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In silico Target Based Computational Drug Repositioning of Tolazamide with Canagliflozin

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ABSTRACT
Diabetes mellitus is a collection of metabolic infection described by high glucose level that comes out from imperfections in insulin emission. The commonness rate of sort 2 diabetes mellitus in Pakistan is 11.77%. It is the fourth driving reason for death because of its connection with different illnesses i-e cardiovascular and renal disappointment. Currently Tolazamide medicine is used to control diabetes. This research work is aimed to reposition a drug Tolazamide with Canaglaflozin which is used against heart attack but target the same genes as Tolazamide that decreases the side effect of drugs used against diabetes. Drug repositioning was carried out in an off-target profile in which drug information was retrieved, its interactions with already known targeted genes and new target genes are determined, side effects, toxicity class are compared, its associated pathways are identified and docking is done with the interacting targets. It was found that Tolazamide showed strong interaction with KCNJ11 and ABCC8, CACNA1A, CACNA1B, and CACNA1C all these are also the target of Canagliflozin. The side effect of canagliflozin is quite less than Tolazamide. Toxicity class of canagliflozin is 5 and docking showed that the score is 6484, binding energy -407.45. Subsequent to screening an extraordinary number of medications which are utilized to control target protein and furthermore looking at their symptom, it is suggested that Canaglaflozin can be repositioned against KCNJ11, ABCC8, CACNA1A, CACNA1B, and CACNA1C according to all above mention parameters. This research work can be used in laboratories to determine its efficacy and validity.
Keywords: *Diabetes mellitus, drug repositioning, Tolazamide, Canagliflozin, ABCC8.*

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INTRODUCTION

Diabetes mellitus is a collection of metabolic sicknesses with high glucose levels over a drawn-out period, otherwise called basic diabetes. This high glucose causes the sicknesses of unreasonable pee, appetite, and thirst. Diabetes is caused by either the pancreas that does not create enough insulin or by the body's cells that don't react legitimately to the delivered insulin. There are two primary sorts of diabetes mellitus: Type 1 DM is the aftereffect of insulin disappointment in the body and in past the name given to type 1 DM is "adolescent" diabetes or "insulin-subordinate diabetes mellitus.Type 2 Diabetes mellitus begins generally with insulin opposition, a confusion in which the cells don't react appropriately to insulin. As sickness advances, insulin inadequacy can likewise create. This sort was once in the past called "non-insulin-subordinate diabetes mellitus "grown-up just diabetes." The real reason is unnecessary weight and lacking activity. [20].

Type 2 diabetes mellitus prevalence in Pakistan is 11.77% and is likewise the fourth driving reason for death because of its association with different cardiovascular and renal diseases. This disease in guys is higher than in females [17]. In several native populations, the ABCC8 gene has been linked to type 2 diabetes. In insulin secretion, the ABCC8 gene that synthesizes the sulfonylurea receptor plays a key role. The SUR1 protein is the subunit of the ATP-sensitive potassium (K-ATP) found in the beta cells of the pancreas over the cell films. Beta cells secrete insulin, The K-ATP channel controls the insulin emission from and into the circulatory system of beta cells. Changes in ABCC8 interfere with the capacity of the K-ATP channel prompting the steady arrival of beta-cell insulin. In result, glucose is immediately expelled from the circulatory system [22].

Currently, most commonly used drug against diabetes type 2 is Tolazamide which strongly targets the ABCC8 and KCNJ11 but Tolazamide has severe side effects and lies in toxicity class 4 which is not best as compared to class 5 and 6.

Heart attack (myocardial infarction or MI) is a serious mental health emergency within which blood supplies to the heart, normally through a blood clot, are suddenly blocked. People with diabetes type 2 have higher rates of hypertension, dyslipidemia, and obesity, main causes of CVD [19].

Canagliflozin is a drug which is used against diabetic heart attack have fewer side effects, also lie in toxicity class5 and target the same genes as Tolazamide that is used against diabetes and can be repositioned to cure diabetes type 2.

Drug repositioning is the use of available drugs to treat conditions that are different from the original purposes of treatment and to redevelop a compound for use in a different disease. Drug molecule does not only bind to their targets proteins for which it is purposed but it also targets many other protein and genes. Drug target interaction provides a way to predict the unknown target and their pathway and docking provide the satisfaction how well the drug molecule bind to their target protein. [11, 5]. In this study the drug Tolazamide used against diabetes will be repositioned due to its toxicity and more side effects with Canaglaflozin which is used against heart attack but target the same genes as Tolazamide that decreases the side effects and toxicity of drugs used against diabetes.

MATERIAL AND METHODS

Drug repositioning was carried out in an offtarget profile in which the mechanism of pharmacology is unk nown. Candidates for drugs and drugs act on new targets for new therapeutic indications out of the origin al scope [25]. The detailed Methodology is shown in Fig 1.

