Journal of Advances and Scholarly Researches in Allied Education
Vol. 21, Issue No. 7, October-2024, ISSN 2230-7540

DOI: https://doi.org/10.29070/1xcpbp06

Computational Docking Analysis of Protein-Ligand Interactions in Diabetes-Related Complications: Targeting Molecular Pathways for Therapeutic Intervention

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Abstract: A key tenet of the scientific method is the integration of computational resources into the chemical and biological domains to facilitate the discovery and development of new pharmaceuticals. A major public health concern in India is diabetes. An immediate start is required to begin the research and development of a novel diabetic therapy. Type 2 diabetes remains incurable despite the availability of several therapies. Target identification, interactions between proteins and ligands, and residues in the active site form the basis of drug design. Our focus here is on five conserved and very active amino acid residues from five proteins with essential roles in diabetes. A variety of docking methods were used to investigate the binding mechanism and affinities of drug-like compounds, chalcones, some plant chemicals, and other potential anti-diabetic medications from the virtual screening database (ZINC) (free database). The protein data bank was searched for the three-dimensional structural coordinates of 1AH3 (Aldose Reductase) according to the results in literature and the Root Mean Square Deviation (RMSD).

Keywords: Diabetes-Related, ZINC database, data bank, drug design, anti-diabetic

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INTRODUCTION

Diabetes, one of the most common illnesses, impacts around 382 million individuals globally. The International Diabetes Federation (IDF) reports that diabetes is directly responsible for the deaths of almost 1.3 million people annually. By 2045, 629 million people will be living with diabetes, says the International Diabetes Federation. Uncontrolled high blood sugar levels cause insulin resistance and malfunction of the pancreatic β-cells, which are the hallmarks of diabetes. Diabetes changes the metabolism of sugar, fat, and protein, which can lead to complications with the eyes, nerves, kidneys, heart, skin, and major blood arteries. Because people with diabetes account for 12% of overall healthcare spending, this puts a tremendous financial burden on healthcare systems. People of all ages are susceptible to the complicated condition known as type 2 diabetes mellitus (T2DM). High glucose plasma levels are a symptom of type 2 diabetes, which can be caused by inadequate insulin production or action, or both. Diabetes' main metabolic problem is insulin resistance in tissues that need insulin and a relative lack of insulin production by pancreatic β-cells. When the body experiences insulin resistance and, eventually, β-cell failure due to dietary spillover, it changes its fuel balance. Insulin resistance causes the early signs of the illness, such as hyperinsulinemia and β-cell hyperplasia.

Relative insulin insufficiency, caused by β-cells' inability to reverse insulin resistance, leads to the development of diabetes. Diabetes involves a number of physiological processes, including the production of insulin, insulin resistance, and the absorption of glucose. Glucokinase, AMP-activated protein kinase, 11 β-hydroxysteroid dehydrogenases (11 β-HSD), insulin receptor substrate, interleukin1 beta, dipeptidyl peptidase IV, glutamine-fructose-6-phosphate aminotransferase (GFAT), peroxisome proliferator-activated receptor-gamma (PPAR-gamma), tyrosine phosphatases, tyrosine kinase insulin receptor, protein kinase B, and insulin receptor are some of the human proteins that have been recognised as significant regulators in the onset of diabetes. Changes to one's food, more exercise, and the use of anti-diabetic drugs are just a few of the ways that diabetes may be well-managed. It is still up for debate whether or not anti-diabetic drugs effectively manage diabetes, and others say they frequently have major side effects. As a result, the focus has been on foods rich in phytoconstituents that combat diabetes and traditional and alternative medicine. Plants and plant-based products are thought to possess therapeutic properties due to the bioactive components they contain. Some of the ingredients include gum, polysaccharides, short peptides, alkaloids, triterpenes, and glycosides.

