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Molecular Docking Studies of Possible Treatment of Diabetes using Vasicine against Islet Amyloid Polypeptide

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Abstract: Diabetes is the becoming one of the most common problem all over the world. About 1 in 10 persons are suffering from diabetes and most from type 2 diabetes. It occurs due to problem in pancreas which further results defect in the insulin secretion, as insulin maintains blood glucose level. The effect of Alpha-Amyrin Acetate, Myrcene and Vasicine compounds against Islet Amyloid polypeptide (IAPP) protein was seen through molecular docking studies. IAPP acts as complementary to insulin in regulating the sugar level for the treatment of diabetes disease by virtual screening. Different tools and software used in this research were Uniprot, Pubchem, Swiss ADMS, PyRx, Auto dock Vina/MGL tool and PyMOL.
Keywords: Diabetes Mellitus, IAPP, Molecular Docking, Vasicine compound,

I. INTRODUCTION

Diabetes mellitus is a type of metabolic diseases which is characterized by high blood sugar levels and lead to defects in insulin secretion. Diabetes mellitus which is commonly known as diabetes was first identified as a disease associated with "sweet urine". Elevated levels of blood glucose (hyperglycemia) lead to spillage of glucose into the urine; therefore, it is termed as sweet urine.
Blood glucose levels are controlled by insulin, as it is the hormone produced by the pancreas. Presence of insulin maintains the blood glucose level. When the blood glucose elevates, by eating food and any other item, insulin is released by pancreas to maintain the glucose level by promoting the uptake of glucose into body cells. The patients suffering from diabetes, causes the hyperglycemia due to absence or insufficient production of insulin or lack of response to insulin. Diabetes is a chronic medical condition which means that although it may be controlled [1]. Most of the people are suffering from type 2 diabetes and gestational diabetes is temporary type which may occur in some females at the time of pregnancy.
About 34.2 million people of all ages – about 1 in 10 is suffering from diabetes in the U.S. There are about 7.3 million adults aged 18 and older i.e., about 1 in 5 and they are unaware that they have diabetes just under 3% of all U.S. adults. There are number of people who are diagnosed with diabetes increases with age. More than 26% of adults age 65 and older (about 1 in 4) have diabetes. [2]. The protein Islet Amyloid Polypeptide (IAPP) is also known as Amylin. IAPP is having 37-amino acid peptide co-secreted by pancreatic β cells with insulin and is deficient in diabetes. It balances insulin level and IAPP actions are complementary to insulin in regulating plasma glucose concentration. Amylin slows gastric emptying, reduces postprandial glucagon, and it can suppress appetite. [3]

A. Alpha-Amyrin Acetate

Alpha-Amyrin acetate is one of the natural triterpenoids found in the herbs of *Ervatamia divaricata*, it decreases blood engorgement time and also feeding rate and decline fecundity. Alpha-Amyrin acetate also shows the activities of anti-inflammatory and antispasmodic. [4]

B. Myrcene

Myrcene, is also known as β-myrcene, is one of the alkene natural hydrocarbon. Myrcene is strongly precisely classified as a monoterpene (They are dimers of isoprenoid precursors). It is one of the significant component of essential oil of various plants, including cannabis, hops and bay[5][6] Myrcene is produced at 400 °C by pyrolysis of β-pinene, which is procured from turpentine. It is hard toobtainit directly from plants.[7]

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C. Vasicine

Vasicine is one of the quinazoline alkaloid, which is found in *Justicia adhatoda* and also found in *Peganum harmala.*[8] Vasicine also combination with the related alkaloid vasicinone. In both *in vivo* and *in vitro, the* alkaloids in combination in ratio of 1:1 which showed pronounced broncho dilatory activity are respiratory stimulants. Vasicinone is one of the weak cardiac stimulants whereas vasicine has a cardiacde pressant effect; its effect can be balanced by adding the alkaloids. Vasicine natural compound is reported as a uterine stimulant effect. [10][11]

Molecular docking is one of the method used in the field of structural molecular biology and computer-assisted drug design to known its interaction and affinity.[12] Docking is a molecular modeling technique which is used to predict how a protein interacts with small compounds (ligands) like lock and key. It may be used to predict the strength of association or binding affinity between two molecules.[13] Molecular docking is one of the most frequently used methods in structure-based drug design, due to its ability to predict the binding-conformation of small molecule Compounds to the appropriate target binding site.[14][15] Some of the important steps are shown through this flow chart given below.