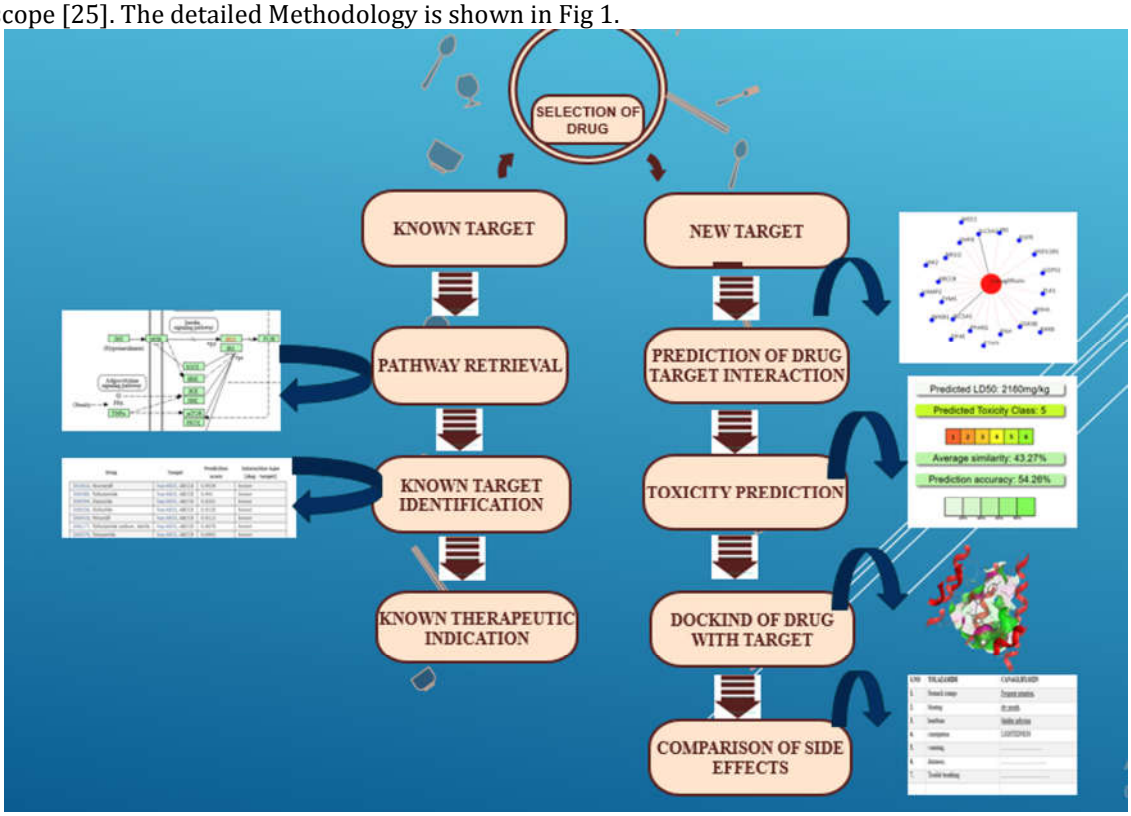

Fig 1: Schematic illustration of the methodology

DRUG SELECTION FOR REPOSITIONING:

This work plan was carried out with some modifications in accordance with the previously published paper [5]. The drug Canaglaflozin used against heart attack and Tolazamide used against diabetes were selected after screening the great number of drug molecule used against diabetes and diabetes-related diseases i-e renal diseases and cardiovascular disease by using online available database DRUG BANK [4].

PREDICTION OF KNOWN TARGET INTERACTION:

Known target and known therapeutic indication were determined by using DINIES [24] tool which gives the list of drugs that are working with ABCC8 target.

PREDICTION OF NEW DRUG TARGET INTERACTION:
Drug target interaction of canagliflozin with their protein that is off-target was predicted by using online available server Balestera web server [18]. The drug that was repositioned (Canagliflozin) can be used against diabetes because it also targets the same gene as Tolazamide. The ADMET properties and toxicity class of Canagliflozin were predicted by using the online server ADMET Psychem and toxicity server protocols [12].

TOXICITY PREDICTION:
Toxicity class of both drugs tolazamide and canagliflozin were determined by using Protox server [2] from where we analyze that tolazamide lies in class 4th which is not suitable as class 5 of canagliflozin.

PATHWAY RETRIEVAL:
All genes that are involved in the diabetes were submitted in enrich net [7] from where 2 significant pathway was found i-e ABC transporter and Type 2 diabetes mellitus.

DRUG DOCKING WITH THEIR OFF TARGET PROTEIN/GENES:
Three dimensional (3d) structure of drugs targeted proteins was predicted and downloaded from the RCSB PDB [18**]** and three-dimensional structure of drug compound was downloaded from Zinc Database [9]. Canagliflozin was docked against ABCC8 and KCNJ11 by using online available server Patch Dock [17] and Auto Dock [18] and determined their scores values.

SIDE EFFECTS COMPARISION AND REPOSITIONING:
Side effects of Canagliflozin were compared with that of Tolazamide and found that Canaglaflozin have fewer side effects as compared to Tolazamide and Canaglaflozin was able to cure diabetes because it targets the mutant gene involved in diabetes so there is no need to use additional drugs to treat patients with diabetes that also suffering from cardiovascular disease. Biological and experimental methods for the discovery of drugs are well known to be time-consuming and costly. New efforts to repurpose drugs through the prediction of drug-target interaction networks using the biological and chemical properties of drugs and targets have been explored [5, 14]. Structure of both drugs Canagliflozin and Tolazamide is shown in Fig 2.

