IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
September 2016 Vol.:7, Issue:2

Antidiabetic Activity of Bioactive Compounds from *Gmelina arborea* Fruit - An *In Silico* Approach

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Kumaresan.P, Dr.K.A.Jeyanthi, Dr.R. Kalaivani

PG & Research Department of Biotechnology, Thanthai Hans Roever College, Perambalur, Tamil nadu, India.

Submission: 10 September 2016
Accepted: 15 September 2016
Published: 25 September 2016

Keywords: Traditional, backbone, nutrition, therapeutic value

ABSTRACT

India is one of the few countries where almost all the known medicinal plants can be cultivated in some part of the country. In almost all the traditional medical systems, the medicinal plants play a major role and constitute their backbone. Moreover, some plants consider as an important source of nutrition and as a result of that these plants recommended for their therapeutic values. Diabetes mellitus is clinical syndrome a group of metabolic diseases. Herbal drugs are prescribed widely because of their effective, less side effect and relatively low cost.

INTRODUCTION

The World Health Organization (WHO) estimates that about 80% of the population living in the developing countries relies almost exclusively on traditional medicine for their primary healthcare needs. The term of medicinal plants include various types of plants used in herbalism and some of these plants have medicinal activities. These medicinal plants consider as rich resources of ingredients which can be used in drug development and synthesis. Moreover, some plants consider as an important source of nutrition and as a result of that these plants recommended for their therapeutic values. India is one of the few countries where almost all the known medicinal plants can be cultivated in some part of the country or the other. India has about 2,000 species of medicinal plants and a vast geographical area with high production potential and varied agro-climatic conditions [1]. *Gmelin arborea* is a fast growing deciduous tree which grows on different localities and prefers moist fertile valleys with 750–4500 mm rainfall [2].

Diabetes mellitus is clinical syndrome a group of metabolic diseases. This high blood sugar produces the classical symptoms of Polyuria (frequent urination), Polydipsia (increased thirst), and Polyphagia (increased hunger).All forms of diabetes have been treatable since insulin became available in 1921, and type 2 diabetes may be controlled with medications. It is the most common endocrine disorder, affecting 200 million. Many herbal medicines have been recommended for the treatment of diabetes. Herbal drugs are prescribed widely because of their effective, less side effect and relatively low cost[3].The International Diabetes Federation (IDF) estimated the global burden of diabetes was 366 million in 2011 and it would rise to 552 million by 2030[4]. Docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. The associations between biologically relevant molecules such as proteins, nucleic acids, carbohydrates, and lipids play a central role in signal transduction[5].

The main target of insulins anti- lipolytic action is believed to be phosphodiesterase 3B (PDE3B), whose phosphorylation by Akt leads to accelerated degradation of the pro-lipolytic second messenger Camp. Glucagon-like peptide-1(GLP-1) is a 30 residue peptide hormone released from intestinal L-cells following nutrient consumption. It potentiates the glucose-

induced secretion of insulin from pancreatic beta cells, increases insulin expression, inhibits beta cell apoptosis, promotes beta cell neogenesis, reduces glucagon secretion, delays gastric emptying, promotes satiety and increases peripheral glucose disposal[6].

MATERIALS METHODS

Plant Materials

The Plant was collected from Thammampatty, Salem District, Tamilnadu. The Plant was identified, authenticated and the voucher specimen has been in our laboratory for the future reference. The fruit was shaded, dried, powdered and passed through a 40 mesh sieve and kept in a well closed contain for further extraction.

Sample Preparation

About 2.0g of the sample was soaked in 100 ml ethanol for 24 hours. The extract was filtered through what man no.1 and the filtrate was concentrated dryness. The extract was diluted with ethanol and used for the experiment.

Ligands and receptor

The compound identified by GCMS method was then drawn using chem. Sketch software. The smiles formula obtained from chem. The structure of PDE3B and GLP-1 was obtained from PDB databank. Using control panel of this stand-alone the software, the ligand molecules attached to the receptor were selected. All the residues surrounding the ligand which comes in 8.0^0A were identified and using Hex software.

Analysis

Active site analysis of GLP-1 and PDE3B receptor were carried out using EXPASY Prosite. Docking result obtained for each compound with the receptor was analyzed. Apart from docking energy, binding mode and interaction of each ligand with the functional residues of the GLP-1 and PDE3B receptor were analyzed in detail by visually inspecting the docked complexes using Hex tool.

