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Investigate the Feasibility of Repurposing Existing Drugs or Identifying Novel Compounds for Diabetes Management Through Computational Docking

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Abstract: One way to manage type 2 diabetes mellitus, a long-term health issue, is to reduce the pace at which carbohydrates are broken down in the body. This may be achieved by blocking the enzyme α-glucosidase. There is a fast rise in the number of instances of type 2 diabetes, and there are currently no effective, safe, or widely used medications to treat it. The research aimed to examine the molecular processes and intended to use medications licensed by the food and drug administration (FDA) against α-glucosidase in drug repurposing. The possible inhibitor against α-glucosidase was identified by refining and optimizing the target protein by adding missing residues and minimizing to reduce conflicts. Following the docking investigation, the most effective compounds were chosen to create a pharmacophore query. This query will be used for the virtual screening of FDA-approved medicinal molecules that have comparable shapes. Based on binding affinities (−8.8 kcal/mol and −8.6 kcal/mol) and root-mean-square-deviation (RMSD) values (0.4 Å and 0.6 Å), the study was carried out using Autodock Vina (ADV). In order to learn about the receptor-ligand specific interactions and stability, two of the most powerful lead compounds were chosen for a molecular dynamics (MD) simulation. In comparison to conventional inhibitors, the docking score, RMSD values, pharmacophore studies, and MD simulations demonstrated that two compounds, namely Trabectedin (ZINC000150338708) and Demeclocycline (ZINC000100036924), had the ability to inhibit α-glucosidase. These projections demonstrated that the drugs Demeclocycline and Trabectedin, which have been authorized by the FDA, might be repurposed to fight type 2 diabetes.

Keywords: drug repurposing, diabetes mellitus, carbohydrate metabolism, pharmacophore, Demeclocycline

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INTRODUCTION

A symptom that may be used to identify diabetes is hyperglycemia. Insulin secretion is reduced and pancreatic β-cell activity might be negatively affected. Severe complications from persistently high blood sugar levels characterize diabetes mellitus, a metabolic disorder. Thus, a metabolic condition is hindered by a vicious cycle of hyperglycemia. The heart, kidneys, nerves, and eyes are just a few of the many organs and tissues that may suffer damage from poorly managed diabetes. Monitoring blood glucose levels is the gold standard for diabetes diagnosis and management.

Glucose, or sugar, is produced when carbs are eaten orally because digestion processes them. Insulin is a hormone that tells cells to take glucose out of the blood and either store it for later use or use it as fuel. Diabetes manifests itself in one of two ways: either the body does not produce enough insulin or it is unable to properly use the insulin it does produce. Type 1 diabetes mellitus (T1DM), type 2 diabetes

mellitus (T2DM), and gestational diabetes are the basic classifications.

In 2004, the idea of pharmacological repositioning—sometimes called drug repurposing—was first put forth. Although the concept of medication repositioning has evolved and become more specific over time, the associated nomenclature is still ambiguous and causes confusion. The process of discovering new applications for drugs outside their original indications is called drug repositioning, repurposing, redirecting, or reprofiling. Drug repositioning makes use of active ingredients such as previously sold medications whose patents have expired, medications that have been pulled from the market due to safety concerns, and compounds that have not met the safety and efficacy standards set by clinical studies. That being said, drug repositioning is not concerned with the structural alteration of active molecules via de novo drug design procedures. Drug repositioning is still being studied by academic research groups and pharmaceutical businesses despite the absence of a specific description. Because it may reduce development time and money by eliminating multiple time-consuming and expensive phases, medication repositioning is welcomed by the pharmaceutical industry as an alternative to traditional drug research and development.

