin.

Key words: *Macaranga denticulate*, Macarangin, molecular docking, antidiabetic.

INTRODUCTION

Now a day's Diabetes mellitus (DM) is a common chronic diseases in the world which is characterized by the high blood glucose level [1]. It is associated with the deficiency of circulating insulin level, responsible for persistent high blood glucose level [2]. Though there are various types of oral hypoglycemic drugs along with insulin for the treatment of DM. But increasing demands of the patients to use the natural product for the anti-diabetic activity because synthetics drugs cause various side effect and toxicity. On the other hand, herbal or natural drugs have less side effect, some times more effective than synthetic drugs and cost effective [3, 4].

Alpha amylases (endo-1, 4-α-D-glucan glucanohydrolase EC 3.2.1.1) are extracellular endoenzymes that indiscriminately cleave α-1,4 linkages between adjacent glucose units in the linear amylose chain and ultimately generate glucose, maltose, and maltotriose units. This category of industrial enzymes constitutes approximately 25% of the enzyme market. Conversion of starch into sugar syrups such as glucose, maltose, maltotriose, dextrins sugar, or fructose syrups, etc. are the major part of

the starch process trade [5, 6]. The spectrum of amylase application has widened in many different fields, like that clinical, medicinal and analytical chemistry; additionally as their widespread application in starch saccharification and within the textile, food, paper and pharmaceutical industries [7-11]. However, enzymes from fungal and bacterial sources have dominated applications in industrial sectors, attributable to advantages like cost effectiveness, less time and space requirement and ease of process modification and improvement [12, 13].

Glucokinase (EC 2.7.1.2) is an enzyme which facilitates phosphorylation of glucose to glucose-6-phosphate. Glucokinase occurs in cells in the liver and pancreas of humans and most other vertebrates. In every of those organs play a very important role to regulation of carbohydrate metabolism by acting as a glucose sensing element, triggering shifts in metabolism or cell perform in response to rising or falling levels of glucose, like occur when a meal or when abstinence. Mutations of the gene for this enzyme will cause unusual types of diabetes or symptom [14].

In silico is an expression used to mean "performed on computer or via computer simulation". In silico methods can help in identifying drug targets via bioinformatics tools. They can also be used to analyze the target structures for potential binding/active sites, generate candidate molecules, check for their drug likeness, dock these molecules with the target, rank them according to their binding affinities, further optimize the molecules to improve binding characteristics The utilization of computers and computational methods permeates all aspects of drug discovery nowadays and forms the core of structure-based drug design [15].

The aim of the study to find the mechanism of action of the isolated compound macarangin from *Macaranga denticulata* was explored the α-amylase and Glucokinase inhibitory activity by molecular docking analysis and ADME/T property studies used to measure the safety of the compound as drug.

MATERIALS AND METHODS

In silico analysis

Molecular docking analysis of isolated compounds from *Macaranga denticulata*

Protein Preparation

The structures of the target receptor binding sites of human alpha amylase (PDB ID: 1PPI) and human glucokinase (PDB ID: 1V4S) were obtained from the RCSB Protein Data Bank. After that, structure was prepared and refined using the Protein Preparation Wizard of Schrödinger-Maestro v10.1. Charges and bond orders were assigned, hydrogens were added to the heavy atoms, selenomethionines were converted to methionines, and all waters were deleted. Using force field OPLS_2005, minimization was carried out setting maximum heavy atom RMSD (root-mean-square-deviation) to 0.30 Å.

Ligand Preparation

Compounds were retrieved from Pubchem databases, i.e. Macarangin (CID 10047854). The 3D structures for these were built by using Ligprep2.5 in Schrödinger Suite 2013 with an OPLS_2005 force field. Their ionization states were generated at pH7.0±2.0 using Epik2.2 in Schrödinger Suite. Up to 32 possible stereoisomers per ligand were retained.

Glide Standard Precision (SP) ligand docking

SP flexible ligand docking was carried out in Glide of Schrödinger-Maestro v10.1within which penalties were applied to non-cis/trans amidebonds. Van der Waals scaling factor and partial charge cutoff was selected to be 0.80 and 0.15, respectively for ligand atoms. Final scoring was performed on energy-minimized poses and displayed as Glide score. The best docked pose with lowest Glide score value was recorded for each ligand.

Ligand based ADME/Toxicity prediction

This test was carried out using Lipinski's "Rule of Five"[16]. This analysis is done by following server,

- ACD/I-Lab (https://ilab.acdlabs.com/iLab2/index.php)
- Molinspiration (http://www.molinspiration.com/cgi-bin/properties)

RESULTS AND DISCUSSIONS

In silico analysis

Molecular docking analysis

In this study, the binding mode of α-amylase enzyme was investigated by doing computational analysis, glide docking. Both glide standard (SP) and extra precision (XP) mode had been introduced, where extra precision mode used for cross validation purpose. The results of docking analysis were described in Table 1 and the docking figure showed in Figure 1. Binding energy is the primary parameter which is generated as a result of molecular docking. It gives us the idea of strength and affinity of the interaction between the ligand and the receptor. The greater the binding energy is, the weaker the interaction is and vice versa. Thus during any docking study, we intend to look for the ligand which displays the least binding energy, thus the best affinity among the test molecules [17]. From our

study it shows that macarangin which is the common compound of macaranga species give anti-diabetics activity in both of Alpha amylase (1PPI) and Glucokinase (1V4S) receptors which indicates that this compound has potent anti-diabetic activity against diabetics malitus.

