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Exploration of Volatile Compounds of Microalgae *Spirulina platensis* as an Inhibitory α -glucosidase Candidate: In Silico Approach

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Abstract

Inhibitors of α -glucosidase are one of the important therapies in controlling diabetes mellitus, a metabolic disease with an increasing global prevalence that requires safer treatment alternatives. This study aims to explore the potential of bioactive compounds from *Spirulina platensis* as antidiabetic candidates using an in-silico approach. The research methods include analysis of bioactive components through GC-MS, prediction of physicochemical properties, pharmacokinetics, and toxicity (ADME-T), validation of docking methods, and simulation of molecular docking against α -glucosidase enzyme (PDB ID: 2QMJ). The results showed that the ten best compounds met the drug-likeness criteria and had good ADME-T profiles, including 3-Buten-2-one; 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)- (β -ionone); 2(4H)-Benzofuranone, 5,6,7,7a-tetrahydro-4,4,7a-trimethyl-; (R)- (Dihydroactinidiolide), 3,7,11-Trimethyl-1-dodecanol (Farnesanol); 9-Octadecen-1-ol, (Z)- (Oleyl Alcohol), Cyclohexanol, 2-methyl-5-(1-methylethyl)-; (1. α ., 2. β ., 5. α .)- ((+)-Carvomenthol); Levomenthol, 2-Buten-1-one; 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-(Damascone); 2,2,6,7-Tetramethyl-10-oxatricyclo[4.3.0.1(1. 7)] decan-5-one (Ketalactone); 7-Acetyl-3,3-dimethylbicyclo [4.1.0] heptan-2-one (7-Acetyl-Bicycloheptanone); and Acetic acid, 6,6-dimethyl-2-methylene-7-(3-oxobutylidene) oxepan-3-ylmethyl ester (ADM-ester). The docking results show that some compounds have good binding affinity and are able to form stable interactions with active residues of α -glucosidase. *Spirulina platensis* has potential as a source of natural α -glucosidase inhibitor candidates for antidiabetic therapy.

Keywords: *Spirulina platensis*, α -glucosidase, GC-MS, molecular docking, in silico, antidiabetic

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease characterized by hyperglycemia due to impaired insulin secretion or action (Alam et al., 2016). The prevalence of DM continues to increase and has become a global health problem, with WHO (2013) reporting 347 million sufferers worldwide (Chan, 2016). Indonesia ranks seventh with 13.7 million cases. Conventional therapies such as α -glucosidase inhibitors (e.g. acarbose) are effective in lowering postprandial glucose, but often cause side effects in the form of gastrointestinal disorders (Kusumawati et al., 2021; Laoufi et al., 2017). Therefore, there is a need to search for new active compounds as candidates for safer therapies based on natural ingredients.

Spirulina platensis is a type of photosynthetic cyanobacterium microalgae that is rich in protein (55-65%), essential amino acids, vitamins, minerals, pigments (phycocyanin, chlorophyll, carotenoids), and secondary metabolites such as flavonoids, phenols, steroids, and saponins. These bioactive contents have been reported to have pharmacological activities, including as antioxidants, anticancer, and antidiabetic (Gheda et al., 2021; Mane & Chakraborty, 2018). Previous in vivo studies have shown that aqueous extracts of *S. platensis* are able to lower blood glucose levels and oxidative stress parameters, although the underlying molecular mechanisms have not been fully elucidated (Aissaoui et al., 2017; Nasirian et al., 2018).

The in silico approach with molecular docking method is an efficient alternative to trace ligand-receptor interactions, especially in identifying the potential of bioactive compounds as inhibitors of α -glucosidase enzyme, which plays a role in carbohydrate hydrolysis (Holidah et al., 2018; Tao et al., 2019). This method can provide early predictions regarding binding affinity and types of molecular interactions, thus accelerating the process of discovering natural drug candidates before in vitro or in vivo (Dona et al., 2019; Velázquez-Libera et al., 2020). In line with this, a number of studies have utilized the in-silico approach to explore the bioactive potential of *Spirulina platensis* against various biological targets. Susantiningsih et al. (2024) reported that *phycocyanin*, *genistein*, and *ferulic acid* compounds from *Spirulina* have the ability to interact with target proteins such as TNF- α and p21 that play a role in aging and inflammatory pathways, with docking results showing strong binding affinity (ΔG *phycocyanin* around -15.0 kcal/mol) and low K_i value of *genistein* (~ 7.3 μ M), thus indicating significant inhibitory potential (Tiwuk Susantiningsih et al., 2024).