Amidst the skyrocketing expense of drug development, medication repurposing has emerged as a potential strategy for discovering new medicines for a wide range of illnesses and conditions, including cancer, heart disease, neuropathy, infectious diseases, psychosis, and uncommon disorders like type 2 diabetic mellitus (T2DM). Type 2 diabetes is a non-communicable illness that is becoming more of a problem in healthcare systems throughout the world. Striking a good balance between the roles of effectiveness, side effects, and patient tolerance is challenging with the primary classes of antidiabetic medicines for type 2 diabetes. So, medication repositioning is a great way to discover new effective treatments for type 2 diabetes without breaking the bank. Cancer, Parkinson's disease, Alzheimer's disease, and cardiovascular disease may occur as a result of the metabolic abnormalities linked to type 2 diabetes, including hyperinsulinemia, inflammation, oxidative stress, and excessive glycation. There is solid evidence that antidiabetic medications may reorient themselves to address these conditions. It used to take a lot of money to find potential new medication indications via random tests. Methods for medication repositioning that are both guided and economical are provided by computational techniques including classical algorithms and machine learning. Machine learning techniques for discovering novel treatments for type 2 diabetes and additional uses for existing antidiabetic medications are the primary emphasis of this study.

LITERATURE REVIEW

Park, Kyung Soo. (2019). Despite the fast advancements in science and technology, the process of developing new drugs has been a lengthy and expensive one during the last few decades. 'Drug repurposing' or 'drug repositioning' has emerged as a substitute method to speed up the drug development process, finding new uses for existing drugs instead of finding new drug compounds from scratch. This strategy now accounts for 30% of newly marked drugs in the US. Meanwhile, a new field of medication repurposing known as computational drug repurposing is being made possible by the massive and rapid expansion of pharmaceutical compound molecular, genomic, and phenotypic data. More specifically, this review summarises the most current developments in computational drug repurposing. Computing approaches that are regularly utilized are summarized after the available repositioning strategies. Then, it

delves into the methods of study repurposing validation. It wraps off by talking on the problems that computational repurposing still has.

Kalita, Nihalini et.al. (2024). The complicated interplay between hereditary and environmental variables leads to the severe and long-lasting metabolic condition known as diabetes. A pandemic of diabetes mellitus has emerged on a global scale. The lengthy and expensive process of creating new pharmaceuticals and agents has hampered medication development. Drug repositioning or repurposing has gained attention in the last 30 years due to the decrease in the number of drugs authorized by the FDA. One potential strategy to alleviate the financial strain that most countries experience while dealing with diabetes mellitus is to repurpose current medications. Objective Various validation procedures were used in the process of repurposing pharmacological compounds for the treatment of Diabetes Mellitus, and this article seeks to explain all of them. Methods In order to compile this review, the writers combed through a mountain of articles found in academic databases such as Web of Science, Google Scholar, and PubMed. Final Product A small number of anti-diabetic medications with additional pharmacological properties were found via drug repurposing. Several drugs have been shown to be beneficial in treating diabetes mellitus. These include celecoxib, buspirone, berberine, diacerein, methazolamide, and bromocriptine. Their mechanisms of action include reducing insulin resistance and hyperglycemia, suppressing glucagon production, and enhancing insulin sensitivity. In summary When it comes to overcoming the challenges posed by complicated illnesses like type 2 diabetes, the area of pharmacological repurposing shows great promise. Significant delays in the identification of viable treatments for illnesses like T2DM have typically been the consequence of traditional drug development procedures, which are marked by lengthy durations and expensive prices. A more efficient and cost-effective approach to medication development is offered by the drug repurposing strategy, however.

Turner, Nigel et.al. (2016). The traditional drug discovery pipelines have been heavily funded by pharmaceutical corporations, but the development of new medications has not kept pace with the rising frequency of numerous illnesses, including type 2 diabetes (T2D). One effective strategy for overcoming the limitations of traditional methods is medication repurposing, which involves using already-existing pharmaceuticals for a different purpose. One way to significantly cut down on medication development times is by repurposing, which makes use of existing data on the molecular pharmacology of therapeutic treatments. This review delves into the latest developments in the quest for novel antidiabetic drugs via the use of repurposing methodologies.

