

In silico investigation of the anti-diabetic potential of garden egg compounds on alpha-glucosidase

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Abstract:

Diabetes mellitus is a chronic metabolic disorder affecting millions of people worldwide. In 2019, diabetes was the direct cause of 1.5 million deaths according to WHO. Alpha glucosidase is an intestinal enzyme that aids digestion of dietary carbohydrates and starches to produce glucose for intestinal absorption, which in turn leads to the increase in blood glucose levels. Hence, this study was aimed at investigating, through in silico approach, the possible inhibitory potential of *Solanum aethiopicum* natural product, solasodine, on alpha glucosidase through binding in the enzyme's active site. Thus, blocking its hydrolytic potential of cleaving oligosaccharides to absorbable monosaccharides. Following a preliminary screening of 149 ligands from PubChem database, seven (7) ligands were selected and their physicochemical and absorption, distribution, metabolism, elimination and toxicity (ADMET) properties were checked using Swiss institute bioinformatics webserver. Further molecular docking studies carried out revealed that Solasodine and Notoryne were the most potent inhibitors of alpha glucosidase with binding affinities of -10.05 kcal/mol and -7.50 kcal/mol, respectively. The findings of this study are believed to serve as a baseline information for further wet lab investigations by pharmaceutical organizations toward the development of new drugs for combating the endemicity of diabetes in this region of the globe.

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1. Introduction

Diabetes Mellitus (DM) is a metabolic disorder characterized by elevated levels of blood glucose (hyperglycemia) resulting from either inadequate insulin production by the pancreas, insufficient cellular response to insulin or a combination of both factors [1]. It is a worldwide pandemic, ranking as the world's fifth leading cause of death. The International Diabetes Mellitus Federation predicts that 592 million people worldwide will have DM by 2035 [2]. As it stands, of the 537 million cases recorded globally in 2021, 24 million cases are from Africa; and Nigeria accounts for over 3 million cases [3]. Beyond its economic implications, DM adversely affects individuals' quality of life contributing to complications such as cardiovascular diseases, kidney failure and neuropathy [1]. In addition, DM exerts significant social and public health impact such as influencing employment opportunities, social relationships and mental health [3].

Alpha glucosidase is a membrane-bound enzyme situated in the epithelium of small intestine, playing a crucial role in enhancing glucose absorption, which is achieved by catalysing the hydrolytic cleavage of oligosaccharides into absorbable monosaccharides [4]. Consequently, the inhibition of this enzyme results in a deceleration of postprandial blood sugar elevation post-meal [5-8], and the

rate of carbohydrate digestion is reduced, thereby decreasing glucose absorption. Nonetheless, in diabetic patients, such therapies of enzyme inhibition have a short-term effect of lowering current blood glucose levels, with a slight long-term reduction in haemoglobin levels [4].

Solanum aethiopicum, known as "Garden egg" or "Scarlet eggplant," is a consumable vegetable crop categorized within the Solanaceae family. The Solanaceae family is one of the most extensive and vital groups of vegetables, primarily originating in tropical regions. *Solanum aethiopicum* is commonly cultivated in Nigeria for its nutritional and medicinal properties [9]. Several *Solanum* species have been reported to have anti-diabetic properties, making them promising plants for developing efficacious and safer medicines for diabetes and its complications [10-15]. Specific researches conducted on the phytochemical compositions of *Solanum* species have shown their abilities to stimulate insulin secretions [16] and lower high sugar diets [17]. Other functions include possessing insulin-like activities through their hypoglycaemic capabilities [18] and suppressing sucrose transfer to the intestines from the stomach [19].

While most studies have delved into the phytochemicals of this species, the present study was designed to investigate, *in silico*, the possible inhibitory

potential of a *Solanum aethiopicum* natural product, solasodine, on alpha glucosidase through binding in the enzyme's active site. Thus, blocking its hydrolytic potential of cleaving oligosaccharides to absorbable monosaccharides.

2. Materials and Methods

2.1 Protein sequence retrieval

The target protein, alpha glucosidase (5kzw), was retrieved from RSCB PDB database (<http://www.rcsb.org/>) [20].

2.2 Target protein preparation and active site prediction

Target protein was processed for docking by adding polar hydrogens, removing hetero-atoms, and then converting the data to ".pdbqt" file format as described earlier [21]. Furthermore, the active site of the targeted protein was predicted using CASTp calculations (Computed Atlas of Surface Topography of proteins) by going to the CASTp server and uploading the target protein pdb ID, then clicking on submit (<http://sts.bioe.uic.edu/>) [22].

2.3 Preparation of ligands for docking

Following a preliminary screening of 149 ligands from PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>) [23], seven ligands were selected and docked to identify the best ligand with the least binding energy. The 3D structure of the ligands were downloaded from PubChem database in ".sdf" format and converted to ".pdbqt" format.

