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In-silico Screening of some Isolated Compounds of *Hemidesmus indicus* and Evaluation of its Antidiabetic Potential

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Abstract

Hemidesmus indicus, widely recognized as anantamul, is often utilized in conventional medical systems to treat liver disorders, diabetes and kidney diseases etc. Some of the compound has been isolated and identified as antidiabetic in nature. Fewer compounds were screened for the *in-silico* study to establish a computational approach of the plant *Hemidesmus indicus* to open a new gateway for the treatment of diabetes. Docking study was carried out by using Autodock 4.2 software and a overall comparison study was performed between different compounds like 2-hydroxy-4-methoxy benzaldehyde, Beta-amyrin palmitate, Hyperoside , Isoquercetin and Vanilin. Among these Beta-amyrin palmitate and Vanilin showed most promising docking score towards different antidiabetic receptor comparison to the internal ligand. Docking score of Beta-amyrin palmitate are -6.37, -6.50, -7.69 and -8.14 for the PDB ID 1X70, 1PPI, 1V4S and 5VEX respectively. Docking score of Vanilin are -2.99, -4.43, -3.72 and -4.43 for the PDB ID 1X70, 1PPI, 1V4S and 5VEX respectively. The above study revealed that Beta-amyrin palmitate was found to be most potent antidiabetic agent according to the *in-silico* study. This Beta-amyrin palmitate was also identified as an antidiabetic agent through *in-vitro* study, from this we can conclude that a *in-vitro* and *in-vivo* correlation can be establish for this compound.

Keywords: *Hemidesmus indicus, Vanilin, Beta-amyrin palmitate, 1X70, 1PPI, 1V4S and 5VEX*

Introduction

Hemidesmus indicus R.Br., often known as "Anantmoola or Anantamul," is a laticiferous, twining shrub that is found throughout the majority of India. *Hemidesmus indicus* was once belongs to Asclepiadaceae family but has currently been moved to the Periplocaceae family based on pollination characteristics. *Hemidesmus indicus* behave as a laxative, diuretic, and diaphoretic and that can be used to treat syphilis, cough, asthma, and leucoderma. It is widely distributed in nature, hence easily available. It exhibits a variety of activities out of which antidiabetic activity is very important [1]. *Hemidesmus indicus* contains a broad range of chemicals, including terpenoids, steroids, flavonoids, phenolic compounds, saponins, tannins, lignins, cardiac glycosides, proteins, and carbohydrates [2,3]. Beta-amyrin palmitate,

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Hyperoside, Isoquercetin, Vanilin, 2-hydroxy-4-methoxybenzaldehyde are some isolated compounds found in the *Hemidesmus indicus* [4]. Diabetes mellitus (DM) is a metabolic condition characterized by a lack of insulin synthesis or action, or both [5]. It prevails in practically every country and continues to grow in numbers and impact as people's quality of life deteriorates, resulting in decreased physical activity and more obesity. This results in long-term hyperglycemia and a wide range of metabolic processes in the human body [6]. According to the World Health Organization (WHO), Diabetes mellitus affects 347 million people worldwide, and it is expected to become the sixth greatest cause of death by 2030. In 2012, diabetes caused a total of 1.5 million fatalities. It was the eighth most typical reason of mortality for both males and females, and the fifth most typical reason of death for females [7]. Different kinds of medications, such as biguanides and sulfonylureas are currently able to be treated diabetes mellitus hyperglycemia. These certain medications have adverse effects, therefore finding a new class of chemicals to solve these issues is critical. The medical profession is still grappling with how to manage diabetes without causing negative effects. Alternative medications are always being sought. The rise of phyto-medicine and the hunt for novel types of antidiabetic from herbal plants has been prompted by the negative effects of synthetic medications, as well as drug resistance [2,8]. S.A. Nair *et al*. [9] in 2014 during evaluating the toxicity effect of Hemidesmus indicus root extracts observed that the root extracts show glucose-lowering properties. Therefore, they are interested to isolate the active compound which has hypoglycemic activity. For the isolation of active compounds from root extracts, they go through different chromatographic techniques. The effective component, Beta-amyrin palmitate, was separated and identified which was then evaluated for the anti-hyperglycemic activity by Glucose tolerance test in alloxan-induced diabetic rats. The effects of 2-hydroxy-4-methoxy benzaldehyde isolated from H. indicus roots on diabetic rats caused by streptozotocin has been thoroughly discussed by Kannabiran K. *et al* [10] in a number of studies. Verma N. *et al* [11] evaluate antihyperglycemic activity of hyperoside by Oral glucose tolerance test (OGTT). Dong Kwon Yang [12] and Hyung-Sub Kang [12] investigate the antidiabetic action of quercetin (QE) in streptozotocin (STZ)-induced diabetic rats by Oral glucose tolerance test (OG-TT). Lu G. *et al* [13] investigate the antidiabetic action of quercetin (QE) in diabetics triggered by streptozotocin (STZ) in neonatal rats by Oral glucose-tolerance test (OG-TT). In the design and layout of novel medications, molecular docking is a crucial methodology. These tactics aim to predict a small molecule's experimental binding mechanism and affinities within the target receptor's binding region. The natural ligand posture, the receptor binding site, and the related physical-chemical molecular interactions must all be accurately predicted using a good docking process [14,15]. The present study gives an insight of interaction between some identified compounds with different antidiabetic receptor by the help of molecular docking and compare the different compounds using docking score.