Jeyabaskar, Dr. Suganya et.al. (2017). Diabetes ranks as the world's third most deadly disease. People with diabetes have a metabolic condition characterized by consistently elevated blood glucose levels. Traditional Chinese medicine made extensive use of camptothecin, an alkaloid substance with enhanced antioxidant potential. Early studies on camptothecin showed that, in comparison to synthetic medications on the market today, it had superior anticancer and antitumor action. The inhibitory action of the chemical over the corresponding target proteins may be better understood by in silico drug development and docking research. When it comes to predicting and evaluating atomic-level binding interactions between receptors and tiny compounds, molecular docking is a potent tool. This work used Arguslab to examine the in-silico binding interaction of camptothecin with three key diabetes targets: Glucokinase, insulin receptor, and PPAR gamma. Molecular docking, which involves studying the interactions between tiny molecules and

their proteins, is done using the ArgusLab program. Tests on the bioactivity and drug-likeness of camptothecin indicated that it would be suitable for use as an oral medication. Results from the docking investigation showed that among the three proteins, camptothecin had the highest binding affinity. Of the three proteins, the one with the lowest binding energy was the PPAR gamma protein, followed by the insulin receptor and Glucokinase, both of which had binding energies more than -8.5 kcal/mol. So, the Camptothecin molecule may be a preferable choice for a lead molecule in the search for novel anti-diabetic medications.

Rao, Monica et.al. (2023). During 2020 and 2022, the globe saw a coronavirus pandemic that posed unprecedented challenges to humankind. Scientists, doctors, and pharmacists were all kept on high alert by the constant battle and sprint to discover a treatment for the illness. The evident drawback of the de novo method—the large time it takes to locate a drug—made it an unworkable choice. Up until today, the public had no idea that scientists may find a path ahead by reusing and recycling current medications. Repurposing medications is giving them a new use in medicine after they've been through the drug development process and either been authorized, withdrawn, or put on the shelf. A number of disorders have responded well to drugs that have been repositioned or repurposed. This article gives a rundown of the computational strategies used for repurposing, including in silico methodologies, molecular docking, and signature mapping, and follows the path of a few repurposed medications. One of the most terrifying illnesses, cancer, is also discussed in the study, along with how repurposing medications may help with various forms of the condition. The time has come for a coordinated effort to investigate this method of medication development. Many medications have been effectively repurposed for the treatment of many disorders, as discussed in the article. One bright spot that may alter the course of drug development is drug repurposing, which has the ability to shorten the long road to finding a permanent cure for a disease.

RESEARCH METHODOLOGY

Target Protein and Its Properties

A literature analysis led to the adoption of α-Glucosidase as a target protein for type 2 diabetes. Its Uniports ID is P10253 and its accession number is NP_000143.2. The target protein's sequence, function, and other details may be retrieved using these IDs. Using the DeepLoc-1.0 and ESLpred web servers, we were able to determine the target protein's subcellular location. Both methods make advantage of features of proteins, including their dipeptide makeup, physicochemical qualities, and amino acid content. Algorithms based on support vector machines (SVMs) employ these features to forecast where eukaryotic proteins will be found inside cells.

Molecular Docking, Validation, and Lead Identification

In drug design, molecular docking is a tool for finding the optimal ligand-protein complex structure. The open-source docking program Autodock Vina was used to perform it. We used Open Babel to transform the small molecule files that were obtained in SDF format into PDB format. Both the ligand and the protein were auto-prepped before docking began. This included desalinizing the macromolecule, adding polar hydrogens, assigning charges, and, in the case of the ligand, selecting torsions. Docking at certain sites required adjusting the grid box surrounding each one. The box size for all three dimensions was 54 × 56 ×

50, while the X, Y, and Z coordinates were 63.750, 87.139, and 71.694, respectively. After the ligand and protein were transformed into PDBQT format, the bonds between them were made rotatable.

Retrieval of Reported Inhibitors and Docking

To aid in the generation of a pharmacophore query based on structural similarities, the already-reported inhibitors/active chemicals were gathered from the literature and the PubChem database. Protein topography, including surface pockets and interior cavities, is crucial for protein function, and CASTp offers this information [25]. The most likely location for binding was selected. Twenty active molecule structures were obtained from PubChem and translated to PDB and pdbqt file formats using Autodock for docking purposes. To prepare the macromolecule, water molecules are removed and polar hydrogens and charges are added. Python Rx was used to do the site-specific docking, while PyMOL was used for analysis.

