In Silico Identification of Antidiabetic Compounds in Ficus deltoidea Research Study

Posted on March 20, 2025

Abstract:

Ficus deltoidea Jack leaf decoction is a traditional remedy used to relieve symptoms of diabetes, hyperlipidaemia and hypertension. This plant has been observed to inhibit α-glycosidase activity in the intestine, block hepatic glucose production, improve insulin sensitivity, suppress hepatic glucose and improve glucose absorption in patients with type 2 diabetes mellitus. The α-glycosidase enzyme has been identified as a potential target receptor for diabetes treatment. It would seem that the chemical compounds found in the leaves of Ficus deltoidea Jack include vitexin, rhoifolin, lupeol, betulin, corymboside and (1ξ)-1,5-anhydro-1-[2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-chromen-8-yl]-D-galactitol. This study aims to analyse the potential activity of chemical compounds from Ficus deltoidea Jack as antidiabetic, specifically with regard to proteins or ligands, through in silico studies (virtual screening) with molecular docking. The research was conducted through molecular docking between chemical compounds in Ficus deltoidea Jack and the α-glucosidase enzyme (PBD ID: 5NN8). In silico method used with Autodock Tools 1.5.6. The observed parameters were the binding energy values of both native and test ligands. The results indicated that vitexin, rhoifolin, lupeol, betulin, corymboside and (1ξ)-1,5-Anhydro-1-[2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-8-yl]-D-galactitol exhibited binding affinities of -6.27, -8.28, -8.08, -7.46, -7.28 and -7.21, respectively. With regard to acarbose, the binding affinity was -5.54. The results indicated that the six chemical compounds from Ficus deltoidea Jack exhibited a lower binding affinity than acarbose. It may be suggested that Ficus deltoidea Jack has potential as an alpha-glucosidase inhibitor against type 2 diabetes.

Introduction:

Diabetes mellitus is a disorder characterised by persistent hyperglycaemia, resulting from partial or complete pancreatic damage that causes an imbalance in carbohydrate, lipid and protein homeostasis. The hyperglycaemic state is the effect of impaired insulin secretion, insulin resistance, or both. In 2021, an estimated 537 million people had diabetes, and this number is projected to reach 643 million by 2030, and 783 million by 2045. In 2021, more than 1.2 million children and adolescents had type 1 diabetes. According to the International Diabetes Federation (IDF) report, the number of people with type 1 diabetes in Indonesia reached 41.8 thousand people in 2022. This figure makes

Indonesia the country with the most type 1 diabetes patients in ASEAN, as well as 34th out of 204 countries on a global scale[1].

Traditional medicines have been used for a long time and play an important role as alternative medicines. Some new bioactive drugs isolated from plants show antidiabetic activities that are more effective than oral hypoglycaemics used in clinical therapy[2]. Ethnobotanical data shows 800 medicinal plants are used for diabetes mellitus. It is clinically proven that only 450 medicinal plants have anti-diabetic properties and 109 medicinal plants have a complete mode of action[3]. Tabat barito (Ficus deltoidea Jack) is a plant that is distributed throughout Malaysia, Thailand, and Indonesia, including Sumatra, Java, Kalimantan, Sulawesi and Maluku. Most people in Kalimantan know Ficus deltoidea Jack by the regional name Tabat barito. Corner classifies Ficus deltoidea into thirteen varieties namely Ficus deltoidea var. deltoidea, var. angustifolia, var. Arenaria, var. bilobata, var. bornensis, var. intermedia, var. kinabaluensis, var. kunstleri, var. lutescens, var. motleyana, var. oligoneura, var. peltata and var. trengganuensis [4]. Ficus deltoidea Jack has long been known by the Banjar and Dayak ethnicities, especially in South Kalimantan, as a sari rapet or special herbal medicine for women. In addition, people also use this plant for skin disorders, lumbago, diabetes and hemorrhoids [5]. The traditional use of Ficus deltoidea by boiling is used as an antidiabetic treatment and tonic after childbirth to tighten the uterus and vaginal muscles, to treat menstrual cycle disorders, and also to treat vaginal discharge[6]. A decoction of its leaves is claimed to have antioxidant, and aphrodisiac properties as well as improving blood circulation and treating gout [6].

Ficus deltoidea Jack has potential as an oral antidiabetic, through insulin-mimetic or insulinotropic activity. Ficus deltoidea inhibits α-glycosidase activity in the gut and blocks hepatic glucose production [7,8]. Improved insulin sensitivity, suppressed hepatic glucose and increased glucose uptake in type 2 diabetes mellitus through PTP1B regulation [9]. Vitexin and isovitexin (flavonoids) in Ficus deltoidea leaves inhibit α-glucosidase so that it can be used as an antidiabetic [10].

The advancement of technology with in silico testing, which is the initial stage of testing a new drug candidate before it is tested in the laboratory, has led to a relatively shorter time for new drug discovery. By using molecular tethering methods, new drug candidates can be predicted for their interactions with their targets. Along with the development of technology, the discovery of new drugs is relatively shorter after the in silico test which is the initial stage of testing new drug candidates before testing in the laboratory. New drug candidates can be predicted for their interaction with the target through in silico testing with molecular tethering methods[11]. Therefore, this study aims to find active compounds of Tabat Barito or Ficus deltoidea Jack that are responsible for having anti-DM activity in silico. The results of this study are expected to help find new anti-DM compounds that can produce better therapeutic effects than before and minimize or eliminate side effects that exist in current drugs.

Materials And Methods:

Materials

The hardware used is an ASUS X409 MA laptop with Intel(R) Celeron(R) Processor, N4020 CPU @ 1.10Ghz, 4.00 GB RAM, Windows 11 operating system. The laptop is connected to the network (Wifi). The software used is Windows 11, AutoDockTools-1.5.6, MarvinSketch, Discovery Studio 2021 Client, Avogadro, PyMol, Notepad and the Protein Data Bank (PDB) site, PubChem site, Swisspdbviewer. Grid Point: (x, y, z) 62, 52, 62 and Grid Center: (x, y, z) -13,925; -38,292; and 95,229[12].

Receptor Selection

The target receptor, the α-glucosidase enzyme, was obtained from the Protein Data Bank website www.rcsb.org in the form of a *.pdb file with code 5NN8. The receptor was chosen based on the method used X-Ray Diffraction, derived from the organism Homo sapiens, and is a receptor akarbosa. The next step is to repair the protein and separate the macromolecule from the natural ligand using Biovia Discovery Studio Visualizer.

