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SHREDDED TUNA FORTIFIED WITH BANANA BLOSSOMS AS AN ANTI-DIABETIC FOOD CANDIDATE: AN INVESTIGATIONAL *IN SILICO* STUDY

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ABSTRACT

Fish shredded is nutritious and has a soft texture, less stringy than shredded beef. The compounds in tuna shredded fortified with banana blossoms and their potential as antidiabetic are not yet known. The purpose of this study was to identify phytochemical bioactive compounds in tuna shredded fortified with banana blossoms and to study its potential as an antidiabetic functional food *in silico*. The 70% fortified tuna shreds were extracted using hexane, followed by ethyl acetate and finally using methanol. The methanol filtrate was evaporated to obtain methanol extract of shredded fish and analyzed using LC-HRMS. Phytochemical compounds were analyzed for antidiabetic potential in silico using Open Babel GUI software version 2.4.1, PyRx 0.8 (The scrips Research Institute), PyMOL™ 1.7.4.5, and Discovery Studio Visualizer (2021). The methanol extract of banana heart fortified tuna fish contained 32 compounds. The results of docking the compounds against the α-glucosidase receptor showed that the compound that had a lower or the same binding affinity with acarbose (-8.00 Kcal/mol) and native ligand (-6.00 Kcal/mol) was flurandrelonide (-9.40 kcal/mol), Quercetin-3β-D-glucoside (-9.30 kcal/mol), sakuranetin (-8.80 kcal/mol), curcumin (-7.70 kcal/mol), ar-turmerone (-7.20 kcal/mol), nootkatone (-7.20 kcal/mol), and ferulic acid (-6.90 kcal/mol). The lower the binding affinity value, the stronger the inhibition of α-glucosidase. Phytochemical compounds in shredded tuna fortified with banana blossoms that may act as antidiabetic agents through in silico α-glucosidase inhibition are flurandrelonide, quercetin-3β-glucosidase, sakuranetin, curcumin, ar-turmerone, and ferulic acid.

Keywords: α-glucosidase, *banana blossoms*, binding affinity, tuna shredded, *in silico*

INTRODUCTION

Shredded fish is a traditional processed product from fisheries, obtained through a drying process of raw materials to which certain spices have been added to improve taste and extend shelf life **(Sulistiyati *et al*., 2022)**. Shredded fish is one of the efforts to diversify fishery product processing products **(Ismail & Putra, 2017)**. **(Suryani *et al*., 2007)** state that shredded fish has the characteristics of a soft shape, delicious taste, distinctive smell, and has a relatively long shelf life of up to about 60 days, is relatively easy to make, and is ready to be consumed directly. The soft character of shredded fish products can also be a problem when compared to shredded beef or other terrestrial animal meats, which have a very fibrous appearance. Various efforts have been made to make fish shredded fibrous, such as by adding other fibrous ingredients **(Suryani *et al*., 2007)**. Efforts to add fibrous material have been carried out on various types of shredded fish, including adding *keluwih* to shredded African catfish **(Rohmawati *et al*., 2019)**, adding jackfruit straw to shredded red tilapia **(Ismail and Putra, 2019)**, added tofu pulp to shredded tilapia fish **(Rahardjo *et al*., 2017)**, added coconut pulp to shredded tuna *pindang* **(Hardoko *et al*., 2015)**, shredded tuna **(Rohmawati *et al*., 2019)**, shredded skipjack tuna **(Djamaludin *et al*., 2022)**, shredded fly fish **(Mamuaja & Aida, 2014)**, and shredded catfish **(Aisah *et al*., 2021)**. In addition, **Alam *et al*. (2020)** added banana and banana peel flour to increase the fiber content of cookies. The addition of banana blossom is also carried out on other products such as meatballs **(Kurnianingtyas *et al*., 2014)**, snakehead fish jerky **(Sulistiyati *et al*., 2017)**, tuna fish jerky **(Hajar & Handayani, 2013)**, tilapia fish nuggets **(Simanullang *et al*., 2021)**, beef sausage **(Fattah, 2016; Fattah & Hidayat, 2015)**. The number of products added with banana blossom shows the important role of banana blossom in various food products in Indonesia. Among other benefits for using banana blossoms in food, they are underused, affordable, and a good source of fiber and anthocyanins that can increase nutritional value and improve health **(Khoirunisa *et al*., 2019)**. Banana plants grow throughout the year, are easy to cultivate, and Indonesia is the largest banana producer in Asia, resulting in high banana blossom **(Lestario *et al*., 2009)**. The health benefits of banana blossom are antioxidant capacity, improving digestion, helping diet, improving blood circulation, increasing red blood cell production, preventing premature aging, increasing breast milk productivity **(Djamaludin *et al*., 2023; Harismayanti *et al*., 2018; Ningrum *et al*., 2011; Pratiwi *et al*., 2021; Wahyuni *et al*., 2012),** and lowering blood cholesterol level **(Ferdinan & Prasetya, 2018)**. Banana blossom contains a lot of natural substances that are good for health such as protein, carbohydrates, minerals, phosphorus, calcium, vitamin B1, vitamin C and the fiber content contained in banana blossom is also high, thus banana blossom is often said to be a food that contains nutrients that are rich in nutrients and quite complete **(Aida *et al*., 2014)**. Banana blossom also contains compounds of alkaloids, saponins, glycosides, tannins, flavonoids, and steroids which are beneficial for health **(Ningrum *et al*., 2011)**. Banana blossom can improve several diseases, one of which is diabetics, who can consume banana blossom because of its low glycemic index (GI) **(Pakaya *et al*., 2015)**. Another important component in banana heart is antioxidants which have health benefits, namely to overcome and prevent oxidative stress which has an important role in degenerative diseases. The benefits of antioxidants are that they can slow the speed of digestion in the intestine, provide a relatively long feeling of fullness, facilitate blood circulation and as an anticoagulant, which prevents blood clots **(Mamuaja & Aida, 2014)**. The antioxidants include phenolic or polyphenolic compounds such as flavonoids which can prevent oxidative reactions so that they can repair beta-pancreatic cell damage and increase insulin secretion **(Bansal *et al*., 2012; Verma *et al*., 2013)**. Natural antioxidants are also often used as anti-aging to repair damaged cells **(Coskun *et al*., 2005)**. Since banana blossom contains high fiber and also phytochemical compounds that are antidiabetic, then when banana blossom is added to shredded fish, it is hoped that the shredded fish product will also be antidiabetic. Therefore, it is necessary to analyze what compounds are contained in banana heart fortified shredded fish and their potential as a functional food as antidiabetic with molecular docking used *in silico*.

