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IDENTIFICATION OF ANTI-DIABETIC ACTIVITY OF *PTEROCARPUS SANTALINUS* LINN (RED SANDALWOOD) COMPOUNDS BY INSILICO APPROACH

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ABSTRACT: Medicinal plants have wide spread properties due to the presence of phytocompounds and are the alternative medicines available for those who cannot be helped by conventional medicine. In this work we have selected bioactive compounds from *Pterocarpus santalinus* Linn medicinal plant extracts. Gas chromatography and Mass Spectrum studies were studied to identify the compounds present in the Methanolic extracts based on the retention time, area and the compounds present in the Extracts of *Pterocarpus santalinus* Linn were identified. The identified compounds were used for anti-cataract activity by insilico method with Alpha glucosidase which plays an important role in causing diabetes mellitus and hence chosen for docking studies with identified compounds. Docking results showed that out of Twenty compounds, Cyclo Hexane, 1-ethyl-1-methyl,2,4-bis(1-methyl, ethanyl) shown best docking energy to the Alpha glucosidase.

KEYWORDS: Anti-Diabetic, Docking studies, Alpha Glucosidase, *Pterocarpus santalinus* Linn.

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1.INTRODUCTION

The World Health Organization (WHO) projects that diabetes deaths are to increase by over 80% in coming decades [1]. This result the demand for medical care in type 2 diabetes will continue to increase. Type 2 diabetes is one of the major life threatening diseases, all over world and is one of the major public health challenges of the 21st century [2]. Glucose control is an important goal to

diminish the risk of long term health complications of type 2 diabetes. Alpha-glucosidase inhibition is one of the powerful interventions and recently recommended as essential target for diabetes management [3]. Alpha-glucosidase is a glucosidase acting upon 1,4-alpha bonds and carbohydrates are converted into simple sugars, which can be absorbed through the intestine [4]. Hence, alpha-glucosidase inhibitors reduce the impact of carbohydrates on blood sugar and are used to establish greater glycemic control over hyperglycemia in diabetes mellitus type 2, particularly with regard to postprandial hyperglycemia [5]**.** These inhibitors are saccharides that act as competitive inhibitors of enzymes needed to digest carbohydrates, specifically alpha-glucosidase enzymes in the brush border of the small intestines. The membrane-bound intestinal alpha-glucosidases hydrolyze oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides in the small intestine [6]. Alpha-glucosidase is intestinal enzyme which catalyzes the degradation of diet polysaccharides to absorbable monosaccharide. Natural or synthetic glucosidase inhibitors are of therapeutic interest to delay postprandial hyperglycemia in type 2diabetes [7]. The objective of this investigation was to characterize and determine the effect of the natural compounds on α-Glucosidase which is an important protein involved in Type 2 Diabetes. Plants like *Pterocarpus santalinus Linn* have shown delaying effect on experimental diabetes. Therefore, it is important to evaluate new plant-derived agents scientifically. *Pterocarpus santalinus Linn* in Indian system of medicine are used traditionally for the treatment for anti-diabetes [8]. Hence, in present study these three Indian medicinal plants were selected to evaluate inhibitory effect on alpha glucosidase.

2. MATERIALS AND METHODS

GC-MS method for identification of compounds

GC-MS analysis was carried out on a GC CLARUS 550 PerkinElmer system comprising a gas chromatograph interfaced to a mass spectrometer (GC-MS) instrument employing the following conditions: column Elite-1 fused silica capillary column (30×0.25 mm ID×1EM df, composed of 100% Dimethyl poly siloxane), operating in electron impact mode at 70 eV; helium (99.999%) was used as carrier gas at a constant flow of 1ml/min and an injection volume of 0.5 EI was employed with split ratio of 10:1injector temperature 250°C; ion-source temperature 280°C. The oven temperature was fixed from 110°C (isothermal for 2 min), with an increase of 10°C/min, to 200°C, then 5°C/min to 280°C, ending with a 9 min isothermal at 280°C. Mass spectra were taken at 70 eV; a scan interval of 0.5 s and fragments from 40 to 550 Da [9].

Collection of alpha glucosidase structure

The structure of Alpha glucosidase (PDB ID: 2QLY) were obtained from PDB database. After the unnecessary chains and hetero atoms were removed using SPDBV software, hydrogens were added to the protein and used for active site identification.

Active site Identification

Active site of Alpha glucosidase (PDB ID: 2QLY) of Homo sapiens was identified using CASTp server. A new program, CASTp, for automatically locating and measuring protein pockets and cavities, is based on precise computational geometry methods, including alpha shape and discrete flow theory. CASTp identifies and measures pockets and pocket mouth openings, as well as cavities. The program specifies the atoms lining pockets, pocket openings, and buried cavities; the volume and area of pockets and cavities; and the area and circumference of mouth openings [10].