Test Compound Preparation

A total of 6 chemical compounds from Ficus deltoidea Jack: vitexin, rhoifolin, lupeol, betulin, corymboside and (1ξ)-1,5-Anhydro-1-[2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-8-yl]-D-galactitol were chosen as ligands for this work, and the compound acarbose as a comparison compound, the compounds were downloaded from https://pubchem.ncbi.nlm.nih.gov/.

Docking Validation

Validation of molecular tethering was done by re-tethering the natural ligand into the 5NN8 receptor using AutoDock Tools version 1.5.6. The parameters observed were RMSD values of less than 2Å.

Docking of Test Compounds

Docking of the test compound was performed by tethering the prepared test ligand to a previously validated tethering site using AutoDock Tools. The result parameters are ΔG (Free bond energy) and Ki (Inhibition Constant) values. The results of the test ligand molecular tethering were visualized and molecular tethering analysis was performed using Discovery Studio Visualizer and Notepad software.

Simulation Result Analysis

The data that will be obtained during re-docking are the RMSD value, bond energy, number of hydrogen bonds and the type of amino acid residues formed. The lower the RMSD value and bond energy, the more similar the resulting position will be to the initial position with standard values. Then the data obtained during docking is the number of hydrogen bonds produced and the bond energy value. The smaller the bond energy and the more number of hydrogen bonds that will be generated, the ligand is thought to be an anti-DM candidate. The data results are then visualized using Biovia Discovery Studio 2021.

Result:

Before performing the docking simulation, the determination of the ligand's active site was carried out using the AutoDock Tools software on the grid box that has been inputted α-glucosidase and ligand. Grid box settings obtained in this study are as follows: Grid Point: (x, y, z) 62, 52, 62 and Grid Center: (x, y, z) -13,925; -38,292; and 95,229. The following is the visualization of natural protein-ligand interaction after re-docking.

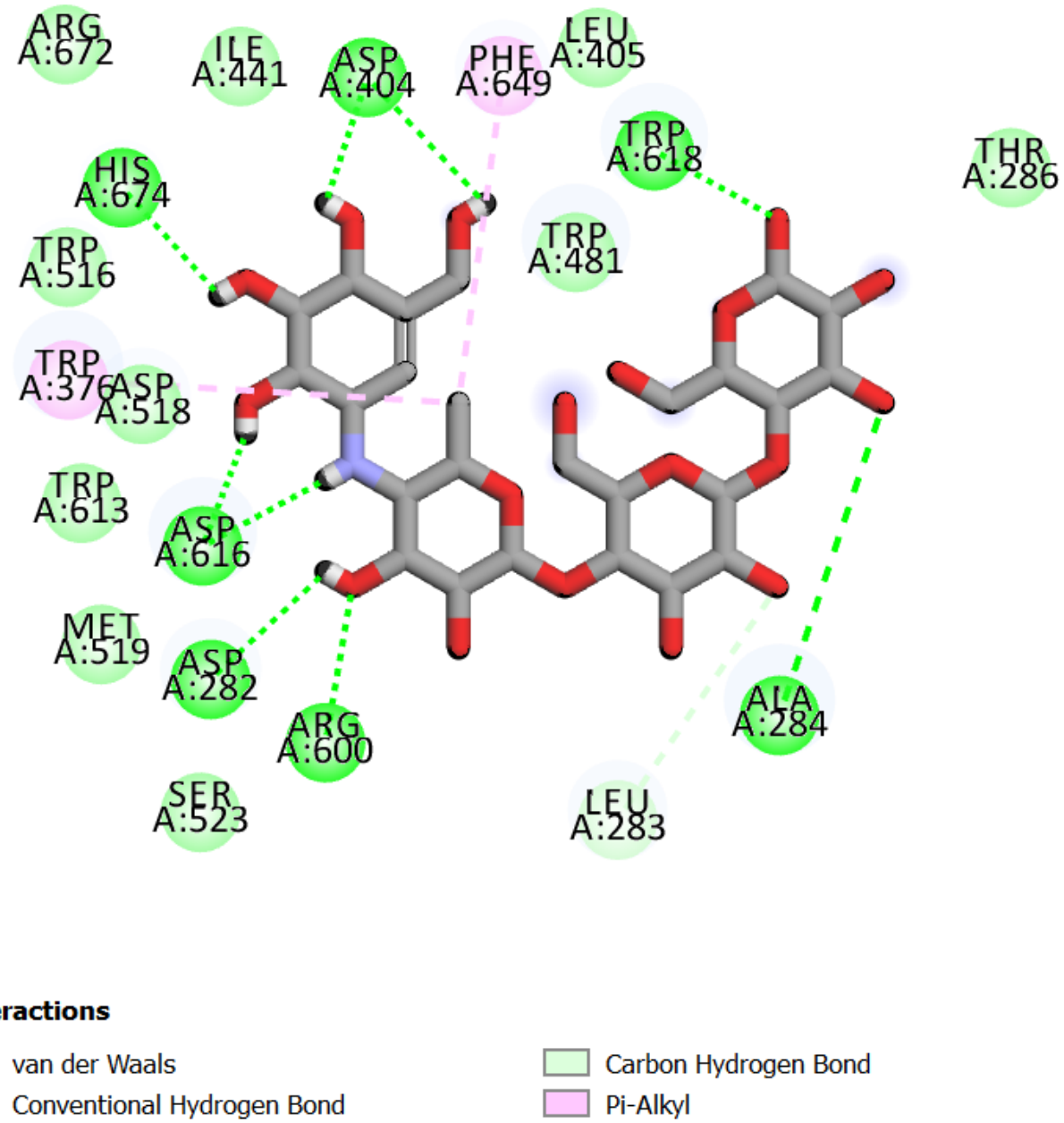


Figure 1. Visualization of receptor-natural ligand bond interactions after re-docking