RESULT AND DISCUSSION

Gmelina arborea is a traditional medicinal plant which was rich in secondary metabolites such as Alkaloids, Carbohydrate, Glycoside, Protein and amino acid, Tannins, Phenolic compounds, Steroids, Triterpenoids, Saponins, and flavonoids. In the present study, the anti-diabetic activity was evaluated using docking by Hex software. From the GC-MS analyses table no 1. The structure was evaluated and mined from the NCBI PubChem database. Further, the active site residues were identified using the EXPASY Prosite is shown in table 2 and 3. Plant-derived flavonoids and phenols are known as potential active compounds that possess a broad range of pharmaceutical properties, antifungal, antiviral anticancer activity [7]. These compounds have also been used as templates for the development of new pharmaceuticals [8]. The energy values obtained for each receptor using Hex is shown in table-4 and 5.

Ligands and receptor

The compound identified by GCMS method was then drawn using chem. Sketch software. The smiles formula obtained from chem. The structure of PDE3B and GLP-1 was obtained from PDB databank. Using control panel of this stand-alone the software, the ligand molecules attached to the receptor were selected. All the residues surrounding the ligand which comes in 8.0^0A were identified and using Hex software. The resulting data of receptor-ligand interactions demonstrates that *in silico* screening method is highly efficient for identifying potential lead compounds against major disorders/diseases [9].

Analysis

Active site analysis of GLP-1 and PDE3B receptor were carried out using EXPASY Prosite. Docking result obtained for each compound with the receptor was analyzed. Apart from docking energy, binding mode and interaction of each ligand with the functional residues of the GLP-1 and PDE3B receptor were analyzed in detail by visually inspecting the docked complexes using Hex tool. To our knowledge, our study is the first to define a role for PDE3B in cardioprotection against IR injury and suggests PDE3B as a target for cardiovascular therapies. GLP-1-based therapies appear to provide gainful effects against atherosclerosis. More randomized data will be required to arrive at conclusive evidence [10].

This result clearly demonstrates that the approach used in the study is successful in finding novel anti-diabetic compounds from plants. Also, the study states and confirms the importance of small molecules from plants, their use in enhancing protein-ligand interaction studies and vital clues that can be used to design new molecules with improved activity.

The active site residues Phosphothreonine and Phosphoserine were predominantly predicted. PDE3B and GLP-1 protein bind to many types of molecules using a wide variety of binding site. They have binding site used by natural ligands. e.g., enzyme active sites and allosteric regulatory sites as well as "novel" binding site at which artificial or non-natural ligands, such as drugs, bind. Proteins are often bound to cofactor or post-translationally modified and these non-protein compounds can have an important influence on the protein binding site [11].

In the present study, docking of isolated compounds from the ethanol fraction of *Gmelina arborea* with PDE3B and GLP-1 receptor indicated that the compounds n-Hexadecanoic and Octadecanoic acid had binding score value shown in table no 5.

Figure 1 represented that target receptor PDE3B docked with n-Hexadecanoic acid and shows score value: 40.50. The target GLP-1n docked with n-Hexadecanoic acids showed in Figure 2. And has the score value of 45.75. The receptor PDE3B docked with the ligand Octadecanoic acid showed in fig 3 with score value 47.24. Figure 4 shows that target receptor GLP-1 docked with Octadecanoic acid and has the score value 48.75.

Graph 1 showed that the comparison of score values for the receptors with n-Hexadecanoic acid. The comparison of score value for the receptor with an Octadeconoic acid represented in the graph. 2.

