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Drug repurposing for diabetes: *In silico* determination of approved drugs against human glucokinase receptor

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Abstract

Diabetes mellitus is a chronic metabolic disorder characterized by abnormal glucose levels. It is a currently leading cause of mortality and morbidity in the world even in developing countries. This study investigates the potential of possible activators of human glucokinase, an important hepatic enzyme in glucose regulation from some selected approved clinical drugs by *in silico* docking simulations. Human glucokinase protein target was selected with its reference compound, piragliatin from the KEGG pathway and the presence of 3D structure in Protein Data Bank. 1545 clinically approved drugs were selected based on their physiochemical properties in relation to piragliatin, the reference drug, with respect to their predicted biological activities. The selected approved drugs were obtained from ZINC database. The protein drug target and the selected approved drugs including the reference drug were prepared for docking simulations using Autodock vina vs- 1.5.6 in a Linux platform. The visualization of the docked results was done using PyMol-vr1-ed win32. Darifenacin hydrobromide and citalopram hydrobromide were found to possess binding affinities of -10.17 and -10 kcal/mol respectively lower than piragliatin with a value of -9.97 kcal/mol. These drugs with lower binding affinities than the binding affinity of the reference drug were predicted to have higher activity against diabetes. Further investigations into the *in vitro* and *in vivo* activities of these drugs are essential in order to validate their use in the management of diabetes.

Keywords: *Diabetes Mellitus*; Human Glucokinase; Molecular Docking Simulations; Piragliatin; Darifenacin Hydrobromide; Citalopram Hydrobromide

1. Introduction

Globally, an estimated 830 million people are living with diabetes, while nearly two million deaths are directly attributed to the condition each year [25]. It is estimated that one in 10 adults worldwide have diabetes, and it is also responsible for 11% of death globally [12]. In Nigeria, the prevalence rate of people with DM was estimated to be 11.2 million [4]

Diabetes mellitus (DM) is a metabolic disorder that is now a global health problem and concern particularly the way it worsens the quality of human life [3,19]. Generally, DM is characterised by high blood sugar (hyperglycaemia) either due to lack or insufficient insulin produced by the body or failure of the body cells to respond to the presence of insulin [22,23]. Diabetes mellitus is not a communicable disease. Diabetes and its complications – including blindness, kidney failure, ischaemic heart disease, stroke and lower-limb amputation – cause premature mortality, significant morbidity, reduced quality of life, and substantial economic burden for individuals, families, health systems and national economies [29].

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Glucokinase (GCK) is a member of the hexokinase family, also known as hexokinase IV. It plays an essential role in glucose metabolism, crucial for sustaining blood glucose levels within normal ranges [10]. It is a pivotal metabolic enzyme that catalyzes the first rate limiting step of glycolysis in the pancreas and liver. GCK is responsible for catalyzing the ATP-dependent phosphorylation of glucose to glucose-6-phosphate (G6P), which triggers insulin secretion in pancreatic β-cells and glycogen synthesis in the liver [14]. GCK is also expressed in other tissues, including the intestine, hypothalamus, pituitary gland, lung, and spleen [18]. The pivotal role of GCK in glucose metabolism, particularly in pancreatic islets and the liver, underscores its significance in maintaining blood glucose homeostasis [2].

In recent years, *in silico* methodologies have become integral to early-stage drug discovery, allowing rapid screening of large compound libraries, prediction of protein–ligand interactions, and prioritisation of candidates prior to laboratory validation [4,5]. Computational approaches such as molecular docking, structure-based virtual screening, pharmacophore modelling, molecular dynamics simulations, and toxicity prediction help to reduce the cost, time, and attrition rates associated with conventional drug development pathways [11,13]. These tools have been widely applied in natural product research and have proven effective in identifying bioactive compounds with favourable drug likeness, predicted safety, and strong binding affinity for validated therapeutic targets [11,24].

The work is aimed at determining the binding affinities of some approved drugs against human glucokinase (PDB ID: 4NO7). It is also aimed to identify front runner approved drugs in the management of diabetes. Molecular docking and computational analyses were performed to evaluate binding affinities and predicted antidiabetic activities.