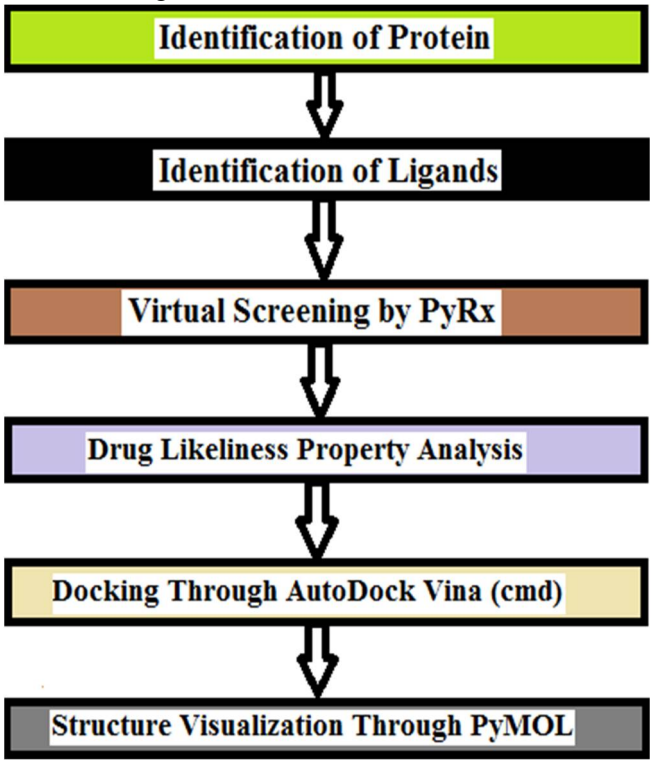


Fig 1: Flow chart of the Process of Molecular Docking

II. MATERIALS AND METHODS

A. Identification of Protein by Uniprot

The Protein Islet amyloid polypeptide which is a diabetes causing protein was retrieved through a database. Structure of protein molecule Islet Amyloid polypeptide (IAPP) was obtained from Uniprot [16][17]. From Uniprot (RCSB PDB) the protein structure was downloaded in ".pdb" format. [18][19].

B. Identification of Compounds by PubChem

The natural compounds Alpha-Amyrin acetate, Myrcene and Vasicine were used for docking study. All these compounds were selected from *PubChem* online database for the docking study [20][21] The 3D structure of compounds were downloaded in *.sdf* format from PubChem online database. Then all these downloaded structures of given compounds were converted from ***.sdf*** format to ***.pdb*** format through '*online SMILES Translator and structure file generator*' [22] and downloaded in *.pdb* format. These *.pdb* format file compounds were used to run PyRx and Auto dock tools/software in further process [23].

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C. Virtual Screening by using PyRx

PyRx is the important software used in molecular docking for virtual screening of the compounds. [24]. Software PyRx was used to screen the compounds and its binding affinity with the given protein target. Compounds were selected based on their minimum binding affinity for further process of drug likeness property analysis. In PyRx procedure the protein molecule was loaded first and it was converted from *.pdb* format to pdbqt format. In next stage natural compounds were imported in *.sdf* format and converted from *.sdf* format to *.pdbqt* fromat, then docking virtual screening process was run through Vina wizard and result were analyzed according to its binding affinity between protein molecule and natural compounds.

D. Drug Likeliness Property Analysis

Online web server Swiss ADME was used for drug likeliness property analysis. In this screened compounds were analyzed for its drug property followed by its Lipinski rule of five. For this process screened compounds were copied from PubChem by its CID number followed by Canonical SMILES given on it. The copied Canonical SMILES were pasted on online web server Swiss ADME dialog box and run the process [25]. It shows all the drug likeliness properties. The compounds were screened followed by Lipinski's rule of five. Lipinski rule of five which states that: -

1) Less than 500- Dalton Molecular mass
2) Less than 5-Hydrogen bond donors
3) Not more than 10-Hydrogen bond acceptors
4) Not more than 5 -Partition co-efficient LogP
5) Not more than 1 rule can be violated.