In addition, volatile analysis with GC-MS also revealed the diversity of volatile metabolites in *Spirulina*, including groups of alkenes, ketones, aldehydes, alcohols, and esters. Paraskevopoulou et al. (2024) even identified up to 128 volatile organic compounds (VOCs), including *hexanal*, *β -ionone*, *nonanal*, *hept-2-enal*, serta *oct-1-en-3-ol* as the dominant components (Paraskevopoulou et al., 2024). Some of these compounds are not only reported to have potential as antidiabetic candidates through α -glucosidase inhibition, but also have antimicrobial, anti-inflammatory, antioxidant, and chemopreventive activities, thus showing broad pharmacological prospects. Based on this background, this study focused on exploring the active components of *Spirulina platensis* through an in-silico approach to identify potential bioactive compounds as α -glucosidase inhibitors.

Method

GC-MS Analysis

Bioactive compounds of *Spirulina platensis* were identified using data from Gas Chromatography-Mass Spectrometry (GC-MS) results that have been conducted in previous studies. The GC-MS process involves the separation of compound components based on their volatility and molecular mass. The sample is put into a chromatographic column to be separated, then ionization is carried out on a mass spectrometer detector to produce a mass spectrum. The detected compounds are compared with a library database to identify the chemical structure. The GC-MS data obtained became the basis for selecting active compound candidates with potential as α -glucosidase inhibitors.

Prediction of Physicochemical, Pharmacokinetic, and Toxicity (ADME-T) Properties

Compounds identified by GC-MS were screened based on Lipinski's rule of five. Parameters observed include molecular weight (≤ 500 Da), logP (≤ 5), number of hydrogen bond donors (≤ 5), and hydrogen bond acceptors (≤ 10) (Nurfadhila et al., 2023). Predictions were performed using *SwissADME* (Anandhy, 2021). Pharmacokinetic evaluation (absorption, distribution, metabolism, excretion) was analyzed with *pkCSM* (Pires et al., 2015). Meanwhile, toxicity prediction included in silico AMES toxicity test, potential hepatotoxicity, and LD₅₀ value.

Molecular Docking

Receptor structure preparation was performed by downloading α -glucosidase protein crystal (PDB ID: 2QMJ) from Protein Data Bank. Water molecules were removed, polar hydrogen atoms were added, and charges were set *AutoDockTools* (Weni et al., 2020). The ligand structure was obtained from *PubChem* in SMILES format, then the energy optimization of the compound structure was carried out and converted into PDBQT. Furthermore, the validation process of the docking method was carried out by re-docking the comparator ligand (acarbose) into the active site of the target protein. The success of validation is determined from the Root Mean Square Deviation (RMSD) value, with RMSD criteria ≤ 2 Å which indicates valid docking results (Velázquez-Libera et al., 2020).

The docking simulation used *AutoDock Vina* on *PyRx* (Dallakyan & Olson, 2015). The initial step with the grid box was directed at the active pocket of α -glucosidase. The docking results were analyzed based on the binding affinity value (kcal/mol) to assess the stability of the ligand-receptor bond. The ligand-receptor interaction was then visualized with *BIOVIA Discovery Studio*, including hydrogen bonds, hydrophobic interactions, and ligand position in the protein active site (Chaudhary & Mishra, 2016).

Result and Discussion

Lipinski Evaluation and ADME-T Prediction

The results of the analysis (Table 1 and Table 2) showed the 10 best compounds of *Spirulina platensis* that met the criteria of drug-likeness and the most favorable pharmacokinetic profile. The ten compounds include, 3-Buten-2-one, 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)- (β ionone), 2(4H)-Benzofuranone, 5,6,7,7a-tetrahydro-4,4,7a-trimethyl-, (R)- (Dihydroactinidiolide), 3,7,11-Trimethyl-1-dodecanol (Farnesanol), 9-Octadecen-1-ol, (Z)- (Oleyl Alcohol), Cyclohexanol, 2-methyl-5-(1-methylethyl)-, (1.alpha.,2.beta.,5.alpha.)- ((+)-Carvomenthol), Levomenthol, 2-Buten-1-one, 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)- (Damascone), 2,2,6,7-Tetramethyl-10-oxatricyclo [4.3.0.1(1.7)] decan-5-one (Ketalactone), 7-Acetyl-3,3-dimethylbicyclo [4.1.0] heptan-2-one (7-Acetyl-Bicycloheptanone), and Acetic acid,6,6-dimethyl-2-methylene-7-(3-oxobutylidene) oxepan-3-ylmethyl ester (ADM-ester). All compounds fulfill Lipinski's rule, with molecular weight, number of hydrogen bond donor-acceptors, and logP within the ideal range. This suggests that the compounds have the potential to be developed as oral drug candidates because they have good membrane permeability (Lipinski, 2004; Pollastri, 2010).