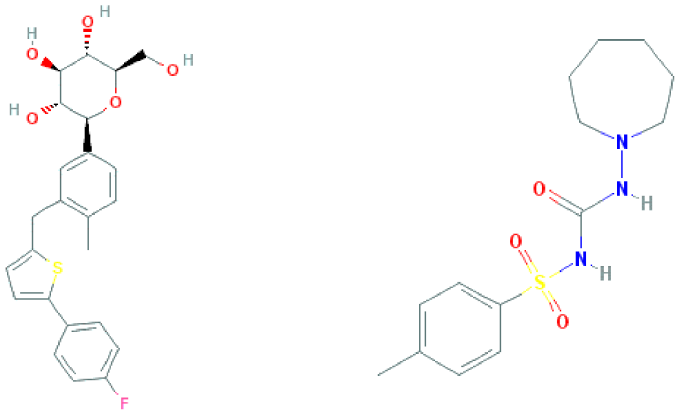

Fig 2: Chemical structures of canagliflozin and tolazamide

RESULT
The drug-target interaction provides us a way to repurpose drug for various other diseases. The interaction of drugs with different targets can probably accomplish adversarial side impacts or purposefulness medications [6].The connecting estimates contrast with the related requirements in an over-performing association of the target interaction of medication, showing similar views between the medicines and the goals. Tolazamide show strong interaction with ABCC8 and KCNJ11 appear in Fig 3 whereas Canagliflozin indicate solid cooperation with SLC5A2 AND SLC5A1 yet it likewise focuses on the ABCC8 quality include in diabetes appear in Fig 4

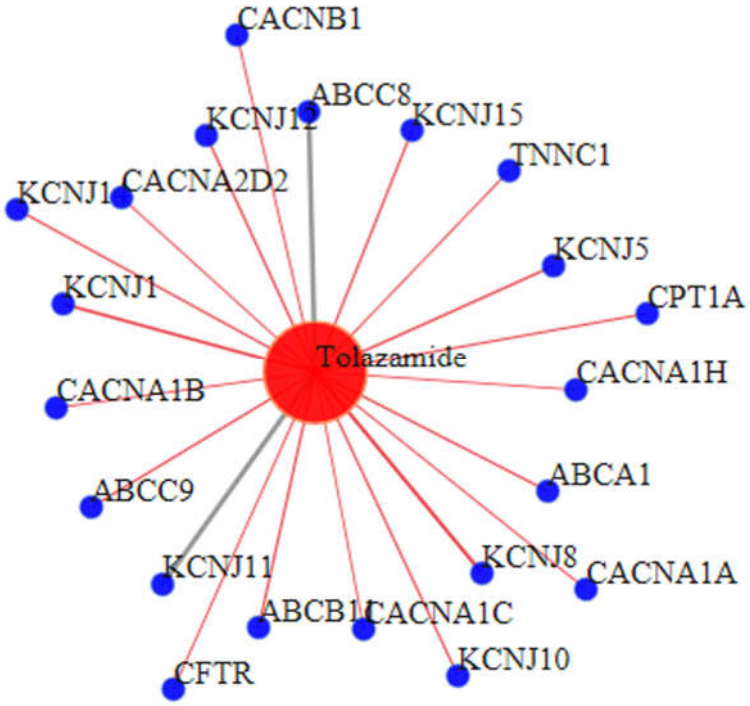

Fig 3: Network of target interactions (Tolazamide)

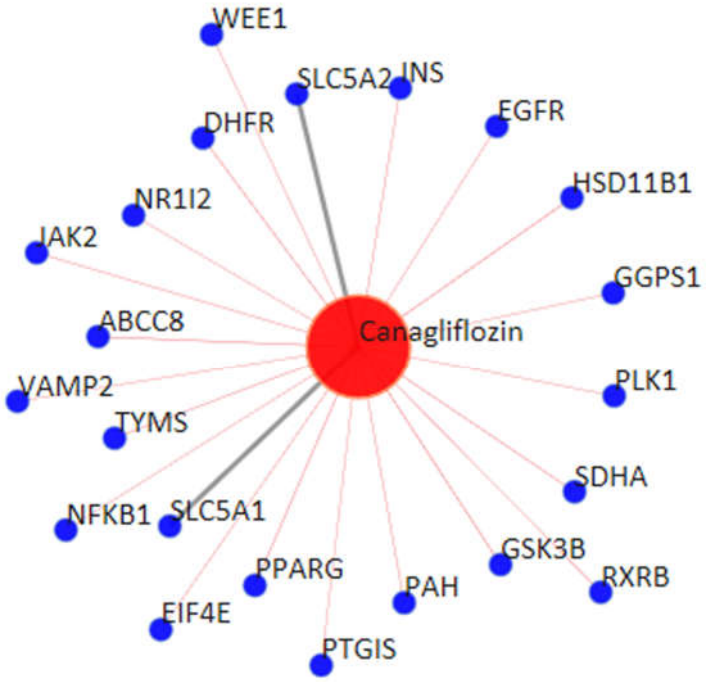

Fig 4: Network of target interactions (Canagliflozin)

Known target and known therapeutic indication were determined which give the list of drugs that are working with ABCC8 target along with prediction score and interacting type shown in table 1 .