E. Docking Through AutoDock Vina (cmd)/MLT tool

In .pdb format the protein target was loaded on graphical windows of Auto Dock Vina [26]. By deleting its water molecules, adding hydrogen polar atoms and by adding Kollman charges of protein target was prepared by going on 'edit' further protein molecule was converted into *.pdbqt* format and finally protein was saved in *.pdbqt* format by going on grid. Compound was imported and it was converted & saved to *.pdbqt* format. After that both the compound and protein in *.pdbqt* format were loaded again on graphical windows and grid box was selected and saved as by grid notepad and followed by config txt on notpad for final command i.e. cmd shown in figure 2. Using given below command prompt results were analyzed and output file was automatically saved in *.pdbqt* format.[27]

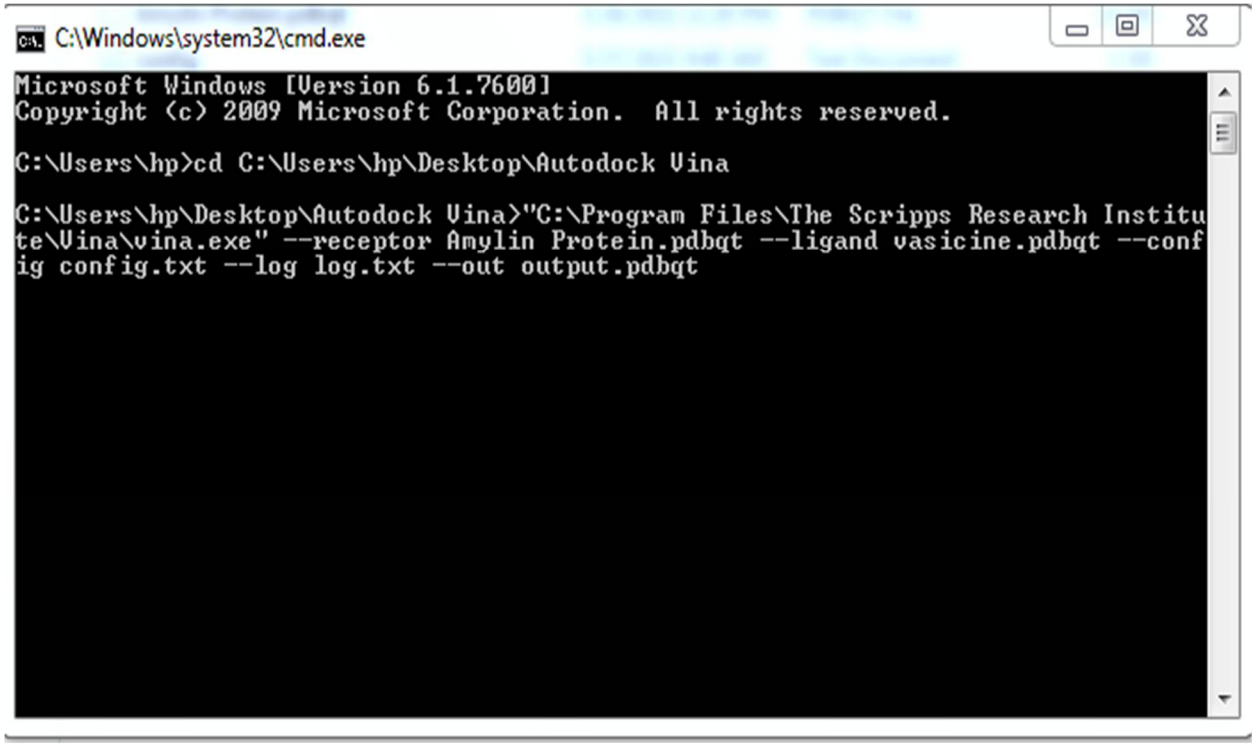


Fig 2 cmd (command) for final auto dock result table

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F. Structure Visualization Through PyMOL

PyMOL tool was used for structure visualization which was a freely available tool. The protein in *.pdbqt* format and output in *.pdbqt* format were loaded on *PyMOL graphical* screen. The protein and compound binding structure was visualized and analyzed.