2. Materials and method

Several software programs were employed to investigate the binding affinities of some approved drugs against human glucokinase receptor through molecular docking and post-docking analyses. These tools have demonstrated high reliability in computational drug-discovery work flows and are widely used in computer-aided drug design. The software included PyMOL, UCSF Chimera, AutoDock Tools (ADT), AutoDock Vina, Open Babel. Biological databases such as the Protein Data Bank (PDB) were utilized for bioinformatics mining. Supporting materials used in the docking workflow included:

- Conf.txt – An Ubuntu configuration file containing binding site coordinates derived from the grid box size and position.
- KEGG pathway – a website used for mining of possible drug targets and ligands.
- ZINC database – a website used for physiochemical properties prediction.
- A Windows 10 Pro workstation – Used for ligand and protein preparation in Chimera and AutoDock Tools.

2.1. Bioinformatics mining- Identification of drug target

KEGG pathway, a type 2 diabetes mellitus reference pathway was used study all possible targets for investigation. Human glucose kinase receptor was selected as a choice of drug target for research. This is because the enzyme regulates carbohydrate metabolism by triggering the cell function in response to rising or falling levels of glucose.

2.2. Preparation of target protein

The experimental crystal structure of human glucokinase (PDB ID: 4NO7) with resolution of 1.70Å was downloaded from Protein Data Bank and was saved as PDB file. The saved file was opened in UCSF Chimera and the containing ligand together with other unwanted components were deleted and saved. The saved file was opened in Autodock tools and polar hydrogen was added and saved as pdbqt (the recognizable file format by Vina).

2.3. Selection and Preparation of Ligands

An activator (piragliatin) was identified through RCSB PDB. Bioactivity score of the activator was done using molinspiration then an in house approved drug database was filtered to obtain 1545 approved drugs similar to the reference activator. Preparation of the ligands and the reference drug was done using the Autodock tool (ADT) by Gasteiger charges computed, all bonds were set to non-rotatable and ligands were saved in PDBQT format for docking.

2.4. Validation of Docking Protocol

Docking validation involved identifying the binding pocket of the target protein. The reference ligand (piragliatin) was isolated in Chimera to determine its orientation within the active site.

In AutoDock Tools:

- The prepared receptor and isolated piragliatin ligand were loaded
- A grid box was generated to completely enclose the binding site
- The grid centre and dimensions were documented (Table 1)

Table 1 Centre and Size of Grid Box

Grid box	Centre	Dimension
X	-12.778	22
Y	-0.611	18
Z	19.944	20

2.5. Molecular Docking

Molecular docking simulations were performed using AutoDock Vina on Ubuntu. All receptor and ligand PDBQT files were placed into a single directory. The directory was opened in the terminal. Docking simulations were executed using the command: bash binbash.sh. Each ligand generated an output log containing its predicted binding affinity values.

2.6. Post-Docking Analysis

Upon completion of the docking runs:

- Binding affinity values for each ligand were extracted and compiled in Microsoft Excel
- Mean docking scores and standard deviations were calculated across four replicates (A1–A4)
- Ligands were ranked, and the top 2 compounds exhibiting the strongest affinities were designated as the front-runner drugs.

These compounds were visualized in PyMOL to examine their binding orientation within the active site. Each ligand was assigned a unique colour for clarity.

Protein–ligand interactions were assessed based on:

- Hydrogen bond formation
- Hydrophobic contacts
- Active-site amino acid residues involved
- Relevant binding-site interactions were captured and saved as PNG images for documentation and reporting.

3. Result

Table 2 Biological activities of the reference compound, piragliatin

Biological activities	Values
G-couple protein receptor ligand	0.20
Ion channel modulator	-0.17
Kinase inhibitor	-0.16
Protease inhibitor	0.36
Enzyme inhibitor	0.28
Nuclear receptor ligand (NRL)	0.06

Table 3 Binding energies (kcal/mol), mean values, and standard deviations for the top-ranking drugs compared with the reference ligand piragliatin

Drugs	**A1**	**A2**	**A3**	**A4**	**Mean**	**S.D**
Darifenacin hydrobromide	-10.2	-10.1	-10.2	-10.2	-10.17	0.05
Citalopram hydrobromide	-10.0	-10.0	-10.0	-10.0	-10.00	0.00
PIRAGLIATIN	-9.2	-10.7	-10.0	-10.0	-9.97	0.61

Figure 1 Human glucokinase receptor in complex with the piragliatin showing the amino acids.