TABEL.2: KNOWN TARGET PREDICTION:

Drug	Target	Prediction score	Interaction type [dug - target]
D01810, Nicorandil	hsa:6833, ABCC8	0.9534	Known
D00380, Tolbutamide	hsa:6833, ABCC8	0.941	Known
D00294, Diazoxide	hsa:6833, ABCC8	0.9201	Known
D00336, Glyburide	hsa:6833, ABCC8	0.9135	Known
D00418, Minoxidil	hsa:6833, ABCC8	0.9113	Known
D06177, Tolbutamide sodium, sterile	hsa:6833, ABCC8	0.9076	Known
D00379, Tolazamide	hsa:6833, ABCC8	0.6992	Known
D02427, Glibornuride	hsa:6833, ABCC8	0.6834	Known
D02430, Gliquidone	hsa:6833, ABCC8	0.6707	Known
D00271, Chlorpropamide	hsa:6833, ABCC8	0.6617	Known
D01111, Nateglinide	hsa:6833, ABCC8	0.6548	Known

Drug target interaction alludes the drug response toward the target when regulated, which increase or decrease the intensity of response (drug target). It also demonstrates the functional similarities to other drugs and all the pathway of drugs. Function similarities of ABCC8 are 14.6%.

The toxicity of Canagliflozin lie in class 5 and LD50 value is higher i-e 2160mg/kg, similarly, the toxicity of Tolazamide lie in class 4 and LD50 value is lower i-e 1000mg/kg. Canagliflozin has low toxicity class i-e class 5 which is best in human life, but Tolazamide lies in toxicity class 4 which is not suitable as compared to class 5. LD50 value of Canagliflozin is high which is good as compared to Tolazamide which is low.

All genes that are involved in the diabetes were submitted in enrich net [7] from where 2 significant pathways were found (Fig 5 and 6) i-e ABC transporter (significance of network distance distribution (XD-score) is 1.014 and significance of overlap (fisher test) 2.3e-05) and Type 2 diabetes mellitus (significance of network distance distribution (XD-score) is 0.946 and significance of overlap (fisher test) 2.3e-05).

ATPcassette couple ATP hydrolysis for active transportation of a wide variety of substrates such as ions, s ugars, lipids, sterols, peptides, proteins, and drugs.

A prokaryotic ABC transporter's framework generally comprises of three parts; typically two essential me mbrane proteins with six transmembrane sections each, two peripheral enzymes binding and hydrolyzing ATP, and a periplasmic (or lipoprotein) substrate-binding protein.On the other hand, the membrane-spanning protein and the ATPbinding protein are fused in a typical eukaryotic ABC transporter, forming a multi-domain protein with membrane-spanning (MSD) domain and nucleotide-binding domain (NBD)

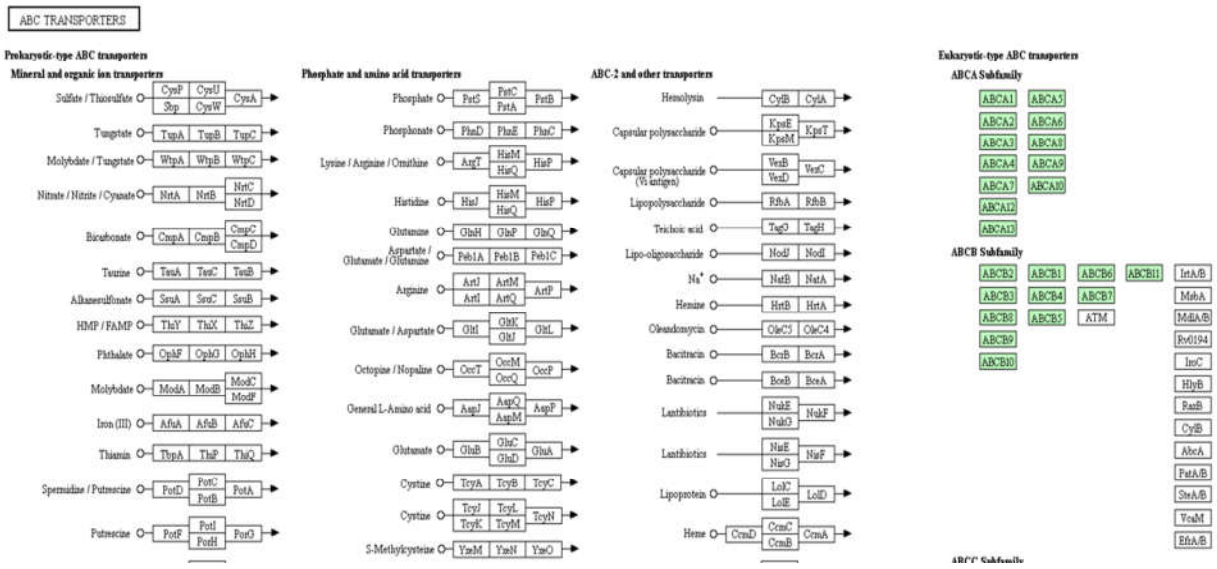

Fig 5: ABC transporter pathway.

