Molecular docking analysis of seagrass (*Enhalus acoroides*) phytochemical compounds as an antidiabetic

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Abstract

Enhalus acoroides have potential to inhibit the α-glucosidase enzyme and as an antidiabetic drug. Twenty-seven phytochemical compounds of seagrass (*E. acoroides*) were analyzed by molecular docking method. All possible candidate compounds predicted ADME pharmacokinetic properties using the swiss ADME website. A molecular docking analysis was carried out using the PyRx 0.8 Autodock Vina software. Furthermore, the interaction analysis between molecules was carried out using PyMOL software and the Discovery Studio Visualizer BIOVIA. There were 17 of the 27 compounds which had the best potency as oral antidiabetic drug candidates. The validation results showed that all ligands had aroot mean score deviation (RMSD) value <2Å with the best value of 0.0. The binding affinity with the strongest bond value was -9.2 (kcal/mol) on the NAMPT bond with tannin, while the weakest value was 40.01 at 3l4y (α-glucosidase) with 3-methyl. The 2h6d receptor can bind to all ligands, and the α-glucosidase receptor can bind to two test ligands. The docking method used in this study was valid, and the phytochemical compounds of seagrass have the potential to be an alternative to antidiabetic drugs.

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Key words: Diabetes mellitus; molecular docking; phytochemicals; seagrass.

Acknowledgements: Authors would like to thank to Dr. Satya Ari Nugraha who assisting in molecular docking application.

Contributions: YF, SS, RNA and EN organize and design research, conduct research, provide research tools, collect and organize data. YF and RNA analyze and interpret data. SS and EN wrote the initial and final drafts of the article. All authors have critically reviewed and approved the final draft and are responsible for the manuscript's content and similarity index. EN supervised the project.

Fundings: This research was funded by a grant from the Ministry of Education and Culture of the Republic of Indonesia with contract number of 1686/E2/TU/2020.

Conflict of interest: The authors declare no conflicts of interest.

Received for publication: 18 October 2021.
Revision received: 21 January 2022.
Accepted for publication: 27 January 2022.

Journal of Biological Research 2022; 95:10224
doi:10.4081/jbr.2022.10224

Introduction

Diabetes mellitus type 2 is a chronic condition and is one of the major causes of mortality worldwide. The disease is caused by high blood sugar levels because the insulin produced by the body isinsufficient to process sugar in the bodyor body resists insulin.[1] The epidemic of diabetes mellitus and its accompanying complications poses a major threat to global health problems. In 2015, 1 in 11 (around 415 million) adults aged 20-79 years had diabetes mellitus.[2] Based on data from the World Health Organization (WHO) in 2019, it was recorded that people living with diabetes reached 422 billion. This number is predicted to continue to increase to reach 642 million people with diabetes mellitus in 2040.[2] Some 90% of people with diabetes have type 2 diabetes as a result of unhealthy lifestyles. According to the International Diabetes Federation (IDF), Indonesia is one of the countries with the seventh most diabetes mellitus sufferers worldwide after China, India, the United States, Pakistan, Brazil, and Mexico.[3]

The high prevalence of type 2 diabetes mellitus sufferers in Indonesia can be treated from an early age by paying attention to some of the initial symptoms that appeared, which are related to the effects of high blood sugar levels.[4] The value of blood sugar levels in diabetes mellitus patients was >126 mg/dL at fasting blood sugar levels, and at the time of the test was >200mg/dL. Early symptoms of type 2 diabetes mellitus can also be detected through a postprandial glucose level test, a blood glucose test done 2 hours after eating.[5]

The recognition of the initial symptoms that appeared can speed up treatment. Some medical treatments widely used for diabetes mellitus sufferers are pharmacological therapy using synthetic drugs and insulin injection. Those treatments have several drawbacks, such as dyspepsia symptoms, cell resistance, allergies due to the immune response for insulin injection, and the high cost. Another treatment method used is metformin, an oral antidiabetic drug for initial treatment. The drawback of administering this drug is that it causes nausea and bloating in sufferers.[6]

The seagrass *(Enhalus acoroides)* is a natural ingredient that can be used as an antidiabetic.[7] It contains bioactive compounds such as flavonoids, alkaloids, phytochemical compounds, and antioxidants.[8] These compounds are known for reducing high blood sugar levels.[9] Delaying sugar absorption through inhibiting carbohydrate hydrolysis enzymes α-glucosidase can control glucose levels in the body.[10]