Figure 2 Validation of docking protocol with the reference compound marked red.

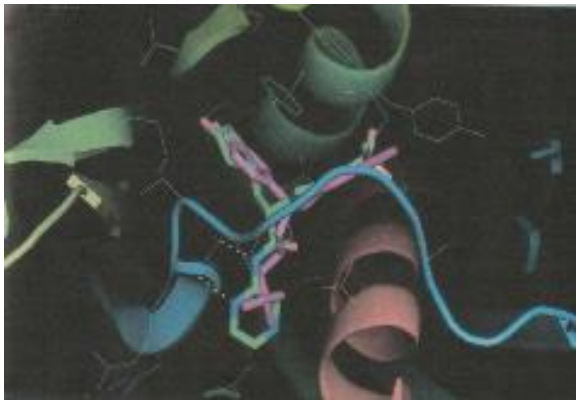


Figure 3 Structural alignment of citalopram hydrobromide marked magneta colour.

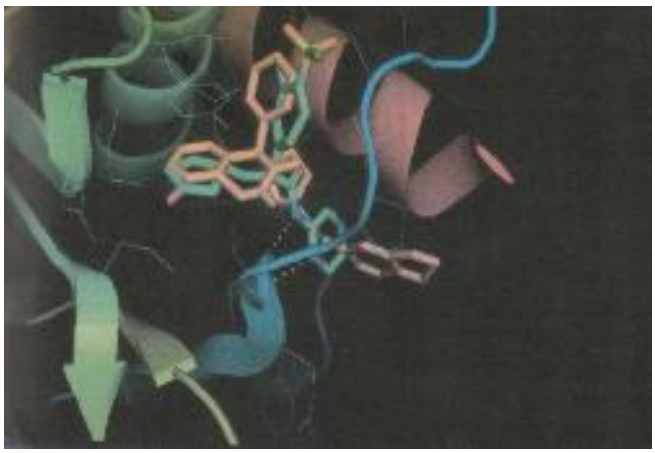


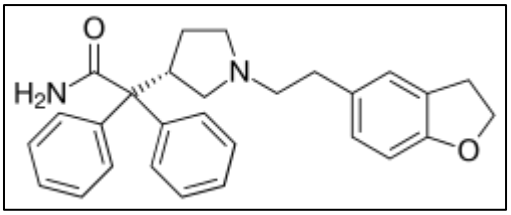
Figure 4 Structural alignment of darifenacin hydrobromide marked orange colour.

4. Discussion

Human glucokinase receptor was selected from the list of available targets using KEGG type 2 diabetes mellitus-reference pathway as a target interest for the management of diabetes. The selection of the preferred PDB structure of human glucokinase was done based on the resolution and the presence of a bound activator and the presence of the activator in ZINC database. The structure with the PDB ID of 4NO7 was selected as the preferred structure because of its low resolution of 1.70Å and the presence of abound potent activator piragliatin. The study was conducted with the total of 1545 clinically approved compounds obtained from drugbank database website. Table 1 shows the 3-D structural position of the reference compound bound to the target which helps in accurate docking results. Table 2 shows the parameters used for the selection of clinically approved drugs which possesss such biological activities. Table 3 shows binding energies in kcal/mol, mean values, and standard deviations for the top-ranking compounds compared with the reference ligand piragliatin.

