Research Article

Computational Screening and Docking Analysis of Natural Compounds Derived From Mangrove Plant against Type-2 Diabetes, Myo-Inositol Oxygenase Enzyme (Miox)

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ABSTRACT

Worldwide diabetes mellitus refers to a group of disorders with different etiologies. In the present study effort has been made to apply the bioinformatics tools to identify the action of mangrove derived compounds against the target protein of the disease diabetes mellitus. The molecular targets, Myo-Inositol Oxygenase (MIOX), the crystallographic structures are available on the Protein Data Bank database as (PDB ID: 3BXD), were used for the docking analysis using the Argus lab programs. The docking studies of the mangrove derived compounds as ligand with target proteins showed that this is a good molecule which docks well with various targets related to diabetes mellitus. Hence the mangrove derived compounds can be considered for developing into a potent anti-diabetic drug.

Keywords: PDB, MIOX, Diabetes, mangrove derived compounds.

INTRODUCTION

Diabetes mellitus refers to a group of disorders with different etiologies. It is characterized by derangements in carbohydrates, proteins and fat metabolism caused by the complete or relative insufficiency of insulin secretion and/or insulin action [1]. It is a chronic metabolic disorder involved in the deregulation of glucose metabolism, β-cell dysfunction, and impaired insulin sensitivity. Glucokinase (GK) promotes glycogen synthesis, while it enhances insulin secretion from pancreatic β-cells [2]. It is characterized by hyperglycemia resulting in the defects of insulin secretion and action. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Hypertension and abnormalities of lipoprotein metabolism are often found in people who are suffering with diabetes. The diabetes mellitus falls into two major categories type-1 and type-2. Type-1 diabetes causes an absolute deficiency of insulin secretion. Individuals at increased risk of developing this type of diabetes can often be identified by serological evidence of an autoimmune pathologic process occurring in the pancreatic islets and by genetic markers. On the other hand type-2 diabetes is much more prevalent category, which causes a combination of resistance to insulin action and an inadequate compensatory insulin secretory response [3]. In type-2 diabetes, the enzymatic control of gluconeogenesis is compromised, thus allowing the production of excessive amounts of glucose resulting in elevated blood glucose levels characteristic of the disease[4].

Type-2 diabetes mellitus (T2DM) is one of the fastest growing metabolic syndromes of multiple etiologies including dyslipidemia. The abnormality of lipoprotein plays a significant role in the development of premature atherosclerosis leading to cardiovascular disease. Further it can impair insulin secretion and action leading to β-cell failure, which involves both a partial loss of β-cell mass and deterioration of β-cell function [5]. Type-2 diabetes is a worldwide diffused disease characterized by insulin resistance that arises from alterations of receptor and/or post-receptor events of insulin signaling 6(Paoli *et al.*, 2013). Throughout the world about 95% of diabetic patients suffer from type-2 diabetes[7].

Diabetes mellitus poses a major health problem on both clinical and social plan. Worldwide more than 220 million peoples are affected by diabetes and its incidence is expected to increase to 400 million by 2030, about 95% of diabetic patients suffer from type-2 diabetes.[8,9]. Altered inositol metabolism is implicated in a number of diabetic complications. The first committed step in mammalian inositol catabolism is performed by myo-inositol oxygenase (MIOX), which catalyzes a unique four-electron dioxygen-dependent ring cleavage of myo-inositol to D-glucuronate. The crystal structure of human MIOX is complex with myo-inosose-1 bound in a terminal mode to the MIOX diiron cluster site. From biochemical and biophysical results the N-terminal deletion mutagenesis and N terminus is important through the coordination of a set of loops covering and shielding the active site, during catalysis. EPR spectroscopy of the unliganded enzyme displays a two-component spectrum that we can relate to an open and a closed active site conformation. Based on site-directed mutagenesis in combination with biochemical and biophysical data, a novel role for Lys (127) was governed to access the diiron cluster[10]. There are different groups of oral hypoglycemic agents for clinical use, having characteristic profiles of side effects[11, 12]. Management of diabetes without any side effects is still a challenge to the medical system. This leads to increasing demand for natural products with antidiabetic activity with fewer side effects.