Table 1: Docking score of different compounds with the receptors.

Compound	Targeted Protein (PDB ID)	Docking energy
Macarangin	Alpha amylase (1PPI)	-5.238
	Glucokinase (1V4S)	-5.638

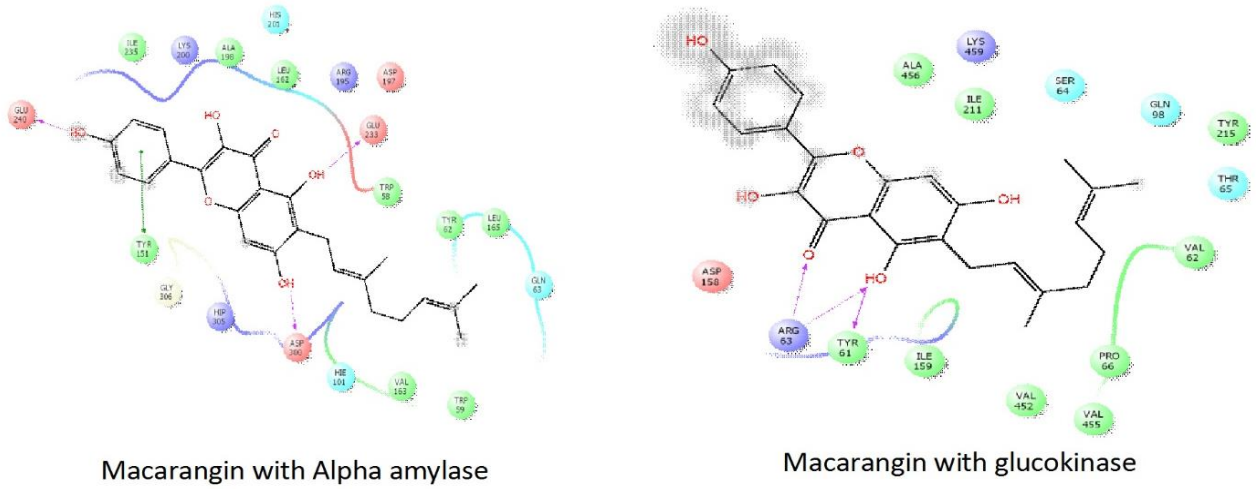

Figure 1: Docking figure of Macarangin with the receptors.

ADME and Toxicity analysis

Ligand based ADME/Toxicity prediction

Drug likeliness, log P, molar refractivity, molecular weight and toxicity risks may be used to judge the compound's overall potential to qualify a ligand as potential drug candidate. The drug-like activity of the ligand molecule in this study was categorized using ADME properties by ACD/I-Lab and Molinspiration. This test was carried out using Lipinski's "Rule of Five" [16]. The distributions of the compound molecular weights (MW), calculated lipophilicity (log P), number of hydrogen bond acceptors (HBA) and number of hydrogen bond donors (HBD) were used to assess the "drug-likeness" of the compounds. It is noteworthy that natural products exhibit a wide range of flexibility, from rigid conformationally constrained molecules to very flexible compounds. The ADME property of the Macarangin was evaluated with ACD/I-Lab and Molinspiration, shown in Table 2. The selected properties are known to influence metabolism, cell permeation, and bioavailability. Predicted properties of Macarangin was within the range for satisfying all the Lipinski's rule of five to be considered as drug like potential.

Table 2: ADME/T Properties of Macarangin.

Name of molecules	MW[α]	HB donor[β]	HB acceptor[€]	Log P[¥]	Molar Refractivity[µ]
Macarangin	422	4	6	4.540502	118.51

[α]Molecular weight (acceptable range: <500).
[β]Hydrogen bond donor (acceptable range: ≤5).
[€]Hydrogen bond acceptor (acceptable range: ≤10).
[¥]High lipophilicity (expressed as LogP, acceptable range: <5).
[µ]Molar refractivity should be between 40-130.

CONCLUSION

Docking studies of the ligand Macarangin with three different target proteins showed that this is a good molecule which docks well with two major targets related to diabetes mellitus. Thus Macarangin can be considered for developing into a potent antidiabetic drug. So, it is need to *in vivo* investigation in future to identify appropriate antidiabetic activity of Macarangin.

COMPETING INTERESTS

The authors declare that they have no competing interests.

ACKNOWLEDGMENT

The authors thank GUSTO (A research group) for providing the software and the financial support.

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