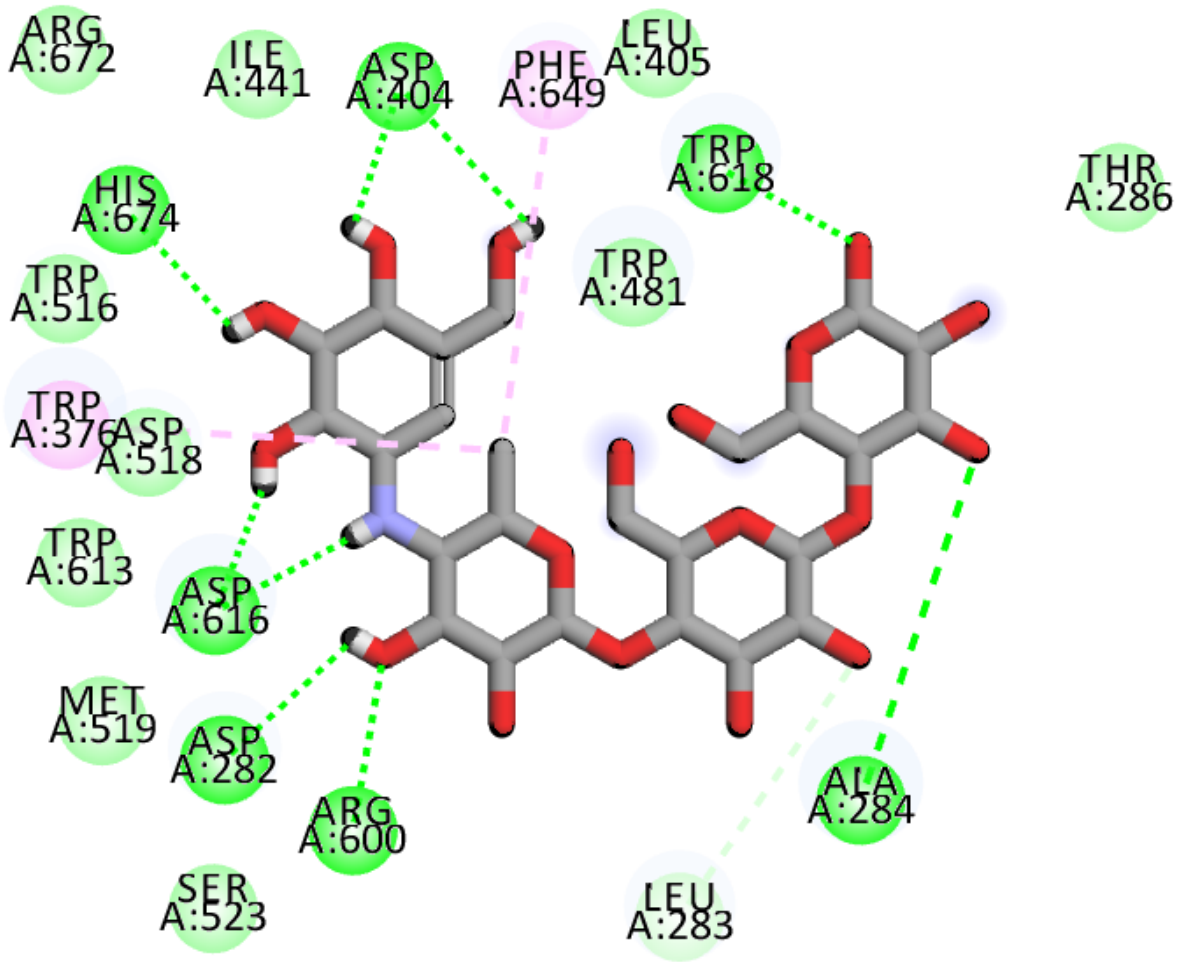
Table 1. Interaction results of α-glucosidase with ligands

No.	Ligand	ΔGbind (kkal/mol)	Category	Chemical Bonding	Amino Acid Residues

1.	Alpha – acarbose (Native ligand)	-8.51	Hydrogen Bonding	Conventional Hydrogen Bond	His 674; Asp 404; Trp 618; Ala 284; Arg 600; Asp 282; Asp 616
				Carbon Hydrogen Bond	Arg 672; Ile 441; Leu 405; Thr 286; Trp 481; Leu 283; Ser 523; Met 519; Trp 613; Asp 518; Trp 516
			Hydrophobic	Pi-Alkyl	Trp 376; Phe 649
2.	Rhoifolin	-8.28	Hydrogen Bonding	Conventional Hydrogen Bond	Ser 676; Asp 282; Phe 525; Asn524
			Hydrophobic	Pi-Pi T-shaped	Phe 649; Trp 481
			Unfavorable	Unfavorable Donor-Donor	Arg 600; Arg 281
3.	Lupeol	-8.08	Hydrogen Bonding	Conventional Hydrogen Bond	Asn 524
			Hydrophobic		Trp 376; Phe649; Trp481; Phe 525; Met 519; Ala555
4.	Betulin	-7.46	Hydrogen Bonding	Conventional Hydrogen Bond	Asn 524
			Hydrophobic		Trp 376; Phe 649; Trp 481; Phe 525; Met 519; Ala 555

5.	Corymboside	-7.28	Hydrogen Bonding	Conventional Hydrogen Bond	Asp 282; Arg 600; Met 519; Asp 518
			Hydrophobic	Pi-Alkyl	Leu 678
6.	(1ξ)-1,5-Anhydro-1-[2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-8-yl]-D-galactitol	-7.21	Hydrogen Bonding	Conventional Hydrogen Bond	Asp 282; Asp 616; Asp 518; Trp 481
			Hydrophobic	Pi-Alkyl	Met 519
				Pi-Pi T-shaped	Leu 678
7.	Vitexin	-6.21	Hydrogen Bonding	Conventional Hydrogen Bond	Leu 677; Arg 600; Asp 282; Asp 616
			Hydrophobic	Pi-Alkyl	Leu 650; Leu 678
				Pi-Pi T-shaped	Phe 649; Trp 481
8.	Acarbose (Comparator)	-5.54	Hydrogen Bonding	Conventional Hydrogen Bond	Phe 525; Asp 616; Asp 518; Asp 404; Trp 481

