M.TECH (BIOINFORMATICS)

SOURABH SHARMA

2023

IDENTIFICATION AND SCREENING OF BACE1 INHIBITORS AGAINST TYPE 2 DIABETES USING DRUG REPURPOSING

A DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE AWARD OF THE DEGREE
OF

MASTER OF TECHNOLOGY
IN
BIOINFORMATICS

Submitted by:

SOURABH SHARMA
2K21/BIO/07

Under the supervision of
Prof. YASHA HASIJA

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DELHI TECHNOLOGICAL UNIVERSITY
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CANDIDATE'S DECLARATION

I, SOURABH SHARMA, 2K21/BIO/07, student of M.Tech (Bioinformatics), hereby declare that the project Dissertation titled " Identification and Screening of BACE1 Inhibitors against Type 2 Diabetes using Drug Repurposing " which is submitted by me to the Department of Delhi Technological University, Delhi in partial fulfillment of the requirement for the award of the degree of Master of Technology, is original and not copied from any source without proper citation. This work has not previously formed the basis for the award of any Degree, Diploma Associatcship, Fellowship, or other similar title or recognition.

Place: Delhi
Date: 13/6/23

SOURABH SHARMA

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CERTIFICATE

I hereby certify that the Project Dissertation titled " **Identification and Screening of BACE1 Inhibitors against Type 2 Diabetes using Drug Repurposing** " which is submitted by **Sourabh Sharma (2K21/BIO/07)**, Department of Biotechnology, Delhi Technological University, Delhi in partial fulfillment of the requirement for the award of the degree of Master of Technology, is a record of the project work carried out by the students 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 elsewhere.

Place: Delhi
Date: 13.06.23

13.06.23

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SOURABH SHARMA

Place: Delhi

Date: 13/7/23

ABSTRACT

Type 2 diabetes (T2D) is a complicated disease that is caused by a complicated combination of hereditary, environmental, and epigenetic factors. Chronic diabetes-related hyperglycemia is linked with dysfunction, long-lasting damage, and failure of several organs, including the blood vessels, heart, eyes, kidneys, and nerves. An interaction involving genes as well as the environment has been linked to diabetes, which is presently the pandemic with the fastest rate of growth.

Research on BACE1 has earlier concentrated on its functions as the β-secretase that regulates the synthesis of β-amyloid beta, which is seen in Alzheimer's disease. BACE1 expression that is pathologically high in cells that have been linked to the emergence of metabolic diseases like type 2 diabetes, heart diseases, and obesity.

Multiple drugs are present in the market to treat the disease, but more drugs are required to be easily accessible to the public. This could be possible when a drug that is normally used for less harmful diseases like fever, nausea, and many more are repurposed to treat chronic diseases like type 2 diabetes (T2D). In this research, anti-viral drugs and anti-hypertension drugs have been repurposed using the in-silico approach of molecular docking which inhibits the BACE1 protein. When this protein is inhibited, it stops the chances of occurrence of type 2 diabetes. Telmisartan, an anti-hypertensive drug, is the best drug to limit the action of BACE1 protein to stop the progression of the disease.

Keywords— Diabetes type 2, β-Secretase 1 (BACE1), Drug Repurposing, Molecular Docking, Telmisartan, *Bioinformatics.*

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
T2D	Type 2 diabetes
Aβ	Amyloid beta
BACE1	β-Secretase 1
EMA	European Medicines Agency
MHRA	Medicines and Healthcare Products Regulatory Agency
ER	Endoplasmic reticulum
GA	Golgi apparatus
GLUT2	glucose transporter 2
UPR	Unfolded protein response
SERCA	Sarco/endoplasmic reticulum Ca2+ ATPase
IAAP	islet amyloid polypeptides
ROS	reactive oxygen species
IL	interleukin
APP	amyloid precursor protein
IRsol	soluble insulin receptor
PKB/AKT	protein kinase B
PDK	phosphoinositide-dependent kinase-1
PDB	Protein Data Bank

CHAPTER 1

INTRODUCTION

One of the most serious global health issues continues to be the cause of type 2 diabetes (T2D). This metabolic disease is brought on by hyperglycemia, which results in insufficient synthesis of pancreatic insulin or resistance to peripheral tissue insulin. T2DM is the result of several epigenetic, genetic, and environmental interactions. Long-term-cell abnormalities can impact insulin levels, which may also have significant glucotoxicity impacts on pancreatic cells and impede insulin production. Insulin resistance describes a time when cells stop responding to insulin as intended, affecting lipids as well as apolipoprotein through modifying the catabolism and inhibiting the action of lipoprotein lipase as a result [1]. In addition to the effect of several genes, being overweight, insulin resistance, and environmental variables, T2D is a complex illness. At a given insulin level, insulin resistance in T2D results in dropped intake of glucose in muscle and adipose tissues alongside a rise in glucose production in the liver. Reduced insulin production brought on by malfunctioning β-cells is another side effect that is insufficient to maintain appropriate glucose levels. The pancreas (β-cells and α-cells), adipose tissue, brain, skeletal muscle, liver, small intestine, and kidneys are some of the organs linked to the emergence of T2D. Inflammation, dysregulation of adipokines, immunological dysregulation, and changes in gut microbiota have all emerged as an important pathophysiological factor, according to emerging research [2].

The brain's involvement in the β-secretase that secretes amyloid beta (Aβ) peptides has historically been the focus of the beta-site amyloid precursor protein cleaving enzyme-1 or BACE1 study. These Aβ peptides build up from the senile plaques that are a hallmark of dementia, resulting in the death of neurons and decreased cognitive function [3]. Although BACE1 is expressed most strongly both in the brain's central nervous system and the pancreas, Numerous cell types also contain BACE1 proteins and mRNA at low levels. BACE1 has been linked pathologically to the emergence of several illnesses, like type 2 diabetes, epilepsy, and schizophrenia. BACE1 is thought to have a physiological function in energy metabolism and homeostasis based on the BACE1 knockout's phenotype in mouse models, which comprise of lower weight growth, and correlations with metabolic illnesses including sugar [4].