2.4 ADMET Analysis

ADMET properties of the selected ligands were checked using Swiss institute of bioinformatics webserver (<https://www.sib.swiss/>) [24]. The ligands were screened for drug likeness by their adherence to Lipinski's "rule of five", and with no more than one (1) violation; and their molecular properties [25].

2.5 Molecular docking using AutoDock

Each ligand was docked with alpha glucosidase protein using AutoDock 4.2.6 software (version 1.5.7). Lamarckian genetic algorithm (LGA) was used as a default search function. The energy value of the docked molecule was noted and calculated in kcal/mol from the output files. Similarly, inhibition constant (K_i) was predicted from the docking process. The binding site of the ligand was selected based on the active site component and the substrate-binding site of the alpha glucosidase protein. The grid box size was set as Size X = 72 Å, Size Y = 66 Å and Size Z = 72 Å. The grid box centre was set as Centre X = - 0.558 Å, Centre Y = -41.04 Å and Centre Z = -18.486 Å. AutoGrid program supplied with AutoDock was used to produce grid map. The spacing between grid points was 0.375 Å. Docked conformations were clustered using a tolerance of 2.0 Å RMSD. Discovery software visualizer (Accelrys, Inc, USA) was employed to visualize and analyse the receptor and ligand structures.

3. Results and Discussion

Solasodine shows promising binding interactions to the target enzyme suggesting potential antidiabetic property. To investigate the inhibitory potential of garden egg compounds on alpha glucosidase *in silico*, seven compounds were docked to the enzyme via Autodock to demonstrate their binding potentials as shown in Table 1.

The table shows their docking score, inhibitory constant (K_i) values, ADMET properties, and interacting residues between the compounds and alpha glucosidase enzyme. It has been established from [25] that a more negative binding affinity indicates stronger binding. Similarly, Figure 1 shows the 2-D putative binding mode of the compounds with alpha glucosidase enzyme. Solasodine displayed the least binding energy score (-10.05 Kcal/mol) against alpha-glucosidase with six different amino acid residues.

Table 1: Selected garden egg compounds from PubChem database used for docking

Ligand	Docking Score (Kcal/mol)	Inhibition K_i (uM)	Lipinski rule of five	Log P	GI absorption	Interacting residues	Molecular weight (g/mol)	Common name
442985	-10.05	43.30	1 violation	4.67	High	Asp356, SO41025, Leu868, Val718, His717, Tyr360	413.64	Solasodine
23427873	-7.50	3.19	Yes	3.76	High	Glu196, Leu195, Pro198, Tyr360, Arg608, Asp365, Thr197, Leu355, Gly359, Val357, Val358	347.68	Notoryne
5281417	-7.28	4.63	Yes	0.62	Low	SO41025, Glu866, Met366, Arg608	340.28	Esculin
76330546	-6.99	7.56	Yes	2.57	High	Glu866, SO41025, His584, Phe362, Pro595, Leu865, Arg594, Val867, Met363, His717, Leu868	224.34	15-Norlubiminol

Ligand	Docking Score (Kcal/mol)	Inhibition Ki (uM)	Lipinski rule of five	Log P	GI absorption	Interacting residues	Molecular weight (g/mol)	Common name
442399	-6.78	10.72	Yes	3.61	High	GLU866, Leu865, His717, His584, Arg608, Arg594, Phe362, Pro595	218.33	Solavetivone
10036509	-6.64	13.67	Yes	2.61	High	Pro198, Leu195, Tyr360	222.32	Aethione
6072	-5.88	48.92	1 violation	0.88	Low	Glu196, His717, Tyr360, SO41025, Phe362, Arg608	436.41	Phlorizin

In this study, molecular docking effectively identified Solasodine as a potential alternative anti-diabetic compound through significant binding interactions to the target enzyme.

Decreasing the absorption of dietary energy molecules can be achieved by inhibiting the enzymes that are responsible for metabolism of carbohydrates, which mainly include alpha amylase and alpha glucosidase [26]. Therefore, one of the targets for the treatment of diabetes is

the inhibition of these enzymes activities [27]. Glycosidic linkages of α -D-(1, 4) in carbohydrates are cleaved by alpha amylase to produce oligosaccharides, which are further cleaved to monosaccharide glucose by alpha glucosidase. Therefore, inhibitors of these enzymes can delay the increase in blood glucose level in people who consume carbohydrate-rich food, and keep the postprandial hyperglycemia under control [27].

