In silico approach for the treatment of Diabetes Type 2 by targeting PTP 1 B With plant derived natural compounds

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SUBMITTED IN PARTIAL FULFILLMENT OF THE

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DEGREE OF

MASTER OF SCIENCE

IN

BIOTECHNOLOGY

Submitted by

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CANDIDATE DECLARATION

I,**Anchal Bansal ,2K22/MSCBIO/63** hereby certify that the work which i presented in the Major Project name **"In silico approach for the treatment of Diabetes Type 2 by targeting PTP 1B with plant derived natural compounds"** in fulfilment of the requirement for the award of the Degree of Masters of Science in Biotechnology and submitted to the department of Biotechnology, Delhi Technological University ,Delhi is an authentic record of my own under the supervision of Prof. Yasha Hasija. The matter presented in the thesis has not been submitted by me for the award of any other degree of this or any other university.

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CERTIFICATE

I hereby certify that the Project dissertation titled "**In silico approach for the treatment of Diabetes Type 2 by targeting PTP 1B with plant derived natural compounds**" which is submitted by **Anchal Bansal, 2K22/MSCBIO/63** Department of Biotechnology, Delhi Technological University, Delhi in partial fulfilment of the requirement, for the award of the degree of Master of Science, is the record for the project work carried out by the student under my supervision. To the best of my knowledge this work has not been submitted in part or full for any degree or Diploma to this university or any other.

Place : Delhi

Date:

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ABSTRACT

Type 2 diabetes is a persistent medical condition characterized by heightened blood sugar levels, also referred to as type 2 diabetes mellitus or adult-onset diabetes. This form of diabetes develops when cells resist the usual effects of insulin in facilitating the movement of glucose from the bloodstream into the cells, a state known as insulin resistance. PTP1B has been associated with inhibiting insulin and leptin functionality both experimentally and clinically. In a preclinical study, substances that target PTP1B in insulin-sensitive tissues demonstrated improvements in insulin function and glucose tolerance. This investigation sought to isolate natural compounds from various plants that displayed potential effects in managing type 2 diabetes. Through the use of in silico methods, the study identified a potent inhibitor of PTP1B with the potential to offer therapeutic benefits for individuals with type 2 diabetes.

Content

LIST OF FIGURES

ABBREVIATIONS

PTP1B - Protein Tyrosine kinase 1 B

GLUT -4 Glucose Transporter

ER - Endoplasmic Reticulum

GS- Glycogen synthase

GSK 3- Glycogen Synthase kinase 3

WHO- World Health Organisation

IGF-IR -Insulin like growth factor 1 receptor

IRS- Insulin Receptor Substrate

JAK 2- Janus kinas 2

KO - Knockout

PDGFR-protein derived growth factor receptor

TNF -Tumor necrosis factor

IL- Interleukin

iNOS- Inducible nitric oxide synthase

RMSD- Root mean square deviation

PDB- Protein databank

CHAPTER 1

INTRODUCTION

According to WHO-1999, 300 million people globally are expected to have type 2 diabetes by 2025. The need to find agents to intervene in type 2 diabetes is increased by this depressing number. Insulin resistance is a condition where there is insufficient insulin action within the cell. Insulin is a major regulator of intermediate metabolism.

A growing prevalent plaguing the developed world (kahn 1999) .When insulin is not taken up by the body tissue for its biological use than it is known as insulin resistance which, in the majority of overweight and obese patients, is linked to an elevated cardiovascular risk profile and is frequently accompanied by glucose high level. This syndrome is linked with multiple disorders, such as aberrant thrombolysis , atherogenic lipid profile, endothelial dysfunction, which increases the risk of cardiovascular disease. Elevations in fasting and postprandial glucose levels in the context of insulin resistance are primarily influenced by the pancreatic βcells' secretory function [Polonsky, K. 1996]. Over hyperglycaemia and frank type 2 diabetes result from the pancreas's growing inability to meet the body's higher insulin requirements. Things which help in insulin role, which includes running ,exercise, weight loss can help in glucose up taken and it reduces the factor associated with disease . As day to day routine is difficult to adjust it is necessary to bring novel medicine for this purpose. While manufacturing drugs for insulin sensitivity, many pathway related to its activity and role have been identified. Particularly knowledge has grown to control the insulin signalling pathway and the component related to phosphorylation of the tyrosine that affects the insulin up taken by the body tissues.

PTP1B is a protein tyrosine phosphatase (PTPase) enzyme that is essential to the insulin action cascade's negative regulation of protein tyrosine phosphorylation [Byon, J. H. 1998]. There are two suggested particular roles for PTP1B: It binds to and dephosphorylates insulin factor, impairing the receptor's capacity to react to insulin binding. JAK 2 is also dephosphorylated which

act as essential mediator for leptin signalling. Because of these reasons, PTP 1B acts as an essential target for artificial inhibitors which can help in the treatment of diabetes type 2.

The physical screening of huge chemical libraries against a protein (high throughput screening) comes out to be predominant method for finding new ligands for novel drug purpose. Molecular docking and visualisation is another method for identifying compounds from different online databases to target the active site of used compound and this can be further calculated using different experiments.