Table-1 GCMS Analysis of *Gmelina arborea*

	Compound analyzed	Retention time	% Area of peak	Molecular formula	Mol. Wt. (In grams)
1	**Cycloheptasiloxane**	13.509	2.66	$C_{14}H_{42}O_7Si_{17}$	518
2	**Cyclooctasiloxane**	16.148	1.35	$C_{16}H_{48}OSi_6$	592
3	**Hexadecanoic acid**	18.651	18.16	$C_{17}H_{34}O_2$	270
4	**n- Hexadecanoic acid**	19.097	18.16	$C_{16}H_{32}O_2$	256
5	**9,12-Otadecanoic acid**	20.262	1.65	$CH_{19}H_{34}0_2$	294
6	**Otadecanoic acid**	20.961	5.32	$C_{18}H_{36}O_2$	284
7	**9-Otadecanoic acid**	22.457	1.01	$C_{18}H_{34}0_2$	282
8	**Eicosanoic acid**	22.702	0.65	$C_{20}H_{40}O_2$	312

Table 2: identification of binding sites in the GLP-1

No of binding sites/hits	Position of binding sites	Binding site profile
1	27 – 32, 78 – 83, 395 – 400, 446 – 451	Myristyl n-Myristoylation
2	31 – 34,49 – 52, 65 – 68, 124 – 127,135 – 138,136 – 139,219 – 222	CK2 Phospho site Casein Kinase 2 Phosphorylation
3	63 – 66,82 – 85,115 – 118	ASN Glycosylation n-Glycosylation
4	129 – 131,225 – 227,378 – 380,432 – 434	PKC Phospho_site Protein Kinase C Phosphorylation

Table-3. Identification of binding site in the PDE3B

No of binding sites	Position of binding site	Binding site profile
1	197 – 263	LEU rich Leucine-rich region
2	770 – 781	PDEASE 1 3'5'-cyclic Nucleotide Phosphodiesterases
3	22 – 25,188 – 191, 280 – 283, 299 – 302,403 – 406,482 –485, 537 – 540,539 – 542, 551 –554 568 – 571,600 – 603,618 – 621 718 – 721,722 – 725,742 – 745 797 – 800,813 – 816,973 – 976 984 - 987	CK2 Phosphosite Casein Kinase 2 Phosphorylation
4	26 – 28, 139 – 141, 310 – 312 402 – 404,479 – 481,548 – 550 562 – 564,574 – 576,579 – 581 641 – 643,702 – 704,737 – 739 1002 – 1004	PKC Phospho_site Protein Kinase C Phosphorylation
5	70 – 73,292 – 295,293 – 296 315 – 318,388 – 391,576 – 579 999 – 1002	CAMP Phospho site CAMP and CGMP dependent Protein Kinase Phosphorylation
6	83 – 88, 205 – 210,238 – 243 250 – 255,253 – 258,256 – 261 346 – 351,350 – 355,376 – 381 423 – 428,452 – 457,457 – 462 476 – 481,505 – 510,543 – 548 715 – 720,749 – 754,865 – 870 956 – 961	Myristyl n-Myristoylation

7	237 – 258	LEUCINE zipper Leucine zipper pattern
8	409 – 412	Amidation amidation
9	466 – 469	ASN Glycosylation n-Glycosylation
10	720–723, 969–972,1042– 1045, 674 – 680	N-linked (glcnac...)

Table 4: Identification of parameters for the docked structures

Ligand with receptors	E-total	E-shape	E-average	Total no of orientation	Average energy top 10	Average energy top 100	Average energy top 1000
PDE3B-n-hexadecanoic acid	-581.5	-581.5	-405.40	828827136	-556.73	-488.36	-410.71
GLP1-n-hexadecanoic acid	-363.52	-363.52	-244.03	828827136	-343.77	-299.81	-247.48
PDE3B-octadecanoic acid	-581.48	-581.48	-289.00	82887136	-457.72	-392.45	-296.40
GLP1-octadecanoic acid	-591.85	-591.85	-407.13	828827136	-550.37	-490.41	-412.75

Table 5: Identification of charged residues for the docked structures

Ligand with receptors	Formal charged residues		Emin	Emax	Atoms	Net formal charge	Score values
	Positive	Negative					
PDE3B-n-hexadecanoic acid	83	97	-581.48	-367.29	1349	-14	40.50
GLP1-n-hexadecanoic acid	18	19	-363.52	-121.05	1110	-1	45.75
PDE3B-octadecanoic acid	83	47	-483.45	-239.88	11930	-14	47.24
GLP1-octadecanoic acid	18	19	-591.85	-366.63	1110	-14	48.75