Globally, diabetes ranks third in terms of cause of mortality, after cancer and cardiovascular disease, according to the International Diabetes Federation. From 415 million in 2015 to 693 million in 2045, that's the number of people with diabetes, according to the World Health Organisation. Although their causes are different, type 2 diabetes mellitus (T2DM) is more prevalent than type 1 diabetes mellitus (T1DM). Two further types of diabetes include type 1 diabetes mellitus and gestational diabetes. Insulin synthesis and insulin activity are disrupted in an unbalanced negative feedback loop, leading to low glucose tolerance in type 2 diabetes.Problems with glucose metabolism lead to a host of complications, including diabetic foot, kidney disease, cardiovascular damage, and many more. These problems can have a detrimental impact on the physical and emotional health of people with type 2 diabetes, and they can worsen with time. Due to the high cost and lifetime necessity of diabetic medicine, health care expenses for those with diabetes are three times higher than those for the general population. In 2015, 67.3 billion USD, or 12% of the world's healthcare budget, went on diabetes care. Therefore, it is crucial to find efficient ways to manage and avoid diabetes.

LITERATURE REVIEW

Sooriyakala Rani Sri Prakash (2023) Validation and the discovery of novel pharmaceuticals both depend on the identification of potential lead chemicals in natural medicines. Ten well-known herbs for type 2 diabetes mellitus (T2DM) were the subjects of this investigation, which used docking studies and network pharmacology to identify their therapeutic mechanisms. Dr. Duke's database and Indian Medicinal Plants, Phytochemistry and Therapeutics were the sources used to compile information on phytoconstituents and medicinal plants. Their medicinal similarity was assessed using MolSoft. The protein targets for the tested phytochemicals were predicted using Swiss TargetPrediction, whereas the list of target genes associated in type 2 diabetes was generated using GeneCards. The following tools were utilised: STRING for network building; Cytoscape for network analysis; PyRx for molecular docking; and Database for Annotation, Visualisation, and Integrated Discovery (DAID) for gene ontology analysis. The progression of type 2 diabetes was shown to include the protein targets EGFR, MAPK1, AKT1, and PI3K. Nimbaflavone also showed a strong binding affinity "for MAPK1 (−8.7 kcal/mole) and PI3K (−9.6 kcal/mole) according to

molecular docking. Contrarily, rutin demonstrated a high binding affinity for AKT1 (-7.4 kcal/mole) and EGFR (-8.1 kcal/mole)", but 10-hydroxyaloin-B had a lower affinity. This study found that flavonoids interact with key protein molecules linked to the MAPK and PI3K-AKT signalling pathways, making them the most essential phytoconstituents for antidiabetic action. Type 2 diabetes is cured by this interaction. Upon activation, these pathways enhance the synthesis of the glucose transporter GLUT4 and alter the activity of Ras-GTPase. The result is the removal of glucose from the bloodstream.

Vishal Chavda (2023) Diabetes and stroke can lead to neurotransmissional defects, decreased synaptic plasticity, and neurodegeneration over time. In order to discover novel drugs for specific diseases, it is necessary to employ computational design to construct a therapeutic agent, molecular dynamic (MD) simulation, and molecular docking. Additionally, efficient and cost-effective approaches for discovering possible therapeutic targets are essential. The virtual screening and identification of structure-based molecular interactions have been made possible by chemical docking technologies such as AutoDock tool v1.5.6, PyRx v8.0, identification Studio Visualiser v19.1.0.18287, and PyMOL v2.3.1. The RCSB-PDB website now has the 3D co-crystal structures of the following receptor/target treatment proteins and their corresponding ligands: BCl-2, Caspase-3, Caspase-8, Caspase-9, IL6, MAPKERK, PI3K, TGF-β, TNFα, and ZO-1. The built structures include a water molecule and a ligand. Prior to docking using Discovery Studio Visualiser, the water molecule must be extracted from the receptor. The last thing to do is use PyRx's AutoDock Vina to turn the structures into macromolecules. The active residues were identified by reviewing previous investigations. A study that utilised in-silico molecular modelling of anti-diabetic medicines with proteins linked to neurodegeneration and stroke generated a robust explanation about the neuroprotective effects of these treatments. Additionally, all biomarker proteins have a higher binding energy for the selected class of anti-diabetic drugs, which includes voglibose, saxagliptin, repaglinide, and dapagliflozin. The biomarker proteins feature BCl-2, caspase-3, caspase-8, caspase-9, IL6, MAPK/ERK, PI3K, TGF-γ, TNF-α, and ZO-1. Some anti-diabetic medications may reduce the risk of stroke and, in severe cases of hyperglycemia, may even be helpful in managing the illness; this study adds to the expanding body of data supporting this claim .