CHAPTER-2

LITERATURE REVIEW

Insulin is released from the pancreas when the glucose level turns up. A tetrameric complex which is a hormone that consist of two -two subunits bind to the receptor . When this hormone binds with the extra-cellular subunit it causes a conformational shift that activate the intracellular subunit's intrinsic activity of tyrosine kinase by auto phosphorylating certain tyrosine residue inside an activated loop. Few of the phosphorylating residue outside the activation loop serve as docking sites of Insulin Receptor Substrates ,IRS which are then phosphorylate through RTk . Phosphorylated IRSs act as adapter proteins that recruit PI 3K through the regulatory subunits. PI 3K then catalyses the conversion of Phosphatidylinositol to the 3, 4 – bisphosphate and 3 , 4 , 5 – trisphosphate activating Phosphoinositide - Dependent Kinase-1 PDK-1. Phospho inositide - Dependent kinase activate PKB or Akt by phosphorylating the crucial threonine as well as serine residues. Protein phosphorylation downstream at insulin receptor leads to glucose absorption into cells via the glucose transporter GLUT 4. This method activates GLUT 4 containing vesicle downstream at PI 3K. A typical PKC and AKT activated by PI 3K phosphorylations has linked to the processes . Akt not only activates GLUT 4 vesicles, but also phosphorylates GSK-3 has constantly increase glycogen production via GS (Moule, 1997). GSK-3 found to be constantly activated and phosphorylate glucose substrate which deactivate it that is necessary for the assembly of Glucose in the form of UDP glucose into glycogens. Akt phosphorylates GSK-3 inactivating the kinases and relieving it inhibition at glucose substrate. Additionally the mentioned mechanism of a PI 3K Independent pathway appeared for the requirement of Insulin Dependent Glucose absorption in cell. This cCbl associated proteins CAP , Cbl dependent pathways appears to give a secondary signals which modulates GLUT 4 vesicles transportation through raft of lipids to affect sugar level. While much is known about the process which originate for propagating signalling of insulin to regulate sugar absorption, the mechanism for understanding termination of signal remain poorly understood. Dephosphorylation of critical tyrosine residues in the receptor's activation loop is becoming a widely accepted notion. Research suggests that receptor

activation is influenced by the balance of phosphorylation and dephosphorylation. PTPs' role in deactivating IR is increasingly important in insulin signalling. Inhibiting IR phosphatase could be an effective therapeutic for Diabetes type 2. Research to find enzymes responsible for dephosphorylating the Insulin receptor led to the identification of several PTPs.

2.1. EFFECT OF PROTEIN TYROSINE PHOSPHATE ON INSULIN PATHWAY

The PTP1B KO mouse and PTP1B ASO therapies in diabetic rodents provide strong evidence that PTP1B plays a role in the insulin signalling system. The PTP1B KO mouse has produced some interesting results and shed light on a number of potential roles for the phosphatase in vivo. Disrupting the PTP1B gene in mice was thought to cause lethality or increased tumor formation. This phosphatase has been shown in cell culture to inhibit growth factor receptor kinase-signalling pathways such as IGF-IR, PDGFR, EDGFR, and IR (Roome, 1988).[Lint, AJ 1999].

None of the scenarios were found, mice found to be alive and long lived and enhancement in the tumor growth was not found. It can be concluded that cell culture could not represent PTP 1B function in vivo. Other PTPs may compensate for the shortage in PTP 1B.We cannot totally rule out compensating effects, but the observed phenotype in PTP 1B KO mice.

PTP1B loss in mice leads to improvement of sensitivity of insulin as evidenced from a considerably reducing in feeding level of glucose which has sustained at medium level of circulating Insulin level . In addition, it showed greater insulin stimulated IR phosphorylation in liver and muscle as well as better clearance of glucose in tested glucose-intolerance level. Deletion of PTP 1B increases activity of insulin indicating that PTP 1B is a negative regulator of insulin signalling. Here at this places PTP 1B is proximate to insulin receptor where it is likely to deactivate the insulin receptor by dephosphorylating it. In additionally or alternatively it has impact on the insulin receptor. PTP 1B by dephosphorylating insulin receptor substrate can inhibit

insulin-signalling or additional dephosphorylating insulin dependent signalling molecule has to be discovered.

The genetic makeup of the PTP 1B SO rat and more recently the outcomes of PTP 1B -ASO therapies of diabetic mice provide many strongest evidence that PTP-1B is engaged in the insulin-signaling pathway. Many unexpected findings have been produced by the PTP1B KO mouse, which has also shed light on several possible in vivo functions of the phosphatase. In the cell-culture it had been reported that multiple Growth Factor Receptor which include kinase signalling pathway such as PDGFR ,IR,IGFIR and EDGFR has been depleted because of the activity of phosphatase. Therefore it has anticipated that because of the destruction of PTP 1B can lead of fetality or can be the major cause for the occurrence of cancer was the important predictor of specificity and binding of substrate to PTP 1B. Latest crystallization in the activation of IR region found associated along PTP 1B provides region for the purpose of selectivity . The tandem p-Tyr residues interact extensively with PTP 1B, with pTyr 1162 situated at the active sites and 1163 p-Tyr binds in the neighbouring secondary p-Tyr sites. These findings suggest that PTP1B may directly dephosphorylate the active IR. The interaction between endoplasmic reticulum ER localized PTP 1B and the activated IR is still unknown. According to many studies it had been claimed that under many situations such as phagocytosis both plasma membrane and endoplasmic reticulum can come close to each and can even get fused with each other . So it appears that IR and the PTP 1B could get dephosphorylated when they come in close proximity. The activated IR may be directed to specific places on the ER for dephosphorylation, similar to how PTP1B dephosphorylates platelet-derived and epidermal growth factor receptors (Haj, FG 2002).