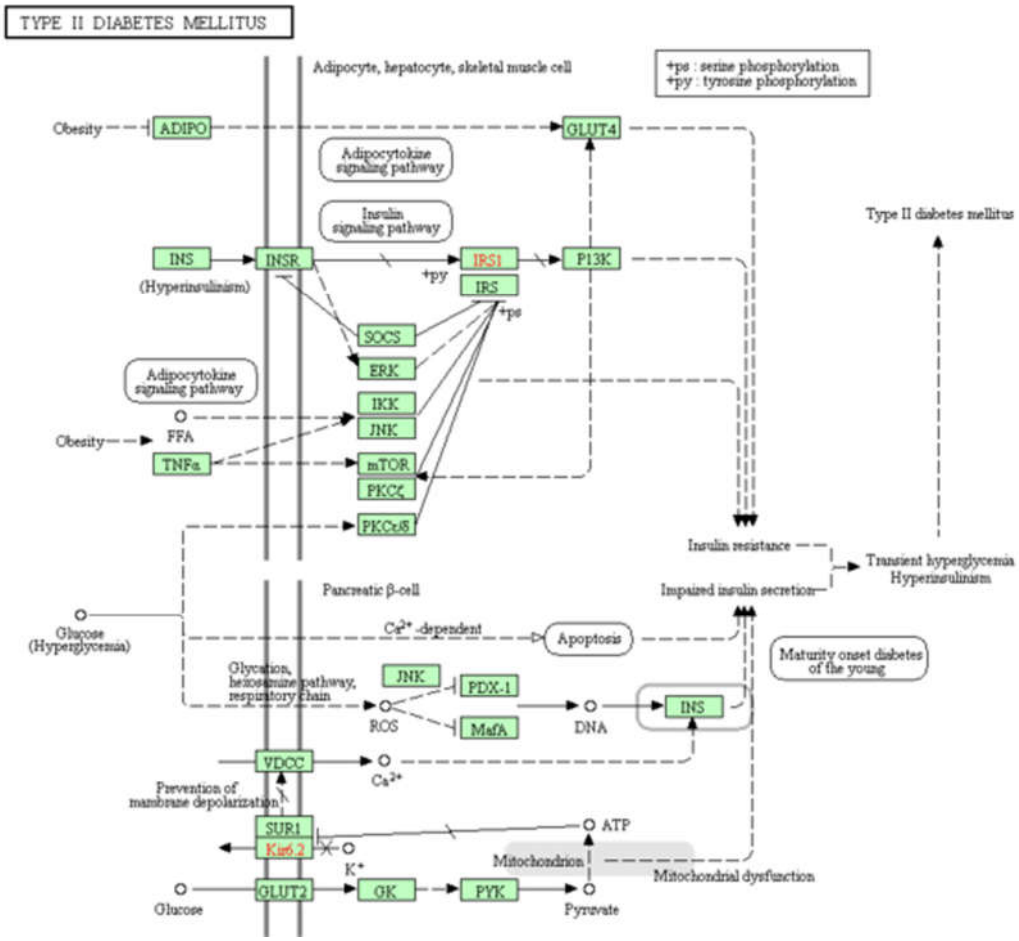

Fig 6: Diabetes pathway

Type 2 diabetes mellitus pathway shows a strong association between insulin resistance diabetes Factors such as FFA, TNFalpha and cellular stress cause insulin resistance by inhibiting IRS1 activities.
The molecular processes activated by them are serine/threonine phosphorylation, association with SOCS, regulation of activity, alteration of cell location, and degradation represent the molecular mechanisms stimulated by them.
This method involves several kinases (ERK, JNK, IKKbeta, PKCzeta, PKCtheta,and mTOR).Type II diabetes growth involves the reduced function of the beta-cell. It has been shown that chronic hyperglycemia induces several flaws in beta-cells. It has been suggested that hyperglycemia leads to big quantities of reactive oxygen substances (ROS) in beta cells, with later harm to DNA elements including P DX-1.Loss of PDX1, a key insulin promoter activity regulator, has also been proposed as an important mechanism leading to beta-cell dysfunction. IRS play central roles in insulin secretion and insulin signal transmission.
Molecular docking is an attractive platform for understanding medication bimolecular communications in the normal structure and disclosure of medications and in the deterministic investigation by just putting a particle (ligand) in the ideal restricting site of the objective explicit locale of the DNA/protein (receptor), essentially in a non-covalent way, to make a steady but startling potential viability and explicitness. The target of ligand-protein docking is to foresee the transcendent restricting mode(s) of a ligand with a protein of a realized 3D structure. One of most imperative components in atomic docking is the scoring capacity; it is utilized to anticipate the coupling partiality between the two particles [16].
In all docked complexes, ASP, ARG, and LYS were common interactive residues. Canagliflozin dock result with ABCC8, KCNJ11, and CACNA1A, CACNA1B and CACNA1C and their 2d interaction are shown in Fig 7 - 11