DATA ANALYSIS

Twenty inhibitors that have been reported were docked to particular sites: acarbose, celgosivir, metformin, migalastat, 1-Deoxynojirimycin, 4-(4-methylbenzenesulfonyl)-N,N-diphenylpiperazine-1-carboxamide (8R, 7S, 6S)The following medications may be prepared using PyRx: -Octahydro-indolizine-1,6,7,8-tetraol, miglitol, NAG, Voglibose, metformin, BGC, GLC, NOJ, SC2, GOL, PGE, PEG, EDO, and MIG. Cilibose (444,020), 4-(4-methyl benzenesulfonyl)-N,N-diphenylpiperazine-1-carboxamide (1,322,817), and Celgosivir (60,734) were among the active compounds studied and used to generate pharmacophore queries (Table 1). In order to find the common characteristics needed to construct pharmacophore searches, conformers were generated by performing flexible alignment on the chosen ligands. For the purpose of pharmacophore query generation, four properties were selected: aromatic groups, hydrophobic groups, hydrogen bond acceptors (HBAs), and hydrogen bond donors (HBDs) (Figure 1).

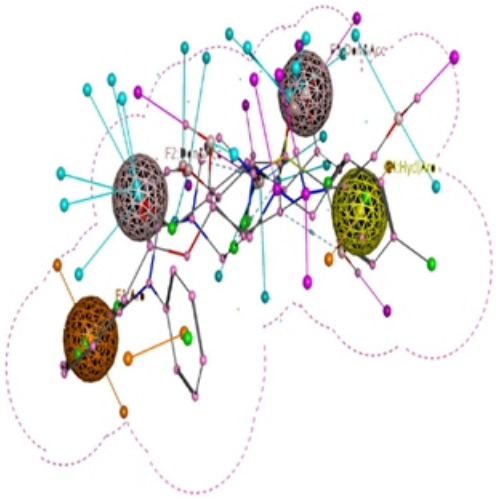

Figure 1. Pharmacophore query for screening purposes. Color balls represent HBA, HBD, hydrophobic, and aromatic groups

Table 1. Most active compounds are used to form pharmacophore queries for screening purposes.

Small Molecules	IC_{50}, and K_d	Structure	HBA	HBD	MW (KDa)	RB	LOG P	Lipinski Violation
Celgosivir	15.95 mM		6	3	259.40	4	−0.8	NO
4-(4-methylbenzenesulfonyl)-N,N-diphenylpiperazine-1-carboxamide	25.1189 µM		4	0	435.4	4	3.8	NO
Voglibose	23.4 µM		8	8	267.28	5	3.1	NO

For computing the binding free energy of small molecules fitted into macromolecules, the MMGBSA method is computationally efficient, cost-effective, and time-efficient. Both compounds' predicted binding energies are shown in Table 2 and the graph (Figure 2). Contributions from Coulombic, covalent, and lipophilic forces are included in the computed energy profiles. Drug discovery and design could benefit from the molecular indications provided by Van der Waals.

Table 2. Binding free energy values in kcal/mol of alpha Glucosidase complexed with Trabectedin and Demeclocycline calculated via MMGBSA method.

Parameters	Trabectedin (Kcal/mol)	Demeclocycline (Kcal/mol)
ΔG_{bind}	−74.36	−78.31
$\Delta G_{bind\_Coulomb}$	−16.15	−16.73
$\Delta G_{bind\_covalent}$	15.66	4.85
ΔG_{bind_Hbond}	−0.98	−2.78
ΔG_{bind_lipo}	−39.11	−34.51
$\Delta G_{bind\_packing}$	−1.42	−0.60
$\Delta G_{bind\_solv\_GB}$	25.53	16.96
ΔG_{bind_vdW}	−57.89	−45.49