Materials and Methods

In-vivo analysis of different isolated compounds

S.A. Nair *et al*. [9] evaluated the antihyperglycemic activity beta amyrin palmitate by Glucose-tolerance test in alloxan-induced diabetic rats. Male-Wistar rats weighing 175–200 g was divided up into four groups of six each to test the effects of various per oral (p.o.) doses of beta amyrin palmitate on glucose tolerance. The substance (5% Tween 80, 1 mL, p.o.) was given to the control group. The experimental groups gained beta-amyrin palmitate in various doses (25, 50, and 100 mg/kg) in the same way. After administering herbal drugs for 30 minutes, 60% glucose (3 g/kg, p.o.; 1 ml/200 g body weight) was given to the rats in all groups. Samples of blood were taken through a retro-

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orbital puncture while the patient was sedated at 0, 1, 30, 90, and 150 minutes following glucose loading.

Kannabiran K. *et al* [10] evaluated antidiabetic activity by a single intra-peritoneal injection of freshly prepared streptozotocin solution in rats. Group I was used as a control, Group II contained STZ-induced diabetic rats that survived, Group III was used as a positive control and got tolbutamide (100 mg/kg) by oral intubation technique, and Group IV contained diabetic rats that were given HMB (500 g/kg) for 7 weeks. At the conclusion of the treatment period, in order to measure plasma glucose using the glucose oxidase method and plasma insulin using a radioimmunoassay kit, blood samples were drawn from the tail vein using aseptic methods and placed in tubes containing potassium oxalate and sodium fluoride.

Verma N. *et al* [11] evaluated antihyperglycemic activity of hyperoside by Oral glucose tolerance test (OGTT). Oral-glucose tolerance testing was accomplished on normal Wistar rats that had fasted overnight (18 hours) to determine the effective dose of hyper insulin. They were split up into four groups, each with six animals. Blood from the tail vein was drawn to assess the initial serum glucose. Orally administered glucose (2 g/kg body weight) was given to normal control rats (Group 1). 30 minutes before the oral administration of 2 g/kg of glucose solution to groups 2 and 3, two separate doses (of 25 and 50 mg/kg body weight) of hyperoside in distilled water were given. Before the glucose load, Group 4 got the usual medication, glybenclamide (20 mg/kg).

Dong Kwon Yang [12] and Hyung-Sub Kang [12] investigated the antidiabetic action of quercetin (QE) in diabetic rats caused by streptozotocin by Oral glucose -tolerance test (OG-TT). The 50 male Sprague-Dawley rats were divided into three (30 mg/kg QE) compound-treated diabetes groups and two normal control groups.

