Virtual Screening of Potent Compounds for Type 2 Diabetes

A Dissertation Report submitted

for the partial fulfillment of the Degree of

Bachelor of Science

By

Nirali Prafulbhai Majithiya

B.Sc. Biotechnology, Sem. VI (2022-23)

Under the supervision of

Dr. Nutan Prakash V.

Associate Professor, Head

DEPARTMENT OF

BIOTECHNOLOGY

ATMIYA UNIVERSITY

'YOGIDHAM GURUKUL' KALAWAD ROAD,

RAJKOT (GUJARAT) – 36000

CERTIFICATE

This is to certify that this dissertation work entitled "**Virtual Screening of Potent Compounds for Type 2 Diabetes**" was successfully carried out by **Miss Nirali Prafulbhai Majithiya** towards the partial fulfillment of requirements for the degree of Bachelors of Science in Biotechnology of Atmiya University, Rajkot. It is an authentic record of her own work, carried out by her under the guidance of Dr. Nutan Prakash V. during the academic year of 2022-23. The content of this report, in full or in parts, has not been submitted for the award of any other degree or certificate in this or any other University.

Head of Department
Department of Biotechnology
Faculty of Science
Atmiya University
Rajkot

Name & Signature of the Head
of the Department

7-04-23

Name & signature
the supervisor

DECLARATION

I hereby declare that the work incorporated in the present dissertation report entitled "**Virtual Screening of Potent Compounds for Type 2 Diabetes**" is my own work and is original. This work (in part or in full) has not been submitted to any University for the award of any Degree or a Diploma.

Nirali

Nirali P Majithiya

Date 07-04-23

INDEX

Virtual Screening Of Potent Compounds for Type 2 Diabetes

Abstract:

Type 2 diabetes, the most common type of diabetes, is a disease that occurs when blood glucose, also called blood sugar, is too high. Blood glucose is the main source of energy and comes mainly from the food we eat. Insulin, a hormone made by the pancreas, helps glucose get into the cells to be used for energy. In type 2 diabetes, the body doesn't make enough insulin or doesn't use insulin well. Too much glucose then stays in the blood, and not enough reaches the cells. The Protein- Ligand interaction plays a significant role in structural based drug designing. In our research work we have taken the adipokines protein and the commercially available drugs against diabetes. The receptor was docked to the different types of drugs and the energy value obtained as follows Metformin (-8.9kcal), Myo-inositol (-7.9kcal) and berberine (-8.8kcal) using the PyRx docking software. Depending on the energy values we have chosen the best three drugs they are Metformin, Myo-inositol and Berberine.

Keywords: Type 2 diabetes, PyRx, Docking

Introduction:

Type 2 diabetes can be develop at any age, even during childhood. However, type 2 diabetes occurs most often in middle-aged and older people. You are more likely to develop type 2 diabetes if you are age 45 or older, have a family history of diabetes, or are overweight or have obesity. Diabetes is more common in people who are African American, Hispanic/Latino, American Indian, Asian American, or Pacific Islander [1].

The report on the state-level disease burden in India stated that the percent change in diabetes prevalence among all ages in India from 1990 to 2016 was 64.3%, while the age-standardized prevalence was 29.3%.The India State-Level Disease Burden Initiative Diabetes study collaborators reported that the prevalence and number of people with diabetes in India increased from 5.5% and 26.0 million in 1990 to 7.7% and 65.0 million in the year 2016. According to this report, Tamil Nadu had the highest prevalence in 2016, followed by Kerala, Delhi, Punjab,