Table 1. Physicochemical Prediction Results

No.	Compound Name	Formula Molecule	Retention Time (min)	Peak %	Molecular Weight (<500 g/mol)	LogP (<5)	H-bond donor (<5)	H-bond acceptor donor (<10)	Lipinski's Rule of Five
1.	3,7,11-Trimethyl-1-dodecanol (Farnesanol)	C15H32O	18,546	24,1	228.41 g/mol	4.20	1	1	Yes
2.	2(4H)-Benzofuranone, 5,6,7,7a-tetrahydro-4,4,7a-trimethyl-, (R)- (Dihydroactinidiolide)	C11H16O2	14,906	19,9	180.24 g/mol	2.37	0	2	Yes
3.	3-Buten-2-one, 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)- (β ionone)	C13H20O	14,092	17	192.30 g/mol	2.94	0	1	Yes
4.	2-Buten-1-one, 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)- (Damascone)	C13H20O	14,092	3,17	192.30 g/mol	2.94	0	1	Yes
5.	2,2,6,7-Tetramethyl-10-oxatricyclo [4.3.0.1(1.7)] decan-5-one (Ketalactone)	C13H20O2	14,914	2,44	208.30 g/mol	2.22	0	2	Yes
6.	9-Octadecen-1-ol, (Z)- (Oleyl Alcohol)	C18H36O	18,446	2,43	268.48 g/mol	4.79	1	1	Yes
7.	Acetic acid, 6,6-dimethyl-2-methylene-7-(3-oxobutylidene) oxepan-3-ylmethyl ester (ADM-ester)	C16H24O4	14,100	1,94	280.36 g/mol	1.78	0	4	Yes
8.	7-Acetyl-3,3-dimethylbicyclo [4.1.0] heptan-2-one (7-Acetyl-Bicycloheptanone)	C11H16O2	14,906	1,49	180.24 g/mol	1.56	0	2	Yes
9.	Cyclohexanol, 2-methyl-5-(1-methylethyl)-, (1.alpha.,2.beta.,5.alpha.)- ((+)-Carvomenthol)	C10H20O	21,372	1,32	156.27 g/mol	2.45	1	1	Yes
10.	Levomenthol	C10H20O	21,372	0,56	156.27 g/mol	2.45	1	1	Yes

Table 2. Pharmacokinetic Prediction Results

No.	Compound Name	Absorption		Distribution		Metabolism				Excretion	Toxicity	
		HIA ^a	Caco2 ^b	VDss ^c	BBB ^d	CYP 2D6 ^e (S)	CYP 3A4 ^f (S)	CYP 2D6 ^g (I)	CYP 3A4 ^h (I)	Total Clearance ⁱ	AMES ^j	LD50 ^k
1.	<i>3-Buten-2-one, 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)- (β ionone)</i>	95.051 %	1.515	0.346	0.822	No	No	No	No	1.303	No	1.684
2.	<i>2(4H)-Benzofuranone, 5,6,7,7a-tetrahydro-4,4,7a-trimethyl-, (R)- (Dihydroactinidiolide)</i>	96.796 %	1.613	0.223	0.286	No	No	No	No	1.051	No	1.987
3.	<i>3,7,11-Trimethyl-1-dodecanol (Farnesanol)</i>	91.753 %	1.504	0.424	0.806	No	No	No	No	1.526	No	1.556
4.	<i>9-Octadecen-1-ol, (Z)- (Oleyl Alcohol)(Oleyl Alcohol)</i>	89.622 %	1.469	0.441	0.826	No	Yes	No	No	1.984	No	1.596
5.	<i>Cyclohexanol, 2-methyl-5-(1-methylethyl)-, (1.alpha.,2.beta.,5.alpha.)- ((+)-Carvomenthol)</i>	95.019 %	1.374	0.133	0.822	No	No	No	No	1.197	No	1.994
6.	<i>Levomenthol</i>	95.257 %	1.376	0.137	0.584	No	No	No	No	1.182	No	1.946
7.	<i>2,2,6,7-Tetramethyl-10-oxatricyclo [4.3.0.1(1.7)] decan-5-one (Ketalactone)</i>	97.426 %	1.5	0.511	0.351	No	No	No	No	0.933	No	2.021

8.	<i>2-Buten-1-one, 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)- (Damascone)</i>	96.422 %	1.229	0.273	0.594	No	No	No	No	1.355	No	1.811
9.	<i>7-Acetyl-3,3-dimethylbicyclo [4.1.0] heptan-2-one (7-Acetyl-Bicycloheptanone)</i>	98.759 %	1.28	0.112	0.409	No	No	No	No	0.121	No	1.89
10.	<i>Acetic acid, 6,6-dimethyl-2-methylene-7-(3-oxobutylidene) oxepan-3-ylmethyl ester (ADM-ester)</i>	96.552 %	1.35	-0.09	-0.041	No	No	No	No	1.312	No	2.164