MATERIALS AND METHODS

Protein Structure

The targeted protein myo-inositol oxygenase (ID: 3BXD), having the resolution of 1.80 A^{o} was retrieved from the protein data bank (PDB) (www.rcsb.org/pdb). Structural and active site studies of the protein were done by using CASTP (Computed Atlas of Surface Topography of Proteins) and pymol molecular visualization software. Six phytochemical ligand molecules namely Stigmasterol, Tretinoin, Tricin,Heritonin, Ascochitine and Taraxasterol retrieved from pubchem database (http://pubchem.ncbi.nlm.nih.gov), were screened against the myo-inositol oxygenase.

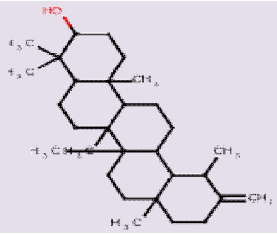
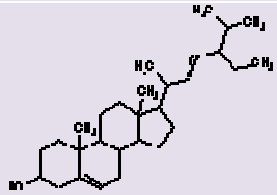
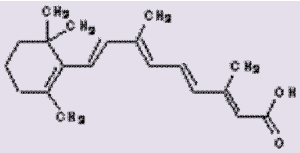
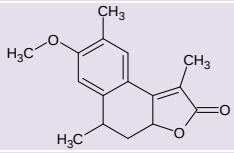
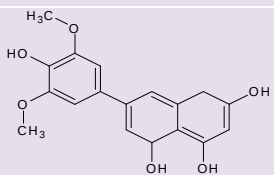
Amino acid binding site

The phytochemical molecules were retrieved from the pubchem database. The selected chemical structures were generated from SMILES notation (Simplified Molecular Input Line Entry Specification) by using the Chemsketch Software (www.acdlabs.com). After successfully binding the structures, geometry optimization and energy minimization were done. The energy minimization process was carried out for 100 cycles using the chimera software. The predicted ligand binding site residues in Myo-inositol oxygenase THR256, PHE28, LYS251, PHE252, TYR255.

Docking methods

Argus Lab 4.01 was used for docking analysis, which is widely distributed public domain molecular docking software. The inhibitor and target protein were geometrically optimized and docked using docking engine Argus dock. The docking simulations in the active sites of 3BXD were performed by the Argus lab program, which has been shown to successfully reproduce experimentally observed binding modes in terms of lowest docking energy. The target protein structure of 3BXD was docked with mangrove derived compounds which provided excellent results as were seen by the least values of the binding energy. The best possible binding modes of the mangrove derived compounds at targeted protein's active sites are displayed.

Table 1: Docking results of mangrove derived compounds against myo-inositol oxygenase

Compound Name	Pubchem ID	Compound structure	Molecular Weight (g/mol)	Hydrogen donor/ acceptor	Docking Energy Level (Kcal/mol)
Taraxasterol	CID:5270604		426.7174	1,1	-14.8894
Stigmasterol	CID: 5280794		269.082	(1,1)	-14.5899
Tretinoin	CID:444795		300.43512	(1,2)	-12.1034
Heritonin	CID:130118		258.31232	0,3	-10.4072
Ascochitine	CID:5464489		276.28454,	2,5	-9.5382
Tricin	CID: 5281702		330.288	(3,7)	-6.9602