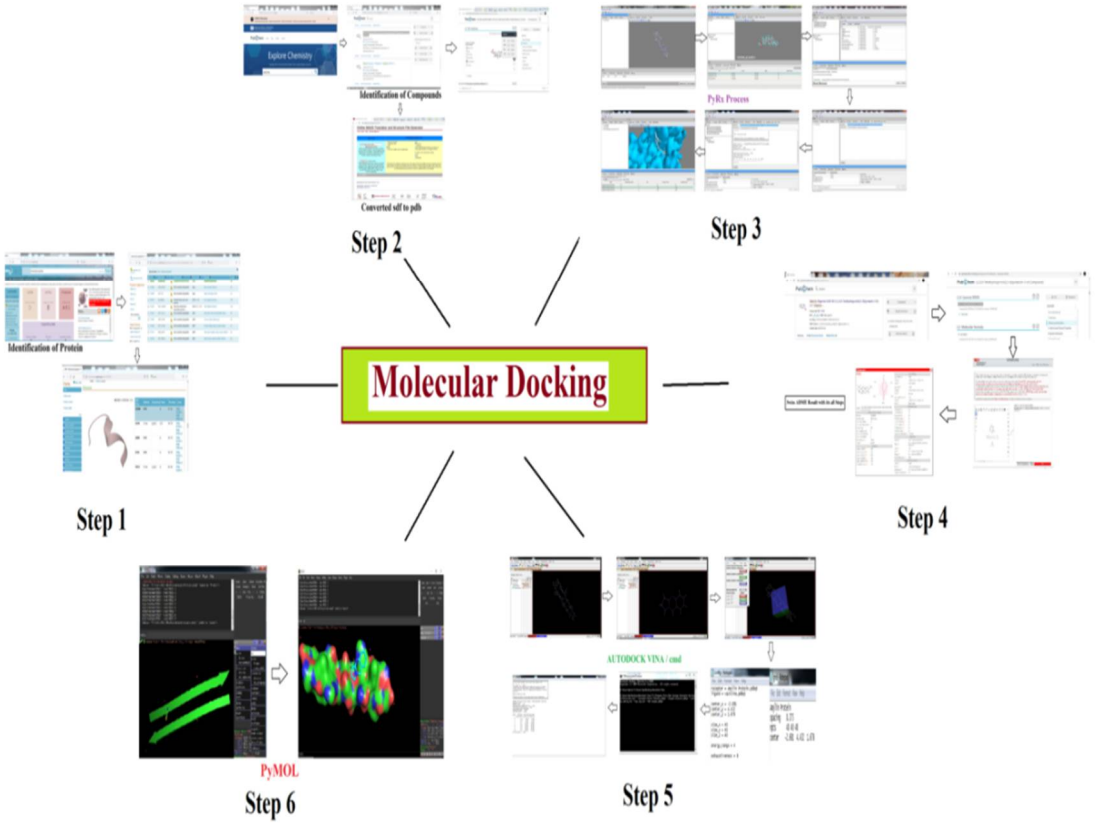


Fig3. Molecular Docking

III. RESULTS AND DISCUSSION

The *Islet Amyloid Polypeptide* (IAPP) protein crystal structure of homosapien (human) was retrieved from Uniprot in .pdb format and 3D structure was retrieved from RCSB Protein Data Bank as shown in its detail in Table1 and Structure in figure 4. The structures of different natural compounds Alpha-amyrin acetate, Myrcene, and Vasicine were downloaded inthe form of *.sdf* & 2D or 3D structure through PubChem on database server details shown in Table 2. Then the downloaded structure was converted into. *Pdb* format through online converter.

Table 1: Selected protein Detail from Uniprot

PDB ID	3FPO
METHOD	X-RAY DIFFRACTION
RESOLUTION	1.50Å
R-VALU FREE	0.154
R-VALU WORK	0.139
R-VALUE OBTAIN	0.140

.

