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Molecular docking studies on phytoconstituents of herbal formulation (Linn).against α-amylase enzyme

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ABSTRACT

The purpose of the study is to evaluate the α-amylase inhibitory activity of active herbal formulation constituents present in using *in silico* docking studies. In this perspective, active plant formulation constituent ligands were prepared for the docking evaluation. Acarbose, a known α-amylase inhibitor was used as the standard. In silico docking studies were carried out using recent version of GLIDE software v5.5 developed by Schrödinger. These results showed that all the active constituents GBDG showed binding energy ranging -9.09kcal/mol when compared with that of the other compound (-8.114 kcal/mol). These molecular docking analyses lead to the further development to identify the potent α-amylase inhibitors for the treatment of diabetes.

Keywords: Antidiabetic; Docking Studies and α-amylase.

1. INTRODUCTION

Diabetes mellitus described as a metabolic disease characterized by hyperglycemia resulting from fault in insulin secretion, insulin action or both. Most effective treatment for type II diabetes is the control of postprandial hyperglycemia after a meal. Stabilization of blood glucose is necessary for diabetic patients, because it prevents hyperglycemia and the Complexity associated with diabetes[1].The properties of diabetes mellitus consist of long-term injury, dysfunction and failure of various organs [2].At the current situation it is predicted that 150 million people, universally have diabetes and that this will increase to 300 million by 2050[3]. Modern medicines such as sulfonylureas, bi-guanides and thiozolidinediones are intended for the treatment of diabetes. Though, they also have undesired effects related with their uses [4].The natural products or medicinal plants reduce the absorption of glucose by reduce the carbohydrate hydrolyzing enzymes, such as pancreatic amylase.

The inhibition of this enzyme slow down the carbohydrate digestion and extend the overall carbohydrate Digestion time, ensuing in the decrease in glucose absorption rate and as a result reduce the postprandial plasma glucose rise. Several indigenous medicinal plants have a great potential in theα-amylase inhibition [5]. Herbal medicines are playing a vital role in the treatment of various chronic diseases when compared to modern synthetic drugs. They are very safe because of its minimum side effects. Proper knowledge of crude drug is very important aspect in the development of herbal formulation, safety and efficacy of the herbal formulation[6,7].

2. EXPERIMENTAL

2.1. Ligand Preparation

The ligands used in this study were prepared using LigPrep module of v2.3 of Schrödinger Suite 2013. LigPrep follows OPLS-AA

(Optimized Potential Liquid Simulations for All Atoms) force fields for energy minimization.

2.2. Protein Preparation

The X-ray crystal structure of α-amylase (PDB: 1HNY) was retrieved from PDB database as raw could not be suitable for molecular docking studies. A typical PDB structure consists only of heavy atoms, waters, Cofactors, metal ions and can be of multimeric. These structures do not have the information about bond orders, topologies or formal atomic charges. So, the raw PDB structure should be prepared in a suitable manner for docking. Protein Preparation Wizard of GLIDE software was used to process and prepare the protein. This also follows the Optimized Potential for Liquid Simulations-All Atoms (OPLS-AA) force fields for energy minimization.

2.3. Docking Protocol

All docking calculations were performed using the „„Extra Precision""

(XP) mode of GLIDE program. The binding site, for which the various energy grids were Calculated and stored, is defined in terms of two concentric cubes: the bounding box, which Must contain the center of any acceptable ligand pose, and the enclosing box, which must Contain all ligand atoms of an acceptable pose, with a Root Mean Square Deviation (RMSD) of less than 0.5 Å and a maximum atomic displacement of less than 1.3 Å were eliminated as redundant in order to increase diversity in the retained ligand poses. The scale factor for van der Waals radii was applied to those atoms with absolute partial charges less than or equal to 0.15 (scale factor of 0.8) and 0.25 (scale factor of 1.0) electrons for ligand and protein, respectively. The max keep variable which sets the maximum number of poses generated during the initial phase of the docking calculation were set to 5000 and the keep best variable which sets the number of poses per ligand that enters the energy minimization was set to 1000. Energy minimization protocol includes dielectric constant of 4.0 and 1000 steps of Conjugate gradient. Upon completion of each docking calculation, at most 100 poses per Ligand were generated[8]. The best docked structure was chosen using a GLIDE score (Gscore) Function. Another scoring function used by GLIDE is E-model, which itself derived from a combination of the Gscore, Coulombic, van der Waals and the strain energy of the ligand [9].

3. RESULTS AND DISCUSSION

GLIDE receptor grid was generated to determine the size of the active site. The most Probable orientation of the ligands in the binding pocket is identified and a scoring function is used to quantify the strength of the interaction a molecule can make in a particular orientation. In order to provide better correlation between good poses and good scores, the LIDE XP precision was favored over the standard mode. The docking analysis was done for the ligands such with the target protein α-amylae using the docking software GLIDE and the docked images are shown. The structures docked by GLIDE are generally ranked according to the GLIDE Scoring Function (more negative). The scoring function of GLIDE docking program is presented in the G-score form. The most straightforward method of evaluating the accuracy of a docking procedure is to determine how closely the lowest energy pose (binding conformation) predicted by the object scoring function. In the present study, Extra Precision GLIDE docking procedure was validated by removing the inhibitor compound with α –amylase protein has been analyzed from the G-score, GLIDE energy and H-bonds. To study the molecular basis of interaction and affinity of binding of ligand analogues to α –amylase protein, all the ligands were docked into the active site of α–amylase. The docking result of these ligands is given in table 1. The interaction energy includes van der Waals energy, electrostatic energy, as well as intermolecular hydrogen bonding were calculated for each minimized complex.