Both PTP 1B KO mice and PTP 1B ASO-treated diabetic animals show enhanced insulin sensitivity (Klaman, LD-2000).Treatment with PTP1B-specific ASO in ob/ob and db/db mice lowered phosphatase protein levels in obesic rat by 70% and in liver, resulting in normalized glucose levels in preclinical insulin-resistant mice. A 70% decrease in PTP 1B proteins level through ASo and genetic is enough for improving sensitivity of Insulin and reduce insulin resistance. This is unclear if the observed change at this model can be due to resistance from insulin because of correcting insulin receptor ,PTP 1B dysregulation is the consequence of a decrease in the levels of a negative regulator, which leads to an overall improvement in insulin activity. It was recently shown that the quantity of functionally active PTP1B present in the cell may be regulated by the reversible oxidation of PTP1B. Goldstein et al. have demonstrated that

when IR is activated, H2O2 is produced along with a simultaneous temporary oxidation and inactivation of PTP1B. Additionally, they have shown that the amount of oxidized inactive PTP1B varied significantly depending on the kind of fat depot, and they have proposed that elevated amounts of active PTP1B may be a factor in insulin resistance. Several studies has demonstrated that the PTP 1B is phosphorylated by the protein kinase and IR which affects the enzyme activity of ptp 1b. By acknowledging the role of PTP 1B along with the interaction with IR will help create effective inhibitors.

2.2. PTP1B

This protein is a 37 KD with a one domain and it is organized into 12 beta sheets and 8 alpha helices. It is a severely twisted with ten beta sheets along the complete length of the molecule Beta12, which is the last strand in the structure's basic sequences is placed close at core place which contains beta3, beta12, beta4, and beta11 in parallel manner. Anti parallel beta strand found flanking by these motifs. Alpha helix-2 is found on the one side of the centre sheet were as alpha helix 3,4 are found on the other side . Along with the chain of alpha4, it forms a four-helix bundle composed of helices alpha5, alpha6, alpha3, and alpha4. A small alpha helices 1, found at the upper part of a beta sheet adjacent to beta 1. Conserved PTP- domain is found to begin from here .An second anti-parallel beta-sheet containing betas 5 and 6 is located above the core beta-sheet. The chain's carboxyl terminus is located at the end of alpha6. The chain's non-conserved amino terminus fold in two -alpha helix called alpha -1 and alpha- 2. NH 2 terminus of alpha 6 is founded wrapped by these helices. The cysteine residue (Cys215) is located on loop 15, a segment that connects beta12 and alpha4. It is crucial to the enzyme's catalytic activity. Entangled loop which connects the secondary structure element are seem to meet at this place .These loops comprise the majority of the 27 invariant residues in PTP domain sequences that have been shown to activate phospho tyrosine containing proteins or peptides. The tertiary structure of the protein is stabilized by the invariant residue which are placed far away from active site.

2.3. PHYTOCHEMICALS

In recent years, a wide range of plant study has been conducted. In addition, numerous plants and fruits have inhibitory properties. Phytocompounds are recognized natural inhibitors of digestive enzymes that work via a variety of ways Researchers are focusing on developing effective and low-risk treatment medicines for T2DM . Medicinal herbs produce secondary metabolites that have effective antidiabetic properties for controlling blood glucose levels. In traditional treatment, various medicinal plants .

2.3.1.BAICALEIN

Baicalein is a major bioactive flavanone that was initially found in the roots of Scutellaria . Among its many biological roles, baicalein's metabolic advantages are being studied intensively. It is found that in mice models having high obesity disorder which is caused by fatty food .Baicalein therapy for117 days substantially reduced level of blood sugar and enhanced effectiveness of insulin Additionally administration of baicalein improved breakdown of glucose and decreased metabolic syndrome. Its therapy reduced kidney abrasion from lowering iNOS and TGF β1 levels and suppressing NF-κB-mediated inflammation. Baicalein therapy significantly alleviated many coexisting metabolic abnormalities in mice with high fat diet-induced metabolic syndrome, including , insulin -resistance , heavy body and gained weight , dys-lipidemia, and aberrant deposited fat along with heptocyte Baicalein’s works majorly on insulin resistance and inflammatory responses because of the role of activated IRS ,PI 3K and AKT pathway and inhibited MAPK pathway. In most of the various pharmacological advantages, its antidiabetic properties as well as its antioxidant, anti-inflammatory, and anti-cancer actions, hold the most promise for therapeutic development.

2.3.2.ELLAGIC ACID

This phytocompound primarily found in pomegranate as well as in dried fruits. It is identified to treat a variety of chronic disorders, including heart disease and neurological disorder , owing to several amazing pharmacological benefits, which include anti inflammatory , anti-oxidant, anti-

cancer properties . Surprisingly, previous research supports ellagic -acid as a significant antidiabetic compound. In diabetes type 2 mice model and its related injury of kidney, this compound therapy effectively reduced , insulin- resistance, hyper glycemia and diabetes nephro pathy via reducing NF KB activity. Its healing property is linked with considerably decreased inflammation response, with significantly lower blood levels of proinflammatory cytokines are TNF alpha ,interleukin 1β and IL-6. Most literature showed prolonged treatment with ellagic acid has been shown to reduce hypertension and stressful behaviour, increase exploration and locomotor activity, as well as restore rational function in diabetes associated rat. Effectively the reasonable effect of this bioactive acid were accompanied by reduced hyper glycemia, mostly modified status of inflammation, and reduction in neurons death . Precisely, ellagic acid curation majorly reduced hyper glycaemia induced kidney injury in KDK rat by inhibiting the group box of 1 toll like receptor 4 NF kB pathway mobility indicating that anti inflammatory role is one of important method for understanding ellagic acid's curing consequences for the healing of diabetes and problems related with it.