Guttula, Satya et.al. (2010). Diabetes mellitus is a multisystem disorder that can impact several human organs, including the kidney, due to metabolic abnormalities and hyperglycemia. The dysfunction of pancreatic beta cells and other forms of tissue damage can be brought about by oxidative stress in individuals with diabetes mellitus due to hyperglycemia. As a result, antioxidants' possible role in diabetic nephropathy therapy appears reasonable. Brain-derived neurotrophic factor (BDNF) is a protein that has a role in glucose metabolism in humans; it is also associated with Alzheimer's disease, depression, and type II diabetes. There is evidence that the Ras homolog gene is associated with diabetic nephropathy. We used the Ligand database to get the astaxanthin and beta carotene ligands and the BDNF and RHOD three-dimensional protein structures. Docking with protein ligands allowed the antioxidant ligands and target proteins to come together. For BDNF and Astaxanthin-Docking, the energy range is shown below: With an Emin of -225.39 and an Emax of. Emin = -220.68, Emax = -69.21 is the energy range for the docking of BDNF and β-carotene. Between -247.72 and -88.39 eV, RHOD and Astaxanthin occupy a range of energies during docking. The docking of β-carotene and Rhod has an energy range of -86.55 and an Emin value of -232.07. Using the energy with the lowest minimum maximises the effectiveness of the docking

procedure. It has been found that astaxanthin has the highest affinity for the target proteins, as its docking score is lower than β-carotene's. At last, astaxanthin's strong antioxidant properties suggest it might help reduce glucose toxicity.

Almasi, Faezeh et.al. (2020). Worldwide, the prevalence of diabetes and associated complications is on the rise; in 2017, an estimated 463 million new cases were recorded. To better prevent and cure diabetes, there has to be an immediate and massive effort. One of the most important things to do, among the numerous problems of diabetes, is to stop the condition from becoming worse instead of merely making it go away. Some drugs used to treat diabetes have unwanted side effects and target carbohydrates in a very specific way. Therefore, a substantial amount of study is required to discover new disease pathways and molecular targets for the treatment of diabetes. This article discusses the therapeutic rationale for using conventional molecular targets to treat diabetes. Additionally, we outline the current and future molecular objectives that library screens ought to aim for.

RESEARCH METHODOLOGY

RCSB Protein Data Bank

The Royal Society of Biology Protein Data Bank (RCSB PDB) is a goldmine for researchers studying biological macromolecule structures, functions, and diseases. Upon its initial formation at Brookhaven National Laboratory in 1971, the PDB gained seven more structures. In 1998, RCSB ("Research Collaboratory for Structural Bioinformatics") assumed control of the PDB. The RCSB is an active participant in the wwPDB in order to keep the PDB archive up-to-date and consistent, making it a worldwide resource for 70 researchers. Through its integrated system RoboHelp, the RCSB PDB website and the data it includes are explained in detail.

PDBSUM and LIGPLOT Interactions

The Protein Data Bank (PDB) has a visual database called the PDBsum that summarises all of the 3D structures recorded within. This is useful for rapid reference. The structure and its constituent components are displayed, including proteins, DNA, ligands, and metal ions, as well as their interactions with one another. By comparing a string to the TITLE, HEADER, COMPOUND, SOURCE, and AUTHOR data in the PDB, the 71-part RasMol molecular graphics tool displays the molecules and their relationships. This tool is extensively used for 3D text search. In order to learn all about the text search's capabilities in more depth. The protein sequence search tool uses the FASTA method to compare user-supplied protein sequences with all of the proteins in the PDB. Presented below are the top results, accompanied by connections to their PDBsum profiles.

