RESEARCH ARTICLE

Docking Techniques for Unravelling the Molecular Mechanisms of Specioside of *Kigelia africana* Fruits

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ABSTRACT

In this study, the inhibitors of α-amylase and aldose reductase, the key of proteins in diabetes mellitus, were isolated as compound speciosides from the *Kigelia africana* fruit Benth. Speciosides were selected as ligands for the receptors of α-amylase and aldose reductase in the molecular docking studies used by PyRx (0.8) for the inhibition of α-amylase and aldose reductase. The results showed that the α-amylase binding energy was 8.1 kcal/mol and aldose reductase was -9 kcal/mol. The ADME process showed that it was easily absorbed orally and distributed through the CNS, metabolized by CYP2D6, and excreted through renal Toxicity studies of speciosides showed no hepatotoxicity or skin sensitization. The *in-silico* studies of specioside compounds led to the development of potent α-amylase and aldose reductase inhibitors used to treat diabetic mellitus**.**

Keywords: Specioside, α-amylase, Aldose reductase inhibitors, ADME.

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INTRODUCTION

The fact that diabetes is a major killer on a global scale is well known.[1] Diets heavy in both fat and sugar inhibit insulin's ability to enhance glucose production *in-vivo* by increasing glucose-6-phosphatase (G-6-Pase) activity in whole-cell homogenates.[2] The initiation, progression, and consequences of diabetes are strongly influenced by elevated ROS and autophagy. Due to the auto-oxidation of glucose in this diet-induced metabolic milieu, free radicals are produced, which leads to oxidative stress. Despite these factors, prolonged consumption of HFD leads to changes in the expression of several genes and/or receptors involved in protein synthesis, metabolic processes, oxidative, stress, inflammation, substrate transport, and modification, and transcriptional control.[3] Knowing the tissue-specific effects of diet composition will make it simpler to choose the best HFD-induced animal model(s) to investigate the etiology of T2DM and related phenotypic abnormalities.[4,5] Currently, there is a huge demand for the utilization of medicinal plants and their constituents to treat diabetes. Studies have shown that specioside glycosides offer therapeutic effects, including their anti-inflammatory, anti-hypertensive, and hypoglycemic activities. According to reports, specioside may increase insulin production, which controls glucose metabolism and lowers blood pressure while acting as an anti-hyperglycemic agent. To determine how specioside affects the proteins in diabetics, this study used molecular docking analysis.

MATERIALS AND METHODS

Docking analysis using a review of the literature, substances were chosen based on their pharmacological characteristics. The proteins α-amylase and aldose reductase, whose structures were acquired from the PDB data library, were docked against the chosen compounds.

Preparation of Protein

The atomic coordinates of the enzymes aldose reducase (PDB ID: 4gca) and α-amylase (PDB ID: 2qv4) were retrieved from RCSB PDB (protein data bank) database before analysis or docking. The protein was docked using Autodock Tool 4 (ADT), and charges were assigned, volumes of the solution and fragments were measured, and fragment volumes were assigned. The Autodock Tool for Molecular Docking (ATMD) was then used to optimize the protein molecule.[6,7] Ligand synthesis After retrieving the 2D structure of specioside from the PubChem database, we used the online grin converter to convert it to the PDB file format. The ligand was converted to PDBQT format and standardized using the PyRx Virtual Screening Tool (python prescription 0.8).[8,9]

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Table 1: Ligands in the dataset's predicted molecular properties and the recommended range of values

Compound	*Molecular weight*	*logP (Octanol/Water)*	*Number of Rotatable bonds*	*Number of H bond Acceptors*	*Number of H bond Donors*
Specioside	508.476	1.6204	7	12	6

