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Active Compounds in Broadleaf Mahogany (*Swietenia macrophylla*) Seeds as Antiaging Agent Based on Molecular Docking Study

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Abstract: *The appearance of brown spots and wrinkles can be a sign of aging which can increase the risk of cancer. Compounds in broadleaf mahogany (Swietenia macrophylla) seeds contains many compounds and is known to have antiaging activity. The search for antiaging compounds requires a long research time, so initial predictions are needed. In addition, there has been no research that predicts anti-aging compounds in S. macrophylla using the molecular docking method. The purpose of this study was to determine the compounds in the seeds of these plants have the potencial compound to antiaging by analyzing their molecular docking interaction on the MMP-1 (matrix metalloproteinase), NEP (neprilysin), PPO3 (polyphenol oxidase).Two compounds that have potentia compound as strong inhibitors towards MMP-1 and PPO3 enzymes, namely β-cytostenone and 3β-hydroxystigmast-5-en-7-on which is a steroid group, as well as germacrena A and germacrena D which are terpenoids. Only compound 3β-hydroxystigmast-5-en-7-on has the potential compound as a strong inhibitor of the NEP enzyme. All compounds have the potential to be strong inhibitors according to the Lipinski rule. Only compounds which binds to the PPO3 enzyme which has better activity than natural ligand based on ΔG and Binding Site Similarity (BSS) values.*

Keywords*: antiaging, MMP-1, molecular docking, NEP, PPO3*

INTRODUCTION

Aging is a process of gradually losing the ability of the tissue to repair and maintain its normal structure and function (Mumpuni and Mulatsari 2018). These changes are caused by the degradation of the extracellular matrix (Widowati et al. 2020). Exposure to UV light is one of the causes of skin aging (photoaging) (Wongrattanakamon et al. 2018). UV rays consist of UVA, UVB, and UVC rays, but UVC rays are absorbed by the ozone layer so ambient sunlight only consists of UVA rays (90–95%) and UVB rays (5–10%). UV exposure can cause up to 80% of signs of skin aging such as dry skin, wrinkles, brown spots, and photoaging correlated with cancer (Amaro-Ortiz et al. 2014).

Another feature of aging is the appearance of brown spots on the skin which can be caused by abnormal expression of the enzyme tyrosinase (PPO3). The tyrosinase enzyme plays a role in regulating the metabolic pathways of melanin. In human skin cells, tyrosinase is the only enzyme that limits melanogenesis and tyrosinase expression has a physiological function in the process of melanoma occurrence and its development (Chen et al. 2019). The most severe manifestation of photoaging is skin cancer. UVB cumulative

damage and aging can cause cancer, for example, the formation of pheomelanin assisted by the PPO3 enzyme (Burke 2020).

ROS which plays a role in stimulating the expression of the MMP-1 enzyme is free radicals. Free radical activity can be slowed down or inhibited by antioxidants (Dompeipen and Simanjuntak 2015). *Swietenia macrophylla* or broadleaf mahogany seeds are known to have antioxidant and anticancer activities. Kalpana and Pugalendi (2011) tested the ethanol extract from *S. macrophylla* seeds, the extract has antioxidant activity. The ethyl acetate fraction of *S. macrophylla* seeds is known to have anticancer activity (Tohir et al. 2020). It has been reported by Moghadamtousi et al. (2013) and Durai et al. (2016) broadleaf mahogany seeds contain many phytochemical compounds such as coumarins and steroids, with the main constituents being limonoids and their derivatives, as well as several fatty acids and terpenoids.

The number of compounds contained in the seeds of *S. macrophylla* needs to be studied further for its activity. These compounds are not possible to be examined in the laboratory because they require a lot of time, energy, and costs. The method that can be applied to estimate the interaction between the tested compound and the target molecule is the molecular docking method. The molecular docking method is a computational method that can predict interactions between two molecules, in this case, compounds in *S. macrophylla* seeds and enzymes that play a role in the aging process (Makatita et al. 2020). Molecular docking methods can be applied to examine the activity of a large number of compounds, resulting in faster and cheaper results.