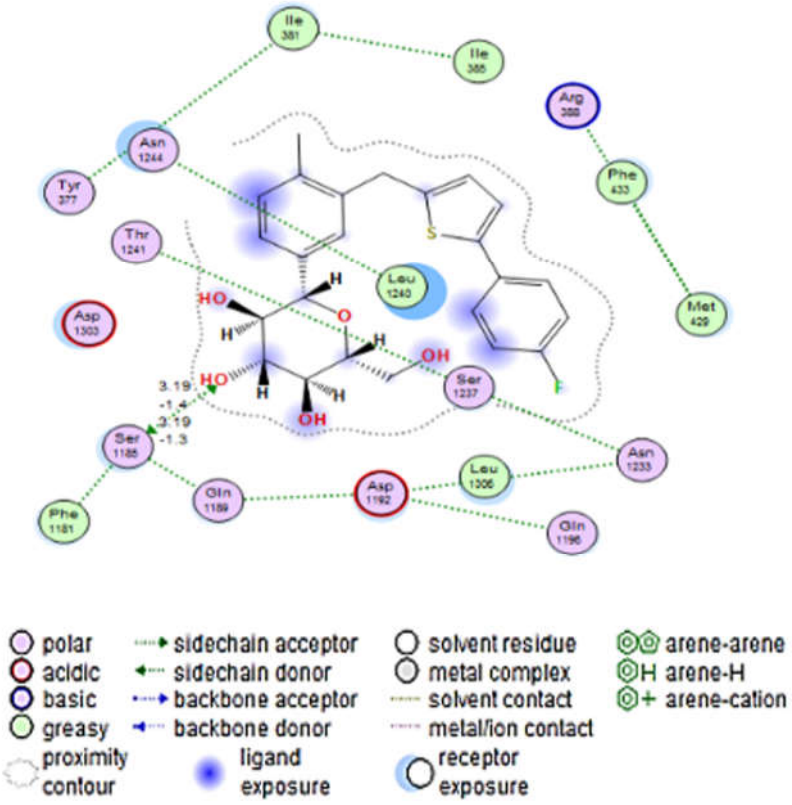

Fig 7: Show the 2 dimension interaction of amino acids residue to the ligand

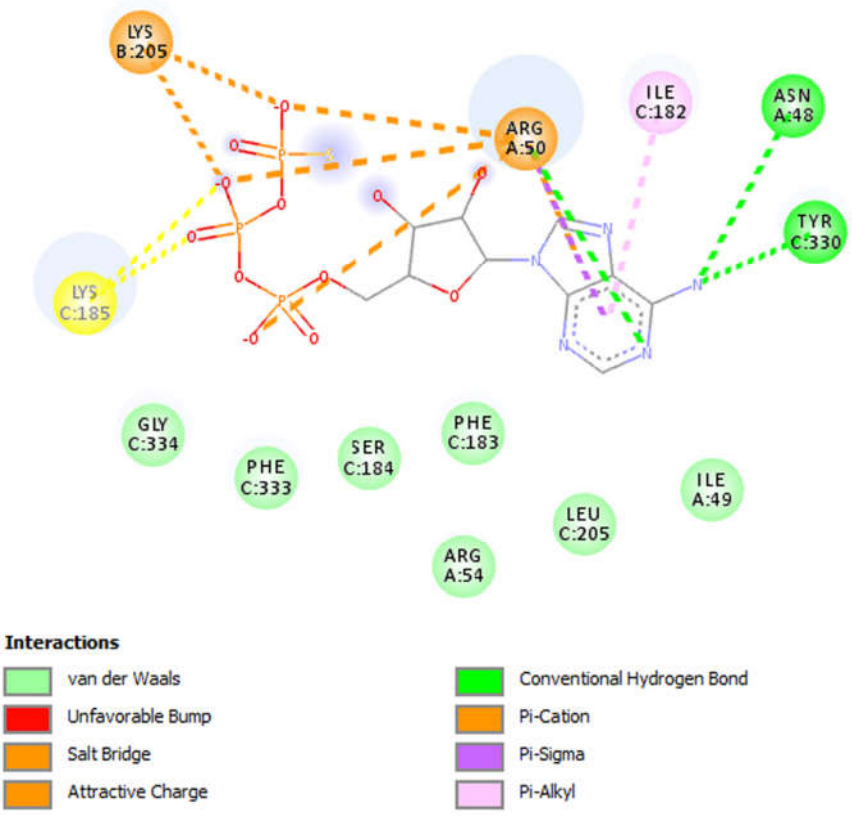

Fig 8: Show the 2 dimension interaction of amino acids residue to the ligand

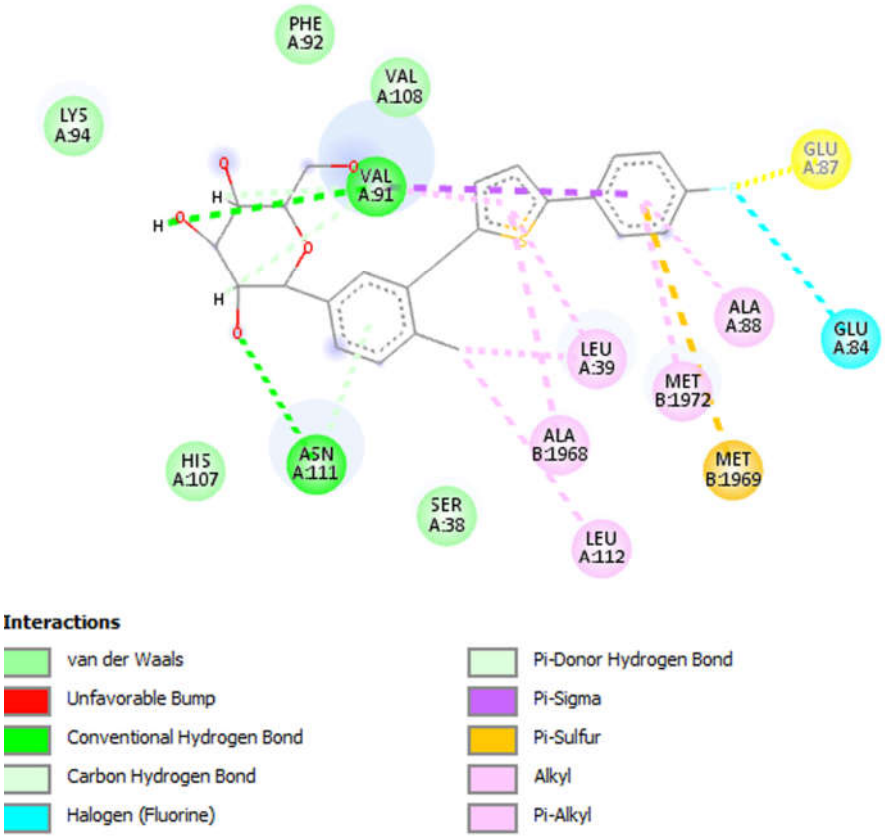