The enzyme α-glucosidase plays a role in the final step in the digestive carbohydrates,[3] and it worksto hydrolyze carbohydrates into sugars that are easier to absorb.[11] The inhibition of α-glucosidase causes the enzyme cannot convert complex carbohydrates into simple sugarsand reduce the absorption in the small intestine. So, the result is to decrease postprandial plasma glucose levels and suppression postprandialhyperglycemia (PPHG).[3] Thus, it will reduce glucose levels in people with type 2 diabetes mellitus.[12]

Materials and Methods

Receptor structure preparation

The tools used in this study were PyRx 0.8 AutoDoc Vina software, PyMOL, and the Discovery Studio Visualizer 2020. The materials used in this study included 2D and 3D receptors and ligand structures. The research began by downloading the receptor structures, namely 3W37, 3A4A, and 3L4Yvia http: //www.rcsb.org/pdb/home/home.do. These receptors are proteins with complex structures of the α-glucosidase receptor. Then, three insulin receptors, namely 2H6D, 4WQ6, and 1BHS were chosen. The receptors were obtained by downloading the receptors' 3D structure on the RCSB PDB (The Research Collaboratory for Structural Bioinformatics Protein Data Bank) website in PDB format (http: //www.rcsb.org/pdb/home/home.do).

Preparation of 3-dimensional structures of compounds as test ligands

The phytochemical compounds of seagrass (*E. acoroides*) were downloaded via the PubChem website (https://pubchem.ncbi.nlm.nih.gov/)and in 2D and 3D structures. Files were downloaded in SDF (Spatial Data File) format and converted to PDB format using the SMILES Translator Online website.[13]

ADME predictions

Prediction of the pharmacokinetic properties of Absorption, Distribution, Metabolism, and Excretion (ADME) was conducted by analyzing phytochemical compounds using the swiss ADME website (http://www.swissadme.ch/index.php). In general, ADME parameters were used to assess the work-range capability of phytochemical compounds after oral administration. Seagrass (*E. acoroides*) phytochemical compoundshave the potential to be the best candidates for the drug with a Topological Polar Surface Area (TPSA) value of <70 $Å^2$(Angstrom = 10^{-10} m).[14]

Validation with PyRx 0.8 Autodock Vina

A total of 17 seagrass phytochemical compounds (*E. acoroides*) had TPSA values <70 ($Å^2$) validated using PyRx 0.8 Autodock Vina. Then, the test ligand re-docked to the target protein. The center of the frame was placed in the ligand center and covered all residue of the binding site. The docking conformation results were aligned with the negative ligand conformation results of crystallographic measurements expressed in the Root Mean Square Deviation (RMSD) value. Validation was confirmed if the RMSD value of the re-docked and crystallographic ligands were less than 2Å.

Molecular visualization using PyMOL and discovery studio

The validation results were used PyRx 0.8 Autodock Vina, which has an RMSD value <2 (Å), then visualized using PyMOL and Discovery Studio Visualizer BIOVIA 2019. Visualization of PyMOL was carried out to see the bond distance in three-dimensional space. Meanwhile, the interactions between molecules in two-dimensional space was determined by Visualization Discovery Studio Visualizer BIOVIA 2019.

Results

ADME prediction (absorption, distribution, metabolism, and excretion)

The phytochemical compounds of seagrass, which were potential as drug candidates, were analyzed using Swiss ADME (Table 1). Swiss ADME was used to assess the rangeability of compounds on oral administration.[12] As much as 17 of 27 phytochemical compounds of seagrass *(E. acoroides)* had the potential as drug candidates with a TPSA value <70 ($Å^2$) (Table 2).

Docking validation

Docking validation aimed to establish the docking method's validity versus conformational 3D ligands to the target protein. Docking validation is expressed by RMSD. The docking validation results showed that all ligands had an RMSD value <2Å with the best value of 0.0 (Table 3). Thus, the docking method used in this study was valid. The binding affinity with the strongest bond value was -9.2 (kcal/mol) on NAMPT (Nicotinamide Phosphoribosyltransferase) bonds with tannin. While the weakest value was 40.01 at 3l4y (α-glucosidase) with 6-fluoro-2-[4-(2-fluorophenyl)phenyl]-3-methylquinoline-4-carboxylic acid (Table 4).