It is predicted that 537 million people globally are likely to have diabetes, with a global incidence of 10.5% among those who are 20 to 79 years old. The diagnosis of type 2 diabetes accounts for about 98 percent of cases worldwide, however, the rate varies widely by country. The overall incidence of confirmed type 2 diabetes among individuals in the United States was 8.5%, according to an investigation from the National Health Interview Survey. Other national databases, including the Centers for Disease Control and Prevention Diabetes Surveillance System, revealed the prevalence of adults with diagnosed diabetes of about 11.3 percent in 2022 (37.3 million people out of which approximately 28.7 million having diagnosed diabetes, and the remaining roughly 8.5 million undiagnosed, and among them, 95% has type 2 diabetes) [5]. There is fear that the number of subjects of diabetes will keep on increasing significantly given the noticeable rise in childhood obesity. This worry is supported by international data, which show that between 1990 and 2019, the overall prevalence rate for type 2 diabetes among young adults and teens of age group between 15 to 39 years climbed from 117 to 183 per 100 thousand people globally.

The process to approve a novel drug is expensive and may span 10 to 15 years. Drug repurposing (repositioning) is a possible alternative approach to shortening the time required to create a medicine as a result of the drawn-out discovery process. After receiving approval from a regulatory agency like the European Medicines Agency (EMA), FDA, or the Medicines and Healthcare Products Regulatory Agency (MHRA), among others, [6] repurposing a drug involves using it for a different indication. Because of the tremendous potential for an accelerated development process, many pharmaceutical firms are actively implementing medication repurposing to revive a few of their previously unsuccessful and FDA-approved pipeline compounds as new therapies for a variety of medical conditions. A new medicine must adhere to strict guidelines in order to be sold. Due to the wide-ranging physicochemical qualities of the chemical entities and the difficulty of expanding the manufacturing, it takes a substantial investment to identify a medicine and subsequently develop it [7], [8]. This restriction further enables pharmaceutical firms or educational institutions to rapidly and effectively use drugs that have already received approval for a novel indicator that isn't yet available to people with the disease. Investigational compounds usually give a strong onset for their revival through repurposing when they fail to demonstrate efficacy for a certain indication. They can be further rediscovered for new indications, eventually developing

into effective medicines, especially helpful when dealing with rare diseases that provide significant treatment, diagnosis, and resource challenges [9]. Due to benefits like cost-effectiveness and a quicker drug development cycle, drug repurposing has become increasingly popular. Its viability is increased by the methodical deployment of repurposing techniques. For instance, computational and phenotypic information retrieval techniques, like the target-based strategy, will yield valuable data with unmatched drug-target validation [8]. Drug repurposing offers a chance to increase our understanding without constricting what is already known. Therefore, medication repurposing can help the pharmaceutical sector, as well as university researchers, produce new, scientifically sound drugs.

CHAPTER 2

LITERATURE REVIEW

2.1 TYPE 2 DIABETES

Diabetes type 2 is a severe metabolic condition that is marked by elevated blood sugar levels caused by insulin resistance and inadequate production of insulin. It is a prevalent and growing epidemic, particularly in developed countries. Unlike type 1 diabetes, lifestyle factors have a significant role in type 2 diabetes, such as poor dietary choices, sedentary behavior, and obesity, along with genetic predisposition. This form of diabetes can have severe health consequences if left unmanaged, including an increased risk of cardiovascular diseases, nerve damage, kidney disease, and other complications. Understanding the symptoms, causes, and management strategies for type 2 diabetes is crucial in addressing this global health concern [10].

A healthy diet, emphasizing reduced sugar and refined carbohydrate intake, along with portion control, is crucial. Regular physical activity, such as brisk walking or aerobic exercises, helps improve insulin sensitivity and maintain a healthy weight. Medications, including oral antidiabetic drugs and insulin, may be prescribed by healthcare professionals to control level of blood sugar effectively.

Type 2 diabetes is a common and developing disease with serious health consequences. Individuals, healthcare professionals, and society as a whole must understand the causes, risk factors, symptoms, complications, and management techniques related with this disorder. We may work towards reducing the impact of type 2 diabetes and enhancing the overall health and well-being of afflicted individuals by introducing preventative measures and taking a proactive approach to managing it [11], [12].

Drug repurposing is a novel method that entails discovering new therapeutic applications for existing drugs that were originally produced for different purposes. Drug repurposing has attracted attention in the context of type 2 diabetes as a viable way to uncover novel therapy options and improving patient outcomes. Researchers and clinicians can investigate the potential of approved drugs in managing type 2 diabetes and its associated problems by focusing on existing knowledge and safety profiles.

One of the most notable benefits of drug repurposing in type 2 diabetes is the potential to drastically reduce the time and expense involved with traditional drug discovery and development because repurposed medications have already been subjected to rigorous preclinical and clinical testing for their original purposes, their safety profiles, doses, and pharmacokinetics are well characterized [13]. This allows researchers to skip time-consuming early-stage trials and focus on studying the drug's efficacy in the context of type 2 diabetes. The total timetable from drug discovery to clinical implementation can be greatly shortened by exploiting existing expertise.

Another benefit of drug repurposing is the possibility of increased patient safety. Repurposed drugs have a well-established safety profile because they have already been approved for usage in humans. This reduces the risks of harmful drug reactions and allows clinicians to confidently prescribe them. Furthermore, repurposing existing pharmaceuticals avoids the need for large-scale manufacturing and distribution operations, which helps to ensure constant drug quality and availability, which benefits patient safety [14].