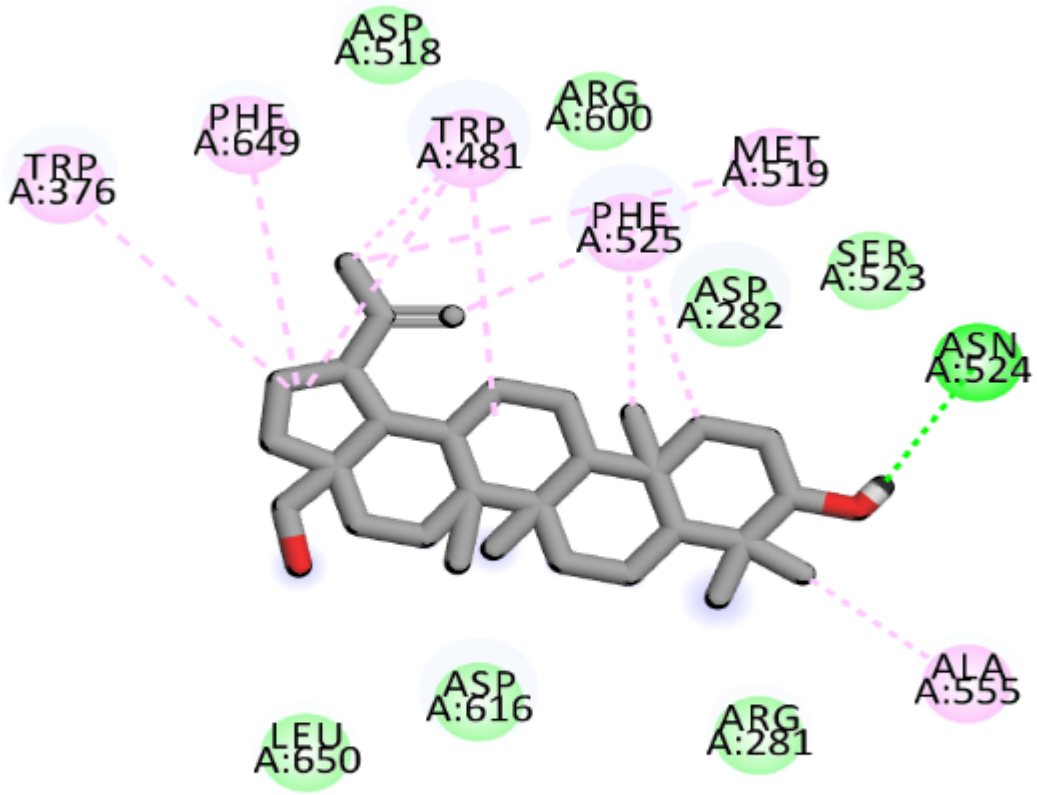
Visualization of the interactions vitexin, rhoifolin, lupeol, betulin, corymboside and (1ξ)-1,5-Anhydro-1-[2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-8-yl]-D-galactitol, acarbose and the amino acid residues of α-glucosidase is shown in Figure 2.