Lu G. *et al* [13] investigated the antidiabetic action of vanillin in streptozotocin (STZ)-induced diabetic in neonatal rats by Oral glucose- tolerance test (OG-TT). Male 2-day-old pups were given 90 mg/kg of STZ intraperitoneally (i.p.) to cause diabetes. The puppies were subsequently divided into four groups at random: control, negative control, diabetic, and vanillin-treated. The vanillin treated groups gained vanillin (100 or 200 mg/kg, p.o.) consistently from the sixth week of age to the tenth week. Vanillin's antidiabetic impact was evaluated by monitoring the insulin, lipid, and blood sugar levels in the diabetic rat's serum.

Molecular docking analysis of isolated compounds

Hardware used

Processor used for this docking is Intel Core i3. CPU Cores are 816, Clock frequency of the hardware is 3GHz, Size of the main memory is 1072 GB, Graphics card is RADEON.

Software used

UCSF Chimera and ChemDraw 15.0 which have academic license are used for this process. For molecular docking, Autodock tools 4.2 is used which is an open source software.

Protein preparation

Three-dimensional structure (Mainly crystal) of different PDB-ID like 1PPI [16] , 1X70 [17], 1V4S [18], 5VEX [19] was chosen for the investigation. From Protein Data Bank (PDB), acquired the 3D X-ray crystallographic structures. The process of getting ready involves accessing the PDB ID to retrieve the protein from the server, uploading the molecule, adding hydrogens, applying specific turning to residues, examining interactions and geometry for all atoms, performing the job, and acquiring the finished protein file.

Ligand preparation

In this investigation, ligands were Beta-amyrin palmitate, Hyperoside, Isoquercetin,

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Vanillin, 2-hydroxy-4-methoxybenzaldehyde. Chemdraw15.0 was used to create the particular structures in concern. The stabilised structure was stored after being downloaded from the server as PDBQT format for the purpose of protein-ligand docking.

Protein-ligand docking

The Autodock-4.2.6 programme (ADP) was used to carry out all molecular docking investigations. ADP tools were used to prepare the protein and ligands. The coordinate values used in grid settings were acquired from re-docking studies, and dimensions of the grid box were 60x60x60 in the x, y, and z directions. In each case, spacing of the grid point was 0.375". Auto grid-4.2 was utilised to create the map files. For search criteria, a genetic algorithm (GA) was employed. The population size was 150, there were 50 GA runs, and there were 2500000 evaluations. Autogrid and Autodock operation was the last step. The molecular docking of individual ligand on the appropriate protein was carried out using Autodock-4.2 and Autogrid-4.2, respectively.

Results and Discussion:

In-vivo results of different isolated compounds

Beta-amyrin palmitate (25-100 mg/kg) had antihyperglycemic effects on rats given glucose orally. The best dosage was 50 mg/kg, and increasing it forward, to 100 mg/kg did not cause a corresponding drop in blood sugar levels. When glucose was delivered, as opposed to oral glucose loading, the medication (50 mg/kg) did not significantly lower blood sugar levels [9].

In comparison to untreated control rats, orally administered HMB's aqueous solution dramatically (F>0.05; P 0.001) decreased blood sugar levels and raised plasma insulin levels to levels close to normal [10].

Hyperoside has been shown to have antihyperglycemic potential when given to diabetic rats caused by streptozotocin, in doses of 25 and 50 mg/kg daily for 30 days. After 120 minutes of an oral glucose tolerance test, rats administered with hyperoside showed a considerable drop in blood glucose levels. In streptozotocin-induced diabetic rats, it was discovered that hyperoside demonstrated dose-dependent and substantial antihyperglycemic activity that was remarkably similar to that of the medication glybenclamide [11].

Quercetin dramatically reduced the increased insulin levels, dyslipidemia, and serum blood glucose levels in diabetic mice [12].

In comparison to the negative control group, the vanilla therapy significantly reduced serum glucose and lipid levels and raised insulin levels. In comparison to the negative control group, the vanillin-treated group had higher insulin sensitivity [13].

Molecular docking results of different isolated compounds

Four distinct proteins connected to glucose metabolism, transport, and utilisation were docked with beta-amyrin palmitate, hyperoside, isoquercetin, vanillin, and 2-hydroxy-4-methoxy benzaldehyde. In order to assess the fitness ratings for the docking of tested compounds with the targeted proteins, this was done. Tables 1, 2, 3 & 4 detail the docking analysis findings, while Figures 1, 2, 3 & 4 display the docking figure. Among all the compounds, β-amyrin palmitate showed well docking score against 1PPI, 1X70, 1V4S and 5VEX respectively.