MATERIALS AND METHODS

Materials and Tools

The raw materials used for the manufacture of shredded tuna fortified with banana blossom, such as tuna (*Thunnus* sp.), banana blossom and spices. The tuna used was obtained from the Blimbing Market, Malang City and has the characteristics of clear eyes, bright red gills, a little slimy, the texture of the flesh is dense and

elastic when touched with a finger and measuring less than 50 cm long and about 2 Kg. The banana blossom used is the type of *kepok* banana obtained from Bunul Market and Muharto Market, Malang City. The seasonings used include garlic, shallots, coriander powder, sugar, table salt, turmeric, galangal, bay leaf, lemongrass, lime leaves, coconut milk and cooking oil. The materials for parameter testing include acetic acid (emsure brand), chloroform (emsure brand), potassium Iodide (emsure brand), aquades, sodium thiosulfate (emsure brand), tapioca flour (Cap Swan), filter paper (Whatman No. 1), tissue, label paper, aluminium foil (Klin Pak 8mx30cm) and plastic wrap (Cling Wrap 30mx30cm). Materials for *in silico* analysis were α-glucosidase (Code 3A4A and 1.6Å resolution of *Saccharomyces cerevisiae*) obtained from the website https://www.rcsb.org/, acarbose and metformin (ligand control) and also GLC (native ligand) were obtained from Pubchem https://pubchem.ncbi.nlm.nih.gov/). The tools used for LC-MS analysis consist of LC Alliance brand LC equipment 2996 (waters) with photodiode-array detector (PDA) 2996 (Waters) and MS type XEVOG2QTOF (Waters) equipment. The tools used during *in silico* process are Acer TravelMate P633-M Laptop, Intel(R) Core™ i5-3230M CPU @ 2.60GHz (4 CPUs), 4096MB RAM Memory, Open Babel GUI, PyMOL, Discovery Studio Visualizer and PyRx software.

The Process of Making Tuna Shredded Fortified with Banana Blossom

The process of making shredded tuna refers to the method of **Hardoko *et al.* (2015)**. Making shredded tuna consists of 3 steps, namely making crushed banana blossom, preparing fish meat, and making seasonings. The formulation of shredded tuna fortified with banana blossoms are tuna 250 g, banana blossom 175 g, garlic, 11 g, onion 21 g, coriander powder 4 g, sugar 21 g, salt 16 g, turmeric 10 g, galangal 25 g, bay leaves 3 g, lemongrass 19 g, lime leaves 3 g, and coconut milk 25 mL. The banana blossom mash is made by washing and cleaning the banana blossom, removing the outer skin to leave a yellowish white inside, steaming for 15 minutes, and then blending it. The crushed banana blossom is squeezed using a filter cloth to reduce the water content, so that the crushed banana blossom juice is ready to be used as an additional ingredient in the manufacture of shredded tuna. While the process of making banana blossom mash, tuna fish are weeded by removing the contents of the stomach, fins, head, and gills, and washed with running water. Clean tuna is steamed for 30 minutes, cooled, and separated from the meat. The tuna meat is then shredded using a grater. While the shredding process is carried out, the seasoning is also prepared by weighing the required spices according to the tuna shredded formulation (Table 1), mixing and mashing the spices with a blender so that a smooth seasoning is obtained. The spices are then mixed with coconut milk, grated fish meat, crushed banana heart, then boiled until boiling or until cooked. Furthermore, the stew of the shredded ingredients is filtered with a filter cloth and squeezed to obtain the residue of the shredded material. The remaining shredded juice is fried for about 5 minutes or until light brown. Abon which has been light brown in colour is removed and the oil is drained using a spinner, in order to obtain a dry floss which is ready to be packaged and analysed for its compounds.

Extraction of Tuna Shredded and Active Compound Analysis

The extraction process for shredded tuna is carried out using the stratified maceration method **Djamaludin *et al.* (2019)**. The maceration process begins with weighing the shredded 50 g and adding hexane solvent in a ratio of 1:5 and macerating at room temperature for 24 hours. The maceration products were filtered with filter paper and the residue was macerated at room temperature for 24 hours with ethyl acetate solvent in a ratio of 1:5. The result of maceration with ethyl acetate was filtered and the residue was macerated at room temperature for 24 hours with methanol solvent in a ratio of 1:5. Furthermore, the results of maceration with methanol were filtered through Whatman filter paper No.1 and the filtrate was taken to be evaporated at a temperature of 50°C at a speed of 100 rpm until the solvent evaporated completely and a methanol extract of shredded fish was obtained for compound analysis using LC-HRMS. LC-HRMS analysis using HPLC Thermo Scientific Dionex Ultimate 3000 RSLCnano with microflow meter. The mobile phase used was A: Water +0.1% formic acid, B: acetonitrile + 0.1% formic acid. The column used is Hypersil GOLD aQ 50x1mmx1.9 particle size. Flow rate 40 L/min. The mass spectrometry used was Thermo Scientific Q Exactive with a full scan at a resolution of 70,000, analysis time of 30 minutes with positive and negative ion modes.

Analysis of Pharmacokinetic (Drug-Likeness)

The drug-likeness analysis of the test compound/ligand is aimed for finding out whether the test compound/ligand complies with Lipinski's rule. The analysis was carried out online through the page http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp **(Jayaram *et al.*, 2012; Lipinski, 2004)**. This stage is carried out before molecular docking *in silico* analysis.