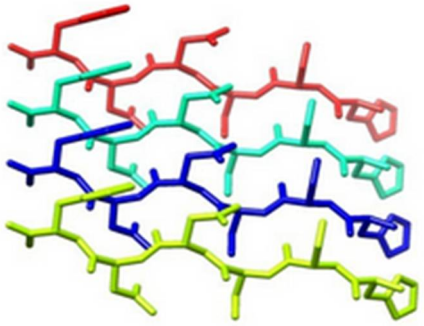
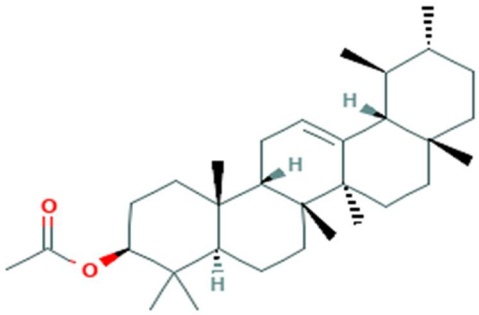
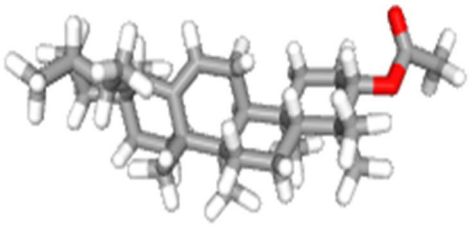


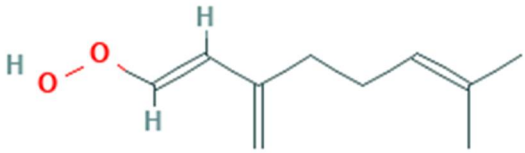
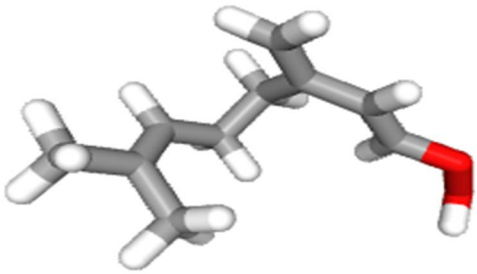
Fig 4 3D structure of Protein

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TABLE 2: Ligand molecule details from PubChem

3.1 -ALPHA –AMYRIN ACETATE	
PUBCHEM CID	13019930
STRUCTURE 2D	STRUCTURE 3D
	
MOLECULAR FORMULAR	$C_{32}H_{52}O_2$
MOLECULAR WEIGHT	468.8 g/mol
X LOG P3-AA	9.6
HYDROGEN BOND DONOR	0
HYDROGEN BOND ACCEPTOR	2

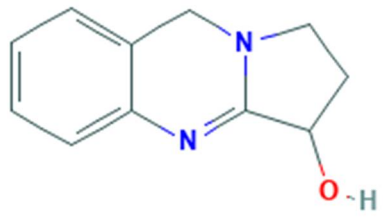
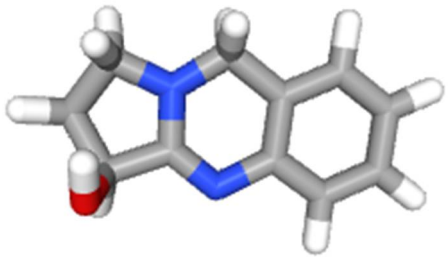
(A)

3.2 - MYRCENE	
PUBCHEM CID	129846599
STRUCTURE 2D	STRUCTURE 3D
	
MOLECULAR FORMULAR	$C_{10}H_{16}O_2$
MOLECULAR WEIGHT	168.23 g/mol
X LOG P3-AA	3.5
HYDROGEN BOND DONOR	1
HYDROGEN BOND ACCEPTOR	2

(B)

3.3 -VASICINE	
PUBCHEM CID	72610
STRUCTURE 2D	STRUCTURE 3D

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MOLECULAR FORMULAR	$C_{11}H_{12}N_2O$
MOLECULAR WEIGHT	188.23 g/mol
X LOG P3-AA	0.4
HYDROGEN BOND DONOR	1
HYDROGEN BOND ACCEPTOR	2

(C)

All these natural compounds Alpha Amyrin acetate, Myrcene & Vasicine were screened virtually through PyRx software to know their binding affinities. The result of PyRx was shown in Table 3 and Table 4. Thus the binding affinities of different natural compounds were Alpha Amyrin Acetate (-5.4), Myrcene (-3.8) and Vasicine (-4.0).