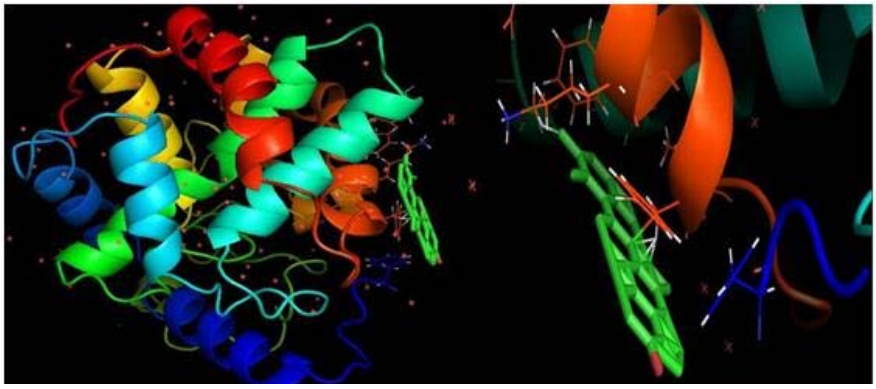


Figure 1: Interaction between residues (myo-inositol oxygenase) and ligand (Taraxasterol), hydrogen bond and polar interaction are shown as green line.

RESULTS

Six chemicals derived from mangrove ecosystem were docked with myo-inositol oxygenase. The docked ligand molecules were selected based on docking energy and good interaction with the active site residues and the results are shown in Table 1and fig 1. From the six ligand molecules, 4 showed the binding energy of greater than -10 Kcal/mol which are Taraxasterol, Stigmasterol, Tretinoin, Heritonin. The binding energies (-14.8894, -14.5899, -12.1034, -10.4072 Kcal/mol) respectively, and the remaining two compounds exhibited the values of less than -10 kcal/mol. The lowest binding energy of -9.5382 and -6.9602 Kcal/mol was found in Ascochitine and Tricin. Thus, the *in silico* docking results, revealed that mangrove derived compounds have the great potential against inhibition of myo-inositol oxygenase

DISCUSSION

Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. Our previous docking studies have already proved the efficacy of mangrove derived compounds against oncoprotein of cervical cancer, NS5 methyltransferase protein responsible for flavivirus and breast cancer protein BRCA1[13-15]. The present study also proved that the coastal mangrove- derived compounds were capable of inhibitor for myo-inositol oxygenase. Ultimately this could lead to inhibition of the growth of Diabetic melitus

The chemical compounds namely Stigmasterol, Tretinoin, Tricin, Heritonin, Ascochitine and Taraxasterol, were identified from mangrove derived compounds and screened against the human myo-inositol oxygenase. (MIOX) complex. The mangrove derived compounds derived compounds were satisfied the Lipinski's Rule of five Not more than 5 hydrogen bond donors (OH an NH groups), not more than 10 hydrogen bond acceptors (notably N and O), molecular weight under 500 g/mol, partition coefficient log P less than 5 and the rotatable bonds less than 10. The chemical compounds docked with targeted protein, the docked ligand molecules were selected based on docking energy and good interaction with the active site residues and the results are shown on the above table 1.

CONCLUSION

Mangrove derived compounds are rich in phenolic compounds of medicinal value. These compounds are ecofriendly, safer and cheaper for application. Natural products and their derivatives have been invaluable as a source of therapeutic agents it possess high chemical diversity, biochemical specificity and molecular diversity within the boundaries of reasonable drug-like properties, from these we make the mangrove derived compounds as attractive targets as lead structures for drug discovery. Here we performed an *in silico* docking methods to determine the mangrove derived compounds were efficacy for anti-diabetic. The results show the best docking score value and also the compounds were satisfied Lipinski's rule of five. We suggest that the Taraxasterol, Stigmasterol has the potential to be developed into a new class of anti-diabetic drugs. The results obtained from this study would be useful in both understanding the inhibitory mode of mangrove derived compounds as well as in rapidly and accurately predicting the activities of newly designed inhibitors on the basis of docking scores. Here we concluded the compounds derived from mangrove ecosystem (Stigmasterol, Taraxasterol, Tretinoin, Heritonin, Ascochitine and Tricin) could be a novel inhibitor for myo-inositol oxygenase.

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