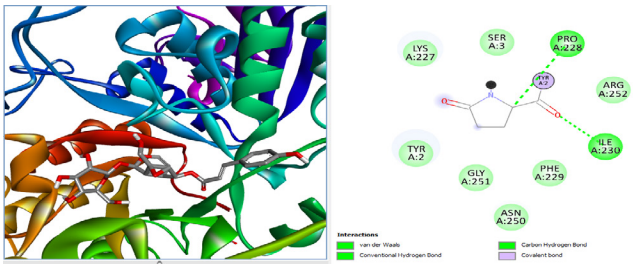

Figure 1: Molecular interaction of specioside with (1) α amylase

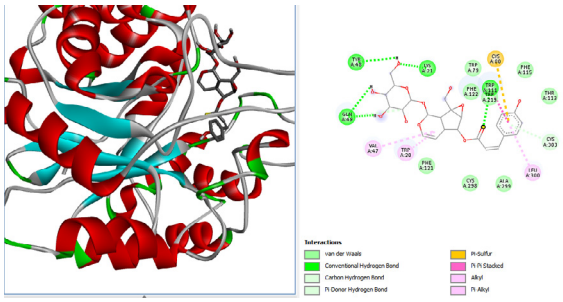

Figure 2: Molecular interaction of specioside with aldose reductase

Molecular Docking

The PyRx Interface employed AutoDock (V. 4.0) to verify the binding properties of the interactions between specioside, α-amylase, and aldose reductase. When they docked, it was thought that the ligand was bendable and the protein was rigid. The implementation was used to guess or figure out which amino acids will interact with ligands in the active protein region. The Pyrex Auto Grid engine was used to make the grid setup file. It was thought that root-mean-quarter deviation (RMSD) numbers less than 1.0 were best. They have been called together to decide on a good bond. The most powerful binding energy was found in a molecule with a high binding affinity.[10]

RESULTS

Specioside and α-Amylase Interact During Molecular Docking

One specific high-affinity of protein molecule is called spicioside. Figure 1 docking analysis results make it abundantly evident that specioside had demonstrated binding to the amylase protein through the interaction of hydrogen bonding. Specioside is shown to bind the α-amylase protein with an energy of -8.1 kcal/mol. When specioside docked with amylase, two hydrogen bonds were created at PRO 228 and ILE 230.

Molecular Docking Interaction of Specioside with Aldose Reductase

According to the findings of docking studies, the binding affinity of specioside with the aldose reductase complex is -9 Kcal/mol. The least binding affinity shows that specioside and aldose reductase form a stable combination. Various amino acids are bound through the proteins LYS-21, GLN-49, TRP-111, ACA 299, CYS 298 and PHE 121, this also forms seven hydrogen interactions Figure 2.

Table 2: Predicted pharmacokinetic (ADME) profiles of compound

Absorption	42.894
Distribution	-4.363
Metabolism	Cyp2D6
Excretion	clearance- 0.85
Toxicity	Mild toxiticy

Predicted Molecular Properties and ADME Profile

We evaluated some of the absorption, distribution, metabolism, elimination, and toxicity (ADMET) predictions to see whether the compounds had any drug-like qualities, as indicated by Table 2, based on the positive biological data previously mentioned. In the pharmaceutical sector, unfavourable ADMET characteristics significantly contribute to drug candidate failure. Using computer modelling tools to comprehend structure–property interactions and forecast possible drug candidates' *in-vivo* behaviour in the human body is known as *in-silico* ADMET prediction.

DISSCUSION

The interactions between specioside, α-amylase, and aldose reductase were examined using AutodockVinaPyRx docking techniques to establish likely binding affinities.[11,12] Based on the strength of their binding, which comprises interactions between proteins and ligands such as hydrogen bonds and other types of bonding, 2 docking complexes' interactions have been contrasted.[13] A summary of docking energy required to construct a ligand-receptor complex in which the ligand was buried in the receptor cavity was shown by the interaction between Specioside and the proteins α-amylase and aldose reductase.[14,15] The minimal docking energies of specioside with α-amylase and aldose reductase proteins are -8.1 kcal/mol and -9 kcal/mol, respectively. The complex was able to achieve the approved state for H-bond interactions. In the pharmacokinetic studies (Tables 1 and 2) of specioside, the absorption was 42.894% through oral, distribution occurred in -4.363% of the CNS, metabolism from Cyp2D6 was excreted through kidney clearance, and there was no hepatotoxicity or skin sensitization.

CONCLUSION

The natural compound specioside was successfully screened for their *in-silico* pharmacokinetic properties. It reveals that specioside possesses optimum pharmacokinetic characteristics naturally and even the same can be improved further by the

latest formulation techniques. Molecular docking studies of specioside proved the significant interaction between enzymes which are crucial in carbohydrate metabolism. It indicates specioside can be used along with other anti-diabetic medications to manage the complications of diabetes mellitus such as diabetic neuropathy. Our research findings open up the door to researchers who are interested in exploring the pharmacological activities of compounds that occur in nature. Furthermore, research studies are required before considering specioside as a viable treatment for complications relevant to diabetes mellitus.

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