2.3.3.RESVERATROL

It is a poly - phenolic phytoene found within various plants, including peanut ,pears, apples, plum. It has been extensively investigated for the diagnosis of multiple disorders due to its numerous remedial characteristics, inclusive anti cancer, anti-diabetic antiobesity, neuro and cardio protective benefits.

2.3.4.NARINGENIN

This phytocompound which is present in grape fruit ,it is a flavonone. A lot of researches suggested that naringenin can be an anti diabetic drug. In P2DM model of a mice stated that it reduced hyper lipidemia, insulin resistance, and hyper glycemia . Naringenin treatment reduced blood glucose levels in mice with glucose intolerance during pregnancy, leading to increased

movement from membrane of insulin responsive glucose transporter GLUT -4 and uptake of glucose through the AMP activated protein kinase pathway into the skeletal muscle cells.

2.4.MOLECULAR DOCKING

Molecular docking is a bioinformatics modelling tool used in structure-based drug development. It has been an invaluable resource for drug discovery and biological system research. It is critical for anticipating the interactions of tiny molecules (ligands) with a protein of interest's binding site. This contributes to the development of more effective and targeted medications.

Virtual molecular screening is a method for docking small molecule compound with macromolecules which assist in finding the lead compounds along their desired biological functionalities. This in silico technique is applied for the purpose of designing noval drug by using computational methods. Here we use PyRx, an open-source software with an intuitive user interface that runs on all major operating systems (Linux, Windows, and Mac OS), for small-molecule virtual screening via docking.

CHAPTER -3

MATERIAL REQUIRED AND METHODOLOGY

The following database and online software were used for the molecular docking

1. PROTEIN DATA BANK
2. PUBCHEM
3. PYRX
4. OPEN BABEL
5. BIOVIA DISCOVERY STUDIO VISUALISER

3.1.PROTEIN SELECTION

- Use PDB (http://www.rcsb .org) to download the structure 6 OMY.
- Put this file into a folder.

3.2.LIGAND SELECTION

- Visit PubChem at www.pubchem.ncbi.nlm.nih.gov.
- Look up ellagic acid as a compound .Download the corresponding 3D conformer in SDF format. Put it in a separate folder.
- Download the 3D structure of baicalein, resveratrol, naringenin in the same way and save it.

3.3.PROTEIN PREPARATION AND LOADING

- The binding location and the binding residue must be know in order to prepare the protein for docking .it involved one chain of protein .Here binding site of protein is already known.
- Open pdb file and delete heta atoms.
- Right results would not be found without removing the already bound ligand.
- Extra chains were removed from protein structure. Here we kept the chain A and rest
- were removed. Now save the file as protein.pdb. Protein structure is ready to be docked.

- Select “file” “Load Molecule” or simply click on the first icon on the upper left corner. Choose the protein structure that you downloaded as “6omy.pdb”.
- Convert pdb format to pdbqt by right click on 6 omy then on display and now select macromolecule.

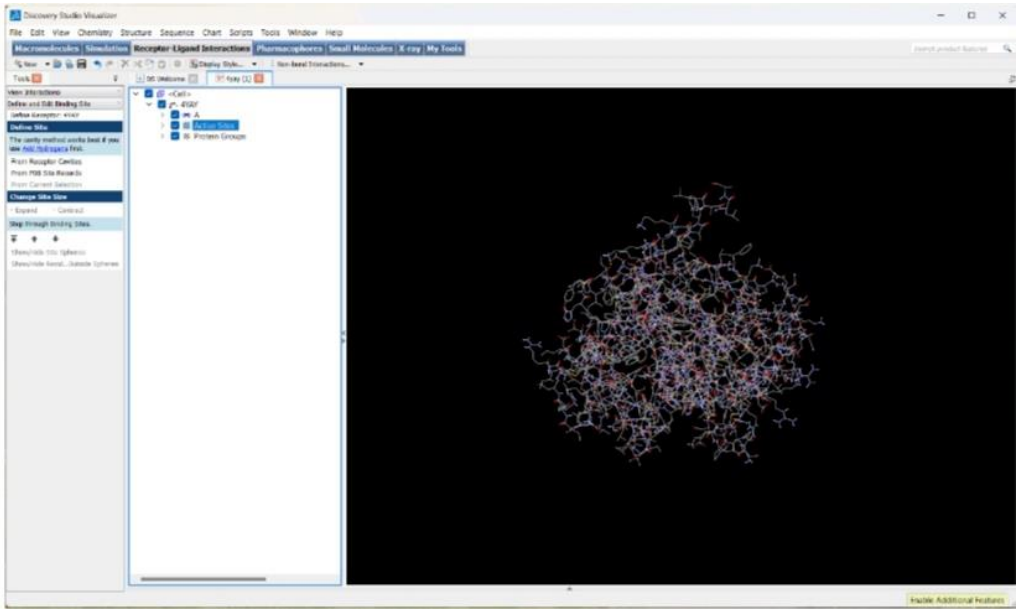

FIGURE 1 – PROTEIN PREPARATION

3.4.LIGAND PREPARATION AND LOADING

- In pyrx.,click on open Babel and select on insert new item present on bottom right corner.
- Now select each ligand one by one and upload it.
- After uploading all ligands, right click on ligand and select minimise all to decrease the energy .Convert all the ligands to pdbqt format.

