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RESEARCH ARTICLE

Molecular docking studies reveal the phytocompound of *Acacia pennata* responsible for the potential inhibition of α-glucosidase

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The aqueous extract of the shoot tips of *Acacia pennata* showed a high enzyme inhibitory activity against α-glucosidase. However, the enzyme inhibiting phytocompound is not known. Identification of the antidiabetic phytocompound will be beneficial in designing drugs with higher efficacy to treat diabetes mellitus. We attempted to identify the compound using molecular docking simulation studies (MDSS). Among the 29 phytocompounds present in *A. pennata*, MDSS revealed that 23 phytocompounds outperformed the co-crystal inhibitor (CCI) of α -glucosidase (PDB ID: 5NN5) in terms of binding affinity. Among the 23 phytocompounds, (2R)-4',7-dihydroxyflavan-(4aà8)-(2R,3S)-3,5,7-trihdyroxyflavan-3"-O-α-L-rhamnopyranoside (compound 25) has the highest binding affinity (-9.2 kcal/mol). Analysis of the protein-ligand interactions revealed that compound 25 formed 5 conventional hydrogen bonds (ASP 282, TRP 481, ARG 600, ASP 616, HIS 674), 3 hydrophobic interactions (TRP 376, TRP 481, LEU 650), 3 electrostatic interactions (MET 519, ASP 616 (n=2)), and 1 carbon-hydrogen bond (ASP 518). The binding pose analysis further revealed that the docking protocol applied in the study was able to re-dock the CCI and dock compound 25 exactly at the active binding site where the CCI was originally positioned. Our in-silico study showed that compound 25 is the phytocompound of *A. pennata* that is responsible for potentially inhibiting the α-glucosidase enzyme. The structure of compound 25 may be modified to design more potent inhibitors of α-glucosidase.

Keywords : *Acacia pennata*, Alpha-glucosidase, In-silico, Molecular docking, Phytocompounds

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Introduction

Diabetes mellitus (DM) is a lifestyle disease wherein there is an abnormally high concentration of sugar in the blood.[1] The International Diabetes Federation estimated that by 2045 a total of 783 million people will have DM.2 In type 1 diabetes, there is a problem associated with the production of insulin from the beta-cells of the pancreas. In type 2 diabetes, there is insulin resistance which results in an abnormally low rate of sugar absorption from the bloodstream into the cells. Type 1 diabetes is treated with the administration of exogenous insulin while type 2 diabetes is treated with hypoglycaemic drugs to lower the blood sugar level.[2] Despite the availability of many drugs, the pharmaceutical management of DM is complicated.[3] This mandates the necessity for the development of new drugs.

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Traditional herbal medicines are an interesting alternative that is being investigated for the treatment of DM.[4]

The aqueous extract of the shoot tips of *Acacia pennata* (L.) Willd. was reported to show in-vitro antidiabetic activity against α-amylase and α-glucosidase.[5] However, the specific phytocompounds that are responsible for inhibiting the enzymes are not yet investigated. Among a plethora of phytoconstituents present in a plant extract, molecular docking simulation studies (MDSS) have made it possible to identify the phytocompound responsible for the inhibition of an enzyme.[6,7] MDSS is an in-silico technique that is used to study the binding affinity, binding pose, and ligand interactions of a compound towards the active binding pocket of a target protein.[8,9] The conventional route of a drug screening process starts with in-vitro tests.[10] However, the advancement in in-silico techniques has made it faster and easy to evaluate the efficacy of phytocompounds against target proteins.[6,11] In this study, we used MDSS to identify a phytocompound of *A. pennata* that is responsible for inhibiting the α -glucosidase enzyme.

Materials and Methods

Retrieval and preparation of protein

The crystal structure of α-glucosidase bearing a protein data bank (PDB) ID 5NN5 was downloaded from the RCSB-PDB website (https://www.rcsb.org/structure/5nn5) in the PDB file format.[12] The structure of the protein was captured with the X-ray diffraction method and it had a resolution of 2.00 Å with an observed R-value of 0.185. The define and edit binding site feature of the Discovery Studio Visualizer (DSV) software v20.1.0.19295 was used to identify the active binding site coordinates of the protein (X = -13.650636, Y = -31.493091, Z = 96.643455). The water molecules and other heteroatoms adhering to the protein were removed with the DSV software. Finally, polar hydrogens were added to the protein with the DSV software. The protein was further processed by adding the Kollman charges with the AutoDockTools v.1.5.6. The PyRx 0.8 virtual screening tool was used to convert α-glucosidase from the PDB file format to the PDBQT file format.