Molecular docking simulations were carried out using the Autodock Vina and Discovery Studio Visualizer. This software is the most commonly used, is open source, easy to operate, and has a low error rate (Trott and Olson 2010, Saputri et al. 2016). The output of those programs is Gibbs free energy (ΔG) which is sorted from the lowest energy, and the number of ligand binding modes. ΔG become the main parameter in the molecular docking simulation. The negative value of ΔG indicates the conformation formed reaction is spontaneous (Chairunnisa and Runadi 2017, Du et al. 2016). Asoka et al. (2022a) and Asoka et al. (2022b) conducted a study using molecular docking to select compounds in ginger essential oil to fight acne and anti-skin aging. Lestari et al. (2022) conducted a search for compounds in black garlic for uric acid. Kintamani et al. (2023) chose an in silico study to select andaliman essential oil compounds that can prevent skin aging. Molecular docking and dynamics by Nurlela et al. (2022) predicted the diterpenoid kaurene compound as a specific antiviral candidate for SARS-CoV-2. This research is expected to improve the knowledge of molecular docking studies in drug development.

There has been no molecular docking research on the potency of the compounds presented in *S. macrophylla* seeds as antiaging agents, and to support the research by Tohir et al. (2020) who stated that the ethyl acetate fraction of *S. macrophylla* seeds had anticancer activity. Therefore, this study aims to determine compounds in *S. macrophylla* seeds that is potential as antiaging and as a support to finding anticancer compounds.

RESEARCH METHODS

Materials and Tools

The tools applied in this study were computers with Intel Core i3 8145U processor specifications, 4 GB RAM, Windows 10 operating system, software in the form of MarvinSketch and MarvinView (downloaded from http://chemaxon.com), Autodock Vina (downloaded from http://vina.scripps.edu/download.html), Autodock Tools (downloaded from http://autodock.scripps.edu/resources/adt), Discovery Studio Visualizer (downloaded from https://discover.3ds.com /discovery-studio-visualizer-download), PyMOL

(downloaded from https://pymol.org/2/#download), and LigPlot+ (downloaded from https://www.ebi.ac.uk/thornton-srv/software /LigPlus/download.html).

The materials applied in this study were the structure of the test ligands in the form of compounds found in *S. macrophylla* seeds obtained from the site https://pubchem.ncbi.nlm.nih.gov in 2D format, and online scientific publications available on Google Scholar, Research Gate, ScienceDirect, PubMed, etc. regarding the compounds contained in *S. macrophylla* seeds, as well as the structure of target proteins that have formed complexes with their natural ligands in 3D form, namely the enzymes MMP-1 (966C), NEP (5JMY), and PPO3 (2Y9X) obtained from the site http://www.rcsb.org.

METHODS

Ligand Structure Preparation

The ligands used in this study were compounds found in *S. macrophylla* seeds as test ligands, N-hydroxy-2-[4-(4-phenoxy-benzene sulfonyl)-tetrahydro-pyran-4-yl]-acetamide, LBQ657, and tropolone as natural ligands. The 2D ligand structure in *.sdf format was transformed into a 3D form using MarvinView software and saved in *.pdb format. All of these ligands were optimized using Discovery Studio Visualizer software by adding hydrogen atoms and stored in *.pdbqt format using Autodock Vina software.

Target Protein Preparation

The 3D structures of the MMP-1 (966C), NEP (5JMY), and PPO3 (2Y9X) enzymes were obtained from the website http://www.rscb.org in *.pdb format. Target proteins were prepared by removing water molecules and ligands using the Discovery Studio Visualizer and saved in *.pdb format. Furthermore, the target protein was optimized using Autodock Tools by adding hydrogen atoms and stored as macromolecules in *.pdbqt format.

Molecular Docking Validation

Molecular docking validation was carried out by re-docking natural ligands to each target protein using Autodock Vina. Validation was carried out with the size of the grid box as well as the spacing and center points of the coordinates according to the position of the natural ligand and the results were stored in .txt format. The molecular docking validation parameter is Root Mean Square Deviation (RMSD).

Molecular Docking Simulation

Molecular docking was performed using Autodock Vina. Prepared protein files in *.pdbqt format are put in the Vina folder. The Vina configuration file was created with the Notepad application and saved with the name config. Molecular docking was carried out according to the validation results of molecular docking. Molecular docking commands were carried out using the “cmd” command prompt program. The programming command to run molecular docking was “C:\vina.exe --config config.txt --out output.pdbqt” then press enter. The results of molecular docking could be seen in the output document with *.pdbqt format and log files which can be opened using the Discovery Studio Visualizer and Notepad software. The log file is a document that contains data on ΔG values in units of kcal/mol.