Criteria: a: (> 30%)

b: (> 0.90 log Papp in 10-6 cm/s)

c: (0.15 –0.45 Log L/Kg)

d: (< -1 logBB)

e-h: (No), i: (> 0.2 log ml/min/kg)

j: (Yes/No)

k: (>5000 mg/Kg)

Pharmacokinetic prediction results (Table 2) showed that all *Spirulina platensis* compounds had excellent human intestinal absorption (HIA), being above 89%, with the highest values shown by oleh 7-Acetyl-3,3-dimethylbicyclo [4.1.0] heptan-2-one (7-Acetyl-Bicycloheptanone) (98.75%) and 2,2,6,7-Tetramethyl-10-oxatricyclo [4.3.0.1(1.7)] decan-5-one (Ketalactone) (97.42%). The permeability values of Caco-2 also all exceeded the criterion of 0.90 log Papp, indicating good oral bioavailability potential. On distribution parameters, most of the compounds showed volume of distribution (VDss) within the normal range (0.133-0.511 log L/kg), with ketalactone having the highest value (0.511 log L/kg), indicating relatively wide tissue distribution. Blood brain barrier (BBB) permeability values were mostly positive, such as 3-Buten-2-one, 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)- (β ionone) (0,822), 3,7,11-Trimethyl-1-dodecanol (Farnesanol) (0,806), dan 9-Octadecen-1-ol, (Z)- (Oleyl Alcohol) (0,826), thus potentially penetrating the central nervous system (Pires et al., 2015).

In terms of metabolism, almost all compounds did not act as substrates or inhibitors of cytochrome P450 enzymes, except 9-Octadecen-1-ol, (Z)- (Oleyl Alcohol) which was detected as a substrate of CYP3A4. This suggests most of the compounds have stable metabolic profiles and low risk of drug interactions. In terms of excretion, the total clearance values varied, with 9-Octadecen-1-ol, (Z)- (Oleyl Alcohol) showing the highest value (1.984 log ml/min/kg) and therefore potentially eliminated faster. Meanwhile, 7-Acetyl-3,3-dimethylbicyclo [4.1.0] heptan-2-one (7-Acetyl-Bicycloheptanone) had the lowest clearance (0.121 log ml/min/kg), indicating a possible longer retention in the body. Toxicity tests showed that all compounds were negative in the AMES test, so they are not mutagenic. LD₅₀ values ranged from 1,556-2,164 mg/kg, which is categorized as low toxicity (Anandhy, 2021; Pires et al., 2015).

Docking Validation Analysis

Validation was performed by re-docking acarbose against α -glucosidase. Docking validation parameters in Table 3 show RMSD ≤ 2 Å which is 1.2358 Å, which indicates the docking method is valid and can be used for simulation of test compounds. Visualization of acarbose interaction in Table 5 shows hydrogen bonding with residues ASP443, ASN207, and ASP542. In addition, akarbose is also involved in hydrophobic interactions with residues TYR299 and PHE575, as well as Van der Waals interactions with residues TRP406, PHE450, and ILE364. The many types of interactions formed confirm the role of acarbose as a stable natural inhibitor of α -glucosidase, thus showing the strongest binding affinity compared to other ligands (FENG et al., 2022; Liu et al., 2021).

Table 3. Docking Validation Parameters

Grid Box						Exhaustiveness
Center			Dimension (Å)			
X	Y	Z	X	Y	Z	
-20.433	-6.3196	-5.7569	14.2586	14.2437	22.5914	

Docking Results of *Spirulina platensis* Compounds against α -Glucosidase

Molecular docking of eleven selected compounds from *Spirulina platensis* was successfully performed using AutoDock Vina on the target protein α -glucosidase. The docking results produced binding affinity values that varied between -4.0 to -6.0 kcal/mol, while the native ligand showed the lowest binding energy of -9.8 kcal/mol. A more negative binding energy indicates a stronger interaction between the ligand and the receptor (Na'Allah et al., 2021; Pantsar & Poso, 2018).

Of the ten test ligands, ADM-ester ranks first with the best binding affinity is *Acetic acid, 6,6-dimethyl-2-methylene-7-(3-oxobutylidene) oxepan-3-ylmethyl ester (ADM-ester)* (−6,0 kcal/mol), diikuti *Levomenthol* (−5,6 kcal/mol), *7-Acetyl-3,3-dimethylbicyclo [4.1.0] heptan-2-one (7-Acetyl-Bicycloheptanone)* (−5,6 kcal/mol), *3-Buten-2-one, 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)- (β ionone)* (−5,5 kcal/mol), dan *2(4H)-Benzofuranone, 5,6,7,7a-tetrahydro-4,4,7a-trimethyl-, (R)- (Dihydroactinidiolide)* (−5,5 kcal/mol). Senyawa lain seperti *2,2,6,7-Tetramethyl-10-oxatricyclo [4.3.0.1(1.7)] decan-5-one (Ketalactone)* (−5,0 kkal/mol), *3,7,11-Trimethyl-1-dodecanol (Farnesanol)* (−5,4 kkal/mol), *9-Octadecen-1-ol, (Z)- (Oleyl Alcohol)* (−5,3 kkal/mol), and *2-Buten-1-one, 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)- (Damascone)* (−5,2 kkal/mol) showed moderate affinity, while *Cyclohexanol, 2-methyl-5-(1-methylethyl)-, (1.alpha.,2.beta.,5.alpha.)- ((+)-Carvomenthol* (−4,0 kkal/mol) had the lowest affinity.