Molecular visualization

Visualization of ligand binding interactions with the target receptor was carried out to determine the chemical bonds that occur and its stability (Figure 1). The application used to visualize the process is Discovery Studio Visualizer 2020. There are several ligands as candidates and then visualized to obtain several ligands with stronger and more stable bond types (Figure 2 and 3). The figure in the form of a dashed line indicates an interaction or bond that occurs. These binding interactions can be in electrostatic interactions, hydrophobic interactions, van der Waals interactions, halogens, and hydrogen bonds. Hydrogen bonding optimizes hydrophobic interactions at the ligand and receptor surfaces. This will increase the binding affinity of the complex molecule. Weak hydrogen bonds will make it easier to break the interaction between the ligand and the receptor, so that it can be exchanged with other ligands. Hydrophobic interactions play an important role in increasing the binding affinity between the ligand surface and the receptor. Binding affinity and drug efficacy correlate with hydrophobic interactions, which are enhanced through interactions on hydrogen.[15] Electrostatic interactions between proteins and ligands play an important role in optimal affinity and selectivity.[16] The interaction between protein and stable ligand can activate the α-glucosidase enzyme to inhibit the absorption of complex carbohydrates.[17]

Table 1. Phytochemical compounds of seagrass (*Enhalus acoroides*).

Phytochemical Compounds	Reference
7-oxo-1H-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylic acid	Ganesh, 2011
Ethyl 7-amino-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate	Ganesh, 2011
Ethyl ester	Ganesh, 2011
2,2,7,7-tetramethyltricyclo[6.2.1.$0^{1,6}$]undec-5-en-4-one	Ganesh, 2011
Benzenamine	Ganesh, 2011
2,4,6-trimethyl-N-(2,4,6-trimethylphenyl)benzenesulfonamide	Ganesh, 2011
Benzene	Ganesh, 2011
1-isocyano-2-methyl-3-nitrobenzene	Ganesh, 2011
Benzenesulfonic acid	Ganesh, 2011
N-[(Z)-[(3Z)-3-hydroxyiminobutan-2-ylidene]amino]benzenesulfonamide	Ganesh, 2011
Benzyl alcohol	Ganesh, 2011
Dibutyl phthalate	Ganesh, 2011
Fumaric acid	Ganesh, 2011
2-O-(3,5-difluorophenyl) 1-O-undecyl oxalate	Ganesh, 2011
Hydrazinecarbothioamide	Ganesh, 2011
2-(phenylmethylene)	Ganesh, 2011
[(2S)-2-[(2R)-4-hexadecanoyloxy-3-hydroxy-5-oxo-2H-furan-2-yl]-2-hydroxyethyl] hexadecanoate	Ganesh, 2011
Methanone	Ganesh, 2011
Phenol	Ganesh, 2011
6-fluoro-2-[4-(2-fluorophenyl)phenyl]-3-methylquinoline-4-carboxylic acid	Ganesh, 2011
Propanoic acid	Ganesh, 2011
Dimethyl (isopropyl) silyl ester	Ganesh, 2011
Trans-3-Ethoxy-b-methyl-b-nitrostyrene	Ganesh, 2011
Saponin	Rina and Antarsih, 2017
Flavonoid	Amudha *et al.*, 2018
Quercetin	Menajang *et al.*,2020
Tannin	Amudha *et al.*, 2018

Table redacted using data from the papers indicated.

Table 2. TPSA values of the phytochemical compounds of seagrass (*Enhalus acoroides*).

Compound	TPSA (Å^2)
Methanone	17.07
1,2,3,4,5,6-Hexahydro-1,1,5,5-Tetramethyl-2,4a-Methanonaphthalen	12.53
1-isocyano-2-methyl-3-nitrobenzene	0.00
2-phenylmethylene	38.66
3-5-difluorophenyl undecyl ester	52.60
6-fluoro-2-[4-(2-fluorophenyl)phenyl]-3-methylquinoline-4-carboxylic acid	50.19
Benzenamine	26.02
Benzene	0.00
Benzenesulfonic acid	62.75
Benzyl alcohol	20.23
Dibutyl phthalate	52.60
Ethyl ester	26.30
Phenol	20.23
Propanoic acid	37.30
Trans-3-Ethoxy-b-methyl-b-nitrostyrene	55.05
Tannin	0.00

Discussion

Identification between ligands and receptors is the key in drug designing to predict drug candidates regarding the potential and side effects of a drug, namely the active potential of a compound that shows a good interaction between protein (receptor) and ligand. In molecular docking, there are two important things, namely structural data as receptor and ligand candidates and the procedures used to model the bonds between receptors and ligands.[13]