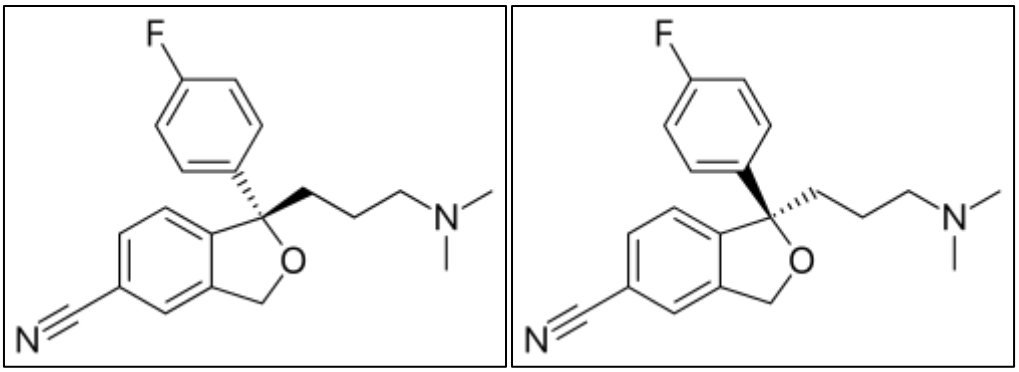
The strength and stability of a protein–ligand complex are governed by the intermolecular interactions formed within the binding pocket, and molecular docking provides a computational means of estimating these interactions through predicted Gibbs free energy (ΔG) values [5,11,24]. More negative binding energies indicate stronger and more thermodynamically favourable interactions, reflecting higher affinity and greater potential for biological efficacy [11]. The binding affinity of a drug molecule explains its degree of interaction with the receptor site. The top drugs as front runners with predicted activities higher than that of the reference compound, piragliatin were darifenacin hydrobromide (-10.17) and citalopram hydrobromide (-10.00).

Darifenacin hydrobromide is a white, crystalline powder with a molar mass of 426.560 $g \cdot mol^{-1}$. Its empirical formula is $C_{28}H_{30}N_2O_2$. It is a medication used to treat urinary incontinence due to an overactive bladder. [8,9]



Darifenacin works by blocking the M_3 muscarinic acetylcholine receptor, which is primarily responsible for bladder muscle contractions. It thereby decreases the urgency to urinate [7]. Its side effects include difficulty breathing, swelling of the face, lips, tongue, constipation, blurred vision, heat prostration due to decreased sweating [7].

Citalopram has an *N, N*- one stereocenter, to which a 4-fluoro phenyl group and dimethyl-3-aminopropyl group bind. As a result of this chirality, the molecule exists in (two) enantiomeric forms (mirror images). They are termed *S*- (+)-citalopram and *R*- (–)-citalopram. It is a fine, white to off-white powder with empirical formula of $C_{20}H_{21}FN_2O$ and molar mass of 324.399 g·mol$^{-1.}$ [16].



(*S*)- (+)-citalopram **(*R*)-(–)-citalopram**

Citalopram is an antidepressant which belongs to the class of selective serotonin reuptake inhibitors (SSRIs). Its mechanism of action is presumed to be linked to potentiation of serotonergic activity in the Central Nervous System (CNS) resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT). It is used to treat depression [20]. Its side effects include drowsiness, dizziness, weakness, anxiety, insomnia, vision changes, nausea, loss of appetite, diarrhea, sneezing, sore throat, increased sweating, decreased sex drive, impotence [1].

However, these drugs do not require screening for their bioavailability and toxicity profile. This is so because they are already in use clinically for the treatment of their respective clinical indications and their pharmacokinetics properties have been analyzed previously and their results within acceptable limits before receiving regulatory approval.

These two clinically approved drugs found to activate the target protein, human glucokinase will serve as valuable candidates for further analysis.

5. Conclusion

This study presents an *in silico* analysis on the identification of potential activators of human glucokinase from clinically approved drugs*. In silico* design helps to improve effectiveness and efficiency of drug discovery and development process, decrease use of animals and increase predictability.

Some of the clinically approved drugs identified as strong activators of human glucokinase, which shall form the basis for further screening for discovering and developing high quality drug candidates for the management of diabetes are: darifenacin hydrobromide and citalopram hydrobromide.

However, the findings from the molecular docking of the selected ligands against a highly promising drug target in humans showed that there is promising prospects towards finding new drug candidates for the management of diabetes.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this work.

Data availability

No new experimental data were generated. All computational data used in this study are available upon reasonable request.

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