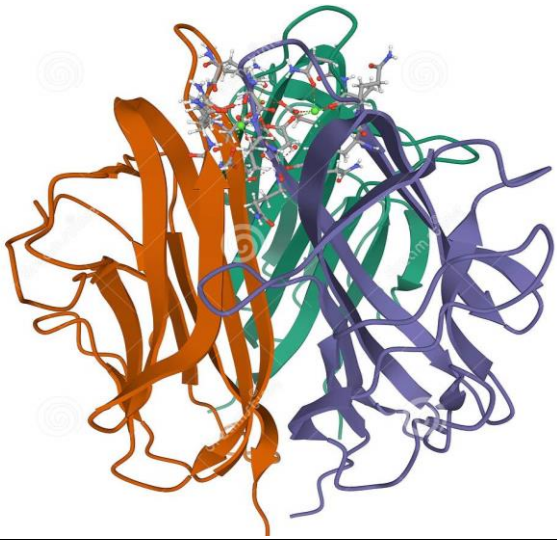
Goa, and Karnataka.[2] Type 2 Diabetes Mellitus (T2DM) is one of the most common metabolic disorders worldwide and its development is primarily caused by a combination of two main factors: defective insulin secretion by pancreatic β-cells and the inability of insulin-sensitive tissues to respond to insulin . Insulin release and action have to precisely meet the metabolic demand; hence, the molecular mechanisms involved in the synthesis and release of insulin, as well as the insulin response in tissues must be tightly regulated. Therefore, defects in any of the mechanisms involved can lead to a metabolic imbalance that leads to the pathogenesis of T2DM [4]. The blood sugar goal for most adults with diabetes is an A1C of below 7%. (A1C is a measure of a person's average blood sugar over a period of about three months.) In many people, diet and exercise are not enough to reach this goal, and one or more medications may be needed. Metformin is a tried and tested medicine that has been used for many decades to treat type 2 diabetes, and is recommended by most experts as first-line therapy. It is affordable, safe, effective, and well tolerated by most people.[5]Computational Biology and bioinformatics have the potential not only of speeding up the drug discovery process thus reducing the costs, but also of changing the way drugs are designed. Rational Drug Design (RDD) helps to facilitate and speedup the drug designing process, which involves variety of methods to identify novel compounds. One such method is the docking of the drug molecule with the receptor (target). The site of drug action, which is ultimately responsible for the pharmaceutical effect, is a receptor. [3] Docking is the process by which two molecules fit together in 3D space. PyRx is a Virtual Screening software for Computational Drug Discovery that can be used to screen libraries of compounds against potential drug targets. PyRx enables Medicinal Chemists to run Virtual Screening from any platform and helps users in every step of this process - from data preparation to job submission and analysis of the results. While it is true that there is no magic button in the drug discovery process, PyRx includes docking wizard with an easy-to-use user interface which makes it a valuable tool for Computer-Aided Drug Design. PyRx also includes chemical spreadsheet-like functionality and powerful visualization engine that are essential for structure-based drug design.[6]

Tools and Materials Used:

For our present study we used bioinformatics tools, biological databases like PubMed, Drug Bank, PDB (Protein Data Bank) and software's like PyRx and Open Babel.

PyRx is a Virtual Screening software for Computational Drug Discovery that can be used to screen libraries of compounds against potential drug targets. PyRx enables Medicinal Chemists to run Virtual Screening from any platform and helps users in every step of this process - from data preparation to job submission and analysis of the results. While it is true that there is no magic button in the drug discovery process, PyRx includes docking wizard with an easy-to-use user interface which makes it a valuable tool for Computer-Aided Drug Design. PyRx also includes chemical spreadsheet-like functionality and powerful visualization engine that are essential for structure-based drug design.[6]

Drug Bank is a unique Bioinformatics/Cheminformatics resource that combines detailed drug (i.e. chemical) data with comprehensive drug target (i.e. protein). Each Drug Card entry contains greater than 80 data fields with half of the information being devoted to drug/chemical data and the other half devoted to drug target or protein data [7]. The PDB (Protein Data Bank) is the single worldwide archive of Structural data of Biological macromolecules, established in Brookhaven National Laboratories (BNL) in 1971 [8].It contains Structural information of the macromolecules determined by X-ray crystallographic, NMR methods etc. PubMed is a free digital archive of biomedical and life sciences journal literature at the U.S. National Institutes of Health (NIH), developed and managed by NIH's National Center for Biotechnology Information (NCBI) in the National Library of Medicine (NLM). PubMed is a free search engine for accessing the MEDLINE database of citations and abstracts of biomedical research articles [9].



Adipokines 3-D Structure [10]

Methodology:

The structure of Adipokines was retrieved from PDB .Using PubChem the structures of the drugs were obtained and they were converted to PDB format by using Open Babel for docking. The docking analysis of Metformin, Prandin, Canagliflozin, Dapagliflozin, Empagliflozin, Actos, Myo-Inositol, Sulfonylurea, Thiazolidinediones and Berberine with Adipokines was carried by PyRx docking software.