Molecular Docking

Molecular docking of the active compound obtained from the LC-MS results of banana heart fortified tuna shredded with α-glucosidase enzyme (3A4A; resolution 1.6Å) as a receptor using PyRx software. The α-glucosidase enzyme as receptor was obtained from the https://www.rcsb.org. The test ligands used were obtained from the active compound content of fortified tuna shredded banana blossom and control ligands in the form of acarbose and metformin, and also GLC as a native ligand. The 3D structure of the ligand was obtained from the PubChem https://pubchem.ncbi.nlm.nih.go in SDF. format. Then it is converted into PDB. format using the Discovery Studio software. Receptor preparation was carried out by separating the C chain structure from the intact structure, then saving it in *.pdbqt format. After being stored, the water molecule was removed and the natural ligand was separated from the enzyme chain C structure. The file was then saved in *.pdbqt format. The molecular docking process is carried out in the PyRx software and the type of docking was blinded docking. After docking is complete, the results of several docking modes along with the value of binding affinity (kcal/mol) are obtained. Next, visualize the docking results in 2D using Discovery Studio software.

Analysis of Toxicity and Bioavailability

The test ligands with the best binding affinity were tested for toxicity predictions one by one using an online toxicity test program accessed on the http://tox.charite.de/protox_II/ **(Banerjee *et al.*, 2018)**. Ligands that showed non-toxic results were tested for bioavailability (ADME) using a program that can be accessed at http://www.swissadme.ch/ **(Daina *et al.*, 2017)**.

RESULTS AND DISCUSSIONS

The results of compound analysis using LC-HRMS from methanol extract of shredded tuna fish fortified with banana blossom identified 32 compounds divided into groups of phytochemical compounds (steroids, alkaloids, flavonoids, terpenoids, and phenolics), organic compounds, fatty acids, and amino acids. Table 1 lists the identified compounds in detail.

Table 1 shows the compounds contained in shredded tuna fortified with banana blossom in the form of phytochemical compounds (steroids, alkaloids, flavonoids, terpenoids, phenolics), nutrients (amino acids and fatty acids), and organic compounds. The group of compounds that have the potential to be bioactive is mainly a group of phytochemical compounds and some organic compounds. The types of phytochemical compounds that can act as bioactive are flurandrenolide (steroid), DL-stachydrine (alkaloid), Quercetin-3β-D-glucoside (flavonoid), sakuranetin (flavonoid), curcumin (flavonoid), nootkatone (terpenoid), ar-turmerone (terpenoids), acetophenone, and ferulic acid (phenolic). The organic compound that is widely reported as bioactive is trans-cinnamaldehyde.

Pharmacokinetic Drug-Likeness Lipinski's Rule

Before docking the ligand to the receptor/enzyme α-glucosidase, each ligand of the active compound of tuna shredded fortified banana blossom was analysed according to Lipinski's rules. The Lipinski rule states that a ligand can be continued for the docking process if (1) the mass is less than 500 g/mol, (2) the Log P value is less than 5, (3) the number of hydrogen bond donors is less than 5, and (4) the number of hydrogen bond acceptors is less than 10 **(Lipinski, 2004)**. The suitability of the test ligand characteristics with the parameters of Lipinski's rule is a requirement that must be met before molecular docking is carried out. The results of the analysis of the suitability of the test ligand characteristics with the Lipinski rule parameters are presented in Table 2.

Table 1 Identified compounds in tuna shredded fortified banana blossom

No.	Retention Time (min.)	Molecule Weight	Formula	Compound	Compound Group
1	2.409	436.22734	$C_{24}H_{33}FO_6$	Flurandrenolide	Steroids
2	2.415	143.0941	$C_7H_{13}NO_2$	DL-Stachydrine	Alkaloids
3	8.702	464.0945	$C_{21}H_{20}O_{12}$	Quercetin-3β-D-glucoside	Flavonoids
4	13.51	286.08324	$C_{16}H_{14}O_5$	Sakuranetin	Flavonoids
5	14.692	368.12517	$C_{21}H_{20}O_6$	Curcumin	Flavonoids
6	17.016	218.1664	$C_{15}H_{22}O$	Nootkatone	Sesquiterpenoid
7	17.372	216.15096	$C_{15}H_{20}O$	(+)-ar-Turmerone	Sesquiterpenoid
8	20.483	120.05732	C_8H_8O	Acetophenone	Phenolic
9	7614	19405744	$C_{10}H_{10}O_4$	Ferulic acid	Phenolic
10	6.949	132.05712	C_9H_8O	trans-Cinnamaldehyde	Organic Compound
11	2.422	145.10976	$C_7H_{15}NO_2$	Acetylcholine	Organic Compound
12	2.826	109.06384	$C_5H_7N_3$	2-Amino-4-methylpyrimidine	Organic Compound
13	3.391	129.07855	$C_6H_{11}NO_2$	L-Pipecolinic acid	Organic Compound
14	3.554	136.038	$C_5H_4N_4O$	Hypoxanthine	Organic Compound
15	3.559	109.05264	C_6H_7NO	4-Aminophenol	Organic Compound
16	3.561	267.09593	$C_{10}H_{13}N_5O_4$	Adenosine	Organic Compound
17	8.54	195.1982	$C_{13}H_{25}N$	N-Cyclohexyl-N-methylcyclohexanamine	Organic Compound
18	22.612	390.27559	$C_{24}H_{38}O_4$	Bis(2-ethylhexyl) phthalate	Organic Compound
19	11.019	255.16155	$C_{17}H_{21}NO$	Diphenhydramine	Antihistamine
20	15.057	250.15611	$C_{15}H_{22}O_3$	3,5-di-tert-Butyl-4-hydroxybenzoic acid	Derivate Benzenoid
21	2.44	228.14672	$C_{11}H_{20}N_2O_3$	Prolylleucine	Amino Acid
22	2.248	203.11516	$C_9H_{17}NO_4$	Acetyl-L-carnitine	Amino Acid
23	2.743	117.0787	$C_5H_{11}NO_2$	Valine	Amino Acid
24	2.787	113.05866	$C_4H_7N_3O$	Creatinine	Amino Acid
25	2.835	155.06894	$C_6H_9N_3O_2$	L-Histidine	Amino Acid
26	2.898	174.11104	$C_6H_{14}N_4O_2$	DL-Arginine	Amino Acid
27	3.56	204.08933	$C_{11}H_{12}N_2O_2$	DL-Tryptophan	Amino Acid
28	8.469	197.11992	$C_{14}H_{15}N$	Dibenzylamine	Aromatic Amina
29	21.613	281.27083	$C_{18}H_{35}NO$	Oleamide	Fatty Acid
30	21.826	255.25545	$C_{16}H_{33}NO$	Hexadecanamide	Fatty Acid
31	22.386	283.28658	$C_{18}H_{37}NO$	Stearamide	Fatty Acid
32	25.762	337.33315	$C_{22}H_{43}NO$	Erucamide	Fatty Acid