Preparation of ligands

According to the protocols described in our previous studies, a total of 29 phytocompounds of *A. pennata* were prepared and saved in the structure data file (SDF) format with the MarvinSketch v.20.10 software.[6,13] The co-crystal inhibitor (CCI) of α-glucosidase (PDB ID: 5NN5) 'acarbose' was downloaded from the PubChem database in the 2-dimensional SDF format (https://pubchem.ncbi.nlm.nih.gov/compound/1-Deoxynojirimycin). A Gasteiger charge was added to each ligand with the AutoDockTools v.1.5.6. Following this, the PyRx 0.8 virtual screening tool was used to minimize the energy of the ligands to attain stability. The parameters used to minimize the ligands' energy was kept default as suggested by the software. Following the energy minimization process, the ligands were converted to the PDBQT file format with the PyRx 0.8 virtual screening tool.

Molecular docking simulation studies

The prepared protein and the ligands were loaded on the PyRx 0.8 virtual screening tool. According to the protocols described in our previous studies, the AutoDock Vina embedded in the PyRx tool was used to execute the MDSS.[14] The molecular interactions of the phytocompounds that showed a better binding affinity than the CCI were further analyzed with the DSV software. The 2D ligand interactions and the 3D binding poses were also generated with the DSV software.

Validation of the docking protocol

According to the protocols described in our previous studies, the docking protocol was validated with the re-docking process of the native ligand at the original binding pocket.[13] The same docking parameters that were used for docking the phytocompounds of *A. pennata* were used to re-dock the native ligand. A comparative analysis was carried out between the originally docked native ligand and the re-docked native ligand.

Results

Molecular docking simulation studies

The binding affinities of all the phytocompounds of *A. pennata* at the active binding pocket of α-glucosidase are given in Table 1. The CCI (positive control) has a binding affinity of -5.7 kcal/mol. Among the 29 phytocompounds, a total of 23 phytocompounds (Compound code: 1, 2, 3, 4, 5, 6, 8, 9, 10, 14, 15, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 28 and 29) showed a better binding affinity than the CCI. Among the 23 phytocompounds, the compound (2R)-4',7-dihydroxyflavan-(4aà8)-(2R,3S)-3,5,7-trihdyroxyflavan-3"-O-α-L-rhamnopyranoside bearing a compound code 25 has the best binding affinity (-9.2 kcal/mol) towards the active binding site of α-glucosidase.

Visualization and analysis of molecular interactions

The 2D and 3D ligand interactions between compound 25 and the active binding site of α-glucosidase are given in Figure 1(a) and Figure 1(c) respectively. The 2D and 3D ligand interactions between CCI and the active binding site of α-glucosidase are given in Figure 1(b) and Figure 1(d) respectively. The 3D binding pose of compound 25

Table 1: Binding affinities of phytocompounds of *A. pennata* towards the active binding site of α-glucosidase

Compound code	Compound Name	Binding affinity (-kcal/mol)
1	Quercetin 4′-O-α-L-rhamnopyranosyl-3-O-β-D-allopyranoside	-7.8
2	Apigenin 6-C-[2″-O-(E)-feruloyl-β-D-glucopyranosyl]-8-C-β-glucopyranoside	-8.4
3	Isorhamnetin 3-O-α-L-rhamnopyranoside	-7.9
4	Kaempferol 3-O-α-L-rhamnopyranosyl-(1à4)-β-D-glucopyranoside	-8.6
5	Isovitexin	-7.3
6	Taepeenin D	-6.8
7	(+)-drim-8-ene	-5.5
8	8,15- labdanediol	-7.2
9	Labdanolic acid	-6.8
10	Quercetin 3-O-β-D-glucopyranosyl-4-O-β- D-glucopyranoside	-7.1
11	Tetracosane	-5.0
12	1-(heptyloxy)-octadecane	-4.9
13	Methyl tridecanoate	-5.2
14	Arborinone	-8.2
15	Confertamide A	-5.8
16	4-hydroxy-1-methyl-pyrrolidin-2-carboxylic acid	-5.3
17	Quercetin-3-O-β-D-glucopyranoside	-7.9
18	Quercetin-3-O-α-L-rhamnopyranoside	-7.9
19	Chrysin-7-O-β-D-glucopyranoside	-8.7
20	Kaempferol 3-O-α-L-rhamnopyranoside	-7.9
21	Pinocembrin-7-O-β-D-glucopyranoside	-8.6
22	Koaburanin	-8.2
23	5,7-dihydroxyflavone 7-O-β-D-glucopyranosyl-8-C-β-boivinopyranoside	-7.8
24	5,7-dihydroxyflavone 6-C-β-boivinopyranosyl-7-O-β-D-glucopyranoside	-8.2
25	(2R)-4′,7-dihydroxyflavan-(4aà8)-(2R,3S)-3,5,7-trihdyroxyflavan-3″-O-α-L-rhamnopyranoside	-9.2
26	(2S)-5,7-dihydroxyflavan-7-O-β-D-glucopyranoside-(4aà8)-epiafzelechin-3-O-gallate	-8.4
27	(2R,3S)-3,5,7-trihdyroxyflavan-3-O-α-L-rhamnopyranoside	-2.0
28	21β-O-[(2E)-6-hydroxyl-2,6-dimethyl-2,7-octadienoyl] pithedu-loside G	-6.2
29	Pitheduloside G	-7.9
30	Standard (positive control)	-5.7