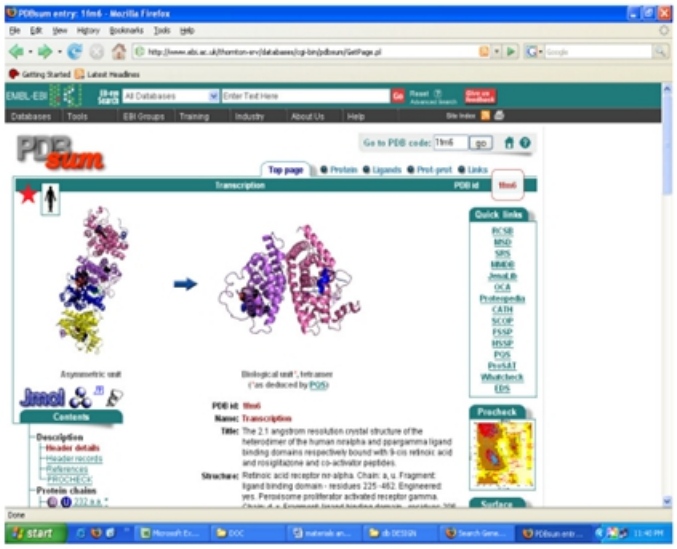

Figure 1 Pdb sum home page

Gene cards

The Gene Cards database contains every human gene along with details on its expression, function, orthologs, disease associations, SNPs, automatically mined genomic and proteomic data, and connections to services that allow users to purchase assays and antibodies. Only the most pertinent and comprehensive data is made available to users via the database. The Gene Cards database was created and is maintained by the Crown Human Genome Centre of the Israeli Weizmann Institute of Science. Originally launched in 1997, the Gene Cards project set out to compile information from a wide variety of specialised sources. Multiple approaches exist for determining which proteins initiate type 2 diabetes. But, proteins used in this study were selected from a gene card database.

Zinc Database

A free database of compounds that are commercially available is ZINC. Use it for virtual screening. ZINC provides over 13,000 compounds in dockable, three-dimensional formats. A source of ZINC is the Shoichet Laboratory in the Department of Pharmaceutical Chemistry at UC San Francisco. The goal of ZINC, in contrast to earlier chemical databases, is to portray the three-dimensional form of the biologically significant molecule. There is a wealth of information available in the ZINC database, which has 727,842 molecules in its library and is constantly being updated with compound catalogues provided by vendors.

Compounds from ZINC Database:

ZINC, which stands for "ZINC is not commercial, a free database for virtual screening," is available at http://zinc.docking.org and includes more than 4.6 million compounds in dockable 3D formats. There are several ways to record the chemical properties of the ZINC molecules. Desolvation energies (both polar and apolar), net charge, ester/isomer ratio, Some of the many numbers included in this collection include molecular weight, computed LogP, chiral centres, chiral double bonds, hydrogen-bond suppliers and acceptors, rotatable bond counts, and many more. Look up 202,134 lead-like compounds and 494,915

Lipinski compatible compounds in the database. These compounds fall under the following categories: molecular weight (150–350), number of hydrogen bond donors and acceptors (three or fewer), and computed LogP value (below 4). Molecular substructure search, vendor-based, ZINC codes, and molecular property constraint are some of the search criteria offered by ZINC.

DATA ANALYSIS

Root Mean Square Deviation (RMSD)

We were able to get the RMSD values by utilising Molegro Virtual Docker to dock these 15 proteins with their co-crystallized ligands. These proteins were selected from a total of 95 structures in the Protein Data Bank that were linked to Aldose Reductase. On the other hand, Table 1 displays the RMSD.

Table 1 Table displaying the relative molecular surface area (RMSD) values of the fifteen proteins docked with their corresponding co-crystallized ligands.

S.No.	PDB ID	RMSD (A°)
1	1AH0	3.14
2	1AH3	0.87
3	1EF3	6.61
4	1EL3	6.70
5	1IEI	1.27
6	1Z89	6.89
7	2IKG	7.85
8	2IKH	1.43
9	2IKI	5.32
10	2IKJ	3.77
11	2NVC	8.37
12	2PDG	2.30
13	2PZN	5.68
14	3DN5	1.44
15	3G5E	3.49

The 1AH3 protein was docked three times with its co-crystallized ligand in order to get consistent results. The data are presented in Table 2.

Table 2: Table showing the RMSD values of 1AH3 in three runs.

S.No.	PDB ID	Run1	Run2	Run3
1	1AH3	0.8736	0.8721	0.670

The ligands of the 15 proteins listed above, as well as inhibitors reported in the literature, were docked with the 1AH3 protein using Molegro and Virtual Docker. Table 3 and Table 4 show the results of the study .

Table 3: A table that displays the docking scores of the 15 co-crystallized ligands that were docked with the 1AH3 protein.