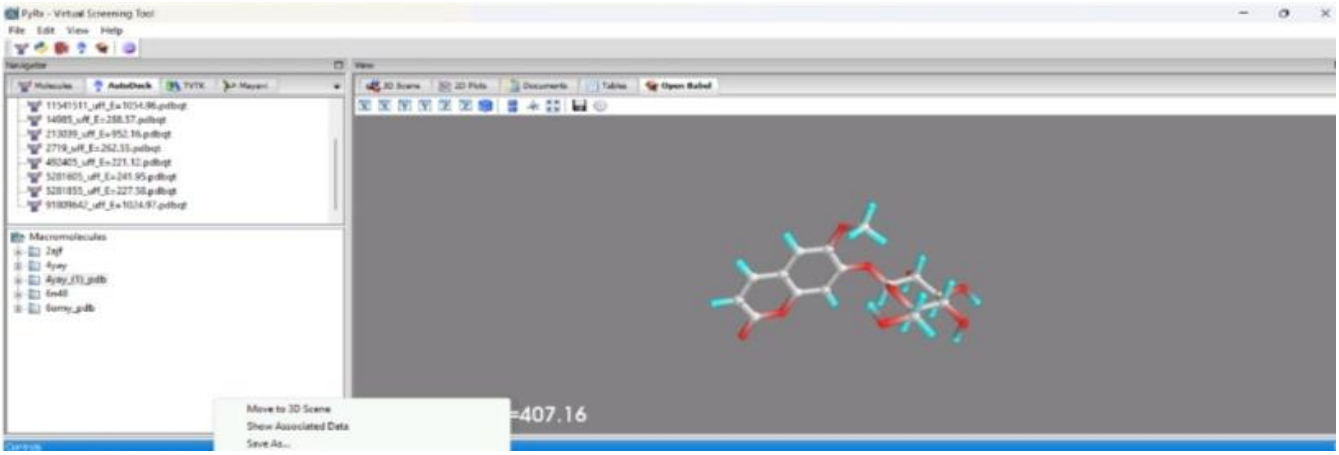

FIGURE 2-LIGAND LOADING

3.5.DEFINING PROTEIN AND LIGAND

- The loaded protein and ligand are shown under the “Molecules” tab. To identify protein and ligand .Right click on protein-<Autodock-<Macromolecule to accomplish that.
- Right click on ligand ,select Autodock and then make ligand pdbqt files are prepared.

3.6.DEFINING GRID BOX

- Now click on vina wizard and select option on the right corner. Select protein and ligand one by one by pressing shift and control button.
- Click on forward .grid box appeared. Return to the molecules tab located on the right corner. Click the loaded protein + symbol.
- All the residue in the chain were visible. To choose the binding residues, right click on residue and choose atom, display, label and atoms. The atoms showed up on the protein. Now properly adjust the grid box so all the residues come inside it.

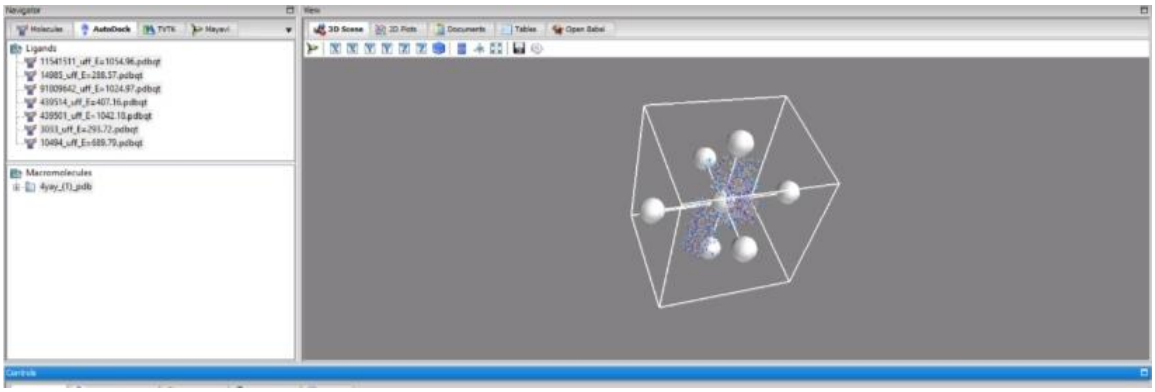

FIGURE 3-DEFINING GRID BOX

3.7.RUNNING AUTODOCK VINA

- To adjust the exhaustiveness, simply enter the desired number in the box located in the left bottom corner. Once everything adjusted press the forward button Docking began and the process was shown. The bottom panel display the poses with the binding affinities after the docking process is completed. It showed all poses along with RMSD value. Save your file in excel sheet.

- Analyse the result and the one ligand which has the highest energy with the negative sign is selected. Again open pyrx tab and click and click Autodock and select macromolecule and ligand with highest binding energy. Now right click and select display then all models of the ligand get displayed and select your desired model and save it in pdb format. Visualise and Analyse the results using Bio via discovery Studio Visualiser.