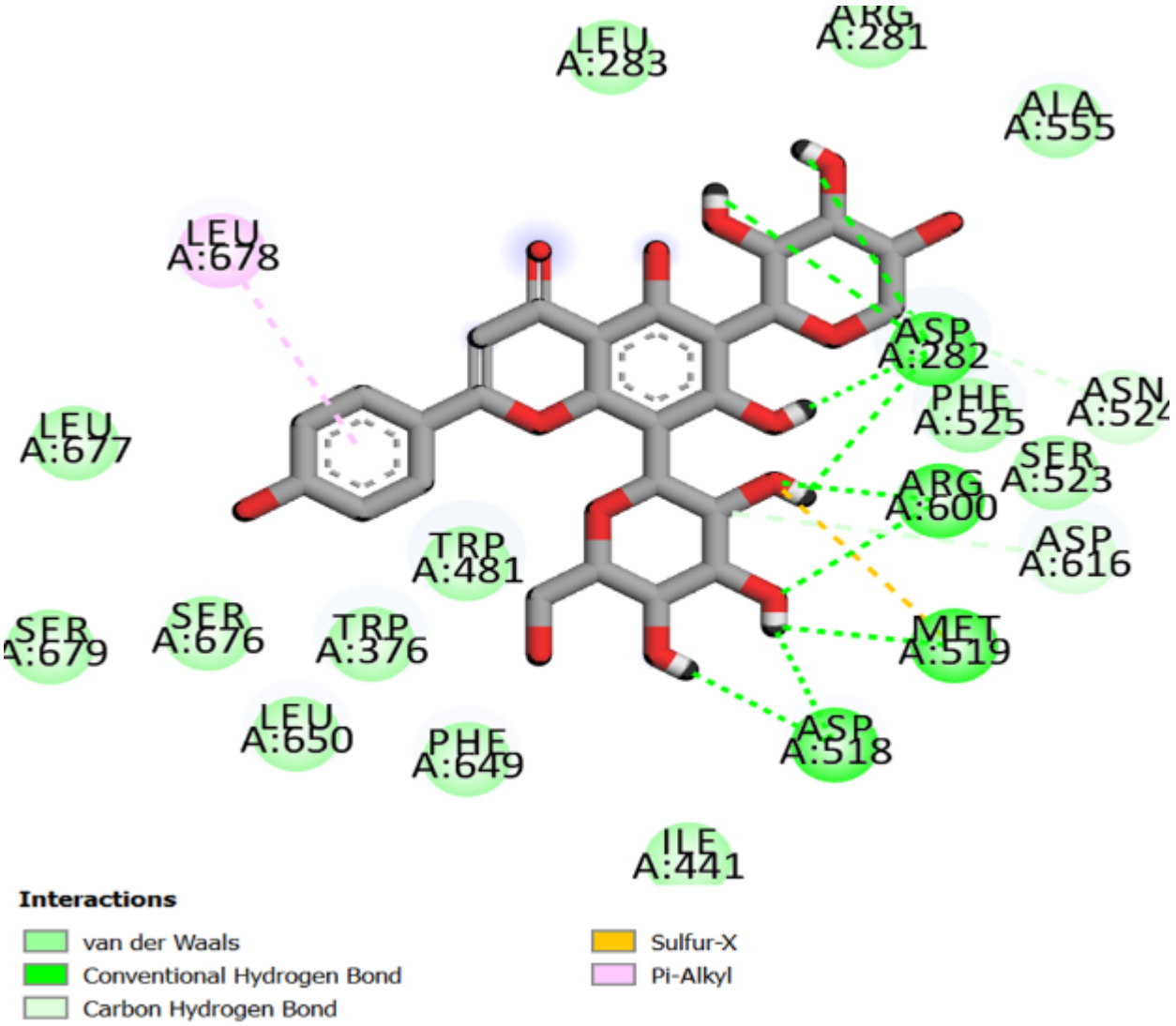
Interactions

- van der Waals
- Conventional Hydrogen Bond
- Carbon Hydrogen Bond
- Pi-Alkyl

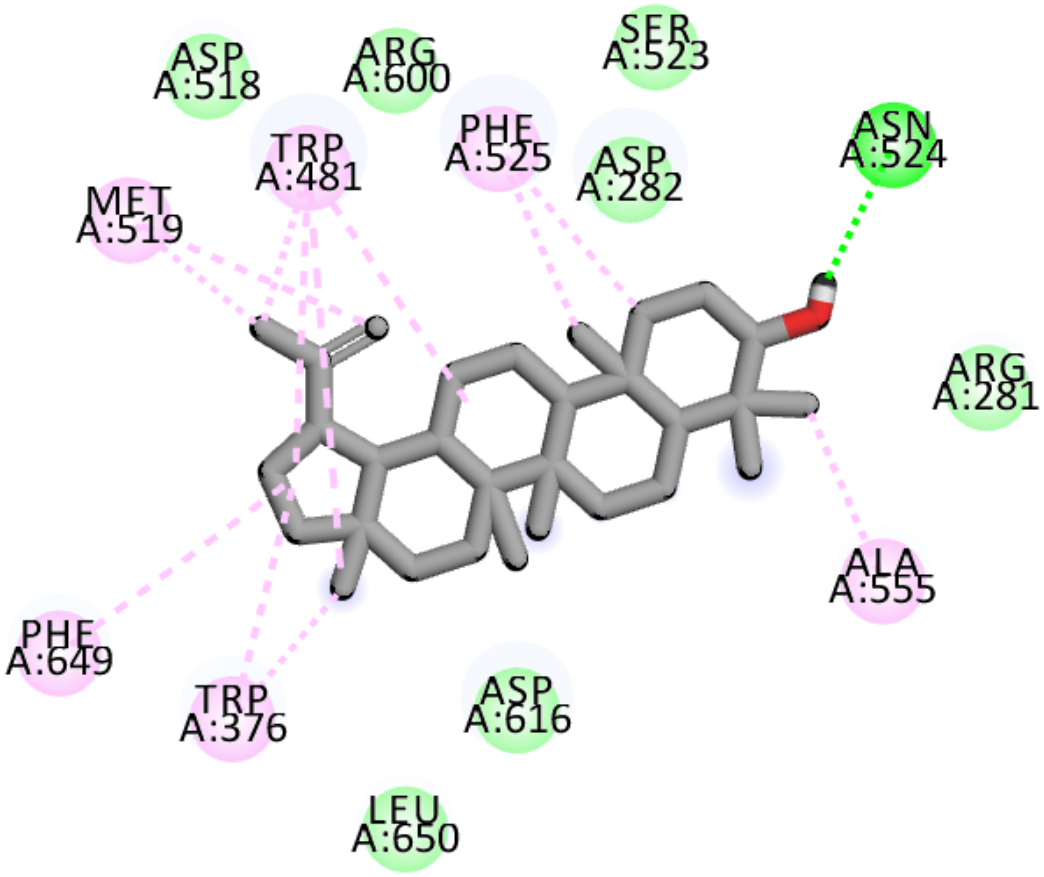
Copyright © 2026 Academic Master.


ASP
A:518
ARG
A:600
PHE
A:649
TRP
A:481
MET
A:519
TRP
A:376
PHE
A:525
SER
A:523
ASP
A:282
ASN
A:524
ALA
A:555
ASP
A:616
ARG
A:281
LEU
A:650
Interactions
van der Waals
Conventional Hydrogen Bond
Alkyl
Pi-Alkyl

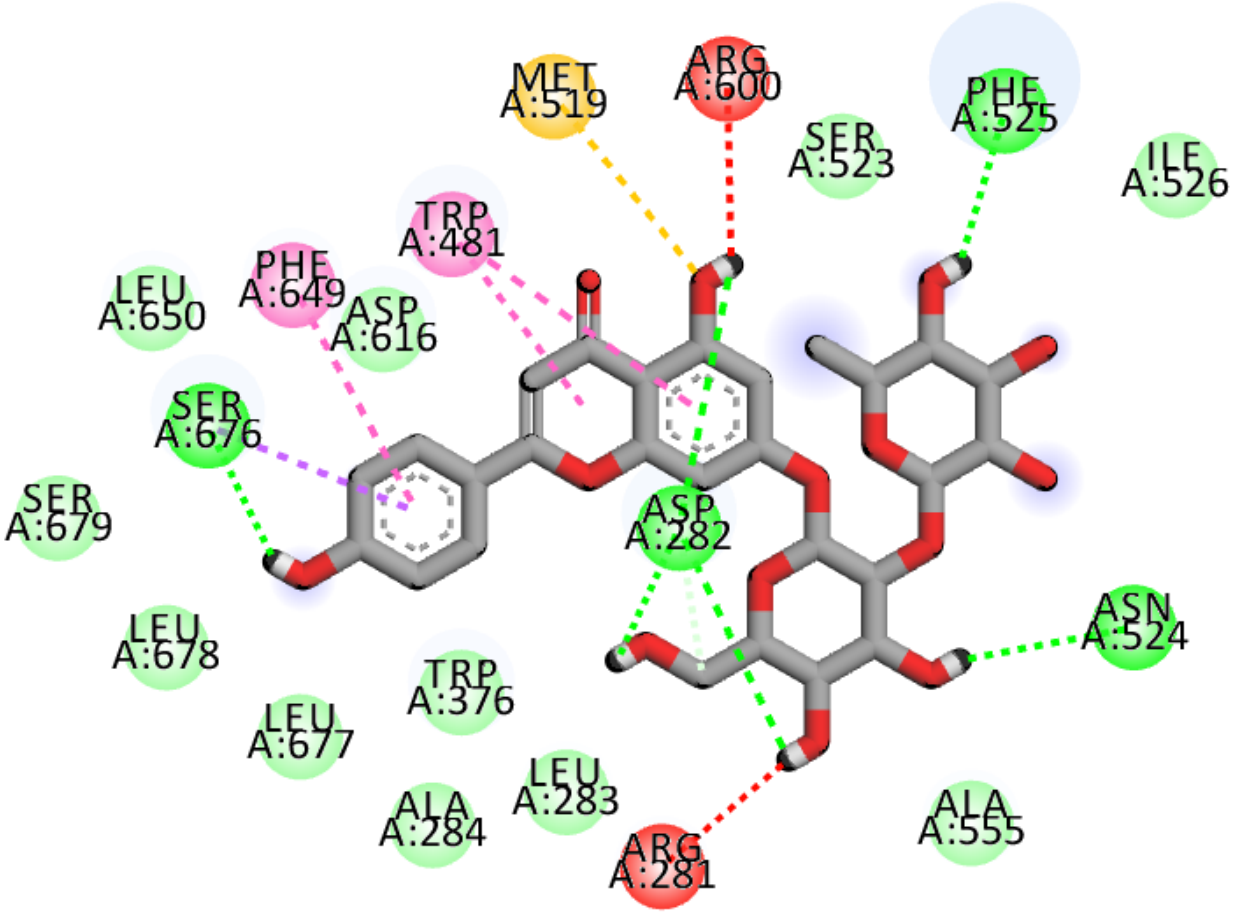
1. (b)



Copyright © 2026 Academic Master.