TPSA <140 (Å²) represents good intestinal absorption. Meanwhile, the TPSA value <70 (Å²) indicates a good value for brain penetration. The ligands of seagrass that havepotential as good drug candidates were shown with TPSA values <70 (Å²), analyzed by six receptors, namely AMP-activated protein kinase, NAMPT, 11-β-hydroxysteroid dehydrogenase 1, and three α-glucosidase receptors to find out the RMSD value and binding affinity.[13] These receptors are fundamental proteins in type 2 diabetes mellitus. AMP-activated protein kinase is involved in the stimulation of glucose transport and fatty acid oxidation. NAMPT is an intracellular regulator of Nicotinamide Adenine Dinucleotide (NAD), regulating the activity of NAD-dependent enzymes.[18] NAMPT is able to modulate the processes involved in insulin resistance. 11 β-hydroxysteroid dehydrogenase 1 causes insulin resistance through conversion of cortisone to cortisol.[19] α-glucosidase is an enzyme present in the small intestine that catalyzes the breaking of α-1,4-glycosidic polysaccharide (or disaccharide) bonds by concurrent conversion to glucose.[20]

The results of the analysis using Discovery Studio Visualizer 2020 shows that there are 11 compounds with the hydrogen bond type with van der Waals forces.[21] The hydrogen bond is a type of bond that plays an important role in the biological activity of a compound. The characteristics of the constituent protons in the hydrogen bond are dynamic.[22] This shows that the type of bond and the conditions of interaction between the ligand and the receptor were stable.[23]

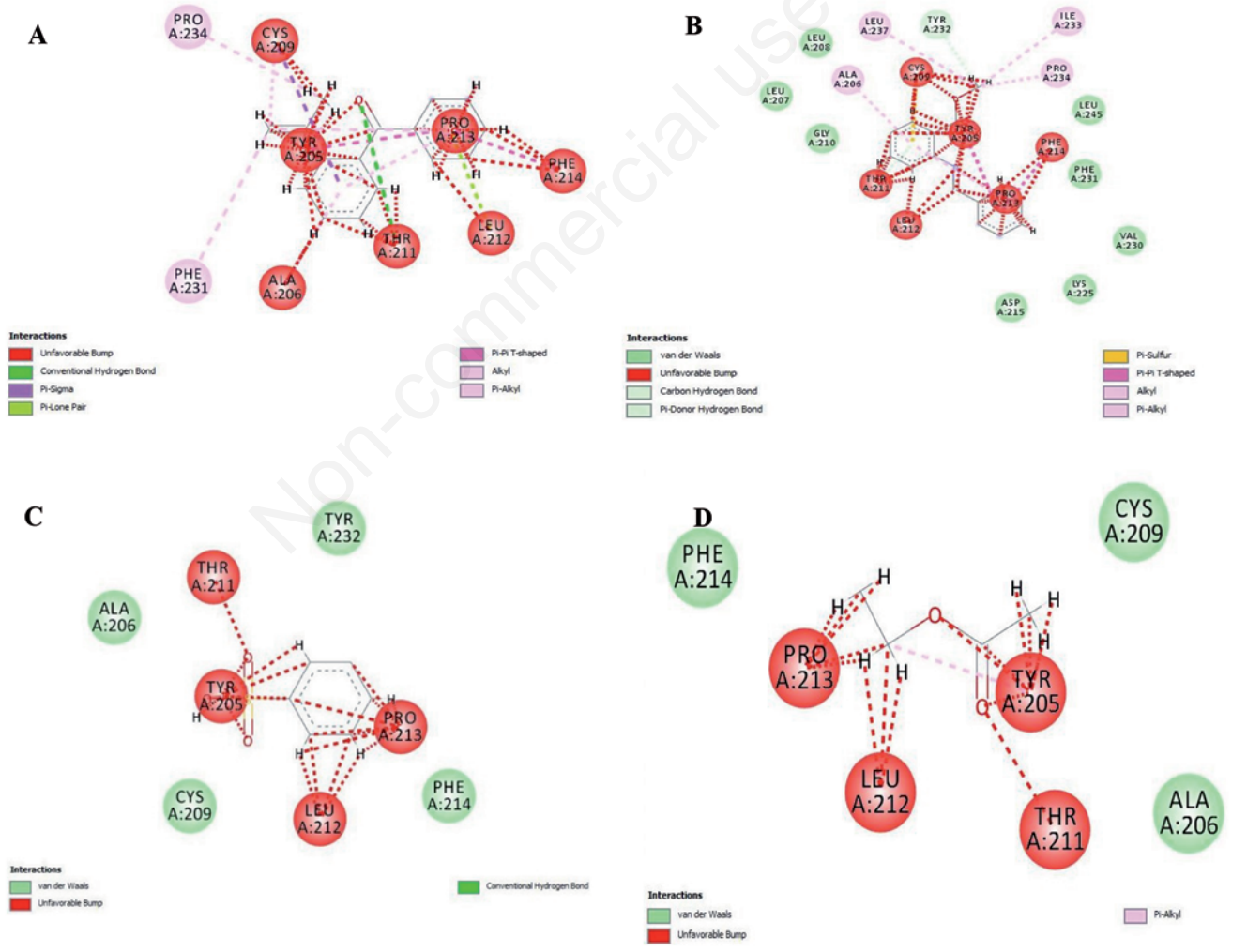

Figure 1. (A) The ligand interaction model methanone with 2h6d; (B) receptors Interaction model of methyl 2-(benzylideneamino) benzoate ligands with 2h6d receptors; (C) The interaction model of the benzenesulfonic acid ligand with the 2h6d receptor; (D) The interaction model of the ethyl ester ligand with the 2h6d receptor.