The region at which a mammalian alpha-amylase is active, Acarbose, a pseudo tetrasaccharide alpha-amylase inhibitor, was used to soak pancreatic alpha-amylase (EC 3.2.1.1), and the X-ray structural analysis revealed an electron density that corresponded to five fully conquered subsites in the active site [PDB ID: 1PPI] [16]. In diabetes people, alpha-amylase breaks down the carbohydrate and

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raises postprandial glucose levels. The inhibition of alpha- amylase enzyme can decrease the post prandial increase of blood glucose that's why it is the potential target for the management of type 2 diabetes.

Table.1 Docking results of β -amyrin palmitate, hyperoside, isoquercetin, vanillin, and 2-hydroxy-4-methoxy benzaldehyde with PDB ID: 1PPI

Compounds Name	Docking Energy	Figure No.
β-amyrin palmitate	-6.50	1(a)
2-hydroxy-4-methoxy-benzaldehyde	-4.73	1(b)
Hyperoside	-5.93	1(c)
Isoquercetin	-4.43	1(d)
Vanillin	-4.43	1(e)

Two hydrogen bond interactions occur between beta-amyrin palmitate with amino acid ASP381 having bond lengths of 2.775 Å & 2.802 Å (Fig No: 1a). Two hydrogen bond interactions occur between 2-hydroxy-4-methoxy-benzaldehyde with two amino acid GLY304 & ASP353, having bond lengths 2.111 Å & 2.106 Å respectively (Fig No: 1b). Three hydrogen bond interactions occur between Hyperoside with amino acid PHE315 and bond length are 2.226 Å, 1.415 Å, 1.413 Å (Fig No: 1c). Three hydrogen bond interaction occur between Isoquercetin with three amino acid MET178, LYS186, LEU69 and bond length are 1.964 Å, 1.902 Å, 2.103 Å respectively (Fig No: 1d). Three hydrogen bond interactions occur between Vanillin with three amino acid VAL467, GLN476, SER478 having bond lengths 2.022 Å, 2.105 Å, 2.188 Å (Fig No: 1e).