ASP
A:518
ARG
A:600
SER
A:523
TRP
A:481
PHE
A:525
ASP
A:282
ASN
A:524
MET
A:519
ARG
A:281
ALA
A:555
PHE
A:649
TRP
A:376
ASP
A:616
LEU
A:650
Interactions
van der Waals
Conventional Hydrogen Bond
Alkyl
Pi-Alkyl

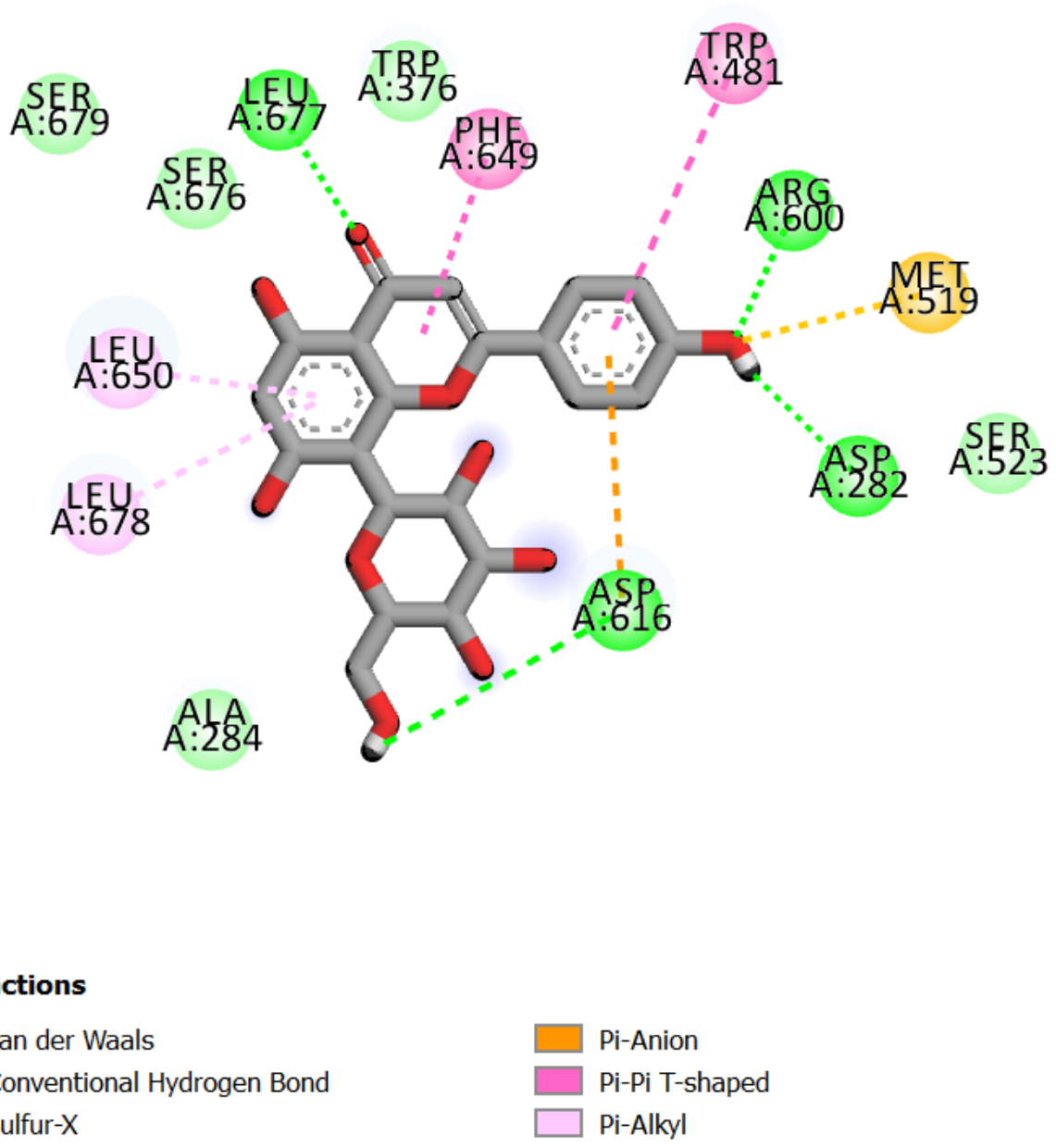
(c) (d)