Furthermore, drug repurposing in type 2 diabetes would lead to the discovery of new mechanisms of action that could improve disease management. Traditional diabetic treatments generally target glucose management and insulin production; however, repurposed drugs may provide additional advantages by targeting inflammation, lipid metabolism, or cardiovascular health pathways. Drug repurposing has the potential to provide more comprehensive and personalised treatment options for people with type 2 diabetes by broadening the range of therapeutic targets.

2.2 PHYSIOLOGY OF β-CELLS AND MECHANISM OF DYSFUNCTION

Pre-proinsulin is the precursor secreted in a native form which upon cleavage turns into insulin. Several enzymes in the endoplasmic reticulum (ER), mature the pre-proinsulin resulting in structural change during the maturation process so that it can become proinsulin. Then, proinsulin gets shipped to the Golgi apparatus (GA) from ER, further, it passes in developing vesicles then breaks down into C-peptide and mature insulin and secreted [15]. Until maturity, the storage of insulin is in granulated form, which upon requirement is released in the body. Glucose elevation serves as a signal for insulin release. It is crucial to keep in mind that a number of other substances, such as fatty acids, hormones, and amino acids, may trigger the secretion of insulin. The principal

mechanism through which beta-cells absorb glucose and the increment in blood glucose is via the glucose transporter 2 (GLUT2), transporter protein which is a solute that in addition it acts as a sensor for glucose for beta-cells. Upon consumption of glucose, its catabolism is initiated. As a result, potassium channels that are ATP-dependent in the plasma membrane start to shut, boosting the ATP/ADP ratio inside cells. The Ca2+ channels which are dependent on voltage open as a result of the membrane depolarizing, allowing the entry of Ca2+ into the cell. An elevation in the cellular Ca2+ concentrates cause the granules made up of secretory insulin to move and infuse into the cellular membrane, which causes the exocytosis of insulin [16].

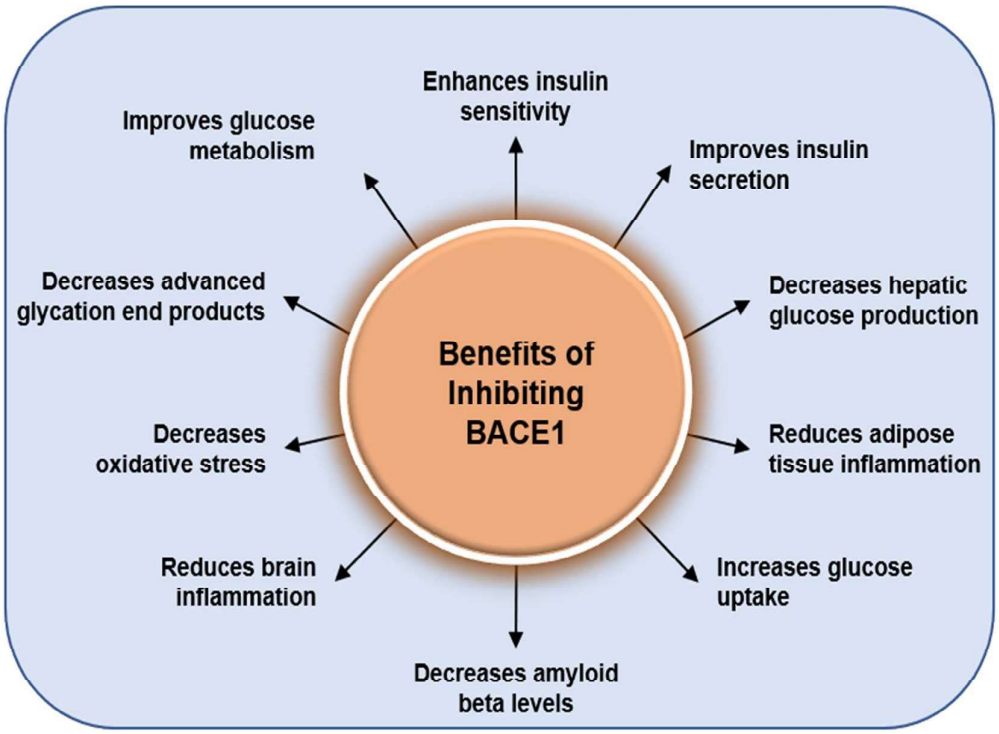


Fig. 1. Benefits of Inhibiting BACE1 in Type-2 Diabetes

Traditionally, cell death has been connected to β Cell malfunction. By triggering the deadly unfolded protein response (UPR) processes, excess FFAs and hyperglycemia produce ER stress, resulting in β-cell dysfunction. In fact, oxidative and metabolic stress caused by weight gain-related lipid toxicity, glucotoxicity, as well as glucolipotoxicity injures β-cells. Higher concentrations of saturated FFAs may cause stress, and this stress may trigger the UPR pathway by inhibiting SERCA (sarco/endoplasmic reticulum Ca2+ ATPase), Which is in charge of IP3 receptor activation, ER Ca2+ mobilisation, or directly impairing ER homeostasis. A sustained high glucose level also increases the

formation of islet amyloid polypeptides (IAAP) and proinsulin in -cells. As a result, there is a rise in the reactive oxygen species (ROS) generation, which is facilitated by oxidative protein folding, as well as a buildup of insulin and IAAP that are misfolded. The physiological mobilization of ER Ca2+ is altered, proapoptotic signals are favored, proinsulin mRNA is promoted to degrade, and interleukin (IL)-1 is released, attracting macrophages, and escalating local islet inflammation [17].

The primary starter of amyloid β(Aβ) formation inside the brain, the primary symptom of Alzheimer's disease (AD), has been referred to as BACE1, an enzyme which cleaves -site amyloid precursor protein (APP). However, recent research has shown that BACE1 is also essential for metabolic control, and mutations in BACE1 result in type 2 diabetes. Here, in this research, we have discovered some already-established drugs for other diseases, which can be beneficial to inhibit BACE1 and stop the progression of type 2 diabetes.