In addition to the energy values, the interaction analysis in Table 4 and Table 5 shows the variety of bond types formed between the ligands and the active residues of α -glucosidase. *Acetic acid, 6,6-dimethyl-2-methylene-7-(3-oxobutylidene) oxepan-3-ylmethyl ester (ADM-ester)*, which ranks first, forms hydrogen bonds with residue ASP542 as well as pi-sigma interactions with TYR299, making it the most promising candidate. Levomenthol interacts with MET444 via hydrogen bonds and with TYR299 via pi-sigma interactions, while *7-Acetyl-3,3-dimethylbicyclo [4.1.0] heptan-2-one (7-Acetyl-Bicycloheptanone)* shows a combination of hydrophobic interactions on aromatic residues that strengthen its binding, *3-Buten-2-one, 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)- (β ionone)* and *5,6,7,7a-tetrahydro-4,4,7a-trimethyl-, (R)- (Dihydroactinidiolide)* interact predominantly through hydrophobic forces with aromatic residues such as TYR299 and PHE575, although they do not form strong hydrogen bonds (Touhtouh et al., 2024). *2,2,6,7-Tetramethyl-10-oxatricyclo [4.3.0.1(1.7)] decan-5-one (Ketalactone)* forms hydrogen bonds with polar residues SER394 and SER395, which play an important role in stabilizing ligand binding (Jyske et al., 2020). Furthermore, the hydrogen bonding surface area analysis of the protein-ligand complexes displayed in Figure 2 provides a visual representation of the strength and location of the hydrogen bonding interactions of each compound with the α -glucosidase protein.

Table 4. Ligand Interaction on Target Protein α -glucosidase

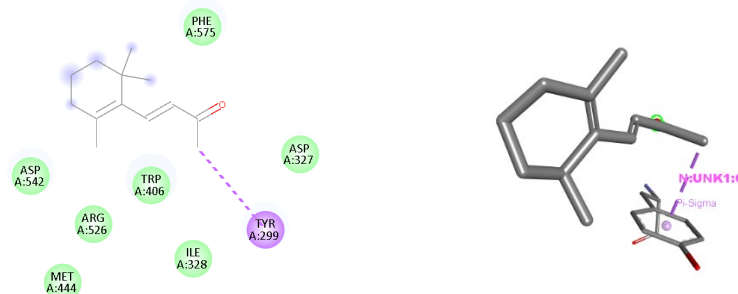
Ligand	Interaction with Amino Acid Residues				
	Binding Affinity (kcal/mol)	Conventional Hydrogen Bonding	Carbon Hydrogen Bonding	Hydrophobic Interaction	Van der Waals Bonding
Acarbose (Native ligand)	-9,8	ASN:207 (2,99), ASP:443 (2,31)	ASP:542 (2,64), ASP:542 (2,70), ASP:542 (1,79), ASP:327 (2,40)	TYR:299, PHE:575 (alkyl, pi-alkyl)	THR:205, ASN:209, ALA:576, ARG:598, TRP:539, TRP:441, HIS:600, ILE:364, ILE:328, MET:444, TRP:406, PHE:450