Table 3: The Binding affinity, RMSD lower bound and RMSD upper bound of different compounds with protein molecules

COMPOUND	CID VALUE	BINDING AFFINITY (Kcal/mol)	RSMD LOWER BOUND	RSMD UPPER BOUND
ALPHA-AMYRIN ACETATE	1309930	-5.4	0	0
MYRCENE	129846599	-3.8	0	0
VASICINE	72610	-4.0	0	0

According to virtual screening through PyRx, compounds Alpha Amyrin acetate and Vasicine showed minimum binding affinity. The screened compounds were used for further analyses to know its drug likeliness property analysis through Swiss ADME which was available online server. Then these compounds were screened basis on the Lipinski's Rule of five for drug likeness property. In drug likeness properties were analyzed based on Lipinski's Rule of five, in which natural compounds were selected based on their Molecular mass, Hydrogen bond (donor & acceptor), Partition coefficient and Lipinski's rule violation as shown in **Table 4**. Through drug likeness property it was analyzed that natural compound Vasicine was having strong binding affinity with protein molecule.

Table 4: Drug likeliness Property Analysis

COMPOUND	MOLECULAR WEIGHT	NO. H-BOND DONOR	NO. H-BOND ACCEPTOR	PARTITION CO-EFFICIENT MLOGP	LIPINSKI/ VIOLATION
ALPHA-AMYRIN ACETATE	468.75 g/mol	0	2	7.08	YES; 1
VASICINE	188.23 g/mol	1	2	1.57	YES; 0

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Based on of drug likeliness property analysis the best compound Vasicine was selected for final docking with protein Islet amyloid polypeptide through Auto Dock Vina. Through Auto Dock Vina software, Compound showed minimum and strong binding affinity with mode RMSD Lower and Upper Bound as shown in **Table 5**. It was considered that Vasicine was the best binding compound against protein target through Auto Dock Vina.

Table 5: AutoDock Vina Result

MODE	AFFINITY (KCAL/MOL)	DIST.FROM BEST MODE	
		RMSD I.B.	RMSD U.B.
1	-4.0	0.000	0.000
2	-3.8	1.785	2.554
3	-3.7	1.241	2.514
4	-3.7	13.726	14.616
5	-3.6	13.053	14.276
6	-3.6	11.492	12.496
7	-3.5	15.317	15.624
8	-3.5	13.943	15.554
9	-3.5	14.475	15.660

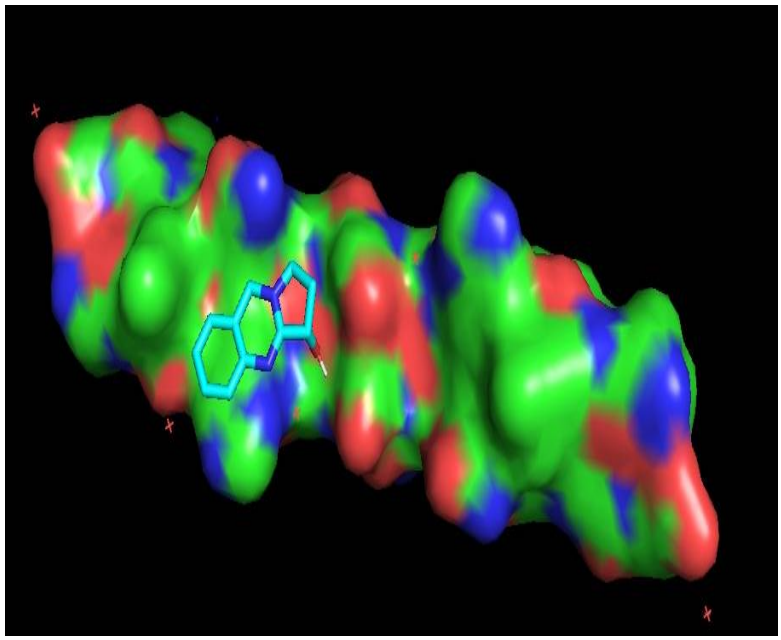


Fig. 5 Result of PyMOL graphical screen of IAPP (Protein) with Vasicine (Compound)

IV. CONCLUSION

It was concluded that molecular docking studies showed the strong binding affinity of Vasicine, toward diabetes causing protein. Thus, it was clear according to docking that the in *in-silico* study, the best natural compound vasicine was best interacted with protein molecule Islet Amyloid Polypeptide and it may act as an inhibitor and may be used as a drug which may control diabetes. Vasicine was found as the best compound having strong binding affinity and followed by Lipinski's rule of five with zero violation. It may be used further as anti-diabetic agent in the treatment of diabetes. Thus, this drug may prevent from diabetes if there are positive results in *in vitro* and *in vivo* studies.