Fig 9: Show the 2 dimension interaction of amino acids residue to the ligand

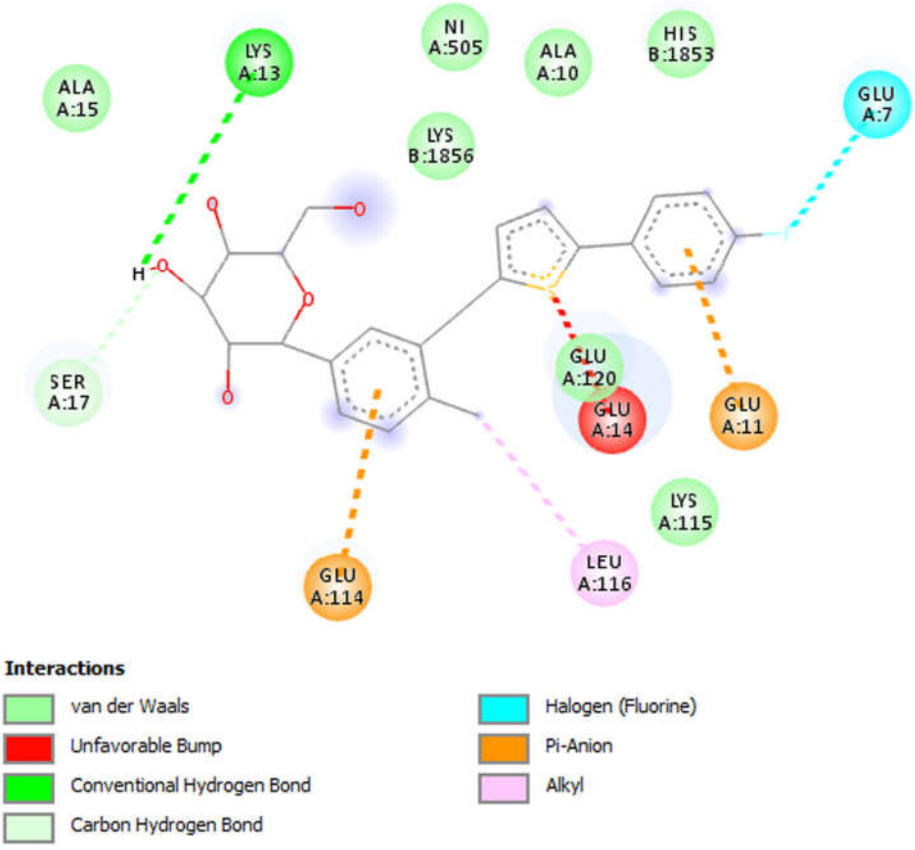

Fig 10: Show the 2 dimension interaction of amino acids residue to the ligand.

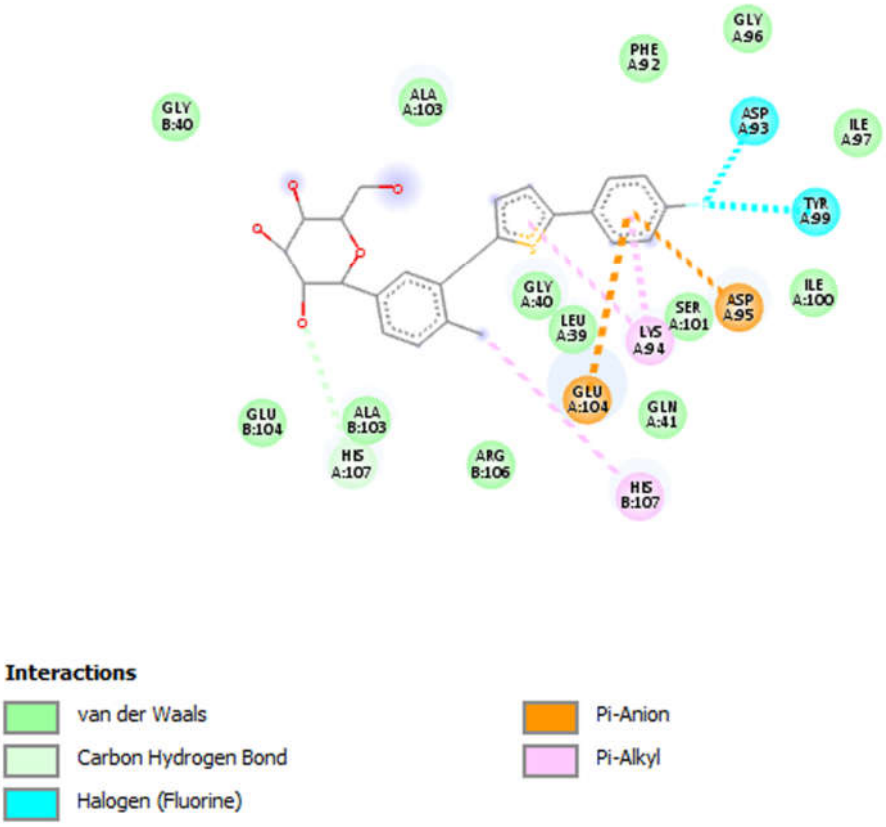

Fig 11: Show the 2 dimension interaction of amino acids residue to the ligand.