<i>Acetic acid, 6,6-dimethyl-2-methylene-7-(3-oxobutylidene) oxepan-3-ylmethyl ester (ADM-ester)</i>	-6	-	ASP:542 (3,56), ASP:542 (3,71)	TYR:299 (<i>pi-sigma</i>)	ILE:328, ASP:327, ASP:443, PHE:575, TRP:406 ARG:526, MET:444, ASP:203, PHE:450
<i>Levomenthol</i>	-5,6	MET:444 (2,62)	-	TYR:299 (<i>Pi sigma</i>), TRP:406 (<i>pi-alkyl</i>)	-
<i>7-Acetyl-3,3-dimethylbicyclo [4.1.0] heptan-2-one (7-Acetyl-Bicycloheptanone)</i>	-5,6	ARG:526 (2,79)	-	-	HIS:600, ASP:443, ASP:542, TRP:539, TRP:441, ILE:364, ASP:327, PHE:575, TRP:406, TYR:299
<i>3-Buten-2-one, 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)- (β ionone)</i>	-5,5	-	-	TYR:299 (<i>Pi sigma</i>)	PHE:545, ASP:327, TRP:406, ILE:328, ARG:526, MET:444, ASP:542
<i>2(4H)-Benzofuranone, 5,6,7,7a-tetrahydro-4,4,7a-trimethyl-, (R)- (Dihydroactinidiolide)</i>	-5,5	-	-	TYR:299 (<i>Pi sigma</i>), PHE:575 (<i>pi-alkyl</i>)	TRP:539, ASP:542, ARG:526, TRP:441, MET:444, ASP:443, ILE:364, ASP:327, ILE:328, TRP:406
<i>3,7,11-Trimethyl-1-dodecanol (Farnesanol)</i>	-5,4	HIS:600 (2,29)	ASP:443 (3,76)	TYR:299 (<i>Pi sigma</i>), TRP:406 (<i>pi-alkyl</i>), ILE:328 (<i>pi-alkyl</i>)	MET:444, PHE:450, ASP:203, ARG:526, PHE:575, ASP:542, ASP:327,

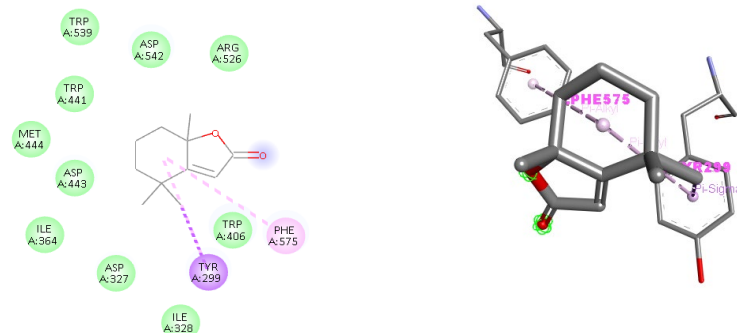
						TRP:441, TRP:329, ASP:443, ARG:598
						TYR:605, GGLY:602, GLN:603, ASP:542, ILE:364, ASP:443, TRP:539, ASP:327, TRP:441, ARG:598, HIS:600, ASP:571
<i>9-Octadecen-1-ol, (Z)-(Oleyl Alcohol)</i>	-5,3	-	-	ALA:576 (<i>pi-alkyl</i>), TRP:406 (<i>pi-alkyl</i>), PHE:575 (<i>pi-alkyl</i>), TYR:299 (<i>pi-alkyl</i>)		
<i>2-Buten-1-one, 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-(Damascone)</i>	-5,2	-	-	ALA:576 (<i>pi-alkyl</i>), PHE:575 (<i>pi-alkyl</i>), TRP:406 (<i>pi-alkyl</i>), TYR:299 (<i>pi-alkyl</i>)	ASP:542, TYR:605, GLY:602, GLN:603	
<i>2,2,6,7-Tetramethyl-10-oxatricyclo[4.3.0.1(1.7)]decan-5-one (Ketalactone)</i>	-5	SER:395 (3,14), SER:394 (3,00)	-			ASP:396, SER:456, SER:454, GLY:547, CYS:483, CYS:458, ASP:485, SER:459
<i>Cyclohexanol, 2-methyl-5-(1-methylethyl)-, (1.alpha.,2.beta.a.,5.alpha.)-((+)-Carvomenthol)</i>	-4	-	-	TYR:299 (<i>pi sigma</i>)		PHE:575, ARG:526, ASP:542, TRP:406, MET:444, PHE:450

Compound	Interaction Visualization
Acarbose (Native ligand)	
Acetic acid,6,6-dimethyl-2 methylene-7-(3-oxobutylidene)oxepan-3-ylmethyl ester (ADM-ester)	
Levomenthol	
7-Acetyl-3,3-dimethylbicyclo[4.1.0] heptan-2-one (7 Acetyl-Bicycloheptanone)	

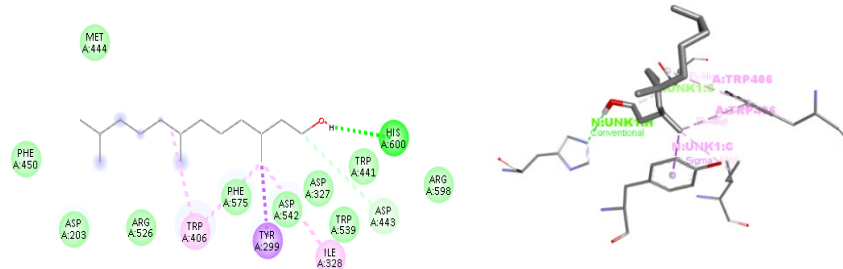
3-Buten-2-one, 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)- (β ionone)