2.3 STRUCTURE OF BACE1

A subgroup of membrane-anchored aspartyl proteases, BACE1 and BACE2, are type 1 membrane proteins. The 501 amino acid preprotein produced by the transcription of the BACE1 gene has five essential domains, including a signal peptide and the cytoplasmic domains, along with pro-catalytic membranes. The BACE1 preprotein is transported by the signal peptide to the endoplasmic reticulum (ER), here the pro-domain of BACE1 is cleaved by furin to create the mature protein. [16] BACE1 is post-translationally activated inside the trans-Golgi network and then it is localized to the late Golgi by the transmembrane domain. The two aspartyl active regions at the locations: D298 and D93, are both necessary for BACE1 to function as a protease. A pH of 4.5 is the ideal level for the activate BACE1 protein to regulate around the plasma membrane in Golgi bodies and endosomes [4]. The functional domains of BACE1's basic structure are shown in Figure 2. There are five domains: cytosolic domain (478-501), transmembrane domain (454–474), catalytic domain (47–454), signal peptide (1-23), and pro-peptide (23–47).

Fig. 2. The functional domains of BACE1

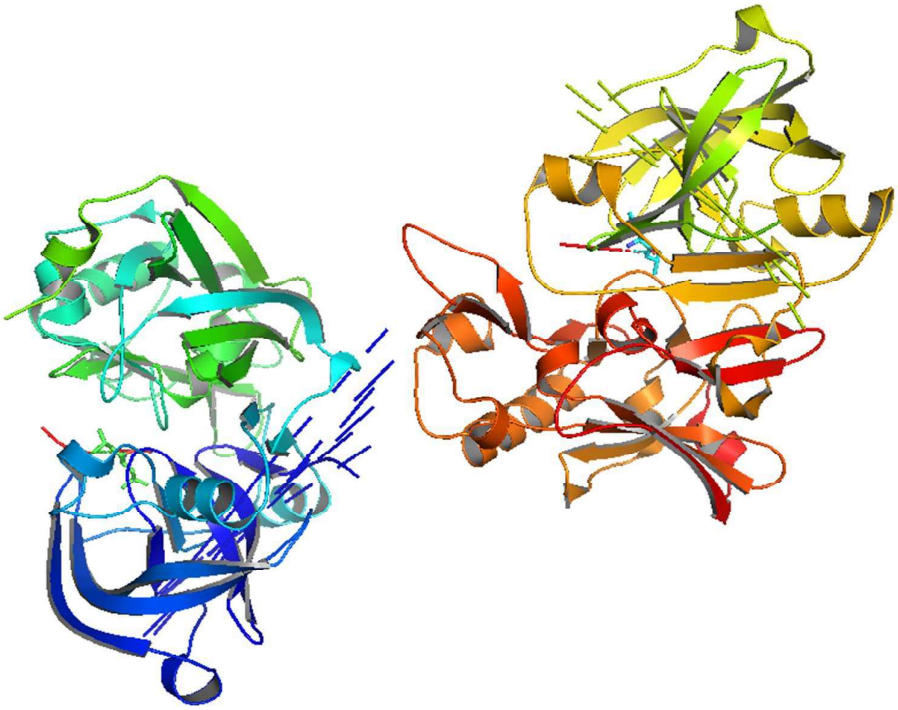


Fig. 3. The BACE1 structure using the structure 1FKN from the RSCB PDB

2.4 BACE1 REGULATION OF INSULIN PATHWAYS

Through the signalling pathway of insulin, BACE1 is connected to the pathophysiology of T2D. Normally, more insulin is produced in the pancreas in response to elevated blood sugar levels, which is then released into the bloodstream and transported to tissues that respond to insulin, including adipose tissue, the liver, and skeletal muscle [18].Through insulin receptors, cells sense elevated insulin levels, which triggers a phosphorylation cascade [19]. As a result, there are impacts that are particular to tissues like

overexpression of genes for fatty acid synthase and malic enzyme, glucose uptake, inhibition of lipolysis, stimulation of lipogenesis, protein synthesis stimulation, and glycogenesis simulation. Together, these effects reduce blood sugar levels while preserving homeostasis and vasodilation [20].

When BACE1 levels are high, insulin signalling and glucose absorption are inhibited, and when BACE1 levels are low, these effects are reversed. BACE1 is essential for efficient insulin signalling. PTEN and PTP1B, two negative regulators that are reported to decline in response to BACE1 inhibition, play a role in how BACE1 affects insulin signalling [21], [22]. In addition, BACE1 can lower the expression of IRs that are physiologically active on cell surfaces by cleaving its ectodomain in a way that is dependent on glucose. (Figure 4). The amount of bioavailable insulin decreases due to the ability of the soluble IR (IRsol) that has been released to bind insulin, further compromising insulin signalling. Patients with T2D had increased plasma IRsol levels and tissue expression of BACE1, which supports the idea that the disease is caused by BACE1 cleavage of IR [23], [24].