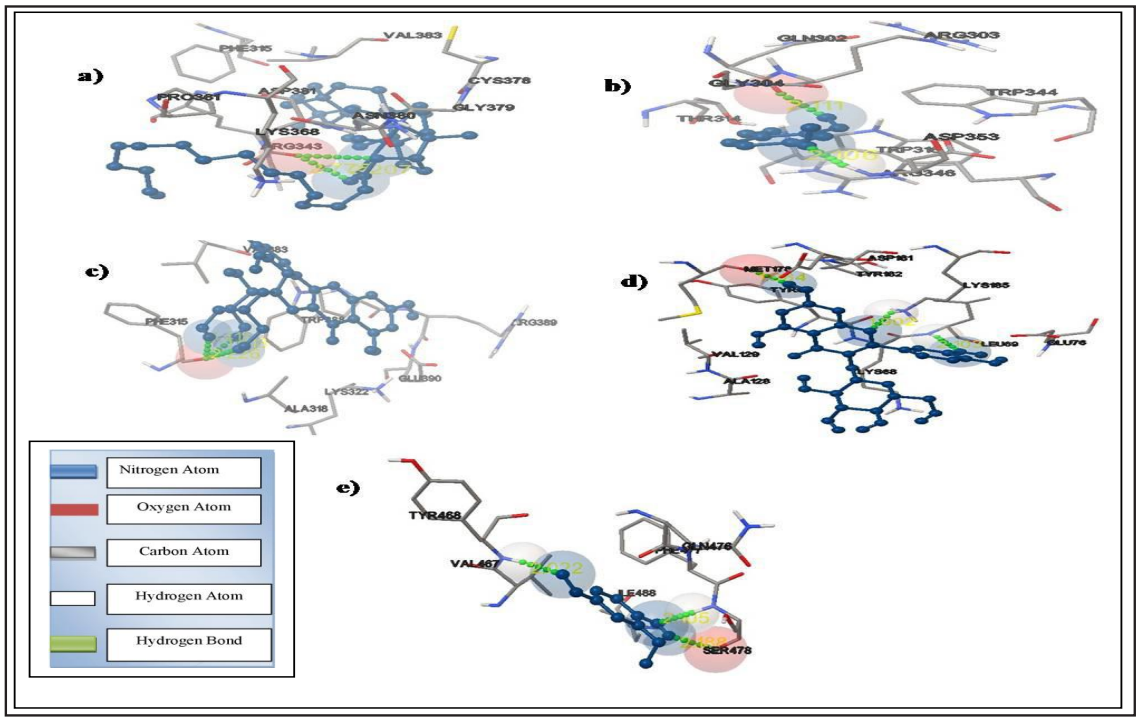

Figure 1: 1(a) Interaction between 1PPI with β-amyrin palmitate, 1(b) Interaction between 1PPI with 2-hydroxy-4-methoxy-benzaldehyde, 1(c) Interaction between 1PPI with hyperoside, 1(d) Interaction between 1PPI with Isoquercetin, 1(e) Interaction between 1PPI with Vanillin

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Beta Amino Acid Inhibitor Complexed With Human Dipeptidyl Peptidase IV (DPP-4) [PDB ID: 1X70] [17]. An enzyme called DPP4 degrades the incretin hormone. Incretins assist the body in producing more insulin only when necessary and lower blood glucose levels. By blocking DPP-4, incretin hormone becomes inactive, which in response produces more insulin so it's a potential target for the management of type 2 diabetes.

Table No-2 Docking results of β -amyrin palmitate, hyperoside, isoquercetin, vanillin, and 2-hydroxy-4-methoxy benzaldehyde with PDB ID: 1X70

Compound Name	Docking Energy	Figure No.
715 (Internal Ligand)	-7.98	2(a)
β-amyrin palmitate	-6.37	2(b)
2-hydroxy-4-methoxy-benzaldehyde	-3.20	2(c)
Hyperoside	-3.71	2(d)
Isoquercetin	-1.79	2(e)
Vanillin	-2.99	2(f)

Internal ligand 715 co-crystallized with Human Dipeptidyl Peptidase IV (PDB ID: 1X70) was re-docked and dock score was -7.98. One hydrogen bond interaction occurs between 715 amino acid GLU205 having a bond length of 2.725 Å (Fig No: 2a).

One hydrogen bond interaction occurs between beta-amyrin palmitate with amino acid ALA593 having bond length of 2.687 Å (Fig No: 2b). Three hydrogen bond interactions occur between 2-hydroxy-4-methoxy-benzaldehyde with three amino acid ARG611, GLU364, ARG581 bond length are 2.125 Å, 1.855 Å, 1.994 Å respectively (Fig No: 2c). Three hydrogen bond interactions occur between Hyperoside with amino acid MET638, ARG691, GLY599 having the bond lengths 2.379 Å, 2.199 Å, 2.061 Å (Fig No: 2d). Three hydrogen bond interactions occur between Isoquercetin with three amino acid GLN718, ASP725, GLU693 the bond lengths being 2.149 Å, 1.639 Å, 1.761 Å respectively (Fig No: 2e). One hydrogen bond interaction occurs between Vanillin with amino acid LYS721 having a bond length of 2.111 Å (Fig No: 2f).