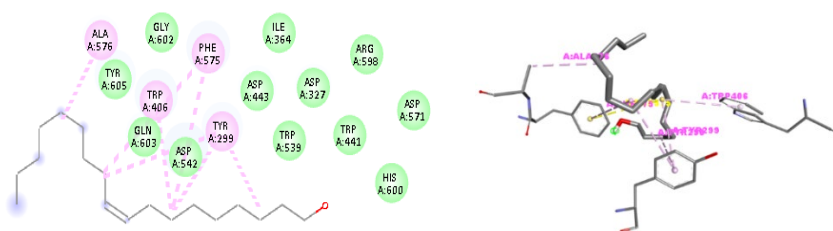
2(4H)-Benzofuranone, 5,6,7,7a-tetrahydro-4,4,7a trimethyl-, (R)- (Dihydroactinidiolide)



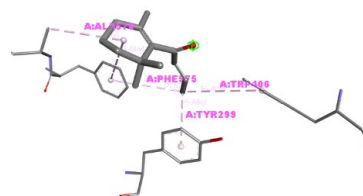
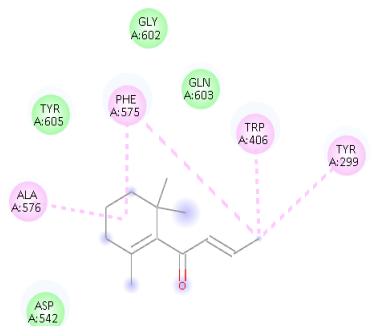
3,7,11-Trimethyl-1-dodecanol (Farnesanol)



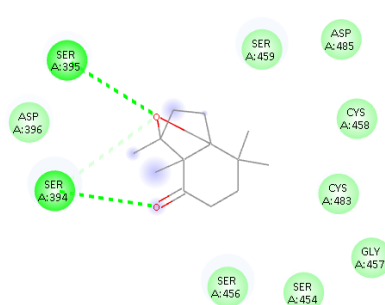
9-Octadecen-1-ol, (Z)- (Oleyl Alcohol)



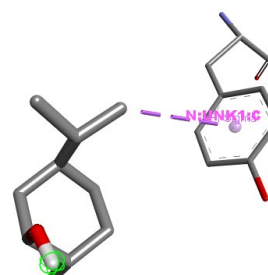
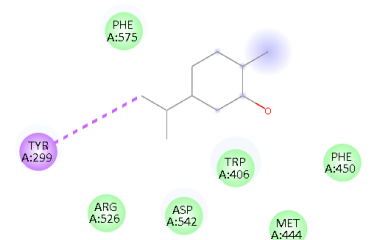
2-Buten-1-one, 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)
(Damascone)



2,2,6,7-Tetramethyl-10-oxatricyclo [4.3.0.1(1.7)] decan-5-one (Ketalactone)



Cyclohexanol, 2-methyl-5-(1-methylethyl)-, (1.alpha.,2.beta.,5.alpha.)- ((+)-Carvomenthol)



Interaction Type Description:

	van der Waals		Pi-Sigma
	Conventional Hydrogen Bond		Amide-Pi Stacked
	Carbon Hydrogen Bond		Alkyl
	Unfavorable Donor-Donor		Pi-Alkyl

