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INSILICO STUDY AND DRUG TARGET FOR TYPE II DIABETES FROM A NATURAL COMPOUND

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ABSTRACT

Diabetes is the most common disease in the world. Especially in India 90 to 95 % people have diabetes. People with type II diabetes tend to have two problems: they don't make quite enough insulin and the cells of their bodies don't seem to take in glucose as eagerly as they should. Anti-diabetic drugs treat diabetes mellitus by lowering glucose levels in the blood. But still no complete remedy performed to eradicate diabetes on the whole. Our present study focuses on inhibitory concept in cellular level can give drug target for typeII diabetes. It was realized that inhibition of all or some of the enzymes like α - amylase, α - glucosidase by inhibitors could regulate the absorption of carbohydrate and these inhibitors could be used therapeutically in the oral treatment of the non insulin dependent diabetes mellitus. Mangiferin is a xanthone isolated from roots of *Salacia chinensis* L. is a competitive inhibitor of α - glucosidase.

KEY WORDS : Diabetes,α - amylase, α – glucosidase, *Salacia chinensis.*

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INTRODUCTION

Diabetes mellitus (DM) often simply referred to as diabetes—is a condition in which a person has high blood sugar, either because the body doesn't produce enough insulin, or because cells don't respond to the insulin that is produced. Here are three main types of diabetes. Type 1 diabetes: results from the body's failure to produce insulin, and presently requires the person to inject insulin. Type 2 diabetes: results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. Type 3 Gestational diabetes: is when pregnant women, who have never had diabetes before, have a high blood glucose level during pregnancy [1]. It may precede development of type 2 DM. As of 2000 at least 171 million people worldwide suffer from diabetes, or 2.8% of the population. Type 2 DM is by far the most common affecting 90 to 95% of the Indian diabetes population[2]. There are two kinds of medicines: oral medications (pills) and insulin shots. Diabetes pills are not insulin. People with type 2 diabetes tend to have two problems: they don't make quite enough insulin and the cells of their bodies don't seem to take in glucose as eagerly as they should. Anti-diabetic drugs treat DM by lowering glucose levels in the blood[3]. With the exceptions of insulin, exenatide and pramlintide are administered orally and are thus also called oral hypoglycemic agents or oral antihyperglycemic agents. There are different classes of anti-diabetic drugs, and their selection depends on the nature of the diabetes, age and situation of the person, as well as other factors[4]. DM type 2 is a disease of insulin resistance by cells. Treatments include (1) agents which increase the amount of insulin secreted by the pancreas, (2) agents which increase sensitivity of target organs to insulin and (3) agents which decrease the rate at which glucose is absorbed from the gastrointestinal tract[6]. Development of drug concentrate on two ways: target of localization and targets of drugs. By closing the potassium channels of the pancreatic beta cells, they open the calcium channels, hence enhancing insulin secretion. Since antiquity, diabetes has been treated with plant medicines. Recent scientific investigation has confirmed the efficacy of many reparations, some of which are remarkably effective[5]. Only those herbs that appear the most effective are relatively non-toxic and have substantial documentation of efficacy. Herbal remedies, dietary supplements, and correct life style changes, all together in combination, may reduce or eliminate the need for medication in diabetics[11]. It also helps in preventing some of the tissue and organ damage associated with uncontrolled blood sugar levels. Diabetes has been treated with plant medicines. Those herbs that are most effective are relatively non-toxic[12]. Effective blood glucose control is a key step in the management of type II diabetes to prevent related metabolic complications associated with this disease[7]. Certain plant extracts like *Terminalia chebula* are known to exert insulin like action[3]. In the 1970s it was realized that inhibition of all or some of the enzymes like pancreatic amylase and α - glucosidase by inhibitors could regulate the absorption of carbohydrate and these inhibitors could be used therapeutically in the oral treatment of the non insulin dependent diabetes mellitus[8]. *Salacia chinensis* L.contains mangiferin a xanthone and a potent competative α - glucosidase inhibitor[9]. It is more potent than commercial acarbose. Thus mangiferin provides an alternative to the conventional medical use α - glucosidase inhibitors[10].

METHODS

Retrieving PDB: (Protein Data Bank)[A]

The X-ray crystallographic structure of the enzyme α - Amylase(3M07)[D], α - Glucosidase(2F2H)[E] was collected from the Protein Data Bank.