and the CCI at the active binding site of α-glucosidase is given in Figure 1(e) and 1(f) respectively. The superimposition of compound 25 and the CCI is given in Figure 1(f).

Compound 25 formed a total of 5 conventional hydrogen bonds with ASP 282 (bond length = 2.61 Å), TRP 481 (bond length = 2.88 Å), ARG 600 (bond length = 1.90 Å), ASP 616 (bond length = 2.38 Å) and HIS 674 (bond length = 2.00 Å); 3 hydrophobic interactions with TRP 376 (bond length = 4.48 Å), TRP 481 (bond length = 5.52 Å), and LEU 650 (bond length = 3.60 Å); 3 electrostatic interactions with MET 519 (bond length = 5.23 Å), ASP 616 (bond length = 3.73 Å, bond length = 4.43 Å); and 1 carbon-hydrogen bond with ASP 518 (bond length = 3.22 Å). On the other hand, the CCI formed only 3 conventional hydrogen bonds with ASP 404 (bond length = 2.41 Å), ASP 518 (bond length = 2.80 Å), and ASP 616 (bond length = 1.76 Å); and 1 carbon-hydrogen bond with HIS 674 (bond length = 3.48 Å). Between compound 25 and CCI, the common interacting active site residues are ASP 518, ASP 616, and HIS 674.