Table 3. RMSD and Binding Affinity values of seagrass phytochemical compounds (*Enhalus acoroides*).

Receptors	Ligand	RMSD (Å)	Binding Affinity (kcal/mol)
2h6d (AMP-activated protein kinase)	Methanone	1,584	-7.4
	1,2,3,4,5,6-Hexahydro-1,1,5,5-Tetramethyl-2,4a-Methanonaphthalen	0.0	-6.9
	1-isocyano-2-methyl-3-nitrobenzene	0.0	-3.6
	2-phenylmethylene	1,659	-7.2
	3-5-difluorophenyl undecyl ester	0.556	-6.8
	6-fluoro-2-[4-(2-fluorophenyl)phenyl]-3-methylquinoline-4-carboxylic acid	0.0	-4.2
	Benzenamine	0.0	-4.2
	Benzene	0.038	-3.9
	Benzenesulfonic acid	0.0	-5.2
	Benzyl alcohol	0.0	-4.5
	Dibutyl phthalate	0.0	-6.4
	Ethyl ester	0.0	-3.7
	Phenol	0.0	-4.2
	Propanoic acid	0.0	-3.3
	Trans-3-Ethoxy-b-methyl-b-nitrostyrene	0.0	-6.8
	Tannin	0.029	-7.8
4wq6 (Nicotinamide phosphoribosyltransferase (NAMPT))	Methanone	0.0	-7.0
	1,2,3,4,5,6-Hexahydro-1,1,5,5-Tetramethyl-2,4a-Methanonaphthalen	0.0	-5.7
	1-isocyano-2-methyl	0.0	-3.7
	2-phenylmethylene	0.0	-7.0
	3-5-difluorophenyl undecyl ester	0.977	-6.7
	6-fluoro-2-[4-(2-fluorophenyl)phenyl]-3-methylquinoline-4-carboxylic acid	0.0	-6.2
	Benzenamine	1,799	-4.1
	Benzene	0.121	-3.8
	Benzenesulfonic acid	0.0	-5.0
	Benzyl alcohol	0.041	-4.6
	Dibutyl phthalate	0.1	-5.8
	Ethyl ester	0.0	-3.3
	Phenol	0.0	-4.1
	Propanoic acid	0.0	-3.2
	Trans-3-Ethoxy-b-methyl-b-nitrostyrene	0.0	-5.8
	Tannin	0.016	-9.2
1bhs (11 β-hydroxysteroid dehydrogenase 1)	Methanone	0.0	-6.7
	1,2,3,4,5,6-Hexahydro-1,1,5,5-Tetramethyl-2,4a-Methanonaphthalen	0.0	-6.8
	1-isocyano-2-methyl	0.0	-3.6
	2-phenylmethylene	0.0	-7.1
	3-5-difluorophenyl undecyl ester	0.068	-6.1
	6-fluoro-2-[4-(2-fluorophenyl)phenyl]-3-methylquinoline-4-carboxylic acid	0.0	-8.1
	Benzenamine	0.0	-4.6
	Benzene	0.0	-3.8
	Benzenesulfonic acid	0.0	-5.6
	Benzyl alcohol	0.0	-5.0
	Dibutyl phthalate	0.0	-5.7
	Ethyl ester	0.0	-3.6
	Phenol	0.0	-4.7
	Propanoic acid	0.0	-3.7
	Trans-3-Ethoxy-b-methyl-b-nitrostyrene	0.0	-8.5
	Tannin	0.0	-6.3
3a4a (α-glucosidase)	Methanone	0.0	-7.3
	1,2,3,4,5,6-Hexahydro-1,1,5,5-Tetramethyl-2,4a-Methanonaphthalen	0.0	-7.4
	3-nitrobenzene	0.0	-3.6
	2-phenylmethylene	0.0	-7.1
	3-5-difluorophenyl undecyl ester	0.0	-6.5
	6-fluoro-2-[4-(2-fluorophenyl)phenyl]-3-methylquinoline-4-carboxylic acid	0.0	-2.2
	Benzenamine	0.023	-4.4
	Benzene	0.0	-3.9
	Benzenesulfonic acid	0.0	-5.6
	Benzyl alcohol	0.042	-4.7
	Dibutyl phthalate	0.0	-6.3
	Ethyl ester	1,046	-3.6
	Phenol	0.0	-4.6
	Propanoic acid	0.0	-3.4
	Trans-3-Ethoxy-b-methyl-b-nitrostyrene	0.0	-6.5
	Tannin	0.013	-8.2

To be continued on next page

Table 3. Continued from previous page.