Table 2 Ligand parameters to comply with Lipinski's rules

No.	Ligand	Mass (g/mol)	Log P	H Bond Donor	H Bond Acceptor
1	Flurandrenolide	436.000000	2.498700	2	6
2	DL-Stachydrine	143.000000	-1.024900	0	2
3	Quercetin-3β-D-glucoside	463.000000	-1.143710	4	8
4	Sakuranetin	274.000000	0.318340	2	5
5	Curcumin	350.000000	0.439250	2	6
6	Nootkatone	218.000000	3.904199	0	1
7	(+)-ar-Turmerone	196.000000	0.682600	0	1
8	Acetophenone	120.000000	1.889200	0	1
9	Ferulic acid	194.000000	1.498600	2	4
10	trans-Cinnamaldehyde	132.000000	1.898700	0	1
11	Acetylcholine	146.000000	0.255700	0	2
12	2-Amino-4-methylpyrimidine	109.000000	0.367220	2	3
13	L-Pipecolinic acid	129.000000	0.213100	2	3
14	Hypoxanthine	136.000000	-0.187100	2	4
15	4-Aminophenol	109.000000	0.974400	3	2
16	Adenosine	267.000000	-1.980000	4	8
17	N-Cyclohexyl-N-methylcyclohexanamine	195.000000	3.583599	0	1
18	Bis-(2-ethylhexyl) phthalate	388.000000	3.698699	0	4
19	Diphenhydramine	255.000000	3.354199	0	2
20	3,5-di-tert-Butyl-4-hydroxybenzoic acid	250.000000	3.685399	2	3
21	Prolylleucine	362.000000	2.403100	2	7
22	Acetyl-L-carnitine	203.000000	-1.235701	0	4
23	Valine	117.000000	0.054300	3	3
24	Creatinine	113.000000	-1.226900	2	4
25	L-Histidine	155.000000	-0.635900	4	4
26	DL-Arginine	174.000000	-1.548100	4	6
27	DL-Tryptophan	204.000000	1.122300	4	3
28	Dibenzylamine	197.000000	2.976400	1	1
29	Oleamide	281.000000	3.509200	2	2
30	Hexadecanamide	255.000000	3.952999	2	2
31	Stearamide	283.000000	3.062230	2	1
32	Erucamide	337.000000	4.083392	2	1

The results of the analysis (Table 2) showed that all ligands of the active compound of tuna shredded fortified banana blossom did not show any deviation from Lipinski's rule (no violation). Lipinski's rule aims to determine the physicochemical properties of ligands, so as to determine the

hydrophobic/hydrophilic character of a compound. So that it can pass through cell membranes by passive diffusion. Lipinski's first rule is mass, in which molecules having a mass of more than 500 g/mol cannot diffuse across the cell membrane. A total of 32 test ligand candidates from the active compound of tuna shredded fortified banana blossom had a mass of less than 500 g/mol. The greater the molecular weight of the ligand, the more difficult it is for the ligand to be adsorbed **(Jasim & Mustafa, 2022; Whatin et al., 2023; Yadav & Khan, 2013)**.

The second Lipinski rule is the water/octanol partition coefficient or known as the Log P value. The Log P value represents the fat/water solubility coefficient which has a range of -0.4 to 5. A total of 32 test ligand candidates from the active compound of tuna shredded fortified with banana blossom have Log P values less than 5 and more than -0.4 (lowest -1.980000; highest 4.083392). The larger the Log P value, the more hydrophobic the molecule. Molecules that are too hydrophobic tend to have a high level of toxicity because they will be retained longer in the lipid bilayer and distributed more widely in the body so that the selectivity of binding to the target enzyme is reduced. A log P value that is too negative is also not good because the molecule cannot pass through the lipid bilayer membrane **(Jasim & Mustafa, 2022; Whatin et al., 2023; Yadav & Khan, 2013)**.

Lipinski's third and fourth rules are the number of hydrogen bond donors and acceptors. The number of hydrogen bond donors and acceptors describes the higher the hydrogen bonding capacity, the higher the energy required for the absorption process to occur. A total of 32 test ligand candidates from the active compound of tuna shredded fortified with banana blossom had less than 5 hydrogen bond donors (lowest 0; highest 4) and hydrogen bond acceptor number less than 10 (lowest 1; highest 8). The high number of hydrogen bond donors and acceptors can affect the distribution of ligands across the cell membrane. Thermodynamically, the high number of hydrogen bond donors and acceptors makes it more difficult for the ligand to pass through the cell membrane, because entering the lipophilic environment requires a desolvatation process or the release of water molecules from the compound **(Giménez *et al*., 2010)**. **(Kunnumakkara *et al*., 2008)** described the higher the hydrogen bonding capacity, the higher the energy required for the absorption process to occur.

Molecular Docking Active Compound Tuna Shredded Fortified Banana Blossom

Various active compounds from natural ingredients have multi-functions for health, one of which is as antidiabetic. The initial method to determine the potential of the active compound as an antidiabetic is the *in silico* molecular docking method, namely the binding of the active compound as a test ligand to the target antidiabetic receptor/enzyme, such as α-glucosidase. Prior to molecular docking, the docking method validation must first be carried out. The validation of the molecular docking method was carried out with the aim of re-docking the ligand on the active site of the α-glucosidase receptor/enzyme by selecting a conformation similar to the natural ligand conformation that was known through re-docking **(Hevener *et al*., 2009)**.

At this stage, grid box measurements are carried out to determine the area where the test and control ligands will attach. The grid box obtained shows that the two types of ligands will attach to the centre position X 21.2771; Y -0.7586; and Z 18.6326 and the dimensions (Å) X 56.7368; Y 75,1330; and Z 68.4370. The docking process is carried out in 10 repetitions and then the docking results are selected by looking at the conformation that is most similar to the native ligand. The overall ligand conformation that has been selected is then calculated the Root Mean Square Deviation (RMSD) value using the Discovery Studio application. The results of molecular docking that show good performance have an RMSD value less than 2Å **(Hernández-Santoyo *et al*., 2013)**. The RMSD value resulting from the validation of re-tethering between the receptor and the natural ligand showed the lowest value of 0Å and the highest value of 1.3521. This molecular docking validation is said to be valid or appropriate since the average RMSD value obtained is less than 2Å.