When Canagliflozin is docked with ABCC8, KCNJ11 (score is 6484, binding energy -407.45), CACNA1A (score is 4924, binding energy is -277.95), CACNA1B (score is 4512, binding energy is -124.41) and CACNA1C (score is 5182, binding energy is -112.24) the interacting residue are Asp, Gln, Leu, etc. Canagliflozin best fit into their all protein binding site. Basically, docking allows analysts to screen a compound database and anticipate strong inhibitors with different scoring capabilities [5]. Docked complexes show the high value of scoring function which indicates the best docking results. According to all the above results it is proposed that Canagliflozin can be repositioned to cure diabetes. Side effects of Canagliflozin were compared with to that of Tolazamide it was found that Tolazamide has greater numbers and severe side effects which is listed below in table 2.

TABEL.2: Comparison Of Side Effects of Canagliflozin And Tolazamide

S.NO	TOLAZAMIDE	CANAGLIFLOZIN
1.	Stomach cramps	Frequent urination,
2.	bloating	dry mouth,
3.	heartburn	bladder infection
4.	constipation	LIGHTEDNESS
5.	vomiting,	……..
6.	dizziness,	……..
7.	Trouble breathing.	……..

The table 2 shows that Canagliflozin has fewer side effects as compared to Tolazamide so it can be repositioned against Tolazamide to cure diabetes.

Canagliflozin is the best drug, according to the all above measure parameters i-e high scoring function in docking, binding energy, bond length, side effects, toxicity class, etc. All parameters are according to the standard value that is suitable for any drug.

DISCUSSION

Understanding both the strong relationships between the drugs, their proposed goals different biological processes that can affect them is essential to enable the improvement of post-marketing drugs. Exploring drug-target interactions increases our awareness of drug activity and its negative effects on patients. Therefore, their computer research offers applications to match patients with optimal medications and also to explore new clinical evidence of certified medicines so this work is done to reduce the side effects of drug on patients [23].

The introduce of rising and propelled novel computational strategies and publicly supporting methodologies that permit the joint investigation of genomic, biomedical and pharmacological information is to encourage educated, viable and precise repositioning of medications. Regardless of whether this presupposition accelerates tranquilize advancement pipelines and its amount makes an interpretation of specifically into another restorative development and influences human wellbeing, specific tending to quick needs(for example uncommon and dismissed sicknesses), stays to be found in a positive light [15].

Metformin is a first-line sedate used to treat type 2 diabetes and has likewise been recognized to diminish cancer-causing hazard and repress the development of malignancy cells I-e dependent on its impacts on tumor hindrance, metformin is probably going to hinder the development of cervical disease cells and metformin's viability is estimated in vitro but there is no research study of diabetes and their drugs side effects so we repositioned the drug of diabetes due to its more side effects [1].

Droperidol, glimepiride, risperidone, and other FDA-affirmed drugs have been repositioned as potential multi-target possibility for the treatment of Alzheimer's ailment utilizing a ligand-protein turn around docking and quality articulation information mining PC pipeline to investigate potential medications for AD treatment but in this study canagliflozin been repositioned as potential multi-target possibility for the treatment of Alzheimer's ailment utilizing a ligand-protein turn around docking and quality articulation information and investigate for diabetes [13].

Phenoxybenzamine and idazoxan ADRA2A (Alpha-2A adrenergic receptor) had a generally new sign for the determination of sort 2 diabetes A system of diabetic metabolites and proteins has been created to give an outline of how diabetes represses metabolites This guide can be utilized to recognize degenerate metabolic chemicals in diabetic patients, however, the lethal impacts of these two medications was not the best but our repositioned drugs have good impacts on patients because their toxicity class is higher as compared to the drugs described above[23].

Canagliflozin is an inhibitor of sodium-glucose cotransporter 2 that reduces cardiovascular risk. New evidence of Canagliflozin is to cure type 2 diabetes because it has low side effects and low toxicity as compared to already existing drugs used to cure diabetes. It cures diabetes on a dose of 300 mg per day. It is useful for those patients who have cardiovascular diseases caused by diabetes [21].

CONCLUSION

This investigation inspected canagliflozin and examined their collaborations with other off-focused proteins and qualities. It demonstrated noteworthy collaborations with ABCC8 and the reactions of canagliflozin were straightforwardly contrasted and those of tolazamide recorded in the tables and it was reasoned that canagliflozin has insignificant symptoms and show preferred cooperation scores over the Tolazamide drugs. After docking the basic amino acid residues are common in both drugs. On the bases of all above-estimated parameter vital for repositioning of any medication, it was inferred that Canagliflozin is repositioned to fix diabetes type 2

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