Docking method

Docking was carried out using GOLD (Genetic Optimization of Ligand Docking) software which is based on genetic algorithm (GA). This method allows as partial flexibility of protein and full flexibility of ligand. The compounds identified in GC-MS are docked to the active site of the Alpha glucosidase of Homo sapiens. The interaction of the Caffeine with the active site residues are thoroughly studied using molecular mechanics calculations. The parameters used for GA were population size (100), selection pressure (1.1), number of operations (10,000), number of island (1) and niche size (2). Operator parameters for crossover, mutation and migration were set to 100, 100 and 10 respectively. Default cutoff values of 3.0 A° (dH-X) for hydrogen bonds and 6.0 A° for vanderwaals were employed. During docking, the default algorithm speed was selected and the ligand binding site in the targets were defined within a 10 A° radius with the centroid as CE atom of active residues. The number of poses for each inhibitor was set 100, and early termination was allowed if the top three bound conformations of a ligand were within 1.5A° RMSD. After docking, the individual binding poses of compounds were observed and their interactions with the protein were studied. The best and most energetically favorable conformation of Caffeine ligand was selected [11-14].

Gold Score fitness function

Gold Score performs a force field based scoring function and is made up of four components: 1. Protein-ligand hydrogen bond energy (external H-bond); 2. Protein-ligand vander Waals energy (external vdw); 3. Ligand internal vander Waals energy (internal vdw); 4. Ligand intramolecular hydrogen bond energy (internal- H- bond). The external vdw score is multiplied by a factor of 1.375 when the total fitness score is computed. This is an empirical correction to encourage protein-ligand hydrophobic contact. The fitness function has been optimized for the prediction of ligand binding positions.

GoldScore = S (hb_ext) + S (vdw_ext) + S (hb_int) + S (vdw_int)

Where S (hb_ext) is the protein-ligand hydrogen bond score, S (vdw_ext) is the protein-ligand van der Waals score, S (hb_int) is the score from intramolecular hydrogen bond in the ligand and S (vdw_int) is the score from intramolecular strain in the ligand [15-19].

3. RESULTS AND DISCUSSION

Gas chromatography method was used to identify the compounds present in the Methanolic extracts of *Pterocarpus santalinus Linn*. From the PDB databank, the PDB files were collected and the final stable structure of the Alpha glucosidase of Homo sapiens obtained is shown in Figure 1. The ligands present in the crystal structure were removed along with hetero atoms for docking studies [20-28].

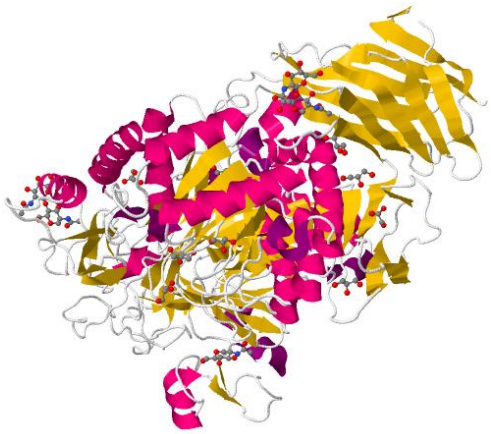

Fig 1: Alpha glucosidase

Active site Identification

After the final model was built, the possible binding sites of Alpha glucosidase was searched based on the structural comparison of template and the model build and also with CASTP server and was shown in Figure 2. Infact from the final refined model of Alpha glucosidase domain using SPDBV program, it was found that secondary structures are highly conserved and the residues shown below [28-34].