CHAPTER-4

RESULT

All the identified compound ellagic acid, resveratrol ,baicalein, Naringenin were docked into the active site of PTP1B using pyrx Auto dock vina. The lowest docked conformation was selected and taken into account.

STRUCTURE OF THE STUDIED PHYTOCOMPOUND

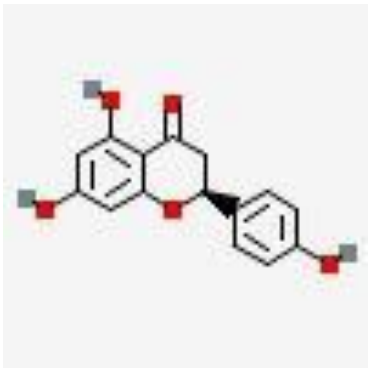

Figure 4 Naringenin.

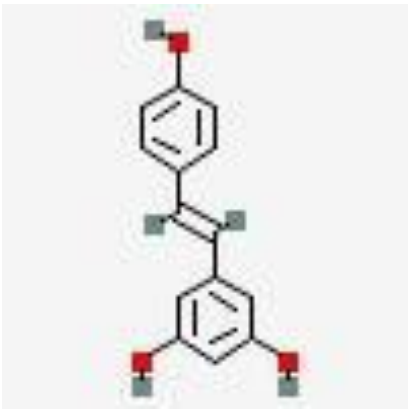

Figure 5 Resveratrol

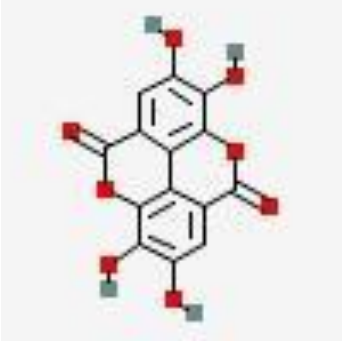

Figure 6- Ellagic Acid.