Validation of docking protocol

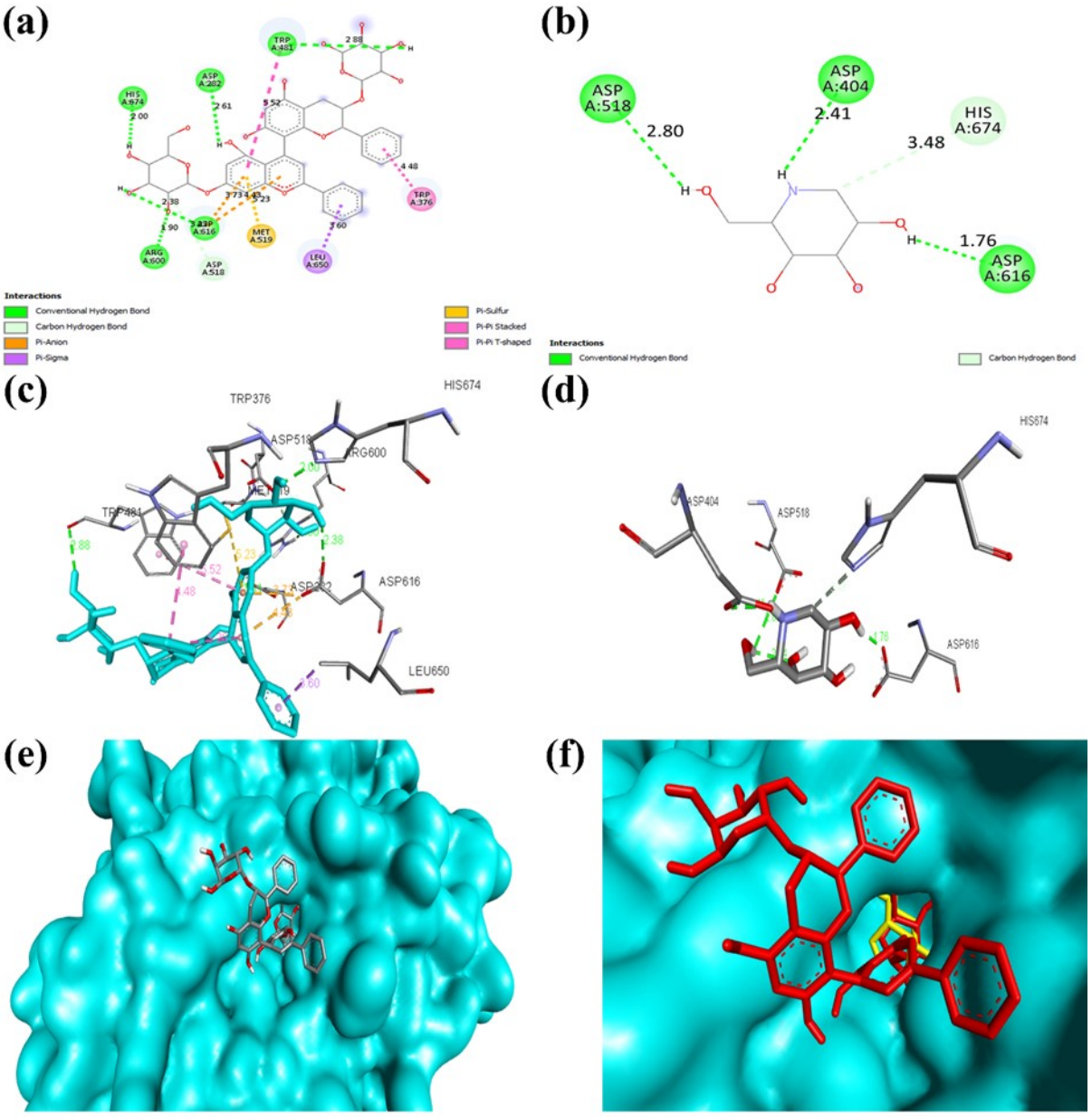

Figure 1: (a) 2D ligand interactions of compound 25 with the active site residues of α-glucosidase. (b) 2D ligand interactions of CCI with the active site residues of α-glucosidase. (c) 3D ligand interactions of compound 25 with the active site residues of α-glucosidase. (d) 3D ligand interactions of CCI with the active site residues of α-glucosidase. (e) Binding pose of compound 25 at the active binding pocket of α-glucosidase. (f) Superimposition of compound 25 and CCI at the active binding pocket of α-glucosidase.

The superimposition technique was used to validate the docking protocol used in the study. The superimposed image of the original binding pose of the CCI and the re-docked CCI at the active binding pocket is given in Figure 2. The original binding pose of the CCI was coded as yellow color while the re-docked ligand was coded as blue color. The CCI was re-docked at the active binding pocket of α-glucosidase with the docking protocol that was used in the study.

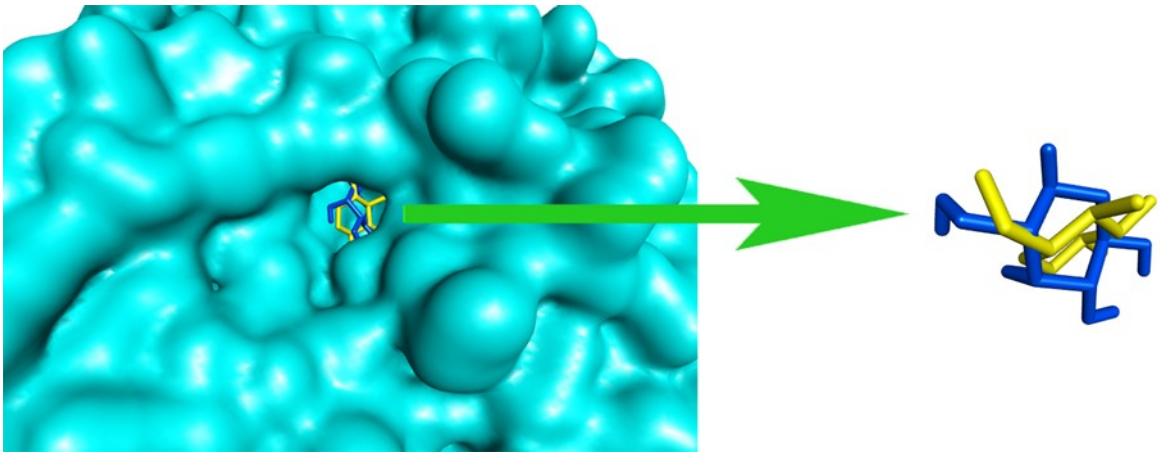

Figure 2: Validation of the docking protocol through the re-docking of the CCI and superimposing their 3D binding poses at the active binding pocket