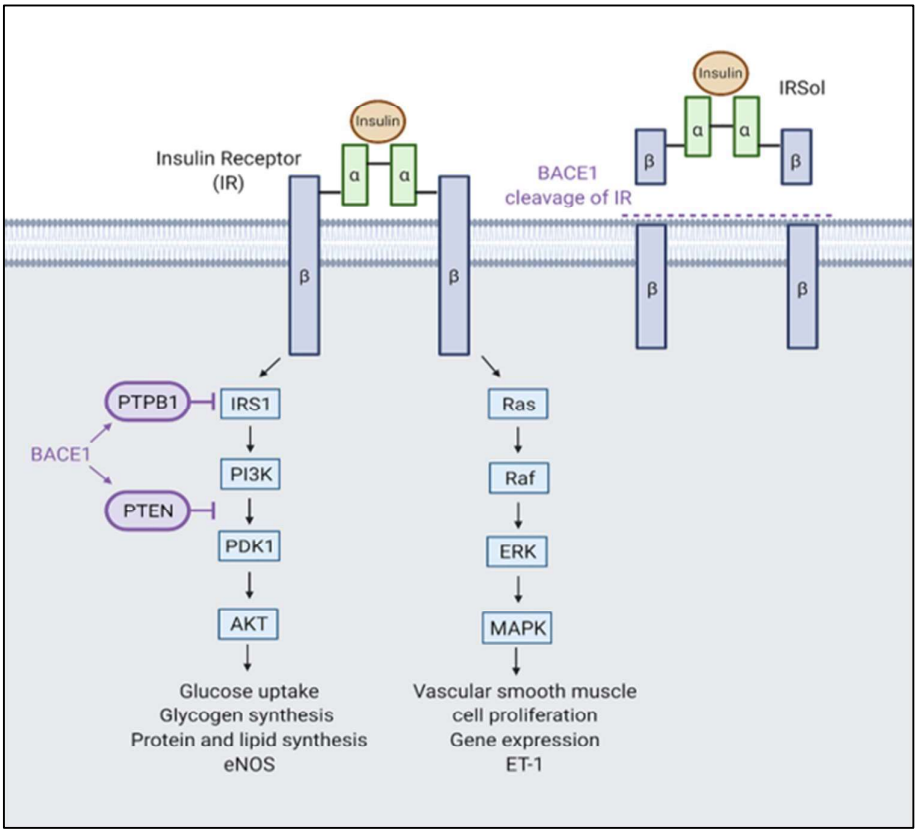


Fig. 4. Role of negative regulators in BACE1-mediated insulin signaling pathway

BACE2 has also been linked to the trafficking and cleavage of the IR in zebrafish, where it is thought to negatively regulate insulin signalling. Additionally, pharmacological suppression of BACE2 in mice is associated with improved glucose homeostasis, more insulin production, and enhanced pancreatic beta-cell function and mass, most likely due to its part in the Tmem27 cleavage [25].

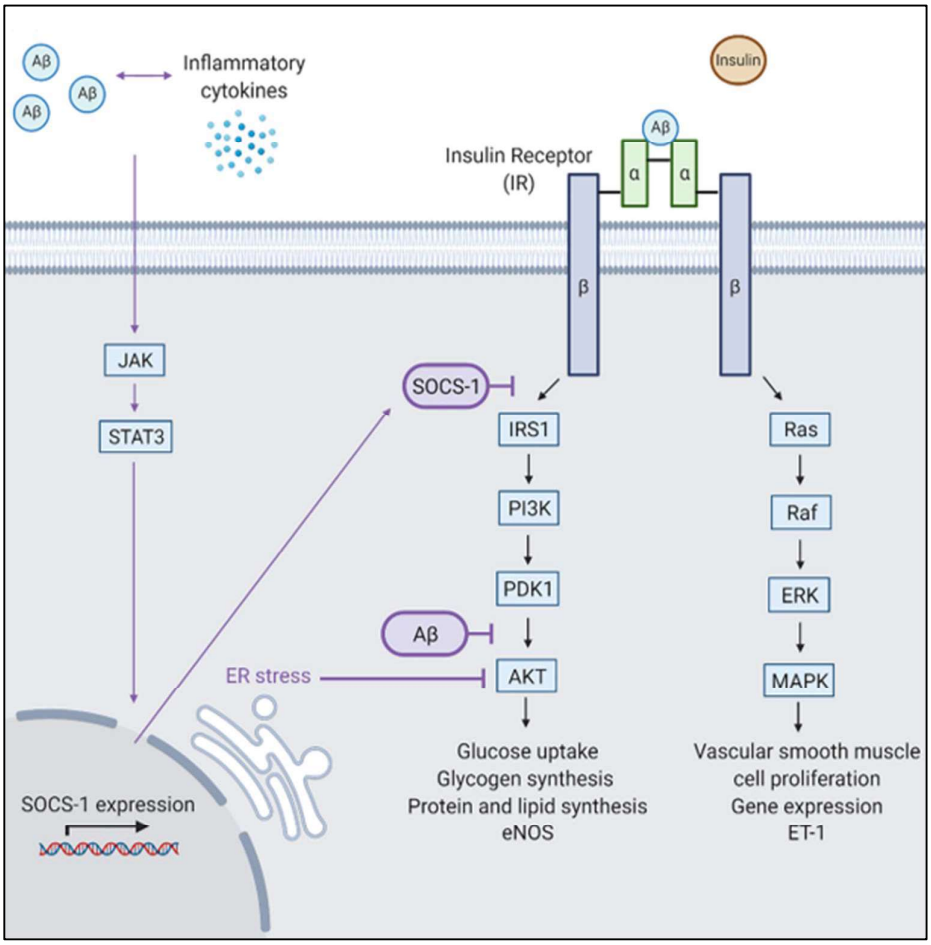


Fig. 5. Interrelationship between BACE1, Aβ production, and insulin signaling pathway

Through the generation of Aβ, BACE1 and BACE2 activity can indirectly modify sensitivity of insulin. BACE2, APP, and BACE1 are all expressed in the liver, and when expression of APP in a mouse model was confined to hepatocytes, there was a 30% rise in circulating Aβ [26].It is known that a variety of cell types can produce Aβ, with platelets being the main producer of 90% of the Aβ circulating in the blood [27] and glial cells are another important source [28]. Due to the similar tertiary structures of IR and insulin, Aβ is a competitive inhibitor that can lower the sensitivity of insulin in cells (Fig. 5) [29], [30].