V. ACKNOWLEDGEMENT

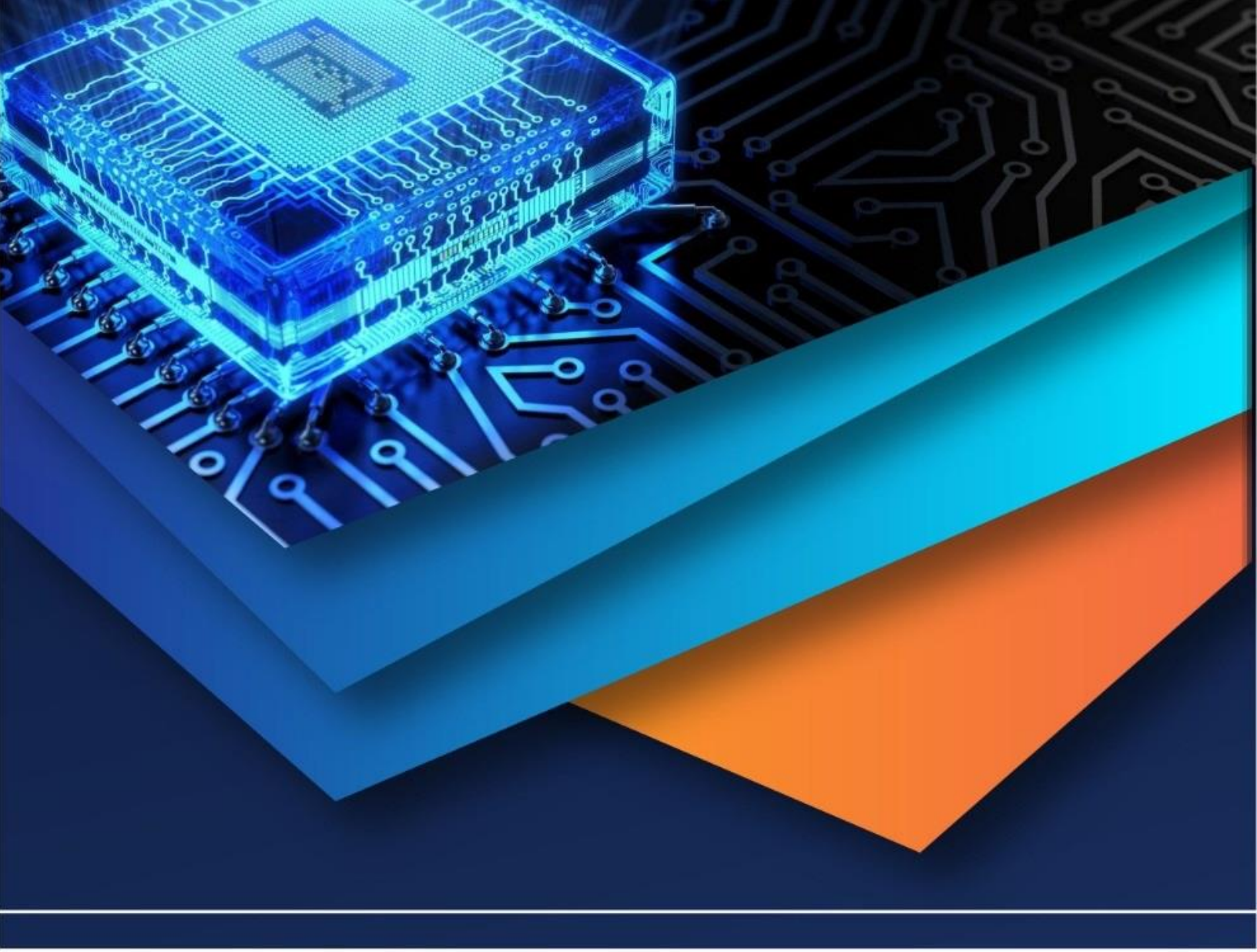
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