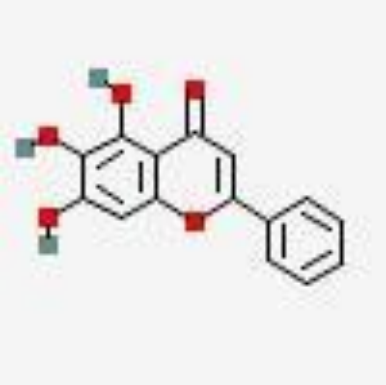

Figure 7 – Baicalein

DOCKING OF ELLAGIC ACID AGAINST PTP 1B

Docking results in binding between ellagic acid and ptp1b shows

Binding energy -8.6 kcal/mol

RMSD- 0

E score. -56.496

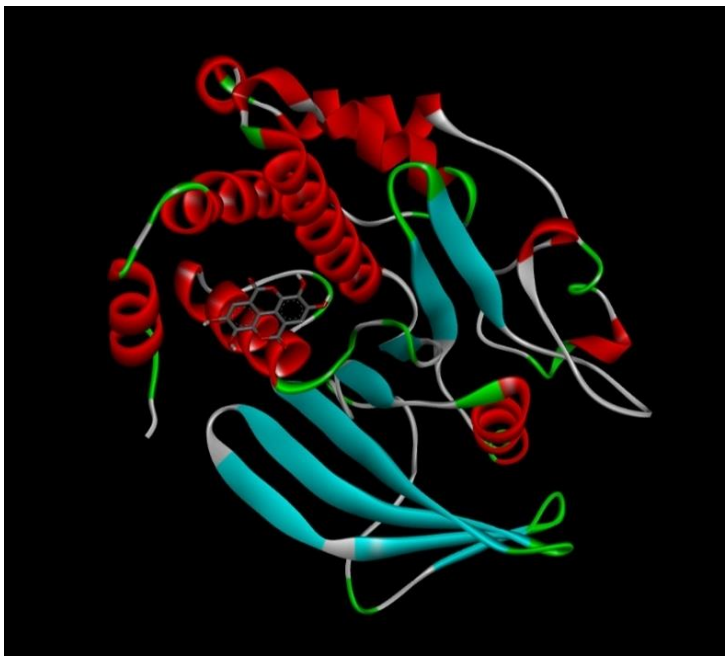

Figure 8-Docking of Ellagic Acid with PTP1B

DOCKING OF BAICALEIN AGAINST PTP1B

Docking results in binding between the Baicalein and ptp1b showed

Binding energy -7.9kcal/mol

RMSD-30.14

E score -51.087

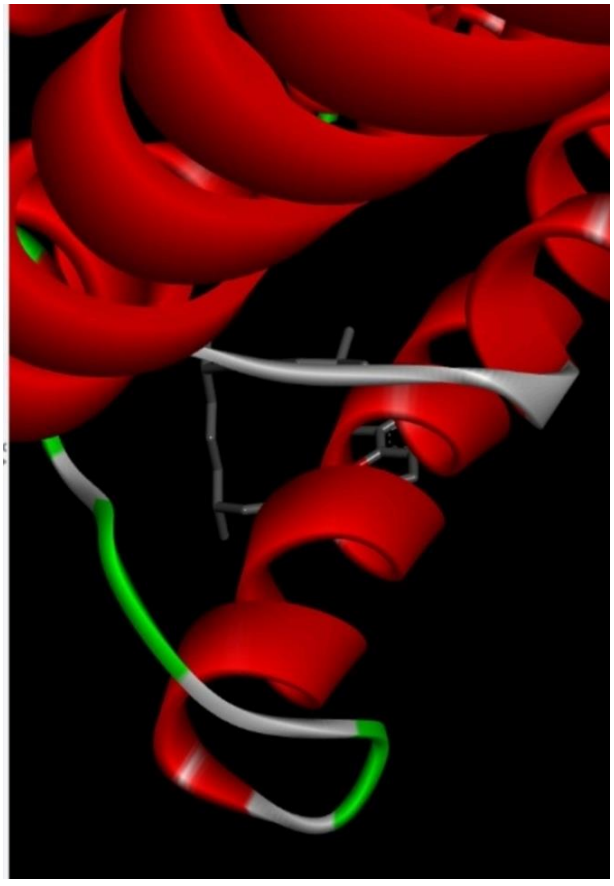

Figure 9-Docking of baicalein with PTP 1B

DOCKING OF RESVERATROL AGAINST PTP1B

Docking result in binding between the resveratrol and ptp1b showed

Binding energy. -7.55 kcal/mol

RMSD-0

E score. - 50.45

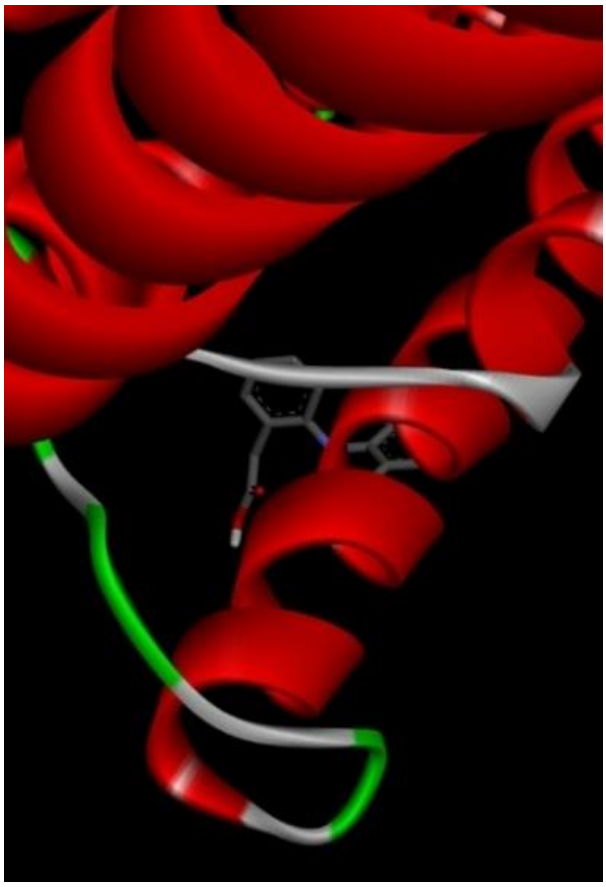

Figure 10 -Docking of resveratrol with PTP 1B

DOCKING OF NARINGENIN AGAINST PTP1B

Docking in between the naringenin and ptp1b showed

Binding Energy -5.6kcal/mol

RMSD. 26.59

E score. -23.45

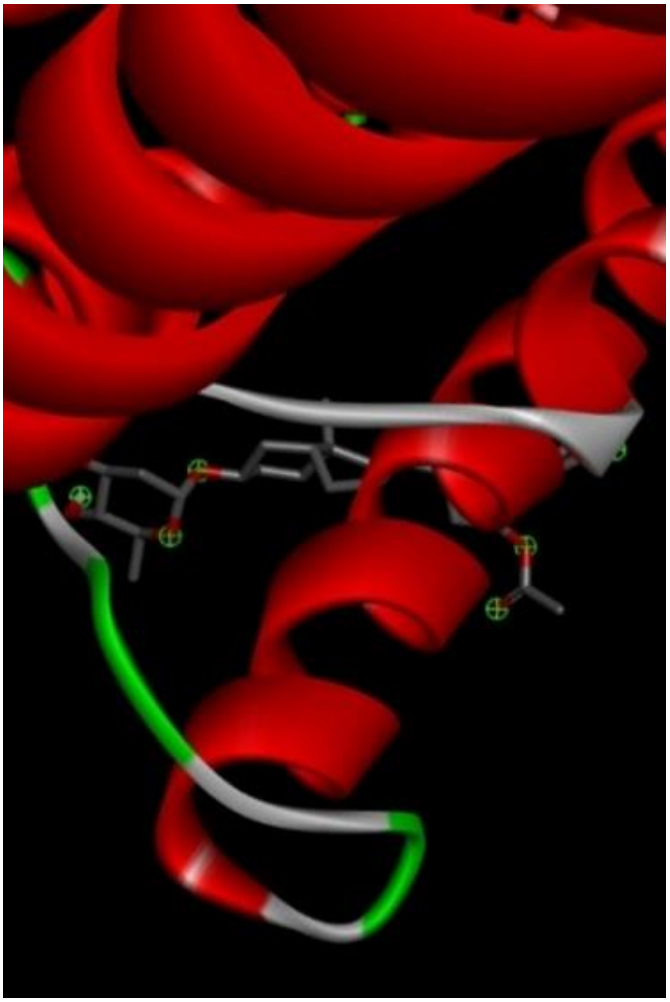

Figure 11- Docking of naringenin with PTP 1B

4.1. DISCUSSION

Here an approach is made to identify potential ligand for the selected protein in the treatment of diabetic type 2 by using molecular docking process. The identification of the best docked ligand allowed us to know the binding mode of compound .Binding energy of the protein and ligand interaction is essential for interpreting