Molecular Docking Visualization

Visualization of the results of molecular docking was carried out in 2D and 3D forms. Compounds resulting from the molecular docking of each target protein with the lowest ΔG value were selected to be visualized using Ligplot+ and PyMOL software. The

selected ligand model was combined with the target protein using PyMOL software into *.pdb format, opened using Ligplot+ software, and performed 2D visualization, followed by 3D visualization using PyMOL software.

Physicochemical Analysis

All the test ligands with the lowest ΔG values were subjected to physicochemical analysis by uploading the structure of the compounds in *.sdf form to the website http://www.swissadme.ch, then converting them into SMILES code. The physicochemical data needed are five Lipinski rules, namely molecular weight, hydrogen bond donors, hydrogen bond acceptors, and LogP.

RESULTS AND DISCUSSION

Antiaging Compounds Screening in Swietenia macrophylla using Molecular Docking

Skin is a body tissue consisting of the epidermis, dermis and hypodermis layers. The main function of the skin is to protect the body from the external environment. Therefore, the skin encounter some problems, one of which is aging. This is also caused by external factors such as pollution and UV rays that directly expose the skin. UV radiation increases the expression of matrix metalloproteinase (MMP-1) enzymes by skin fibroblasts stimulated by excess reactive oxygen species (ROS) and causes photoaging. The MMP-1 enzyme that also called collagenase may cause damage to collagen. This enzyme is a type of collagenase whose activity is mostly affected by UV light. The MMP-1 enzyme can facilitate tumor invasion in melanoma (Pittayapruek et al. 2016). Melanoma is a malignant tumor of the skin that originates from the degeneration of melanocyte pigment cells (Hanum and Supriana 2019). MMP-1, secreted by melanoma, contributes to melanoma progression in two ways. Firstly, it promotes melanoma invasion and metastasis by destroying interstitial collagen. Secondly, it promotes tumor invasion and vascularization through the expression of the protease activator receptor-1 (PAR-1) gene (Pittayapruek et al. 2016). Neprilysin enzymes (NEP) also play a role in the aging process. The NEP enzyme known as elastase originates from skin fibroblasts, and its regulation during aging is associated with loss of skin elasticity and wrinkle formation (Huertas et al. 2018).

Analysis of anti-skin aging activity can be conducted by molecular docking method. Molecular docking is a computational method for predicting interactions between ligands and receptors. One of them is for the preparation of ligands and receptors. The enzyme structure was prepared and optimized by removing water molecules and ligands, and only taking one protein chain in the NEP and PPO3 enzymes. The natural ligands used for validation are only those bound to the binding site, so the ligands used are N-hydroxy-2-[4-(4-phenoxy-benzene sulfonyl)-tetrahydropyran-4-yl]-acetamide, LBQ657, and tropolone.

Ligand structure is an important component in the molecular docking process. The ligands used in this research were ligands originating from *S. macrophylla* seeds as many as 80 ligands and three natural ligands. A total of 80 test ligands were successfully prepared and optimized to in 3D format *.pdbqt by adding hydrogen atoms using Autodock Tools and Discovery Studio Visualizer software developed by BIOVIA. As many as 43 of the 80 tested ligands were limonoid group compounds, this was in accordance with the statement of Moghadamtousi et al. (2013) that the most abundant compound in *S. macrophylla* comes from the limonoid class. There were also other compounds such as fatty acids, terpenoids, and coumarins in *S. macrophylla* seeds. Apart from the ligands, protein structure is also required for molecular docking simulation. The target proteins used in this study were the

MMP-1 (966C), NEP (5JMY), and PPO3 (2Y9X) enzyme The preparation and optimization of the enzyme structure was carried out by removing molecules water and ligands, and only take one protein chain in the NEP and PPO3 enzyme.