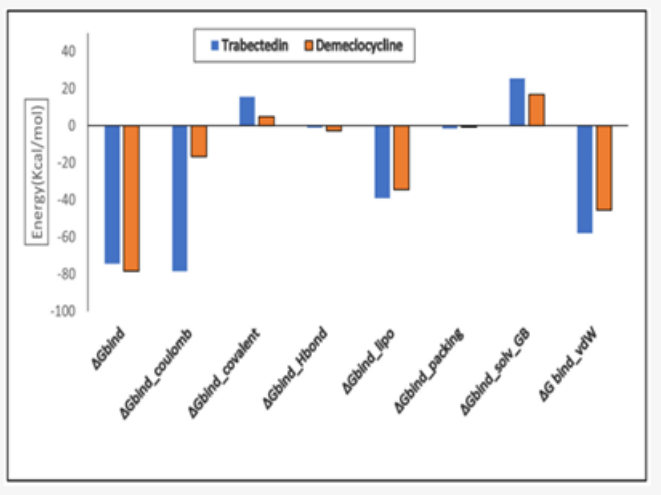

Figure 2. Histogram of calculated binding free energy values of the two best compounds in contact

with receptor via the MM-GBSA method

To further verify the docking validation, we used the receiver operating characteristics (ROC) assessment technique to differentiate between active and inactive ligands (Figure 3). The capacity of the model to distinguish between active and inactive chemicals is shown by a ROC curve near to 1, while a curve close to 0 suggests the inverse. AUC levels between 0.8 and 0.9 are excellent, AUC values between 0.7 and 0.8 are satisfactory, and AUC values between 0.6 and 0.5 are bad. With an area under the curve (AUC) of 0.822 and a ROC curve around 1, the ROC produced trustworthy findings. The chemicals in question were then subjected to further testing.

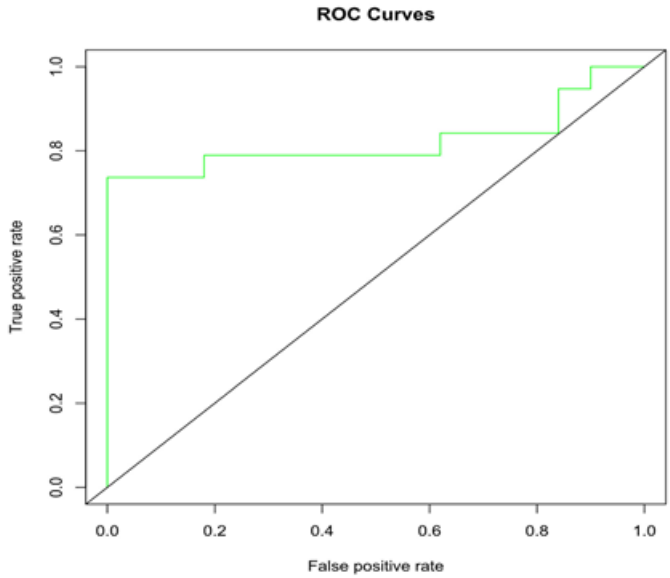

Figure 3. The ROC curve for the validation of docking and the area under the ROC curve calculation quantifies the overall docking results. The green line represents AUC (0.822).

CONCLUSION

α-glucosidase is seen as a crucial target in type 2 diabetes because it has a role in the absorption of glucose and fructose, which are digesting carbohydrates, and in the development of hyperglycemic situations. The proper functioning of several organs and tissues depends on a steady blood glucose level. The severity of type 2 diabetes may be mitigated by reducing glucose production and intestinal glucose absorption. In order to regulate hyperglycemic situations and locate a potential anti-diabetic medication with few or no side effects, a library of chemicals licensed by the FDA is employed to find inhibitors of α-glucosidase. Both the FDA and the EMA have given their stamp of approval to drug repurposing, which is a fast and cheap way to find new ways for already-approved medications to work against different ailments. The research used an in silico technique to screen 1600 medicines licensed by the FDA for molecules that showed anti-diabetic properties against α-glucosidase. The findings reveal that the two drugs authorized by the FDA, Trabectedin and Demeclocycline, bind firmly to the active site of α-glucosidase and inhibit it effectively. A higher incidence of cancer and cardiovascular disease is seen in patients with type 2 diabetes. One of the main ingredients, Trabectedin, is an anticancer drug with marine origins that has been authorized by the FDA to treat soft tissue sarcoma. Demeclocycline, the second leading contender, is used to treat bacterial infections, Lyme disease, bronchitis, UTIs, malaria, and more, and it has received FDA

clearance.

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