SOCS-1 overexpression induced by Aβ, an interferon gamma pathway inhibitor, has an impact on insulin sensitivity as well. Aβ increases SOCS-1 expression through the JAK2/STAT3 pathway, which results in providing resistance to insulin [31]. Leptin regulates JAK/STAT3 signalling, which is significant since it connects to other components of the metabolic syndrome [32]. By referring to the research by Lee et al., Aβ inhibits the activity of the protein kinase B (PKB/Akt) target enzyme phosphoinositide-dependent kinase-1 (PDK), that ultimately causes insulin resistance [33]. Additionally, as seen in obese people with T2D, ER stress and inflammation brought on by palmitate impede insulin signalling. While sAPPβ mimics BACE1, it can restore insulin signalling in this situation [34].

It has been established that BACE1 and BACE2 are expressed in skeletal muscle. In adult muscle that is normally functioning, these were discovered at the neuromuscular junctions, [35] and they have also been discovered to colocalize with Aβ in diseased muscle [36]. The majority of the glucose receptors GLUT4 are present in adipose and muscle tissue, making this significant and are responsible for transporting about 70 percent to 80 percent of blood glucose to the skeletal muscle. DIO mice have reduced muscle glucose transport, and insulin-resistant diabetes compromises GLUT4 receptor-mediated transport,[37], [38] with signalling processes downstream to the receptors for insulin to be connected to GLUT4 trafficking If the expression of BACE1 reaches a level that leads to the generation of excessive amyloid beta (Aβ) in skeletal muscle, it indicates the possibility of its abundant presence capable of cleaving the insulin receptor (IR), The aforementioned scenario has the capacity to influence insulin signaling through direct modulation of the cleavage process of the insulin receptor (IR) and, indirectly, by promoting skeletal muscle to produce amyloid beta (Aβ). This is corroborated by the discovery that the direct processing of APP in C2C12 myotubes impacts glucose absorption and translocation of GLUT4 [39]. As a result of the widespread expression of APP and BACE1, local Aβ synthesis may possess an impact on signalling in several tissues and cells.

All of these shows that BACE1 has a significant physiological role in insulin signalling. This finding could have significant implications concerning the interplay between Type 2 diabetes (T2D) and obesity, offering potential mechanistic insight into the elevated risk of Alzheimer's disease (AD) observed in individuals with T2D.

2.5 THE IN-SILICO APPROACH IN IDENTIFYING BACE1 INHIBITING DRUGS

In the domain of drug development and discovery, the traditional approach of screening large chemical libraries to identify potential drug candidates can be time-consuming, expensive, and often yield limited success. However, with advances in computational techniques and bioinformatics, the in-silico approach has emerged as a valuable tool for identifying potential drug candidates and accelerating the drug discovery process. One area where the in-silico approach has shown promise is in identifying inhibiting drugs to target specific enzymes, such as Beta-Secretase 1 (BACE1), an important enzyme requires in the synthesis of beta-amyloid peptides implicated in Diabetes disease.

The in-silico method revolves around the use of computational techniques, including molecular modeling and virtual screening, to detect potential drug candidates that can bind and inhibit the activity of specific target proteins, such as BACE1. By utilizing information about the protein's structure and binding site, as well as extensive databases of chemical compounds, in-silico methods can efficiently narrow down the search for potential drug candidates. In virtual screening, large chemical libraries are computationally screened to find molecules with the ability to bind to the target protein. Various methods, including ligand-based virtual screening as well as structure-based virtual screening,[40] are employed to prioritize and select compounds with the desired properties. Molecular docking is a crucial step in the in-silico approach, where potential drug candidates are docked into the binding site of BACE1 to predict their binding affinities and interactions. Docking algorithms assess the complementarity between the drug candidate and the protein's active site, allowing for the identification of compounds that have a high likelihood of binding and inhibiting BACE1 effectively.

The current study deals with the repurposing of drugs to inhibit BACE1 in order to cure T2D. To accomplish this result we performed virtual screening and molecular docking to understand drugs and protein targets at a deeper level computationally. PyRx, which is an application of AutoDock Vina has been used to study the binding affinity of drugs. The optimization method is effectively given a "sense of direction" from a single assessment by the computation of the gradient. Performing this work computationally saved us from fear of unsuccessful wet lab experimental results, and has been cost-effective and time savior.