how fit the ligand bind to the target molecule. By using in silico analysis ellagic acid found in berries and pomegranate found to exhibit a good binding interaction with ptp1b ,Ellagic acid has the lowest binding energy for ptp1b that is – 8.6kcal/mol and E score -56.496 and baicalein isolated from Scutellaria root and resveratrol found in grapes ,plum turned up second with binding energy -7.8 kcal/mol and -7.55kcal/mol and E score -51.087 and - 50.45 respectively. Free energy binding and surface interaction between ligand and protein target influence the inhibitory activity of selected bioactive compound on ptp1b. Thus the in silico method adopted in the present study helped in identifying online tools for the treatment of diabetes type 2.This knowledge is important for the development of novel drug for the treatment of diabetes type 2 disorder.

CHAPTER -5

FUTURE PROPOSAL

Molecular Dynamic simulation will be carried out to give more detailed view of the binding complex. The stability of the binding complex is of paramount importance. MD simulation are good indicator of this parameter. If the findings after process comes out to be good, these result can help in the novel drug for the treatment of diabetics type 2.

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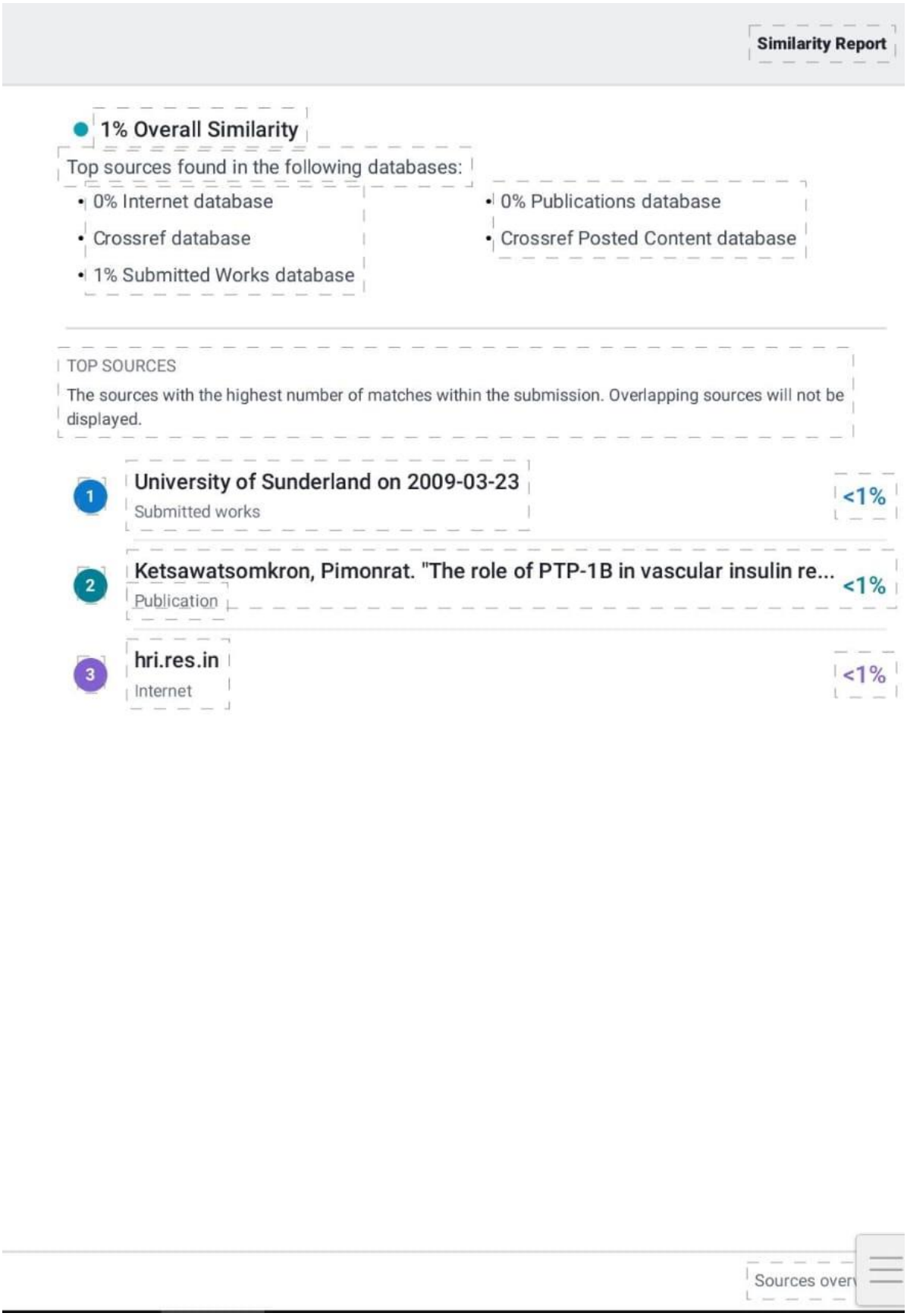
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