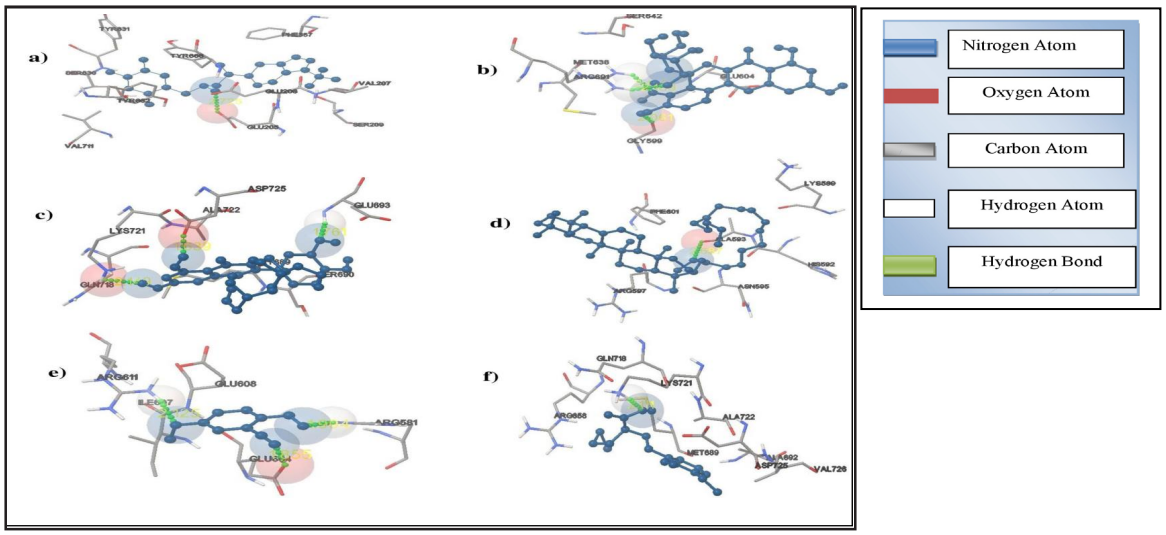

Figure 2: 2(a) Interaction between 1X70 with 715, 2(b) Interaction between 1X70 with β-amyrin palmitate, 2(c) Interaction between 1X70 with with 2-hydroxy-4-methoxy-benzaldehyde, 2(d) Interaction between 1X70 with Hyperoside, 2(e) Interaction between 1X70 with Isoquercetin, 2(f) Interaction between 1X70 with Vanilin

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It is a Crystal structure of human glucokinase [PDB ID: 1V4S]. A gene called glucokinase is crucial in determining how high the body's blood glucose levels are. The pancreas uses it as a "glucose sensor" so that when blood sugar levels rise, so does the amount of insulin produced. The crystal structures of active and inactive glucokinase show that glucose binding causes extensive conformational changes, including domain restructuring. This discovery offered the mechanistic underpinnings for glucokinase activation as a potential treatment for the management of type 2 diabetes [18].

One hydrogen bond interaction occurs between beta-amyrin palmitate with amino acid ASN64 having a bond length of 2.863 Å (Fig No: 3a). One hydrogen bond interaction occurs between 2-hydroxy-4-methoxy-benzaldehyde with two amino acid GLN91, with a bond length of 2.006 Å (Fig No: 3b). One hydrogen bond interaction occurs between Hyperoside with amino acid LYS33 and bond length is 1.833 Å (Fig No: 3c). Three hydrogen bond interactions occur between Isoquercetin with three amino acid ASN84, PHE83, GLY82 having bond lengths of 1.958 Å, 2.066 Å, 1.792 Å respectively (Fig No: 3d). One hydrogen bond interaction occurs between Vanillin with amino acid LYS86 having a bond length of 2.947 Å (Fig No: 3e).

Table 3 Docking results of β -amyrin palmitate, hyperoside, isoquercetin, vanillin, and 2-hydroxy-4-methoxy benzaldehyde with PDB ID: 1V4S

Compounds Name	Docking Energy	Figure No.
β-amyrin palmitate	-7.69	3(a)
2-hydroxy-4-methoxy-benzaldehyde	-3.06	3(b)
Hyperoside	-0.64	3(c)
Isoquercetin	-1.98	3(d)
Vanillin	-3.72	3(e)

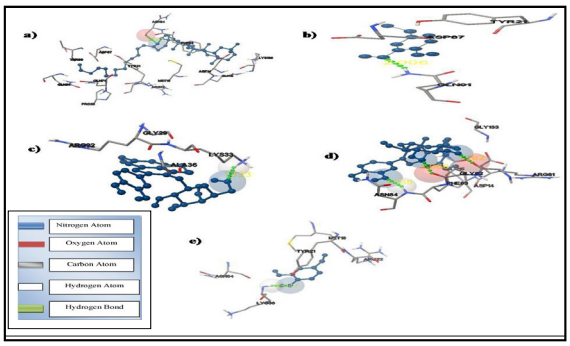

Figure 3: 3(a) Interaction between 1V4S with β-amyrin palmitate, 3(b) Interaction between 1V4S with 2-hydroxy-4-methoxy-benzaldehyde, 3(c) Interaction between 1V4S with hyperoside, 3(d) Interaction between 1V4S with Isoquercetin, 3(e) Interaction between 1V4S with Vanillin