Receptors	Ligand	RMSD (Å)	Binding Affinity (kcal/mol)
3w37 (α-glucosidase)	Methanone	0.0	-3.4
	1,2,3,4,5,6-Hexahydro-1,1,5,5-Tetramethyl-2,4a-Methanonaphthalen	0.0	-3.7
	1-isocyano-2-methyl-3-nitrobenzene	0.0	-3.1
	2-phenylmethylene	0.0	-2.6
	3-5-difluorophenyl undecyl ester	0.0	-3.7
	6-fluoro-2-[4-(2-fluorophenyl)phenyl]-3-methylquinoline-4-carboxylic acid	0.0	35.6
	Benzenamine	0.0	-4.4
	Benzene	0.067	-3.9
	Benzenesulfonic acid	0.0	-4.1
	Benzyl alcohol	0.0	-3.6
	Dibutyl phthalate	0.0	-4.0
	Ethyl ester	0.0	-3.8
	Phenol	0.0	-4.7
	Propanoic acid	0.0	-4.2
	Trans-3-Ethoxy-b-methyl-b-nitrostyrene	0.0	-4.4
	Tannin	0.0	-3.9
3l4y (α-glucosidase)	Methanone	0.0	-3.7
	1,2,3,4,5,6-Hexahydro-1,1,5,5-Tetramethyl-2,4a-Methanonaphthalen	0.0	-2.1
	1-isocyano-2-methyl-3-nitrobenzene	0.0	-4.2
	2-phenylmethylene	0.0	-3.0
	3-5-difluorophenyl undecyl ester	0.0	1.2
	6-fluoro-2-[4-(2-fluorophenyl)phenyl]-3-methylquinoline-4-carboxylic acid	0.0	40.01
	Benzenamine	0.01	-5.0
	Benzene	0.004	-4.5
	Benzenesulfonic acid	0.012	-6.3
	Benzyl alcohol	0.002	-5.5
	Dibutyl phthalate	0.0	-2.5
	Ethyl ester	0.0	-4.1
	Phenol	0.0	-5.1
	Propanoic acid	1,541	-3.9
	Trans-3-Ethoxy-b-methyl-b-nitrostyrene	0.0	-5.6
	Tannin	0.002	0.1

Table 4. Interactions between ligands and target proteins.

Receptors	Ligands	Amino acid residue involved
2h6d	Methanone	Thr211, Cys209, Leu212, Tyr205, Phe214, Pro234, Pro213, Phe231, Ala206.
	2 phenylmethylene	Tyr232, Thr211, Cys209, Tyr205, Phe214, Ile233, Pro234, Leu237, Ala206, Leu245, Phe231, Wal230, Lys225, Asp215, Gly210, Leu207, Leu208
	Benzenesulfonic acid	Thr211, Asp16, Arg311, Ser275, Ile309, Tyr188, Ala379
	Ethyl ester	Tyr205, Phe214, Cys209, Ala206
4wq6	2 phenylmethylene	Asp219, Edo607, Ser241, Val242, Po4602, Arg196, Tyr18, Phe193, His191, Pro273, Pro307, Ala244, Ile351, Asp16, Arg311, Ser275, Ile309, Tyr188, Ala379.
	Tannin	Asp219, Edo607, Ser241, Val242, Po4602, Arg196, Tyr18, Phe193, His191, Pro273, Pro307, Ala244, Ile351
1bhs	Methanone	Leu111, Lys159, Leu162, Phe160, Cys156, Ser158.
	Benzenamine	Val115, Leu162, Ser158
3w37	Dibutyl phthalate	Ile821, Gly820.
	Tannin	Ile821, Gly820.
3a4a	Tannin	Arg213, Arg442, Glu277, His351, Asp352, Asp69, Asp215, Asp69, Tyr72.
3l4y	1,2,3,4,5,6-Hexahydro-1,1,5,5-Tetramethyl-2,4a-Methanonaphthalen	Val398
	Tannin	Val398