Discussion

In people with diabetes, their body has trouble controlling their blood sugar levels. This can lead to high blood sugar levels after meals, which can be problematic, especially for people with type 2 diabetes as they may produce insulin but struggle to use it effectively.[15] α-glucosidase is an enzyme that plays a key role in the digestion of carbohydrates in the small intestine. Researchers have targeted α-glucosidase in the development of drugs to treat diabetes. When α-glucosidase is inhibited, the digestion of carbohydrates in the small intestine is slowed down. These leads to a slower and more gradual increase in blood sugar levels after meals, which can help improve blood sugar control in people with diabetes.[16]

Binding affinity is a numerical score that is used as a metric to rank the affinity of compounds towards certain binding sites in a protein.[17] Based on the binding affinity, a total of 23 phytocompounds outperformed the CCI. However, since compound 25 has the best binding affinity, it was selected for further studies.

In the next study, the molecular interactions between compound 25 and α-glucosidase were studied. Compound 25 formed 5 conventional hydrogen bonds, 3 hydrophobic interactions, 3 electrostatic interactions, and 1 carbon-hydrogen bond. Among all types of protein-ligand interactions, the conventional hydrogen bond is the most important interaction as it is directly associated with the catalytic activity of the protein.[18] In all cases of protein-ligand interactions, it is desirable to have a higher number of conventional hydrogen bonds. As the number of conventional hydrogen bonds increases, the chances of drug resistance also decrease. Compound 25 was able to form 5 conventional hydrogen bonds while the CCI was able to form only 3 conventional hydrogen bonds. The hydrophobic interactions and electrostatic

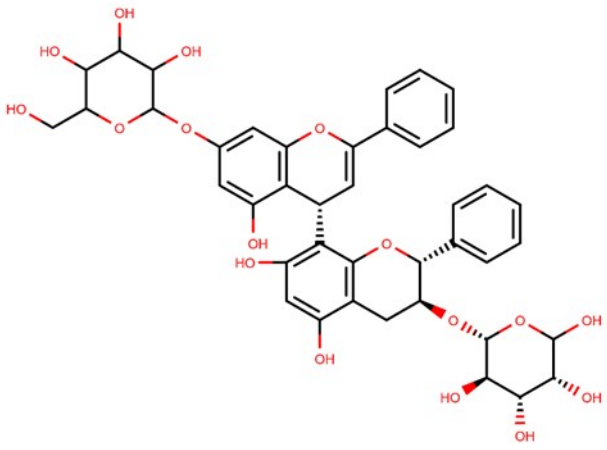

Figure 3: Chemical structure of (2R)-4′,7-dihydroxyflavan-(4aà8)-(2R,3S)-3,5,7-trihdyroxyflavan-3″-O-α-L-rhamnopyranoside

interactions contribute to the stability of the protein-ligand complex.[19] Compound 25 was able to form 3 hydrophobic interactions and 3 electrostatic interactions while the CCI was not able to form any interactions of such type. Therefore, compound 25 outperforms the CCI of α-glucosidase in terms of molecular interactions as well.

Validation of the docking protocol is an integral part of MDSS. It is important to make sure that the docking protocols that are applied for docking can dock the test phytocompounds at the exact location where the CCI was present.[13] In the study, the docking protocol was validated with the re-docking and superimposition technique by analyzing the binding poses. Analysis of the binding pose reveals that the re-docked CCI was docked exactly at the active binding pocket where the CCI was originally present. The binding pose of compound 25 also revealed that the compound was also docked at the active binding pocket where the CCI was originally positioned. The protein-ligand interaction of compound 25 revealed that the re-docked CCI and compound 25 shared 3 similar interacting active site residues. This showed the validity and accuracy of the docking protocol used in the study.

Conclusions

Based on the binding affinity, molecular interactions, and binding poses, we conclude that C25 ((2R)-4′,7-dihydroxyflavan-(4aà8)-(2R,3S)-3,5,7 -trihdyroxyflavan-3″-O-α-L-rhamnopyranoside) is the leading potential inhibitor of α-glucosidase from the 23 tested phytocompounds of *A. pennata*. The structure of compound 25 may be modified to design more potent inhibitors of α-glucosidase.

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