The results of the molecular docking of the active compound of tuna shredded fortified banana blossom can be seen in Table 3. Based on the docking results data (Table 3), it can be seen that the *in silico* analysis of the activity of the tuna shredded fortified banana blossom with the α-glucosidase enzyme predicts that the more stable ligand to the α-glucosidase receptor/enzyme is ligand or compound flurandrenolide from the steroid group with a value of binding affinity is -9.40 kcal/mol. The results of method validation obtained RMSD values less than (<) 2Å. These results show that the calculation of the docking between protein and ligand gives results that are almost similar to the position of the native ligand since it has an RMSD value less than (<) 2Å. In addition, the data presented in Table 3 contains only test ligands that have binding affinity values lower than natural ligands (GLC), control ligands acarbose and metformin, while test ligands with binding affinity values greater than natural ligands (GLC), control ligands acarbose and metformin are not shown. Because these ligands have a very low affinity for binding to the α-glucosidase receptor/enzyme. **Toppo *et al*. (2021)** explained that the lower the binding affinity value of the interaction of the ligand-receptor complex, the stronger the potential to bind and the higher the inhibitory ability of the ligand to the target receptor/protein.

Table 3 Results of docking of phytochemical compounds from tuna shredded fortified banana blossom against α-glucosidase enzyme

No.	Compound	Receptor/Enzyme	*Binding Affinity* (kcal/mol)
1	Flurandrenolide (Steroid)	α-glucosidase	-9.40
2	Quercetin-3β-D-Glucoside (Flavonoid)	α-glucosidase	-9.30
3	Sakuranetin (Flavonoid)	α-glucosidase	-8.80
4	Curcumin (Flavonoid)	α-glucosidase	-7.70
5	(+)-ar-Turmerone (Terpenoid)	α-glucosidase	-7.20
6	Nooktatone (Terpenoid)	α-glucosidase	-7.20
7	Ferulic Acid (Phenolic)	α-glucosidase	-6.90
8	Trans-Cinnamaldehyde	α-glucosidase	-6.00
9	Acarbose (Positive Control)	α-glucosidase	-8.00
10	Metformin (Positive Control)	α-glucosidase	-5.60
11	GLC (Native Ligand)	α-glucosidase	-6.00

When referring to the binding affinity value of acarbose as ligand control (-8.00 kcal/mol), the compound that can bind strongly to the receptor and have the potential as an antidiabetic is a compound that has a lower binding affinity value than acarbose, i.e. ligand flurandrenolide (-9.40 kcal/mol), ligand quercetin-3β-D-Glucoside (-9.30 kcal/mol) and ligand sakuranetin (-8.80 kcal/mol). However, when referring to the binding affinity value of the control ligands for metformin (-5.60 kcal/mol) and native ligands (6.00 kcal/mol), other ligands such as ligand curcumin (-7.70 kcal/mol), ligand ar-Turmeron (-7.20 kcal/mol), ligand nootkatone (-7.20 kcal/mol), ligand ferulic acid (-6.90 kcal/mol), and ligand trans-cinnamaldehyde (-6.00 kcal/mol). This supports the results of research that banana blossom methanol/aqueous extracts were able to reduce blood sugar levels in diabetic rats **(Kifle *et al*., 2021; Vilhena *et al*., 2020)** and were able to inhibit the α-glucosidase enzyme **(Aiemcharoen *et al*., 2022)**. This is because banana blossom extract contains active compounds belonging to the steroid group.

The flavonoid compound quercetin-3β-D-glucoside, sakuranetin and curcumin from tuna shredded have better antidiabetic potential than acarbose control ligand. This supports *in vivo* research that flavonoid extracts from *Ipomea batatas* leaves **(Li *et al*., 2009)**, *Anredera cordifolia* leaves **(Djamil *et al*., 2017)**, and *Sophora davidii* leaves **(Huang *et al*., 2018)** can reduce levels of diabetic rat blood sugar. Quercetin and curcumin compounds were able to improve pancreatic beta-cell structure and glucose metabolic activity in the liver in STZ-induced rats **(Chuengsamarn *et al*., 2012; Yang & Kang, 2018)**.

The interaction between the α-glucosidase enzyme as receptor and the ligand/compound flurandrenolide, quercetin-3β-D-glucoside, and sakuranetin can be seen in Figure 1. The flurandrenolide-α-glucosidase complex has a lower binding affinity value than the acarbose-α-glucosidase complex because it contains one hydrogen bond which is stabilized by 3 hydrophobic interactions (p-sigma, p-alkyl, and alkyl) and one halogen bond, whereas the acarbose-α-glucosidase complex has 10 hydrogen bonds (8 conventional hydrogen bonds and 2 carbon hydrogen bonds and two hydrogen bonds), unfavourable donors. For this reason, it seems that the number of hydrogen bonds is not the main factor in forming a lower binding affinity. This is supported by **Ezzat & Razik (2021)** stated that the high binding affinity is supported not only by hydrogen bonding, but also by hydrophobic interactions such as Pi-Pi stacking. The amino acid residues of the receptor bound by acarbose are also different. Table 4 shows the interaction form of each ligand complex of the active compound of tuna shredded fortified banana flower against α-glucosidase receptors/enzymes.