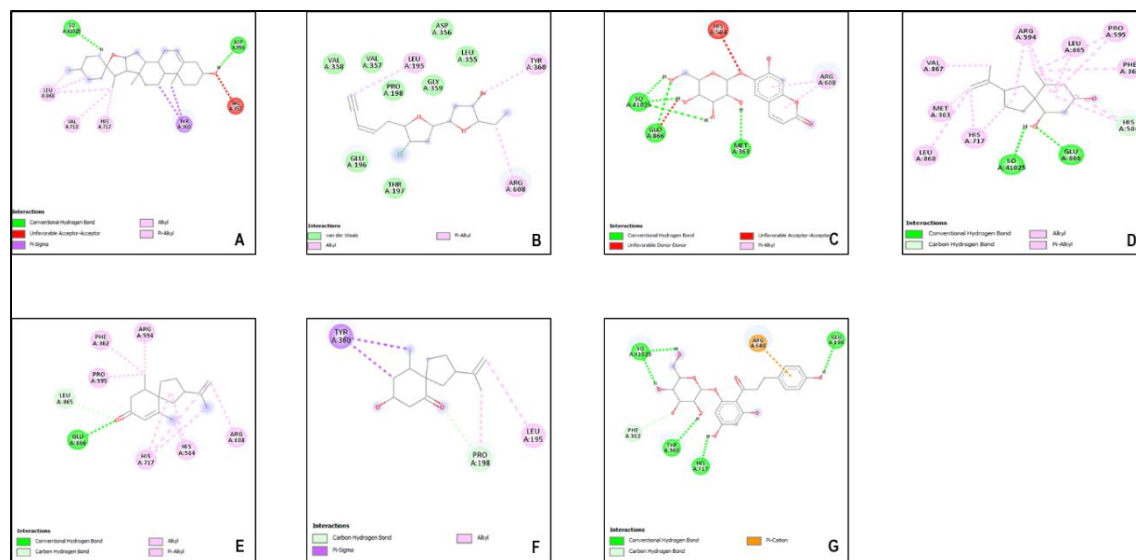


Figure 1: Putative binding mode of the seven garden egg compounds with alpha glucosidase. A: Solasodine; B: Notoryne; C: Esculine; D: 15-Norlubiminol; E: Solavetivone; F: Solavetivone; G: Phlorizin

These inhibitors are essentially other sugar molecules that compete with these enzymes. Alpha glucosidase inhibitors have been shown to effectively lower blood glucose levels by delaying the digestion and absorption of complex carbohydrates, improving blood sugar control in non-insulin-dependent diabetes mellitus patients [4]. Other alpha glucosidase inhibitors studied include commercial drugs such as acarbose, miglitol and voglibose [28]; and plant natural products such as Taxumariene F, Akebonoic acid, Morusin, Rhaponticin, Procyanidin A2, Alaternin, Mulberrofuran K and Psoralidin [5,29-30]. However, the use of these commercial drugs has imparted negative side effects such as abdominal distention and pain [31]. Notably, previous docking study with acarbose showed that it had a binding energy of -9.08Kcal/mol on lysozyme [32]. Therefore, the docking result obtained with Solasodine in this study with the binding energy of -10.05 kcal/mol suggests a possible better prospective anti diabetic drug on the alpha glucosidase enzyme. As determined through post docking

analysis, the molecular structure of *Solanum aethiopicum* natural compounds actively support hydrophobic interaction and form strong hydrogen bonds with adjacent amino acids. Consequently, this enhances the stability of the complex between the ligands and the enzyme, thereby increasing the effectiveness of enzyme inhibition.

Previous investigations have revealed the pharmacological activities associated with garden eggs, particularly their potential anti-ulcer [33], anti-oxidant [34], and anti-inflammatory properties [35-36]. Nonetheless, it is worth noting that this plant is often considered underutilized, possibly due to the limited knowledge and scientific information available about it [9]. Garden egg's composition is notable for its high crude fiber content, low fat content, and low dry matter, characteristics that may offer protection against various ailments such as constipation, colorectal carcinoma, diverticulitis, and atherosclerosis [37]. These attributes may also contribute to the observed weight reduction effects associated with the consumption of the

plant [37-38]. Additionally, garden egg boasts a noteworthy potassium content, an essential electrolyte that plays a vital role in maintaining cardiac function and regulating blood pressure. Others include iron, zinc, magnesium, sodium copper, manganese and calcium [39-40]. Furthermore, garden eggfruits contain polyphenols that inhibit key enzymes linked to type-2 diabetes and hypertension, potentially helping manage or prevent these degenerative conditions [39]. Other phytochemicals from *Solanum* spp studied to reduce postprandial glucose levels include phenols and polyphenolics [38-39], and sesquiterpenoids [41].

More so, general phytochemicals identified in *Solanum* spp include flavonoids, terpenoids, steroids, anthraquinones, tannins and phenols [40, 42]. Other phytochemicals with varying occurrence in *Solanum* spp include saponins and alkaloids [40].

4. Conclusion

In this study, the interaction between Solasodine and alpha glucosidase has offered valuable insight into molecular foundation that supports the established evidence regarding the antidiabetic attributes of the constituents of garden egg. Hence, the ability of this study to elucidate the relationship between binding affinities of the various biomolecules with respect to inhibition of alpha glucosidase could perhaps, serve as a baseline information in developing new antidiabetic drug.

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