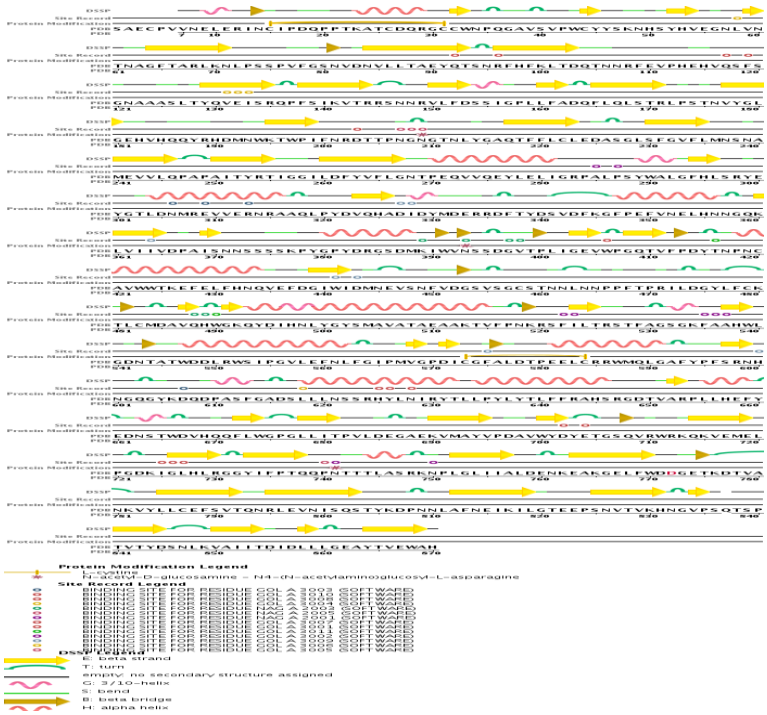

Fig 2: active site of Alpha glucosidase

Docking of inhibitors with the active site

Docking of the compounds with Alpha glucosidase was performed using GOLD 3.0.1, which is based on genetic algorithm. This program generates an ensemble of different rigid body orientations (poses) for each compound conformer within the binding pocket and then passes each molecule against a negative image of the binding site. Poses clashing with this 'bump map' are eliminated. Poses surviving the bump test are then scored and ranked with a Gaussian shape function. We defined the binding pocket using the ligand-free protein structure and a box enclosing the binding site. This box was defined by extending the size of a cocrystalized ligand by 4A. This dimension was considered here appropriate to allow, for instance, compounds larger than the cocrystallized ones to fit into the binding site. One unique pose for each of the best-scored compounds was saved for the subsequent steps. The compounds used for docking was converted in 3D with SILVER. To this set, the substrate corresponding to the protein was added. Docking of best inhibitor with the active site of protein showed the activity of the molecule on protein function (Fig 3 and 4) [35-38].

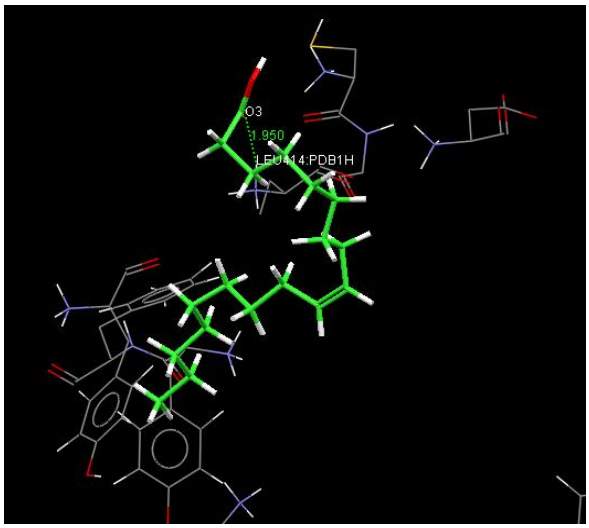

Fig 3: Pregnon-20-0ne

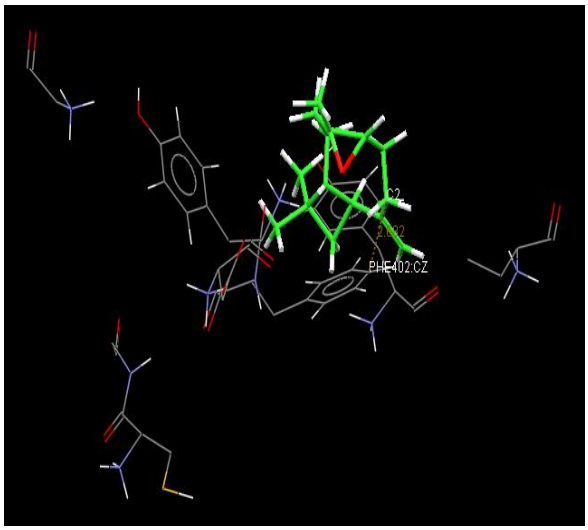

Fig 4: CycloHexane, 1-ethyl-1-methyl,2,4-bis(1-methyl,ethanyl)

4. CONCLUSION

The phytocompounds were identified through GC-MS studies and structural conformation was done by Mass Spectrum analysis. The identified phytocompounds were docked to the alpha glucosidase for their anti-diabetic activity. Among the phytocompounds docked, Cyclo Hexane, 1-ethyl-1-methyl,2,4-bis(1-methyl, ethanyl) showed best docking value with alpha glucosidase.

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CONFLICT OF INTEREST

Authors have no conflict of interest

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