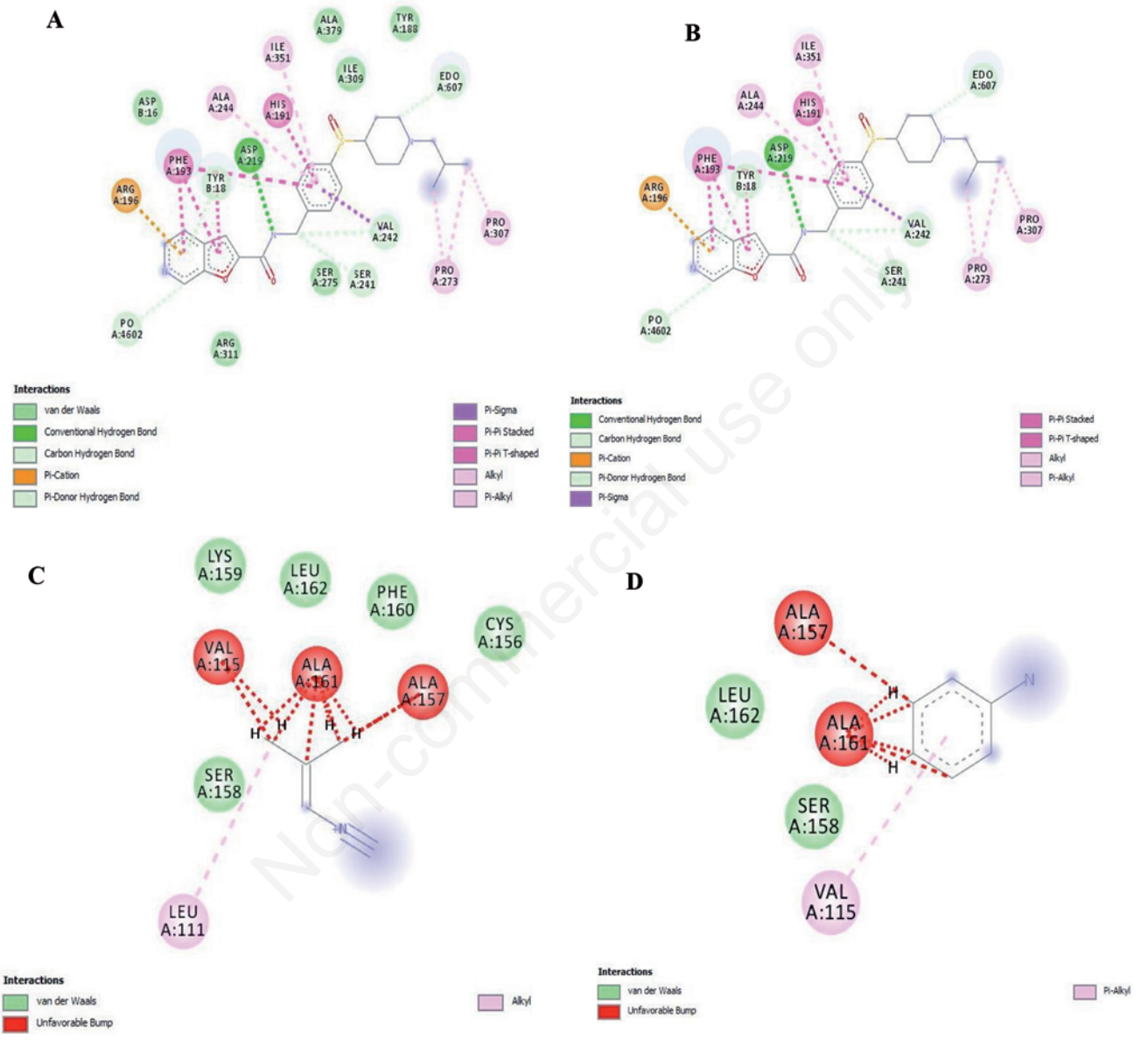

Figure 2. (A) The interaction model of the methyl 2-(benzylideneamino) benzoate ligands with the 4w6q receptor; (B) The interaction model of the tannin ligand with the 4w6q receptor;(C) The interaction model of the 1-isocyano-2-methyl-3-nitrobenzeneligand with the 1bhs receptor; (D) Model of the interaction of the benzenamine ligand with the 1bhs receptor.

Conclusions

Molecular studies show that phytochemical compounds of seagrass can inhibit α-glucosidase activity and have the potential to be antidiabetic drugs. Inhibitor α-glucosidase are effective in lowering insulin release, insulin requirement, and some can lower plasma lipids. Inhibition of the activity of α-glucosidase will decrease blood sugar levels in the body. Further in vivo and in vitro tests and studies are needed to confirm the compound is responsible for this favourable effects and molecular mechanisms of seagrass phytochemical compounds as an antidiabetic drugs.