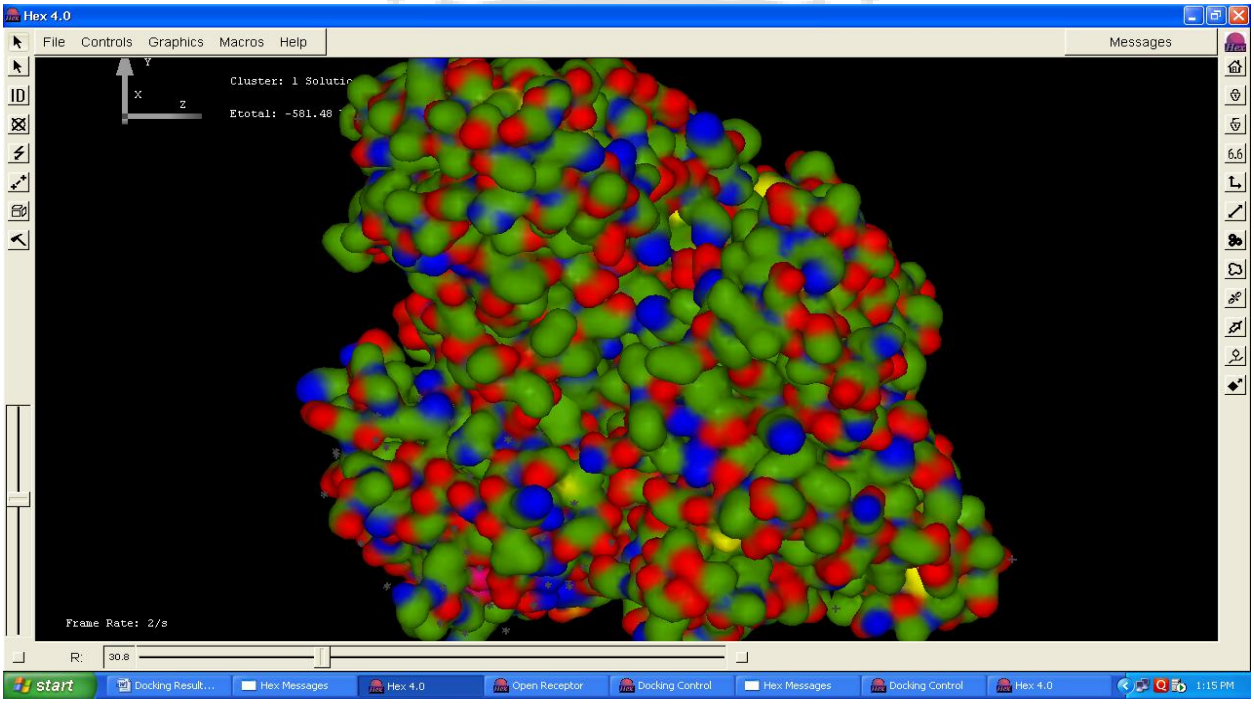


Fig 1: Target Receptor PDE3B docked with n-Hexadecanoic acid

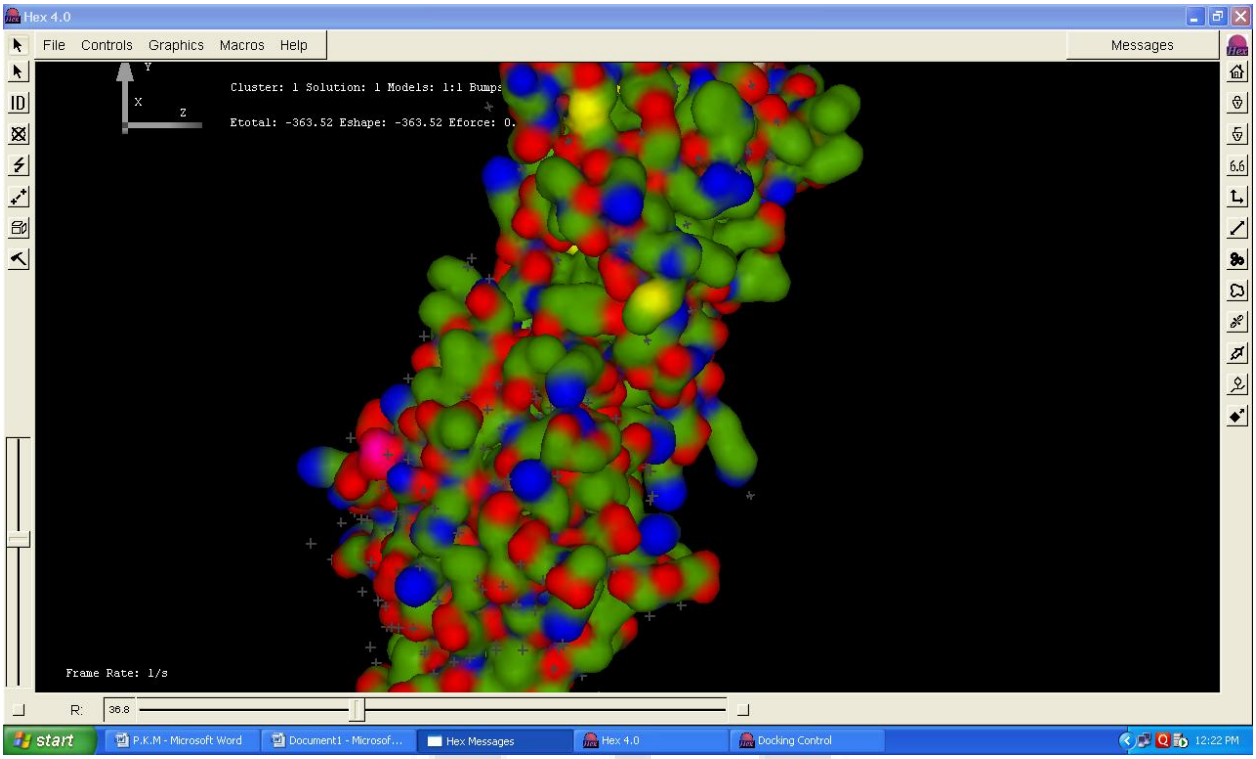


Fig 2:Target Receptor GLP1 docked with n-Hexadecanoic acid

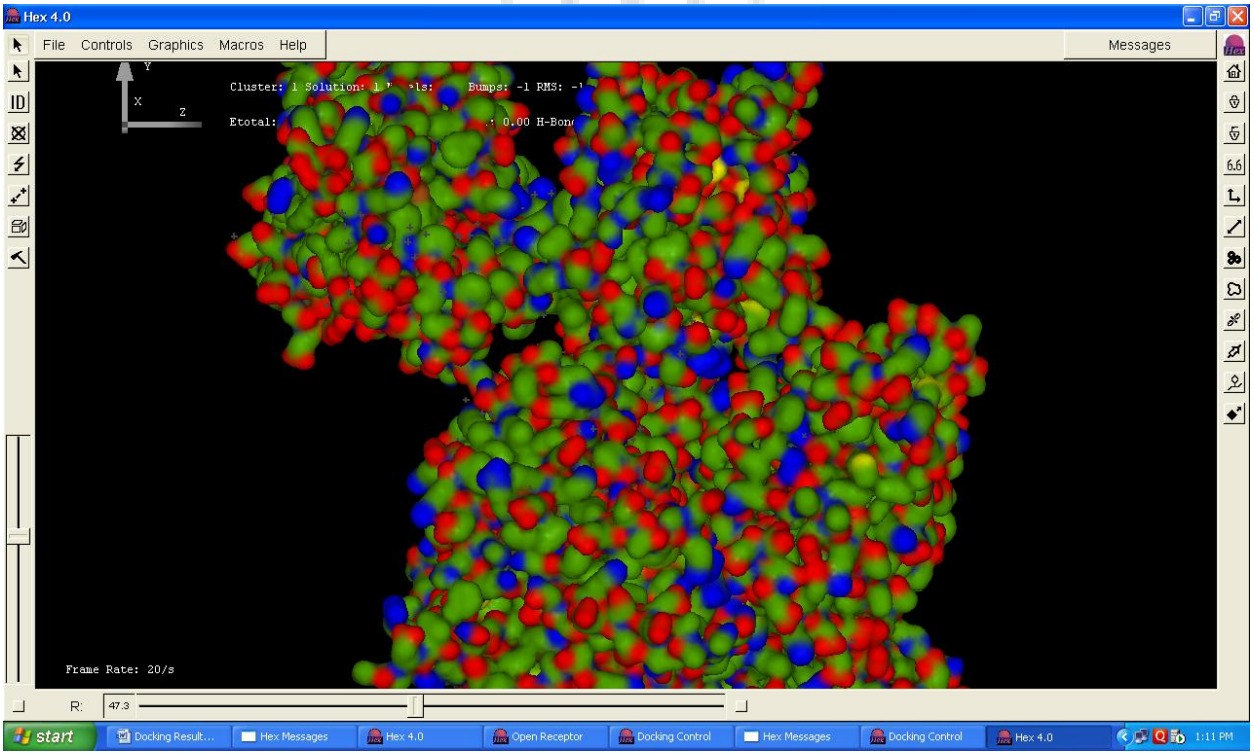


Fig 3: Target Receptor PDE3B docked with Octadecanoic acid