Finding Active Site of the protein(Receptor)[G]

What if (Please check the word)server was used to predict the active site of the protein. Total number of active sites of the protein(receptor) 10 based on energy based active site prediction and the residues have been identified[15].

Ligand Preparation

The set of ligand molecules studied in this work include mangiferin and its structurally similar bioactive compounds. The ligand molecules were retrieved from NCBI-PubChem Compound database [13,H]

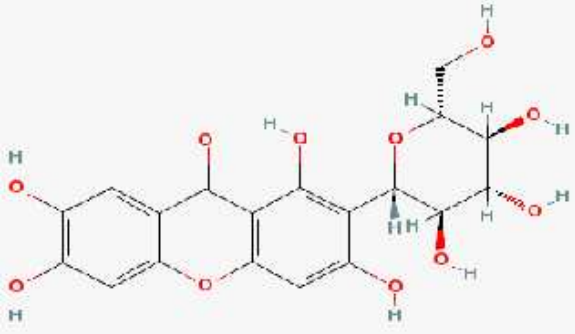

Figure 1
2d Representation of Mangiferin [Pubchem ID CID_5281647]

Docking Simulation

In order to carry out the docking simulation, we used the AutoDock 4.0 suite as molecular-docking tool. It is suitable software for performing automated docking of ligands to their macromolecular receptors. The Graphical User Interface program "AutoDock Tools" was used to prepare, run, and analyze the docking simulation[14]. Results of interaction were viewed using the Molecular visualization software like PyMol.