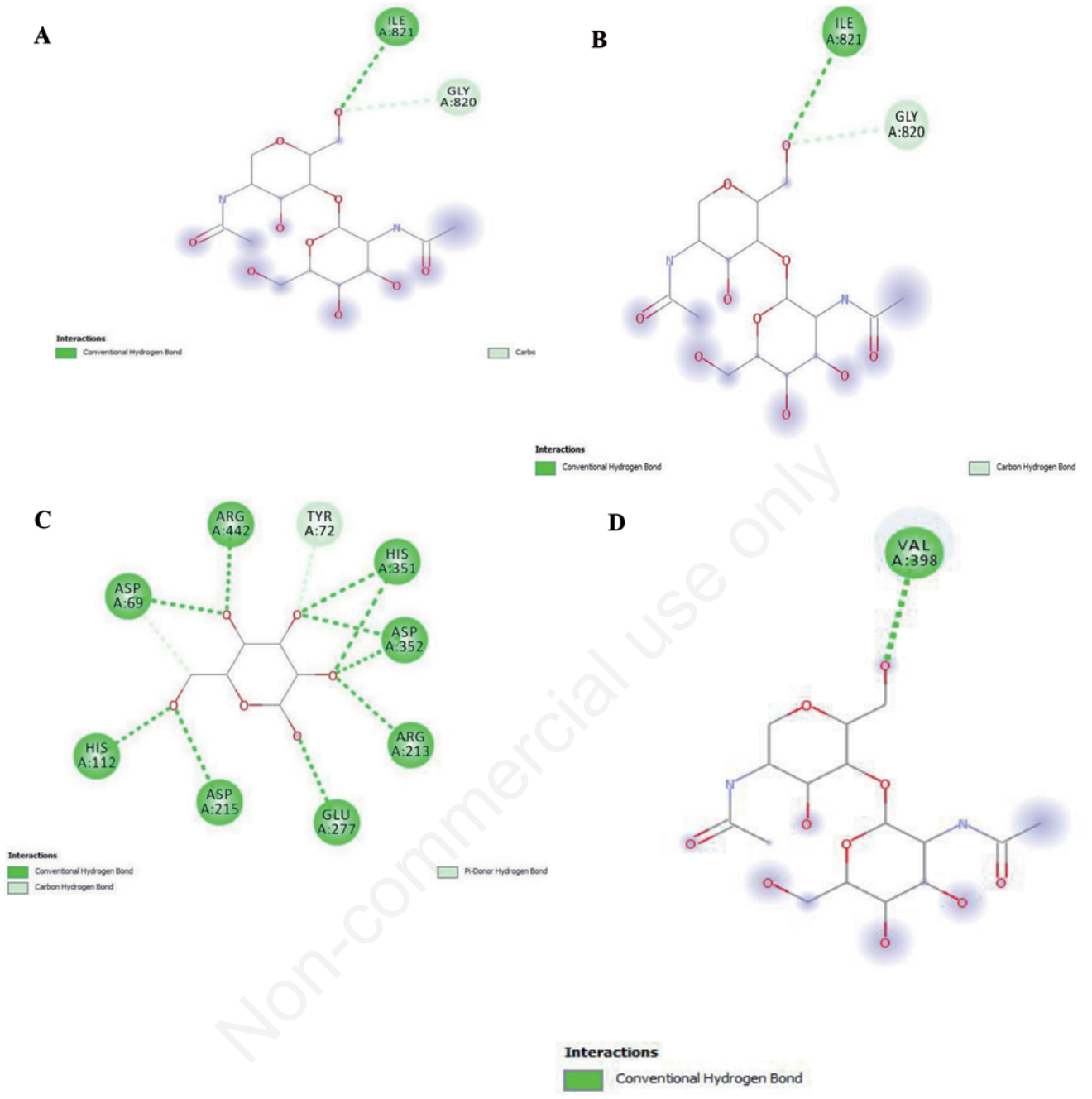

Figure 3. (A) The interaction model of the dibutyl benzene-1,2-dicarboxylate ligand with the 3w37 receptor; (B) Model of the interaction of the tannin ligand with the 3w37 receptor;(C) The interaction model of the tannin ligand with the 3a4a receptor; (D) The interaction model of the 1,2,3,4,5,6 Hexahydro 1,1,5,5 Tetramethyl 2,4a-Methanonaphthalen ligand with the 3l4y receptor.

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