Docking allows the scientist to virtually screen a database of compounds and predict the strongest binders based on various scoring functions. It explores ways in which two molecules, such as drugs and a protein, Adipokines fit together and dock to each other well, like pieces of a three-dimensional jigsaw puzzle. The molecules binding to a receptor, inhibit its function, and thus act as drug. The collection of drugs: Metformin, Prandin, Canagliflozin, Dapagliflozin, Empagliflozin, Actos, Myo-Inositol, Sulfonylurea, Thiazolidinediones and Berberine was identified via docking and their relative stabilities were evaluated using molecular dynamics and their binding affinities, using free energy simulations.

The parameters used for the docking process were:

- Binding Affinity
- Grid Dimension
- RSMD Upper Bound
- RSMD Lower Bound

Results:

Docking results tabulated between Adipokines and the conventional drug Metformin as well as with the newfound drug compounds are shown below along with their bond affinity.

SR.NO	COMPOUND	BOND AFFINITY
1)	METFORMIN	-8.9KCAL/MOL
2)	PRANDIN	-7.6KCAL/MOL
3)	CANAGLIFLOZIN	-7.5KCAL/MOL
4)	DAPAGLIFLOZIN	-7.7KCAL/MOL
5)	EMPAGLIFLOZIN	-8.0KCAL/MOL
6)	ACTOS	-4.5KCAL/MOL
7)	MYO-INOSITOL	-7.9KCAL/MOL
8)	SULFONYLUREA	-8.1KCAL/MOL
9)	THIAZOLIDINEDIONES	-6.9KCAL/MOL

10)	BERBERINE	-8.8KCAL/MOL

A good bond affinity value is -20KCAL/MOL but it only compounds gets up to -15 KCal/Mol.

At this point, I have reached to a conclusion that we can replace metformin with different various drugs for better results and less side-effects varying person to person. But right now, metformin and berberine for adipokines targeted diabetes type 2 is better.

Discussion:

Bioinformatics is seen as an emerging field with the potential to significantly improve how drugs are found, brought to the clinical trials and eventually released to the marketplace. Computer – Aided Drug Design (CADD) is a specialized discipline that uses computational methods to simulate drug – receptor interactions. CADD methods are heavily dependent on bioinformatics tools, applications and databases [3]. The structure of Adipokines was retrieved from PDB. The docking analysis of Metformin, Myo-Inositol and Berberine with Adipokines Protein was carried by PyRx docking software.

Conclusion:

The Protein-Ligand interaction plays a significant role in structural based drug designing. In the present work we have taken the Adipokines protein and identified the drugs that were used against Type 2 diabetes. When the receptor was docked with the drugs the energy value obtained was; Metformin (-8.9kcal), Myo-inositol (-7.9kcal) and berberine (-8.8kcal). In future research work the ADME/T (Absorption, Distribution, Metabolism, Excretion / Toxicity) properties of these compounds can be calculated using the commercial ADMET tools available thus reducing the time and cost in drug discovery process.

A good bond affinity value is -20KCAL/MOL but it only compounds gets up to -15KCAL/MOL. At this point, I have reached to a conclusion that we can replace metformin with different various drugs for better results and less side-effects varying person to person. But right now, metformin and berberine for adipokines targeted diabetes type 2 is better.

***Acknowledgments*:**

I thankfully acknowledge my University, Atmiya University, and my guide and head of the department, Dr. Nutan Prakash V. I also extend my thanks to all the staff members and non-teaching staff who played a role in carrying out this research work.

References:

1)https://www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes/type-2-diabetes

2)https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8725109/#R11

3)"Computational Biology and Drug Discovery: From single - network Drugs", Current Bioinformatics, 2006, 1, 3-13.

4)https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7503727/#:~:text=Type%202%20Diabetes%20Mellitus%20(T2DM,to%20respond%20appropriately%20to%20insulin.

5)https://www.health.harvard.edu/blog/type-2-diabetes-which-medication-is-best-for-me-2020110521256

6)https://pyrx.sourceforge.io/home/35-introduction/53-index

7)"Drug Bank; a comprehensive resource for in silico drug discovery and exploration", Nucleic Acids Research, 2006, Vol.34, Database Issue.

8) "The Protein Data Bank", Nucleic Acids Research 2000, Vol. 28, Oxfords University Press.

9) "PubMed: Online Search Engine for science and biomedical articles, www.pubmedcentral.nih.gov

10) https://www.dreamstime.com/structure-trimeric-globular-domain-adiponectin-also-referred-to-as-gbp-apm-adipoq-acrp-protein-hormone-adipokine-image206197886