It is a structure of the NNC0640 containing human GLP-1 receptor complex [PDB ID: 5VEX]. The glucagon like peptide 1 receptor (GLP 1R), a member of the secretin-like class B family of G-protein-coupled receptors (GP-CRs), and the glucagon receptor (GC-GR), play opposite physiological functions in insulin release and glucose homeostasis. In a glucose-dependent manner, the inhibition of glucagon secretion and promotion of insulin secretion are essential components in the management of type 2 diabetes [19].

Internal ligand 97v co-crystallized with human GLP-1 receptor (PDB ID: 5VEX) was re-docked and dock score was -9.00. One hydrogen bond interaction occurs

Table 4 Docking results of β -amyrin palmitate, hyperoside, isoquercetin, vanillin, and 2-hydroxy-4-methoxy benzaldehyde with PDB ID: 5VEX

Compound Name	Docking Energy	Figure No.
97v (Internal Ligand)	9.00	4(a)
β-amyrin palmitate	-8.14	4(b)
2-hydroxy-4-methoxy-benzaldehyde	-4.37	4(c)
Hyperoside	-4.88	4(d)
Isoquercetin	-5.42	4(e)
Vanillin	-4.43	4(f)

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between 97v with amino acid ASN304 having a bond length of 2.290 Å (Fig No: 4a).

One hydrogen bond interaction occurs between beta-amyrin palmitate with amino acid TYR1088 having a bond length of 2.983 Å (Fig No: 4b). Three hydrogen bond interactions occur between 2-hydroxy-4-methoxy-benzaldehyde with three amino acid ARG1014, LYS1016, LEU1015 having bond lengths 1.969 Å, 1.978 Å, 1.975 Å respectively (Fig No: 4c). Three hydrogen bond interactions occur between Hyperoside with three amino acid GLY1107, LEU1032, HIS1031 having bond lengths of 2.816 Å, 1.934 Å, 2.199 Å respectively (Fig No: 4d). Four hydrogen bond interactions occur between Isoquercetin with three amino acid GLY1030, LEU1032, GLU1108, THR1109 having the bond lengths 1.978 Å, 2.240 Å, 1.931 Å, 1.974 Å respectively (Fig No: 4e). Two hydrogen bond interactions occur between Vanillin with two amino acid GLY1030, LEU1032 respectively having bond lengths of 1.694 Å, 1.972 Å (Fig No: 4f).