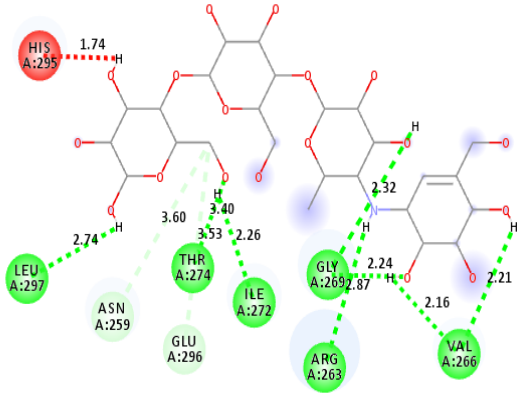
Table 4 Types of Interaction of Ligand-Receptor Complex Compounds

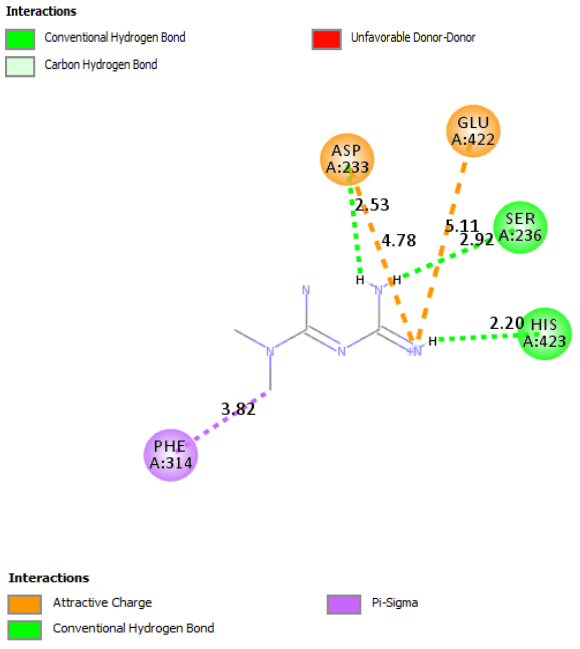
No.	Ligand-Receptor Complex Compounds	Amino Acid Residues	Distance (Å)	Interaction	Type
1	[Metformin-α-glucosidase]	ASP-233	4.78	other	Attractive Charge
			2.53	Hydrogen	Conventional Hydrogen
		SER-236	2.92	Hydrogen	Conventional Hydrogen
		PHE-314	3.82	Hydrophobic	Pi-Sigma
		GLU-422	5.11	other	Attractive Charge Conventional
		HIS-423	2.20	Hydrogen	Hydrogen
2	[Acarbose-α-glucosidase]	ASN-259	3.60	Hydrogen	Carbon Hydrogen
		ARG-263	2.87	Hydrogen	Conventional Hydrogen
		VAL-266	2.21	Hydrogen	Conventional Hydrogen
			2.24	Hydrogen	Conventional Hydrogen
		GLY-269	2.32	Hydrogen	Conventional Hydrogen
		ILE-272	2.26	Hydrogen	Conventional Hydrogen
		THR-274	3.40	Hydrogen	Conventional Hydrogen
		HIS-295	1.74	other	Unfavorable-Donor Donor
		GLU-296	3.53	Hydrogen	Carbon Hydrogen
		LEU-297	2.74	Hydrogen	Conventional Hydrogen
3	[Native Ligand-α-glucosidase]	GLY-160	3.27	Hydrogen	Carbon Hydrogen
		ASN-235	2.46	Hydrogen	Conventional Hydrogen
		SER-236	1.82	Hydrogen	Conventional Hydrogen
		ASN-415	2.86	Hydrogen	Conventional Hydrogen
4	[Flurandrenolide-α-glucosidase]	TYR-158	3.38	Hydrophobic	Pi-Sigma
			5.33	Hydrophobic	Pi-Alkyl
			5.35	Hydrophobic	Alkyl
		ASP-242	2.57	Hydrogen	Conventional Hydrogen
		PHE-303	5.38	Hydrophobic	Pi-Alkyl
		ARG-315	3.98	Hydrophobic	Pi-Alkyl
			5.04	Hydrophobic	Alkyl
		GLU-411	2.82	other	Halogen (Fluorine)
5	[Quercetin-3β-D-glucoside-α-glucosidase]	HIS-280	5.47	Hydrogen	Conventional Hydrogen
		ALA-281		other	van der Waals
		ASN-302		other	van der Waals
		PHE-303		other	van der Waals
		SER-304	3.35	Hydrogen	Conventional Hydrogen
			3.84	Hydrogen	Conventional Hydrogen
			4.99	Hydrogen	Conventional Hydrogen
		ASP-307	4.27	Hydrogen	Conventional Hydrogen
		VAL-308	4.67	Hydrophobic	Pi-Alkyl
			6.07	Hydrophobic	Pi-Alkyl
		GLY-309	3.83	Hydrogen	Conventional Hydrogen
		THR-310	4.12	Hydrogen	Conventional Hydrogen
		VAL-319		other	van der Waals
		PRO-320	5.29	Hydrogen	Conventional Hydrogen
		PHE-321		other	van der Waals
		ASP-325		other	van der Waals
		ILE-328		other	van der Waals
		ALA-329	5.02	Hydrophobic	Pi-Alkyl
		GLU-332	3.61	Hydrogen	Conventional Hydrogen
6	[Sakuranetin-α-glucosidase]	ARG-263	2.57	Hydrogen	Conventional Hydrogen
			3.87	Hydrophobic	Pi-Alkyl
		VAL-266	5.00	Hydrophobic	Pi-Alkyl
		SER-298	3.06	Hydrophobic	Pi-Donor Hydrogen
		ILE-272	5.45	Hydrophobic	Pi-Alkyl
		THR-274	2.72	Hydrogen	Conventional Hydrogen
7	[Curcumin-α-glucosidase]	LYS-156	4.90	Hydrophobic	Pi-Alkyl
		TYR-158	2.82	Hydrogen	Conventional Hydrogen
			4.29	Hydrophobic	Pi-Pi Stacked
			4.78	Hydrophobic	Pi-Pi T-shaped
		GLN-279	1.28	other	Unfavorable Donor Donor
			2.46	Hydrogen	Conventional Hydrogen
		ASN-415	2.13	Hydrogen	Conventional Hydrogen
8	[ar-Turmeron-α-glucosidase]	LYS-156	4.73	Hydrophobic	Pi-Alkyl
		ASN-235	2.16	Hydrogen	Conventional Hydrogen
		PHE-314	4.58	Hydrophobic	Pi-Alkyl
		ALA-418	3.83	Hydrophobic	Pi-Alkyl
			5.42	Hydrophobic	Alkyl
		ILE-419	3.93	Hydrophobic	Pi-Alkyl
			4.94	Hydrophobic	Alkyl
		HIS-423	5.15	Hydrophobic	Pi-Alkyl
9	[Nooktatone-α-glucosidase]	ARG-263	4.49	Hydrophobic	Pi-Alkyl
			4.84	Hydrophobic	Alkyl
		VAL-266	3.78	Hydrophobic	Pi-Alkyl
		ILE-272	4.99	Hydrophobic	Pi-Alkyl
		THR-274	3.70	Hydrogen	Conventional Hydrogen
		HIS-295	5.14	Hydrophobic	Pi-Alkyl
		SER-298	3.71	Hydrogen	Conventional Hydrogen