Interactions

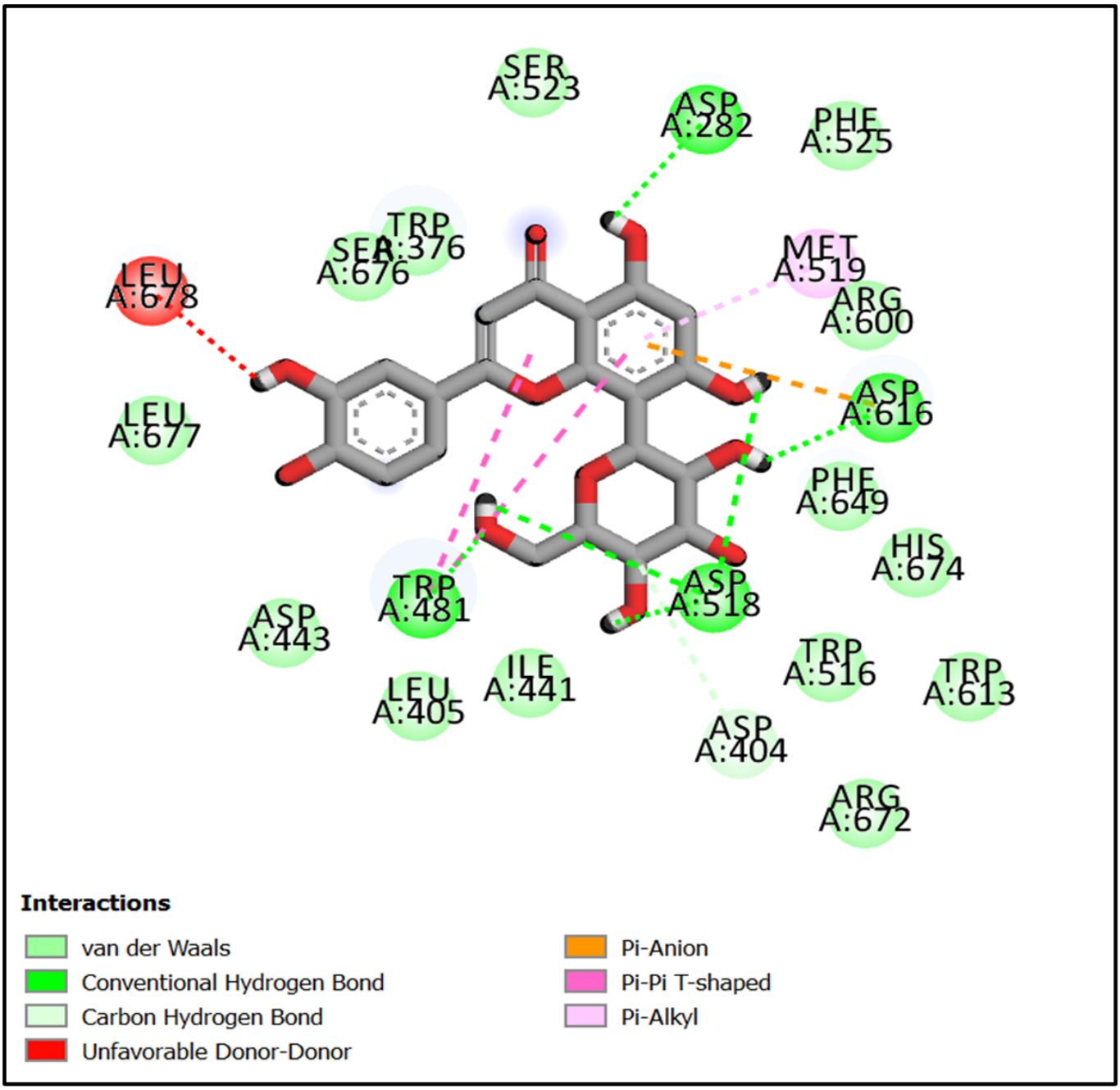
- van der Waals
- Conventional Hydrogen Bond
- Carbon Hydrogen Bond
- Sulfur-X
- Unfavorable Donor-Donor
- Pi-Sigma
- Pi-Pi T-shaped

Copyright © 2026 Academic Master.

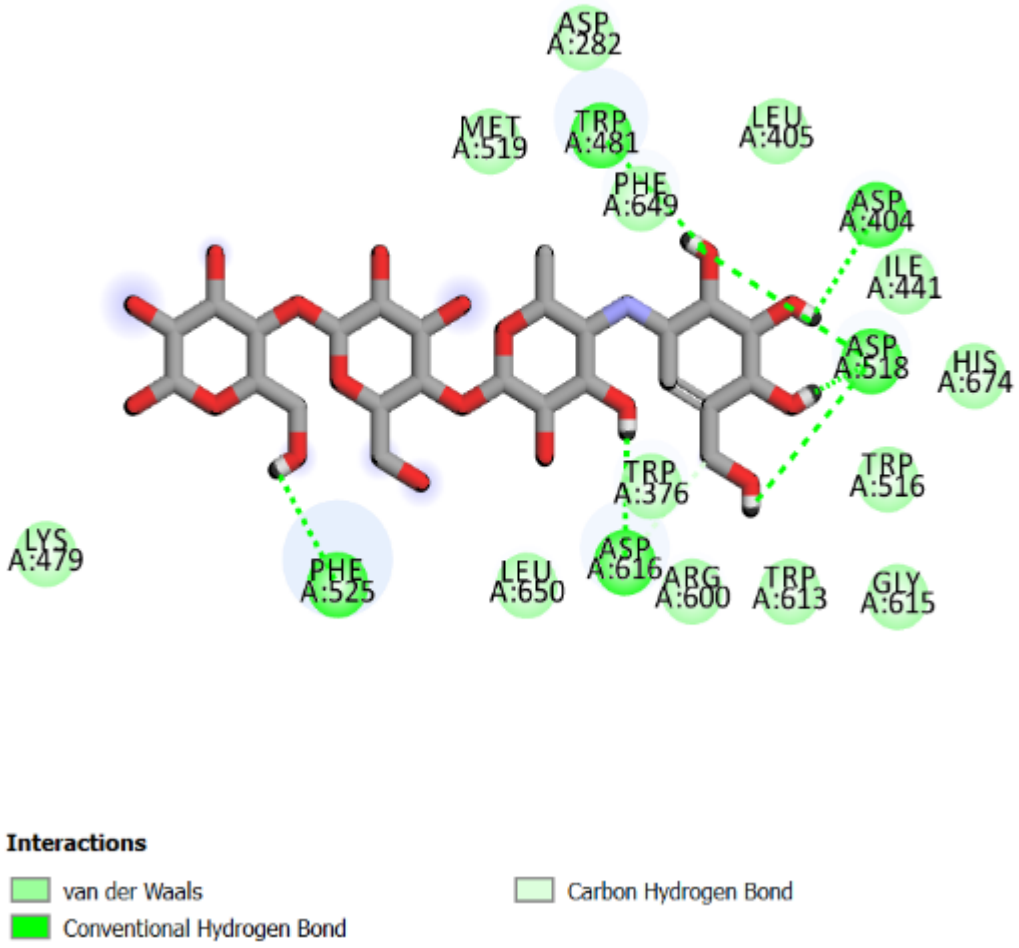


(e) (f)

Copyright © 2026 Academic Master.



Copyright © 2026 Academic Master.