Table - 1: The docking result of these ligands

Compound docked	Glide score
GBDG	-9.09
Mangeferin	-8.114
Quercetin	-7.91
Oleolinic acid	-7.502
Plumbagin	-7.243
Chebulic acid	-6.928
Shikmic acid	-6.928
Ferulic acid	-6.831
B-amyrin	-5.472

The docking score using GLIDE varied from-5.472 to -9.09 against α-amylase. The GLIDE Score for, a standard Acarbose docked with α –amylase was found to be-6.3. This proves that chemical constituent present in the plant could be potential drugs for Anti- diabetic activity drug development. The GLIDE score can be used as a semi-quantitative descriptor for the ability of ligands to bind to a specific conformation of the protein receptor. Generally speaking, for low GLIDE score, good ligand affinity to the receptor may be expected. Especially, compounds GBDG and Mangeferin were found to be potent with a docking score of -9.09and -8.144 respectively.

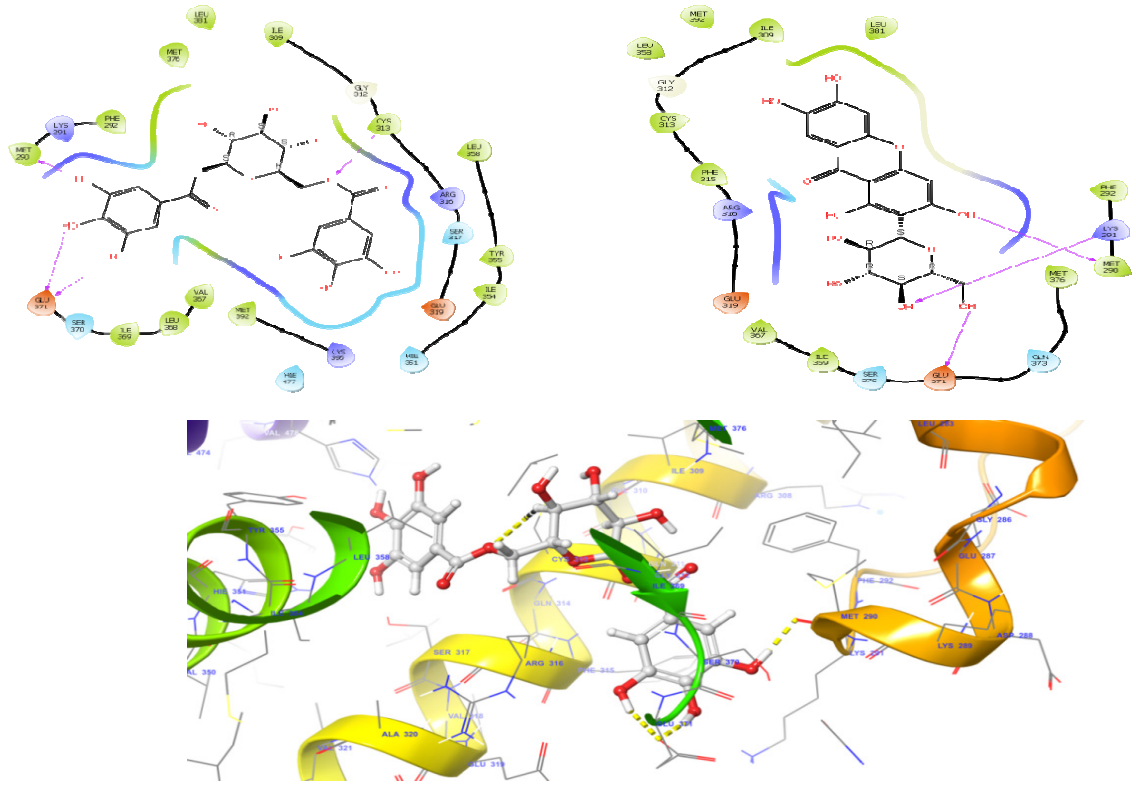

Figure - 1: The docking result of these ligands.

We found a very good agreement between the localization of the inhibitor upon docking and from the crystal structure of the protein. Conformational analysis of different docked complexes also shows that residues ASP 197, ALA 198, LYS 200, HIS 201, GLU233, ILE 235,HIS 305 and ALA 307 for α –amylase protein plays important role in this receptor‟s activity. Docking studies performed by GLIDE has confirmed that above inhibitors fit into the binding pocket of the α–amylase protein. From the results, we may observe that for successful docking, intermolecular hydrogen bonding and lipophilic interactions between the ligand and the receptor are very important. The main reason for the increase in GLIDE score is due to the penalties for close intra-ligand.

3. CONCLUSION

In conclusion, the results of the present study clearly demonstrated that, GBDG and mangeferin formulation excellent binding sites and interactions with α-amylase compared to the standard. Further investigations on the above compounds and in vivo studies are necessary to develop potential chemical entities for the prevention and treatment of diabetes.

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