α - Amylase vs Mangiferin

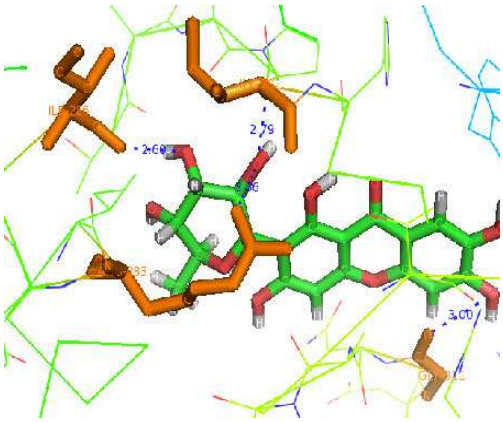

Figure 2(a)
Stick representation

α - Glucidase vs Mangiferin

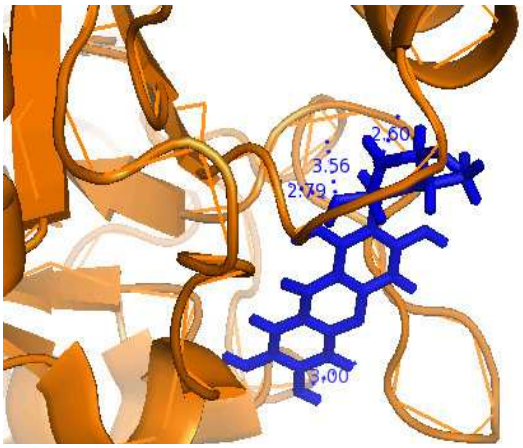

Figure 2(b)
Cartoon Representation

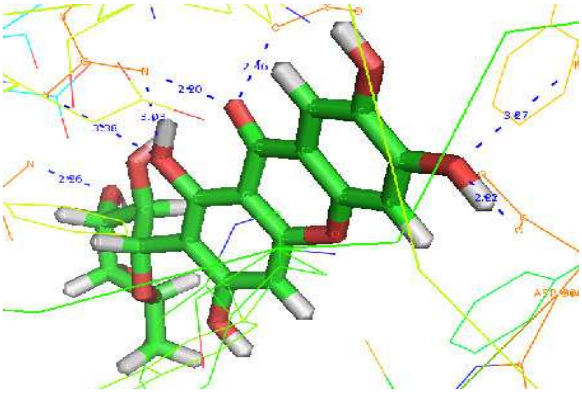

Figure 3(a)
Stick representation

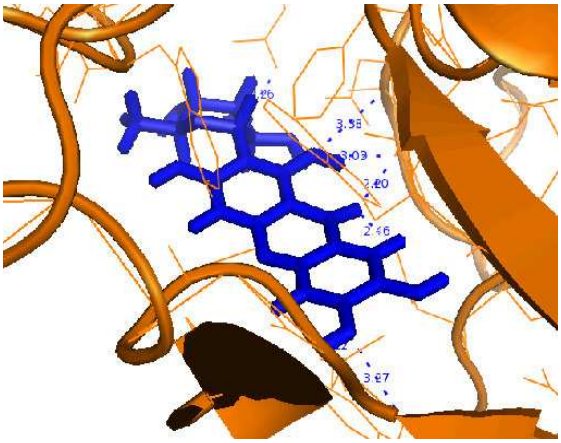

Figure 3(b)
Cartoon Representation

Table 1
Interaction Profile

Receptor Vs Mangiferin	Residues	Atom types		Bond Length	No. H Bonds
		Receptor	Ligand		
α - Amylase	ILE 291, ARG	NI, NB	OA, OB4	2.79Ă, 3.56 Ă,	4
	283,ILE 286, GLY 311	OA, OBA	OBI, OBI	2.60 Ă, 3.00 Ă,	
α - Glucosidase	ASP 482, ARG 466, HIS 540,	NI, NB, NAI,NO	OA,OB4, OBI,OAI,	2.46 Ă, 3.38 Ă, 3.03 Ă, 2.20 Ă,	6
	ASP 306	OA,OBA	OA2,ODI	3.27 Ă, 2.22 Ă,	

Figure 2(a,b): α – Amylase vs Mangiferin
- Residues from receptor ILE 291, ARG 283, ILE 286, GLY 311 and its atom types N1, NB - (Nitrogen), OA, OBA - (Oxygen), interacting with Ligand atom types OA, OB4, OB1, OA1 (Oxygen), correspondingly in the Armstrong distance of bond length as 2.79 Ă, 3.56 Ă, 2.60 Ă, 3.00 Ă.

Figure 3(a,b): α - Glucosidase vs Mangiferin
Residues from receptor ASP 482, ARG 466, HIS 540, ASP 306 and its atom types N1, NB, NA1, NO - (Nitrogen), OA, OBA - (Oxygen), interacting with Ligand atom types OA, OB4, OB1, OA1, OA2, OD1(Oxygen), correspondingly in the Armstrong distance of bond length as 2.46 Ă, 3.38 Ă, 3.03 Ă, 2.20 Ă, 3.27 Ă, 2.22 Ă.

DISCUSSION

In the concise context of above mentioned receptor types that could effectively inhibit Type II diabetes patients from enzymatic process in α - Glucosidase. Mangiferin inhibits more in cellular level progress. Active site prediction of protein shows ten actively participating residues by its energy based prediction. It varies in all two receptor by its prediction. Each predicted active site has minimum 40 residues and used for docking simulation. In theoretically atom-atom constraint sticks with bound energy format. According to autodock score, energy potential and internal energy system must be low in the interaction profile. As it is mentioned, among two kinds of enzymatic inhibition from mangiferin, α - glucosidase shows more inhibitory form. Observation of atomic level interaction shows oxygen and nitrogen atoms paves the way to interact with protein and ligand complex. In the theoretical chemistry, to confirm from bond length we could manage with two atoms and its probable amount of atomic radii. Atomic radii of two atoms forms bond length. Bond length has some limit to manage the energy level in the Autodock procedure. Upper limit and lower limit of the interaction.(Please check the sentence is it heading?) Upper limit considers adding of two atomic radii and lower limit considers minimum possible length to interact. Mangiferin compound has 18 hydrogen atoms, 11 oxygen atoms and 19 carbon atoms. From this atom types from ligand OA, OB4, OB1, OA1, OA2, OD1 occupies the interaction profile with protein(receptor). In the receptor, interaction of atom types contains N1, NB, NA1, NO OA, OBA. All atoms have unique form of identification for programming concept. It is now computationally proved by docking

procedure and its algorithmic form by observing energy value and its number of hydrogen bonds formed between receptor and ligand. It is generally the theoretical consideration of computational hypothesis and applied to our results and observed lower energy value and more number of hydrogen bonds give more stable active compound for the inhibition of type II Diabetes and accepts the protocol of Lennard Jones Potential(LJ) of receptor and Ligand interaction concept more interacting hydrogen bonds and which have least dockink energy score were considered as good inhibitors. While observing the number of hydrogen bonds.

CONCLUSION

Bioinformatic study has been carried out to discover insilico drug to combat the serious disorder diabetes. According to bioinformatic mangiferin had 7 hydrogen bonds with the receptor α- glucosidase. Lower energy value gives more stable compound for inhibition, focusing from this point mangiferin has least binding energy with α – glucosidase. Hence α – glulcosidase is considered as the most suitable drug target to treat diabetes.

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