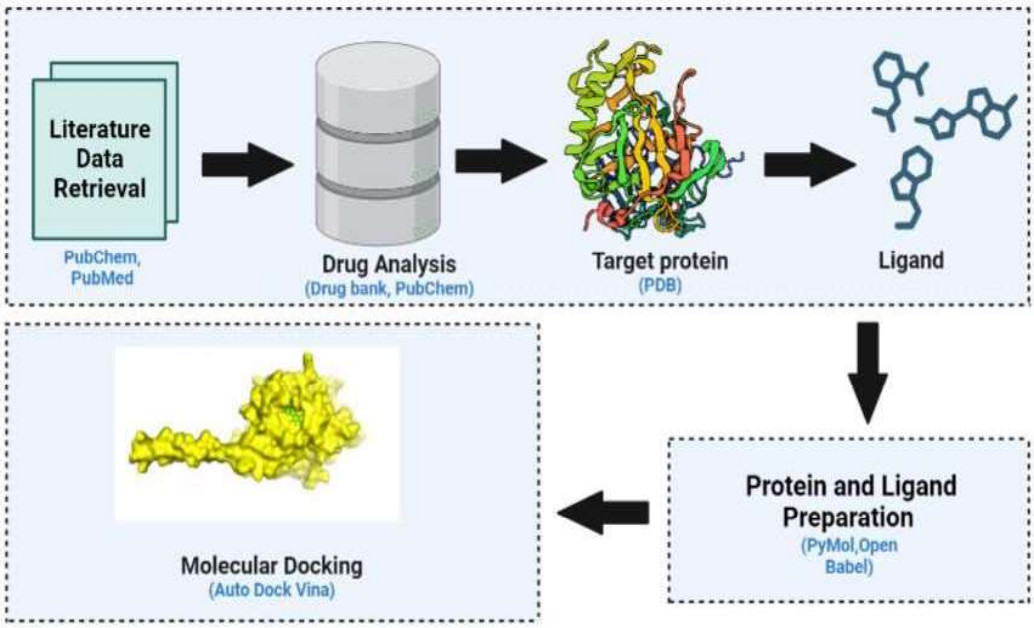


Fig. 6. Diagrammatic representation of the methodology performed

CHAPTER 3

MATERIAL AND METHODS

3.1 COLLECTION OF DATA

The data-gathering process was broken down into many parts, including summarizing the relevant literature, selecting effective drugs, and screening the drugs. In the initial phase, the literature was gathered from databases like Google Scholar and PubMed respectively).

Protein Data Bank, or PDB, served for downloading the chemical structure of drugs and specific protein. This database is used to get the 3-D structure of the molecule. The PDB format file of protein having PDB ID 1FKN is downloaded from RSCB PDB.

The list of Drugs was retrieved from ChEMBL. The European Bioinformatics Institute is in charge of managing the chemical database ChEMBL, which contains details about the bioactive compounds, including information about their capacity to produce drugs. These drugs were used in the in-silico study to produce legit results. The list of drugs that were collected contained a mixture of anti-hypertension drugs and anti-viral drugs.

Then, using PubChem, the SDF structure of all the listed drugs was retrieved from PubChem. The National Center for Biotechnology Information (NCBI) is in charge of the database PubChem, which tracks how chemical compounds perform in tests of biological effectiveness.

3.2 TARGET SELECTION AND PREPARATION

The protein name β-Secretase 1 or BACE1 (PDB ID:1FKN) is been used as the Target protein. BIOVIA Discovery Studio was used to prepare 1FKN.

3.2.1 TARGET PREPARATION:

- Removal of water molecules and heteroatoms from the structure.
- Addition of Polar hydrogen atoms to the target protein.
- Charges are balanced using Kollman charge to a target protein.
- Save the modified file in PDBQT.

3.2.2 GRID PREPARATION:

- Grid box is prepared around the site-specific to the ligand binding site.
- Grid dimensions were saved for future importance.
- The dimensions were 34.86 x 39.07 x 40.6 and the coordinates were 5.669, -4.987, and 12.262 were used to build the grid map for the receptor and ligand.

3.3 LIGAND PREPARATION

- Ligand molecules are downloaded from PubChem in SDF format.
- With the aid of open Babel, we then went on preparing the drugs. Here, file format conversion and energy minimization were carried out.
- Ligands are converted into PDBQT format.
- Ligand rotatable bonds were identified using the torsion tree option.
- The final file is saved in the PDBQT format

3.4 MOLECULAR DOCKING

Molecular docking was performed with the help of AutoDock Vina tool. A computational method used for molecular docking which simulates the atomic-level interactions between proteins and other molecules. For comparison, several accepted standards were established, such as free binding energies of -9 kcal/mol and RMSD values that should be <1 angstrom. The AutoDock Vina software is very effective when juxtaposed with other docking tools. It provides docking results as well as grid map computations. Cross-docking techniques can be used to study antigen-antibody interactions. Induced fit docking, which allows the displacement of binding site side chains, is one of the uses. When the molecular docking is finished, all of the binding energies are analysed, and the top ten drugs with best biding scores are listed.

CHAPTER 4

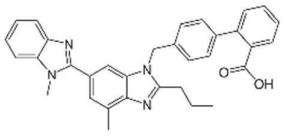
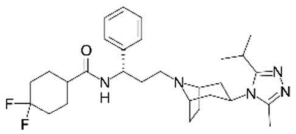
RESULTS

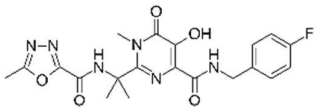
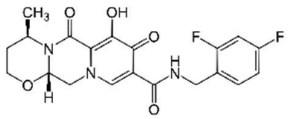
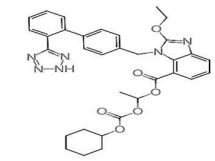
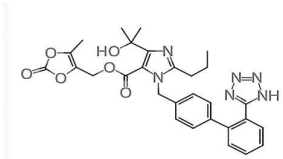
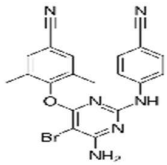
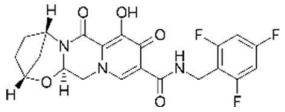
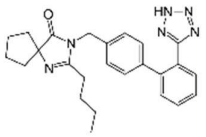
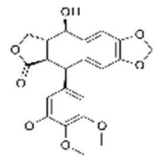
Telmisartan (CHEMBL 1017) was extracted as the best-binding drug with a binding affinity of -10.9kcal/mol. Telmisartan is an anti-hypertension drug. Along with this, 9 more drugs were added to the list of best binding drugs for inhibiting BACE1 which can be fruitful in the cure for type 2 diabetes patients. Other nine drugs were also traditionally used for either hypertension or viral fever.

Telmisartan is sold under the brand name Pritor, Actelsar Hct, Twynsta, Micardis, Micardis-hct, and the drug bank accession number is DB00966. It is an FDA-approved drug but shows minimum side -effects when consumed like vomiting, fever, nausea, allergy, etc. Pregnant women should consult doctors before the consumption of this drug.