In the interaction of the quercetin-α-glucosidase ligand complex, it also shows that the number of hydrogen bonds does not result in a lower binding affinity, but other bonds are needed to stabilize the interaction. This is in contrast to **Patrick (2001)** who stated that hydrogen bonds have stronger bonds than others. The sakuranetin-α-glucosidase ligand complex also has a lower binding affinity than the acarbose-α-glucosidase complex with conventional hydrogen interaction at the amino acid residues ARG-263 and THR-274, hydrogen-donor pi bonds with SER-298 and pi hydrophobic bonds -alkyl with ILE-272 and VAL-268.

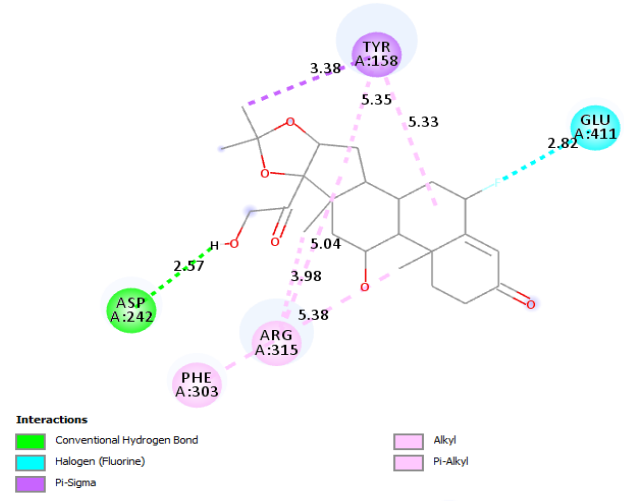
The terpenoid group compounds, i.e. ligands (+)-ar-turmeron and nootkatone also have potential as antidiabetic compounds although their potencies are lower than ligand control acarbose, but still higher than ligand control metformin and native ligand. This also supports the results of *in vitro* and *in vivo* testing of terpenoid compounds. *In vitro* terpenoid compounds from *Potentilla fulgen* were able to inhibit the α-glucosidase enzyme **(Kumar *et al.*, 2013)**, while *in vivo* the terpenoid group compounds were able to reduce blood glucose levels in STZ-induced diabetic rats **(Sheikh *et al.*, 2015)**.

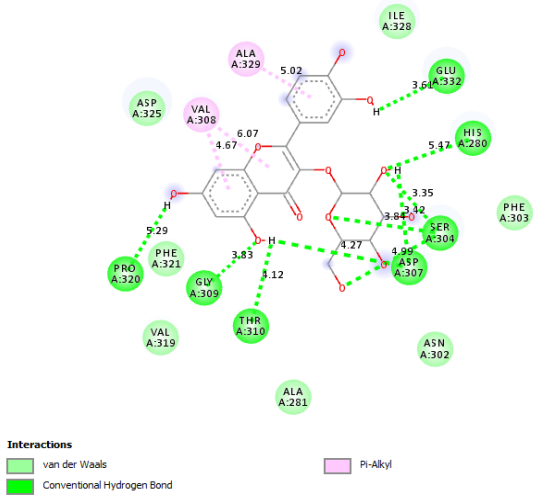
The binding affinity values of ferulic acid and trans-cinnamaldehyde test ligands were also lower than the acarbose control ligand, but still higher than the metformin and native ligands. This supports the research results of **Narasimhan *et al.* (2015)** that ferulic acid exerts an antidiabetic effect by modulating insulin signaling molecules in the liver of type-2 diabetic rats fed a high-fat diet. Ligand cinnamaldehyde has the potential to attenuate rat hyperglycemia through modulation of PPARg, proinflammatory cytokines, and oxidative stress **(Hosni *et al.*, 2021)**.



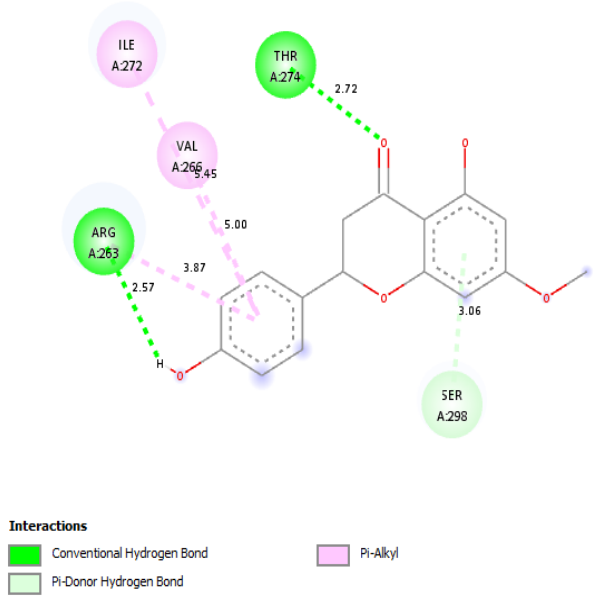


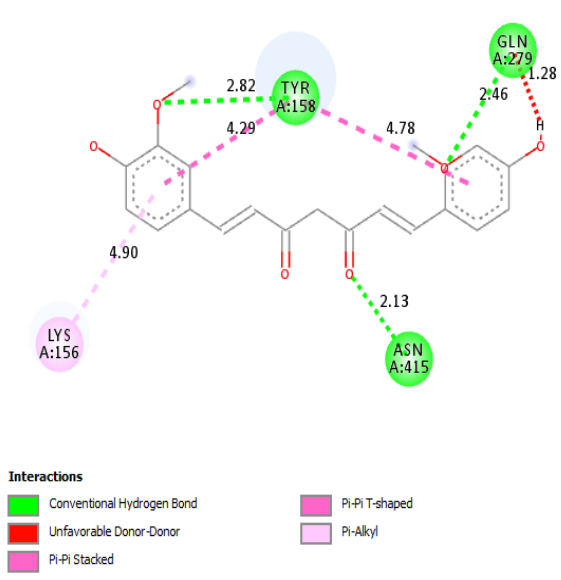
a) [Acarbose-α-glucosidase]
b) [Metformin-α-glucosidase]