S.No	Ligand	Affinity(kcal/mol)
1	Sorbinil	-99.385
2	Tolrestat	-106.995
3	Fidarestat	-110.49
4	IDD384	-145.037
5	Zenarestat	-114.365
6	62P	-115.214
7	BTO	-142.956
8	Nitrofuryl-oxadizol	-129.521
9	IDD388	-132.742

Table 4. The table below displays the docking scores of the inhibitors that were obtained from the literature when they were docked with the 1AH3 protein.

S.No.	Inhibitor	Affinity(kcal/mol)
1	13	-110.472
2	14	-138.726
3	15	-132.434
4	Alrestatin	-89.5063
5	AS-3201	-124.002
6	Epalrestat	-111.721
7	NZ-314	-130.819
8	Ponalrestat	-111.759
9	Risarestat	-131.399
10	Zopolrestat	-142.752

Chemistry of ZINC Compounds:

We searched the ZINC Database using the properties of the fifteen crystallised protein ligands. Table 5 contains the following properties:

Table 5. A table displaying the characteristics of the ligands mentioned earlier.

S.	Ligand	Mol. Wt.	HBA	HBD
1	Sorbinil	236.2002	3	2
2	Tolrestat	357.3495	4	3
3	Fidarestat	279.2251	5	2
4	IDD384	390.4557	4	0
5	Zenarestat	441.6375	5	1
6	62P	324.7415	4	1
7	BTO	277.2341	6	1
8	Nitrofuryl-oxadizol	271.2082	9	0
9	IDD388	416.6280	4	0
10	IDD393	364.7390	4	2
11	ITA	393.3270	6	2
12	47D	351.7670	3	2
13	IDD-393	364.7390	4	1
14	53N	277.2975	5	5
15	IDD740	377.3425	7	2
	Average	341.5927	4.8667	1.6

We searched the ZINC Database using the below-mentioned characteristics' ranges as our lower and upper limits. One thousand one hits were generated in the end. Each of these ligands has a recorded docking score with the 1AH3 protein.

Best compounds from ZINC Database

From the 1001 results produced by the initial ZINC Database search, ten compounds were randomly selected, and their dock scores are displayed in Table 6.

Table 6 Docking scores of the top compounds found in the initial ZINC search are displayed in the following table.

S.No.	ZINC ID	Affinity(kcal/mol)
1	ZINC00447821	-150.707
2	ZINC00005258	-147.748
3	ZINC00844930	-146.974
4	ZINC00712672	-139.608
5	ZINC00225101	-139.243
6	ZINC20357853	-139.185
7	ZINC00156572	-138.731
8	ZINC02138728	-138.431
9	ZINC20357855	-138.292
10	ZINC13298260	-138.085

From the second ZINC Database search, which yielded 837 matches, Table 7 shows the dock scores of the top ten compounds.

Table 7 A table with the docking scores of the compounds found to be most promising in the second ZINC search, organised by item.

S.No.	ZINC ID	Affinity(kcal/mol)
1	ZINC06075556	-186.887
2	ZINC00702980	-184.345
3	ZINC04019626	-181.231
4	ZINC00702964	-180.314
5	ZINC00702957	-179.491
6	ZINC00703016	-179.19
7	ZINC00702960	-177.675
8	ZINC00702959	-176.621
9	ZINC00702953	-176.479
10	ZINC00702951	-176.149

CONCLUSION

The active amino acid residues that form hydrogen bonds with the ligands are also easily accessible to users of the database and members of the scientific community. Making better and easier medications is possible with the help of this database, which can inform you which ligands bind to proteins the best. The five diabetes proteins' valuable information on their highly active amino acid residues is preserved. Medications that require a high binding affinity to their target ligands could find this database helpful. We utilised the gene cards website to identify the protein-coding genes connected to diabetes so that we could construct the current database. A large number of them undergo screening due to the fact that some do not possess ligands and others do not possess a PDB ID. After removing all of them, only proteins that have strong binding sites to ligands are retained. The final five proteins that are considered appropriate are DPP-4, PPAR-γ, PTPN1, Glycogen synthase kinase-3 beta, and Aldose Reductase. All five of these proteins' PDB structures allowed us to identify the conserved amino acids through LIGPLOT interactions. This database will undergo regular updates.

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