(g) (h)

Figure 2. Visualization of the interactions (a) native ligand (alpha acarbose), (b) Betulin, (c) Crombosyde, (d) Lupeol, (e) Rhoifolin, (f) Vitexin, (g) (1ξ)-1,5-Anhydro-1-[2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-8-yl]-D-galactitol, and (h) acarbose as comparator

Discussion:

Ficus deltoidea Jack contains phytochemical compounds, including terpenoids, polyphenols, alkaloids, organic acids, saponins, and their derivatives. Literature shows that different parts of the Ficus deltoidea plant contain different phytochemical compounds. The leaf part contains polyphenols, triterpenoids, saponins, and tannins but contains very few alkaloids Flavonoids, saponins, and alkaloids are found mainly in the stem part, while the fruit mostly contains triterpenoids, alkaloids, and flavonoids [13].

The study of the antidiabetic activity of Ficus deltoidea Jack was also conducted in silico. The term in silico is used to describe experiments conducted with the help of computers. This assay can be used to determine the interaction between a compound and a target molecule, one of which is a receptor. The interaction of compounds with receptors can be visualised by computational methods and can be used to determine the pharmacophore of a compound [14].

The receptor used in this study is the α-glucosidase enzyme (CODE: 5NN8) which has a mechanism of breaking carbohydrates into glucose in the digestive tract and absorption of carbohydrates so that it is an effective approach to lower blood glucose levels. One of the drugs that have an inhibitory mechanism of α-glucosidase enzyme is akarbosa. Interaction between the receptor and its natural ligand. The native alpha-acarbose and 5NN8 ligands that were previously separated during protein preparation were docked again with the redocking process. The redocking process was carried out with the aim of validating the molecular docking method [13]. The docking validation parameters used consist of Root Mean Square Deviation (RMSD) value < 2 Å and the lowest bond energy value and mean centerline shift (RMSD) value that is less than 2 Å. The lower the RMSD value, the more similar the resulting position is to the standard value. Furthermore, the number of hydrogen bonds and bound amino acid residues were used as additional parameters. The docking method was performed using Autodock Tools 1.5.6 software. The docking validation results showed an RMSD value of 1.80 Ǻ which met the RMSD requirement of less than 2Å. This result suggests that the docking method employed is valid and suitable for docking test ligands from Ficus deltoidea Jack.

The interactions between the macromolecule (α-glucosidase) and the test ligands, as well as the native ligand (alpha acarbose), were analyzed using Biovia Discovery Studio software. These interactions encompassed hydrogen bonds and hydrophobic bonds as detailed in Table 1. A higher binding affinity between the ligands and the alpha-glucosidase target structure is shown by the low binding energies. The results indicated that vitexin, rhoifolin, lupeol, betulin, corymboside and (1ξ)-1,5-Anhydro-1-[2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-8-yl]-D-galactitol exhibited binding affinities of -6.27, -8.28, -8.08, -7.46, -7.28 and -7.21, respectively. With regard to acarbose, the binding affinity was -5.54. The following 6 compounds namely vitexin, rhoifolin, lupeol, betulin, corymboside and (1ξ)-1,5-Anhydro-1-[2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-8-yl]-D-galactitol have been proven to show good activity against alpha glucosidase.

Conclusion:

The results indicated that the six chemical compounds from Ficus deltoidea Jack exhibited a lower binding affinity than acarbose. It may be suggested that Ficus deltoidea Jack has the potential as an alpha-glucosidase inhibitor against type 2 diabetes.

Conflict Of Interest:

The authors have no conflicts of interest regarding this investigation.

Acknowledgements:

The authors would like to thank Airlangga University for their kind support during the research

References:

1. Webber, S. IDF Diabetes Atlas. Diabetes Research and Clinical Practice vol. 102 (2021).

2. Tran, N., Pham, B. & Le, L. Bioactive Compounds in Anti-Diabetic Plants: (2020).

3. Verma, S., Gupta, M., Popli, H. & Aggarwal, G. Diabetes Mellitus Treatment Using Herbal Drugs. 10, 1–10 (2018).

4. Corner. The Complex of Ficus deltoidea: a Recent Invasion of The Sunda Shelf. at (1969).

5. Kalman, D. S., Schwartz, H. I., Feldman, S. & Krieger, D. R. Efficacy and safety of Elaeis guineensis and Ficus deltoidea leaf extracts in adults with pre-diabetes. Nutr. J. 12, 1 (2013).

6. Bunawan, H., Amin, N. M., Bunawan, S. N., Baharum, S. N. & Mohd Noor, N. Ficus deltoidea jack: A review on its phytochemical and pharmacological importance. Evidence-based Complement. Altern. Med. 2014, (2014).

7. Adam, Z. Evaluation of antihyperglycemic activity of ficus deltoidea jack and elucidation of its antidiabetic mechanisms using in vitro model. (2012).

8. Farsi, E. et al. Standardized extract of Ficus deltoidea stimulates insulin secretion and blocks hepatic glucose production by regulating the expression of glucose-metabolic genes in streptozitocin-induced diabetic rats. BMC Complement. Altern. Med. 14, 1–13 (2014).

9. Abdel-Rahman, R. F. et al. Ficus deltoidea extract down-regulates protein tyrosine phosphatase 1B expression in a rat model of type 2 diabetes mellitus: A new insight into its antidiabetic mechanism. J. Nutr. Sci. 9, 1–18 (2020).

10. Choo, C. Y., Sulong, N. Y., Man, F. & Wong, T. W. Vitexin and isovitexin from the Leaves of Ficus deltoidea with in-vivo α-glucosidase inhibition. J. Ethnopharmacol. 142, 776–781 (2012).

11. Astalakshmi, D. . et al. Over View on Molecular Docking: A Powerful Approach for Structure Based Drug Discovery. Int. J. Pharm. Sci. Rev. Res. 77, 146–157 (2022).

12. Yuliantini, A. et al. Molecular Docking Phytochemical of Ashitaba (Angelica Keskei) Against A-Glucosidase As A Potential Anti-DMT2 Compound. 8, 21–32 (2023).

13. Ashraf, K., Halim, H., Lim, S. M., Ramasamy, K. & Sultan, S. In vitro antioxidant, antimicrobial and antiproliferative studies of four different extracts of Orthosiphon stamineus, Gynura procumbens and Ficus deltoidea. Saudi J. Biol. Sci. 27, 417–432 (2020).

14. Ekins, S., Mestres, J. & Testa, B. In silico pharmacology for drug discovery: Methods for virtual ligand screening and profiling. Br. J. Pharmacol. 152, 9–20 (2007).