Hypertension is treated with telmisartan alone or in combination with other medications. An increase in blood pressure will increase the stress on the heart and arteries. If that keeps happening for a while, the heart and coronary arteries will fail to perform as intended. This may result in renal failure, cardiac failure, or a stroke by damaging the blood capillaries in the brain, kidney, and heart. Stroke and heart attack risk can be decreased by lowering blood pressure.

Table 1. List of top 10 best binding BACE-1 inhibitors.

Drug Structure	PubChem ID	Compound Name	Binding Affinity (kcal/mol)
	65999	Telmisartan	-10.9
	3002977	Maraviroc	-10

	54671008	Raltegravir	-10
	54726191	Dolutegravir	-10
	2540	Candesartan Cilexetil	-9.9
	130881	Olmesartan Medoxomil	-9.8
	193962	Etravirine	-9.8
	90311989	Bictegravir	-9.8
	3749	Irbesartan	-9.5
	10607	Podofilox	-9.5

In individuals above 55 years and older with heart problems as well as diabetes telmisartan is additionally administered to lower downs the possibility of strokes and cardiac arrest.

Telmisartan blocks the angiotensin II receptor and works by restricting substances in the body that constricts blood vessels and promote vasodilation, and results in the relaxation of blood vessels in the body, resulting in increased oxygen and blood supply to the major organs including brain and heart. Additionally, blood pressure is lowered. Only a prescription from your doctor is required to purchase this medication.

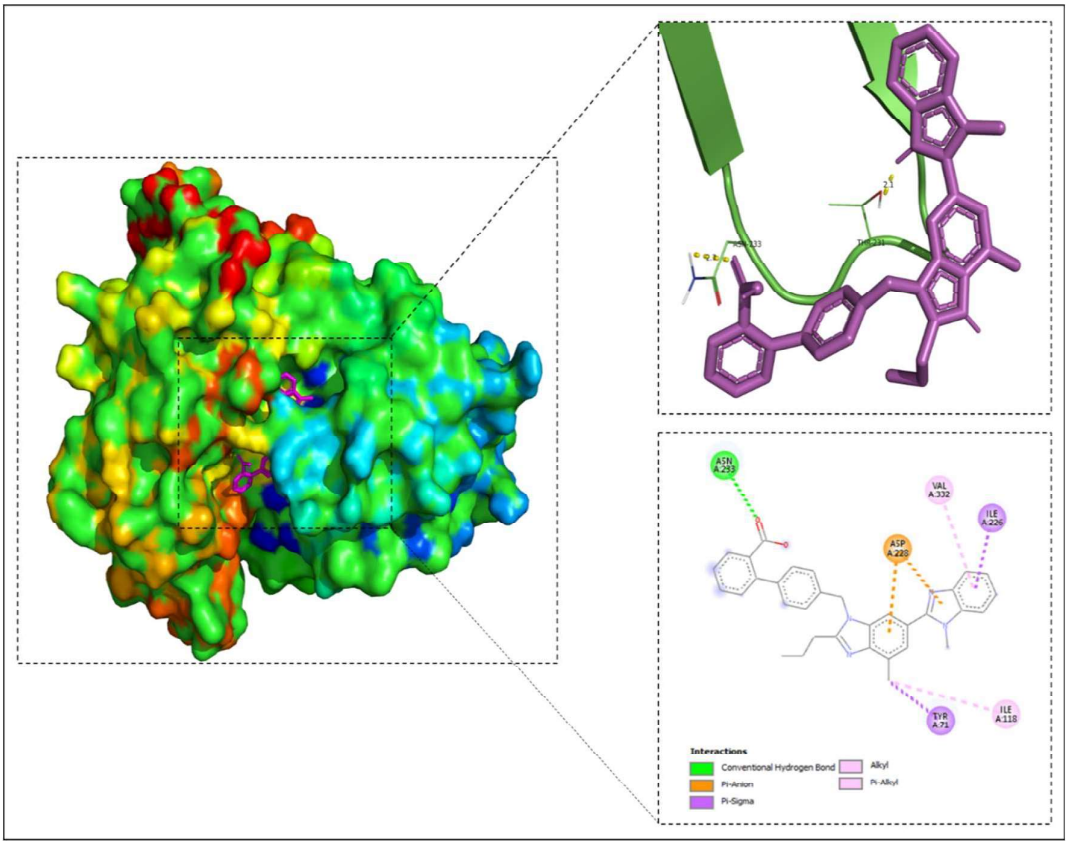


Fig. 7. Protein-Ligand Interaction of 1fkn with Telmisartan and interacting residues are THR-231, ASN-233

CHAPTER 5

CONCLUSION

Type 2 diabetes has become an epidemic all across the globe and it is affecting a substantial number of individuals all over the globe. This disease usually becomes a hindrance in the treatment of other illnesses within the body. Multiple drugs are present to normalize the insulin level in the body but still, medications are required to completely cure type 2 diabetes. Drug repurposing offers a chance to increase our knowledge without constricting what is already known. Therefore, drug repurposing can help the pharmaceutical sector, as well as university researchers, to develop new scientifically sound drugs. Drug repurposing is an exciting area of drug research that aims to find new applications for outdated medications. For instance, Telmisartan, a drug primarily used for hypertension, has shown potential in inhibiting BACE1 and may be considered as a therapeutic option for diabetes treatment. Through computational evaluations, Telmisartan has displayed promising results and can now proceed to be tested on animal models to validate the in-silico results. These experimental validations are critical for verifying the effectiveness of Telmisartan in halting the progression of diabetes and reinforcing the predictions derived from the computational analysis. If the outcomes of the animal model studies align with the in-silico results, further clinical examinations and the approval process by regulatory bodies, such as the FDA, can pave the way for Telmisartan to be utilized as a viable treatment option. The potential repurposing of Telmisartan highlights the importance of exploring existing drugs for new therapeutic applications, ultimately expanding our knowledge against type 2 diabetes and improving patient outcomes.

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