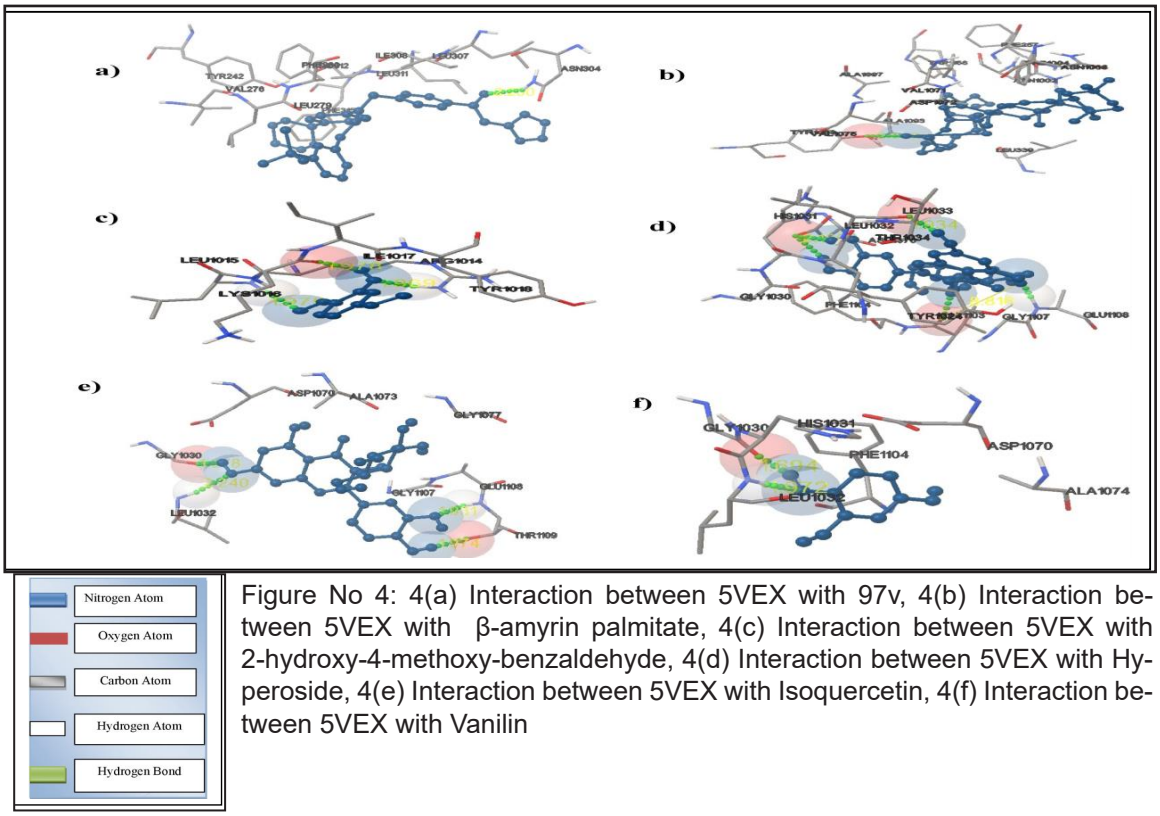

Figure No 4: 4(a) Interaction between 5VEX with 97v, 4(b) Interaction between 5VEX with β-amyrin palmitate, 4(c) Interaction between 5VEX with 2-hydroxy-4-methoxy-benzaldehyde, 4(d) Interaction between 5VEX with Hyperoside, 4(e) Interaction between 5VEX with Isoquercetin, 4(f) Interaction between 5VEX with Vanilin

All around the world, including India, diabetes mellitus is regarded as a serious public health issue. Vascular dysfunction is a result of the metabolic abnormalities that distinguish diabetes, including hyperglycemia, an increase in free fatty acids, and insulin resistance. Ayurveda and herbal remedies are significant alternative treatments that use extracts from many medicinal plants. The evaluation of anti-diabetic activity of isolated compounds from *Hemidesmus indicus* is the focus of this study. The mechanism underlying the extract's ability to treat diabetes was anticipated by an *in-silico* analysis. We can characterize how small compounds behave at the binding site of target proteins and shed light on basic biological processes by using the molecular docking approach to describe the interaction between a

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small molecule and protein at the atomic level. It aids in locating the enzyme's agonists and antagonists. A common technique in logical drug design is docking. A molecular level analysis is required to provide more scientific evidence and a more comprehensive explanation. Docking studies by Autodock 4.2.6 showed that Beta-amyrin palmitate of *Hemidesmus indicus* had the lowest docking score respectively against different antidiabetic protein. Because a compound's potency increases with decreasing docking score, Beta-amyrin palmitate from *Hemidesmus indicus* was found to have a considerable docking score.

Conclusion

Beta-amyrin palmitate outperformed all other chemicals in terms of docking with different antidiabetic protein. Beta-amyrin palmitate, which had the best value in molecular docking. The above study revealed that Beta-amyrin palmitate was found to be most potent antidiabetic agent according to the *in-silico* study. This Beta-amyrin palmitate was also identified as an antidiabetic agent through *in-vitro* study, from this we can conclude that a *in-vitro* and *in-vivo* correlation can be establish for this compound.

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Abbreviations

PDB: Protein Data Bank

DM: Diabetes mellitus

WHO: World Health Organization

OG-TT: Oral glucose tolerance test

QE: Quercetin

STZ: Streptozotocin

ADP: Autodock Program

Å : Angstrom

GP-CRs: G-protein coupled receptors

GLP-1R: Glucagon like peptide-1 receptor

GC-GR: Glucagon-receptor