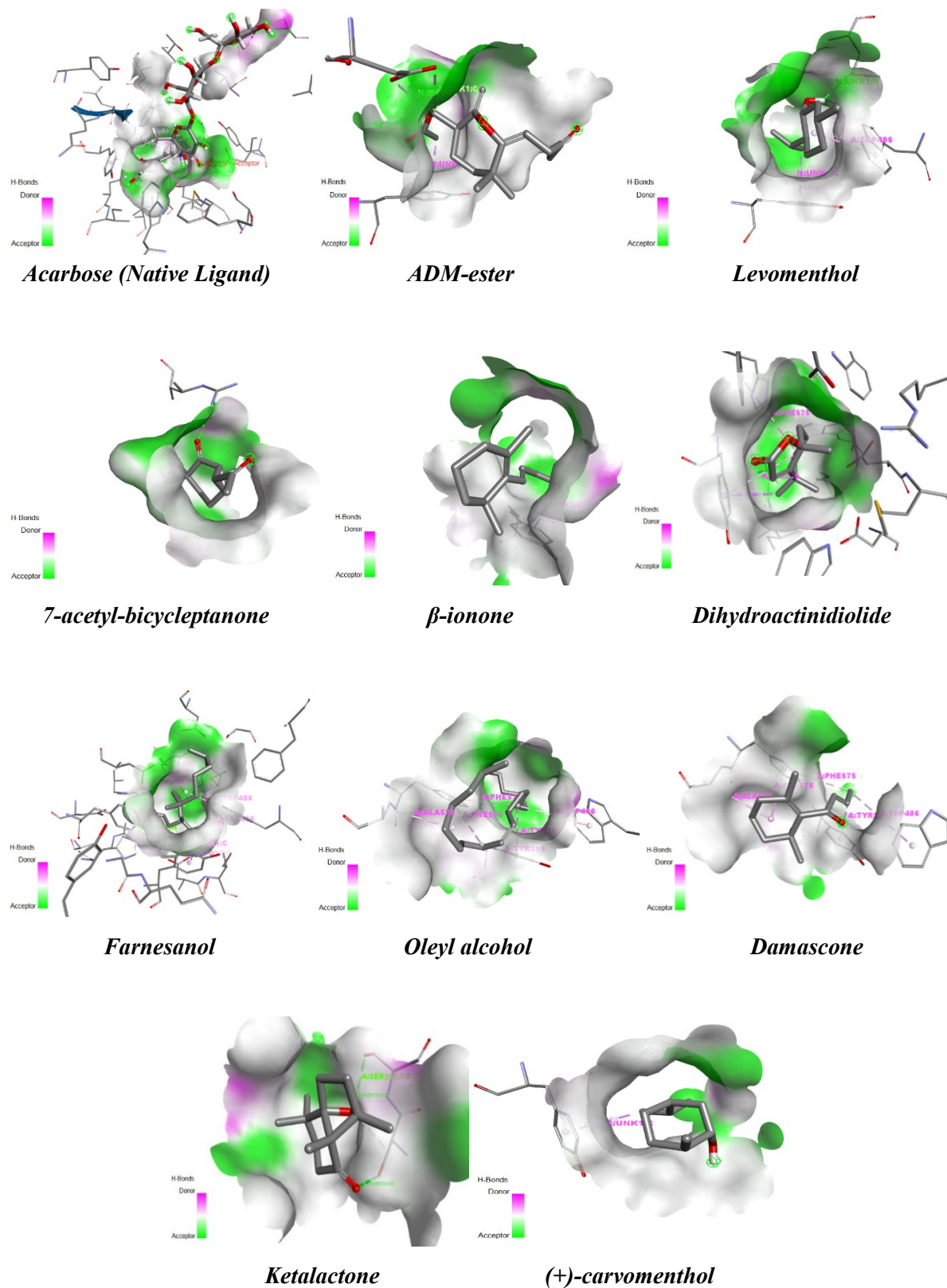


Figure 2. Visualization of hydrogen bonding surface area of protein-ligand complexes in α -glucosidase

Overall, compounds with a greater number of hydrogen bonds, such as *Acetic acid,6,6-dimethyl-2-methylene-7-(3-oxobutylidene) oxepan-3-ylmethyl ester (ADM-ester)*, tend to have higher binding affinities than other ligands that rely solely on hydrophobic interactions (Pantsar & Poso, 2018; Shen et al., 2021). These results confirm that *Acetic acid,6,6-dimethyl-2-methylene-7-(3-oxobutylidene) oxepan-3-ylmethyl ester (ADM-ester)*, *Levomenthol*, and *7-Acetyl-3,3-dimethylbicyclo [4.1.0] heptan-2-one (7-Acetyl-Bicycloheptanone)* can be categorized as the main candidates of α -glucosidase inhibitors from *Spirulina platensis*, which have the potential to be further developed as in silico-based antidiabetic agents.

Conclusion

This study successfully explored the bioactive components of *Spirulina platensis* as candidate α -glucosidase inhibitors using an in-silico approach. GC-MS analysis identified ten main compounds that meet the drug-likeness criteria and have a good pharmacokinetic profile. The results of docking validation with acarbose as native ligand resulted in RMSD value ≤ 2 Å, so the method used was declared valid. The molecular docking showed *Acetic acid,6,6-dimethyl-2-methylene-7-(3-oxobutylidene) oxepan-3-ylmethyl ester (ADM-ester)*, *Levomenthol*, and *7-Acetyl-3,3-dimethylbicyclo [4.1.0] heptan-2-one (7-Acetyl-Bicycloheptanone)* has the most favourable binding affinity towards α -glucosidase enzyme through a combination of hydrogen bonding and hydrophobic interactions on key residues such as ASP542, TYR299, MET444, and SER394. Meanwhile, other compounds such as *3-Buten-2-one*, *4-(2,6,6-trimethyl-1-cyclohexen-1-yl)- (β ionone)* and *5,6,7,7a-tetrahydro-4,4,7a-trimethyl-, (R)- (Dihydroactinidiolide)* tend to interact through hydrophobic forces with moderate affinity. Overall, these findings confirm that bioactive compounds from *Spirulina platensis* have the potential to be further developed as natural α -glucosidase inhibitor candidates for antidiabetic therapy.

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