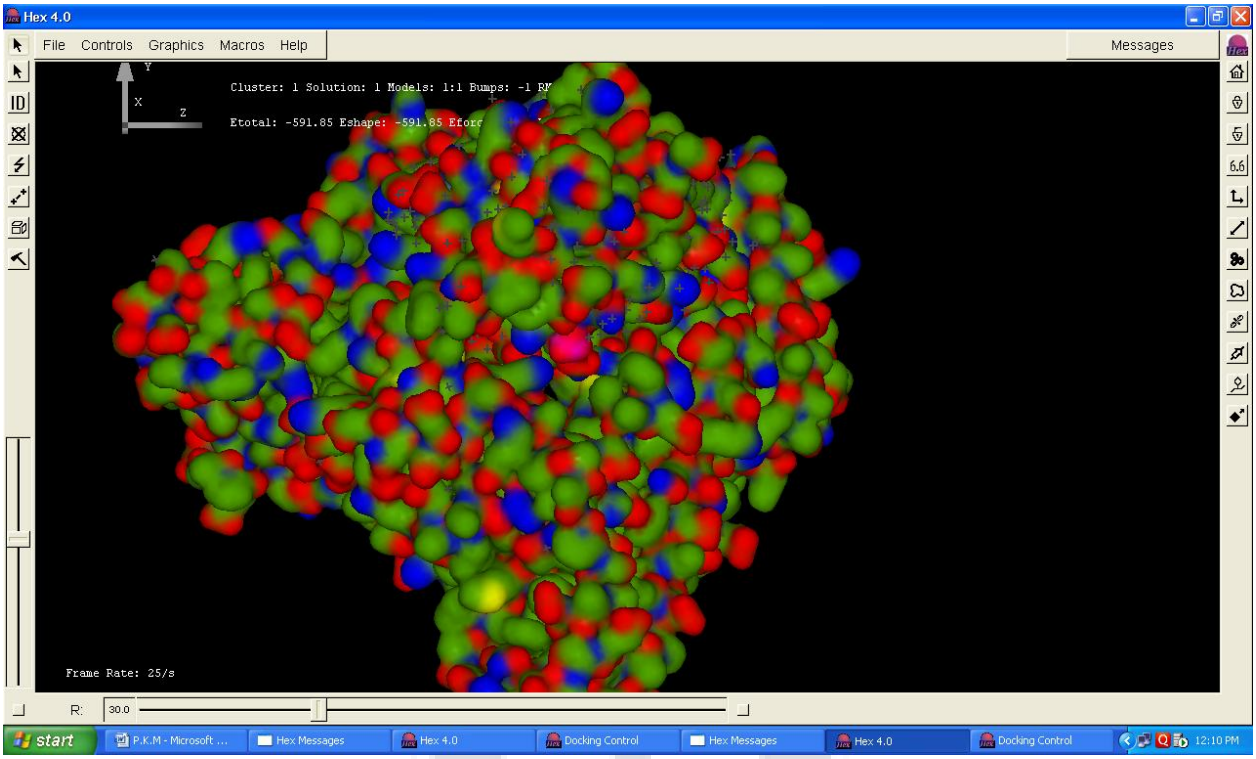
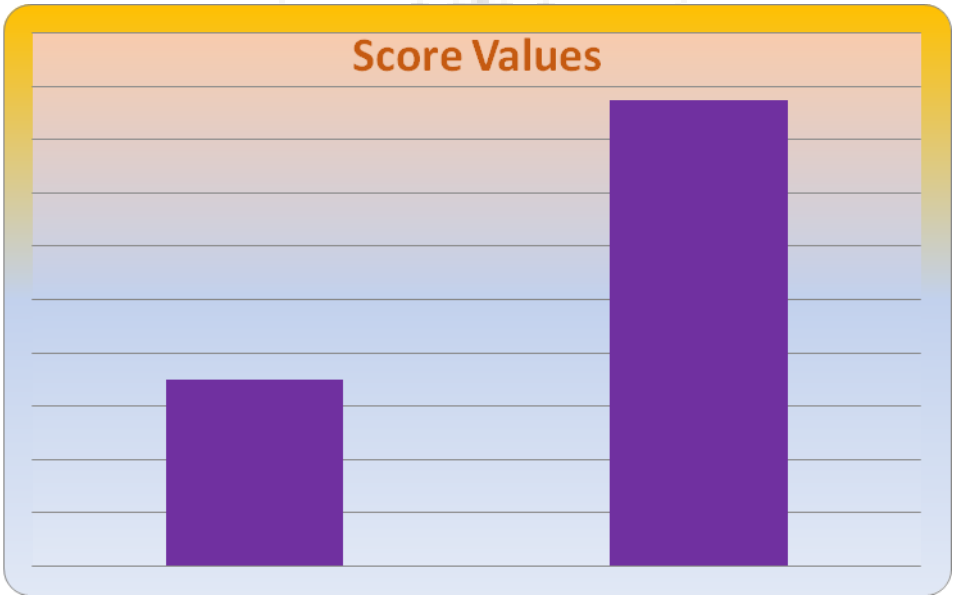
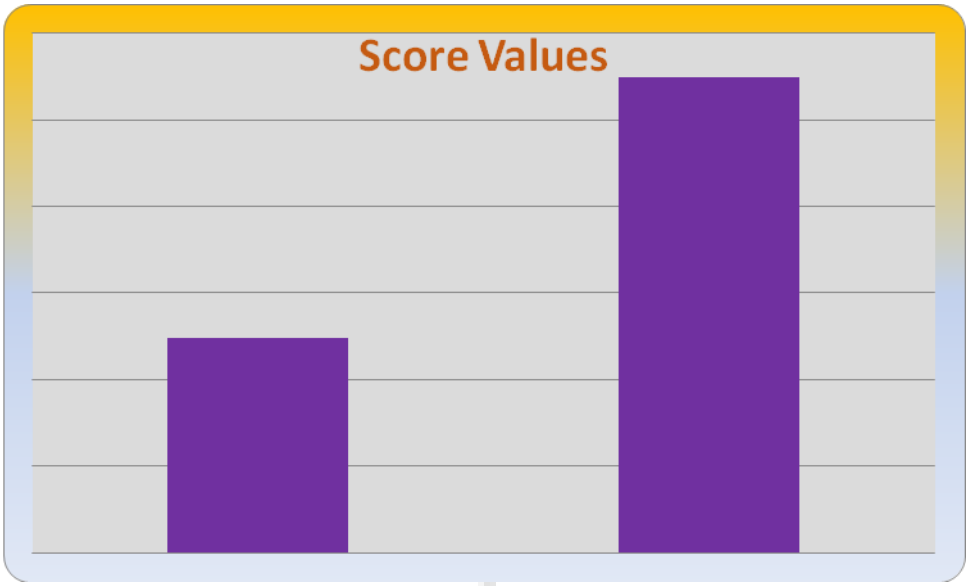


Fig 4: Target Receptor GLP1 docked with Octadecanoic acid



Graph 1: Comparison of score values with Ligand n-Hexadecanoic acid



Graph 2: Comparison of score values with Ligand Octadecanoic acid

CONCLUSION

The field of molecular docking has emerged during last three decades and now is becoming an integral part of drug discovery and development area. The present study helped to identify the potent bioactive constituent present in the ethanolic extract of *Gmelina arborea* attributing anti-diabetic activity. This result clearly demonstrates that the approach used in the study is successful in finding novel anti-diabetic compounds from plants. Also, the study states and confirms the importance of small molecules from plants, their use in enhancing protein-ligand interaction studies and improved the activity.

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