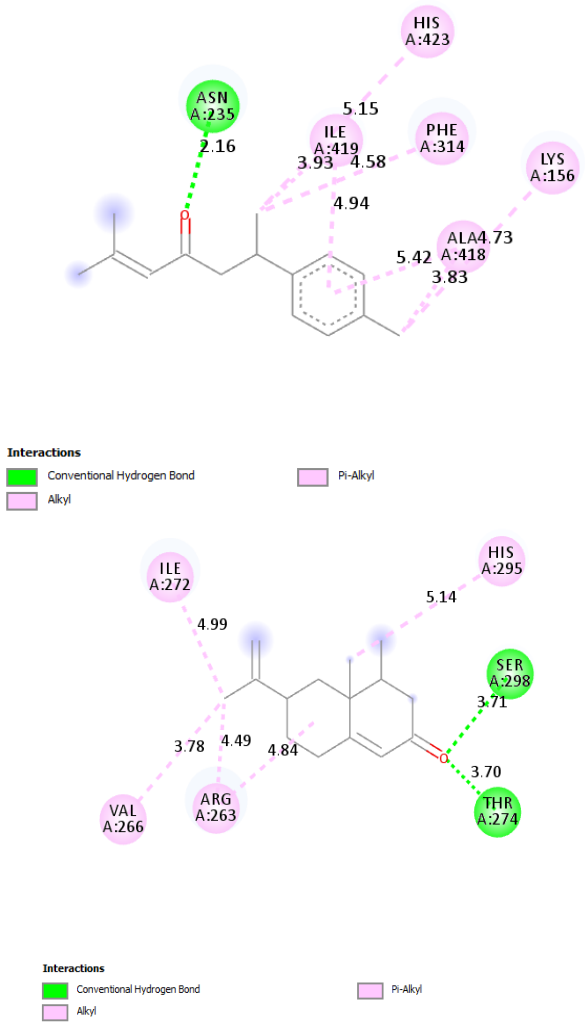


c) [Flurandrenolide-α-glucosidase]
d) [Quercetin-3β-D-glucoside-α-glucosidase]

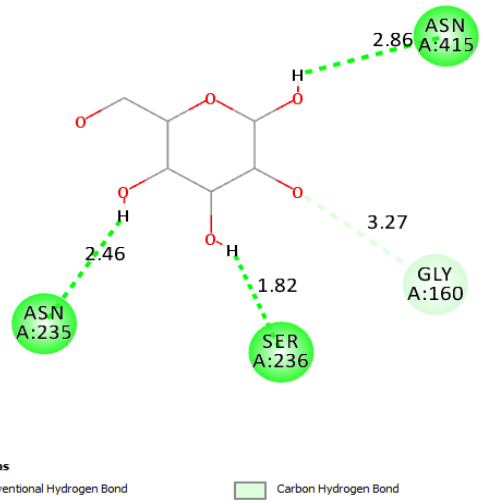




e) [Sakuranetin-α-glucosidase]
f) [Curcumin-α-glucosidase]



g) [(+)-ar-Turmeron-α-glucosidase]
h) [Nooktatone-α-glucosidase]



i) [GLC-α-glucosidase]

Figure 1 2D visualization of ligand complex interaction a) acarbose, b) metformin, c) flurandrelonide, d) quercetin-3β-D-glucoside, e) sakuranetin, f) curcumin, g) (+)-ar-turmerone, h) nootkatone, i) GLC with α-glucosidase as receptor/enzyme

Toxicity and Bioavailability

The results of the pharmacokinetic and toxicity analysis of the potential ligands that have the lowest binding affinity value with the α-glucosidase receptor/enzyme through the http://tox.charite.de/protox_II/ that the test ligand flurandrenolide (steroid group) showed inactive results and are categorized as scale 4 of 6 and LD_{50} 1451 mg/kg. The test ligand quercetin-3β-D-glucoside (flavonoid group) showed inactive results and are categorized as scale 5 of 6 and LD_{50} 5000 mg/kg. The test ligand sakuranetin (flavonoid group) showed inactive results and are categorized as scale 4 of 6 and LD_{50} 2000 mg/kg. This analysis was carried out based on the fact that the material consumed orally should ideally be easily absorbed by the digestive system organs, be able to be distributed specifically to target sites, be able to be metabolized by the body and eliminated without causing any harm to the body's organs **(Drwal *et al.*, 2014)**. Thus, the three test ligand compounds are predicted not to be toxic to body organs.
After knowing the toxicity of the two potential compounds, the bioavailability analysis of these compounds was then carried out. This analysis was carried out online through accessed at http://www.swissadme.ch/. The results of the analysis showed that flurandrenolide (steroid group), quercetin-3β-D-glucoside (flavonoid group) and sakuranetin (flavonoid group) had a high category of human gastrointestinal (GI) absorption.

CONCLUSION

Shredded tuna fortified with banana blossoms contains bioactive components of steroidal phytochemicals such as flurandrenolide, flavonoids quercetin-3β-D-glucoside, sakuranetin, and curcumin, terpenoids ar-turmeron and nootkatone, and phenolic types of ferulic acid. The flurandrenolide, quercetin-3β-D-glucoside and sakuranetin ligands as active compounds of Shredded tuna fortified with banana blossoms have a lower binding affinity value for the α-glucosidase enzyme than the control ligand acarbose or have a higher inhibitory power on the α-glucosidase enzyme than acarbose. This study highlights the potential of presence 3 active compounds that are able to bind α-glucosidase enzymes are more stable than antidiabetic drugs and according to the predicted results of toxicity are not toxic to body organs, then shredded tuna fortified with banana blossoms has the potential to be developed as an antidiabetic functional food.

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