Table 1. The molecular docking validation

Receptors	Coordinates			RMSD (Å)
	X	Y	Z	
MMP-1	9,166	-10,353	38,398	1,069
NEP	-20,579	3,317	-37,541	0,897
PPO3	-10,215	-28,653	-43,443	0,458

Molecular docking method validation was carried out to determine the coordinates and size of the grid box to be used in molecular docking. The validation of this method was carried out by redock the natural ligand to the enzyme in the appropriate position before the natural ligand was separated from the enzyme. The parameter used in the validation of the molecular docking method is the root mean square deviation (RMSD). The RMSD value is used to evaluate the suitability of the molecular docking process, and describes how much the conformational change of the natural ligand before and after validation is carried out. The validation results of the molecular docking method can be accepted if the RMSD value is ≤2 Å. The smaller the RMSD value, the closer the natural ligand position as a result of validation is to the natural ligand position resulting from crystallography. The docking method is carried out under flexible conditions of the ligand, which allows the ligand to adjust the structure to achieve a conformation that can produce a low ΔG (Muttaqin et al. 2019). The ΔG value of the molecular docking simulation results for three enzymes can be seen in Supplementary Material 1.

This method was validated by re-docking the natural ligand to the enzyme in the appropriate position before the natural ligand was separated from the enzyme. The parameter used to validate the molecular docking method is the root mean square deviation (RMSD). Molecular docking validation in this study resulted in RMSD values <2 Å in all target proteins (Table 1), therefore all of protein targets could be used in molecular docking simulation.

Table 2. The affinity energy of several compounds in *S. macrophylla* for the target protein

Ligand	Afinity Energy (kcal/mol)		
	MMP-1	NEP	PPO3
A	-9,9	-	-
LBQ657 (natural ligand)	-	-10,6	-
Tropolon (natural ligand)	-	-	-6
3-hydroxy-4-(1-oxopropyl)-phenyl acetate	-7,6	-7,2	-5,9
3-O-acetylswietenolide	-7	-7,8	-
3-O-propionylproseranolide	-7,5	-7,4	-
3β,6-dihydroxydihydrocarapin	-7,5	-7,3	-
3β-hydroxystigmast-5-en-7-one	-7,9	-7,7	10,5

6-O-acetylswietenin B	-7,7	-7,1	-
7-deacetoxy-7-oxogedunin	-7,7	-8,5	37,8
Febrifugin	-7,7	-7,5	-
Germacrene A	-6,6	-7,5	-6,7
Germacrene D	-6,5	-5,2	-6,6
ɤ-himakalene	-6,6	-5,5	-6,3
Granatumin H	-7,7	-7,1	-
Khayasin T	-7,6	-7,7	-
Scopoletin	-7,5	-7,4	-6,4
Stigmasterol	-7,5	-7,5	28,7
Swielimonoid A	-7,7	-7,8	51,2
Swielimonoid B	-7,5	-7,6	59,9
Swielimonoid C	-7,2	-7,7	-
Swietemahonin E	-7,1	-8	-
Swietemahonin G	-7,9	-7,4	-
Swietenolid	-7,1	-7,6	43,7
α-himakalene	-6,5	-6	-6,5
β-cytostenone	-8,1	-7,7	15
β-sitosterol	-7,7	-7,2	10,6

A: N-hydroxy-2-[4-(4-phenoxy-benzensulfonyl)-tetrahydropyran-4-yl]-acetamide (natural ligand)

Based on the simulation results of molecular docking on the MMP-1 enzyme, the natural ligand N-hydroxy-2-[4-(4-phenoxy-benzene sulfonyl)-tetrahydropyran-4-yl]-acetamide produces ΔG -9.5 kcal/mol. A total of 80 ligands have been docked to the MMP-1 enzyme, and only 16 ligands produced the lowest ΔG which can be seen in Table 2. The β-cytostenone test ligands produced the lowest ΔG of -8.1 kcal/mol. Among the best tested ligands, stigmasterol, swielimonoid B, 3-O-propionylproseranolid, and 3β,6-dihydroxydihydrocarapin yielded the highest ΔG of -7.5 kcal/mol. All interactions of the test ligands with the MMP-1 enzyme were spontaneous because they produced a negative ΔG. However, none of the tested ligands had better activity than the natural ligands in terms of ΔG values.

The natural ligand LBQ657 docked to NEP yielded ΔG -10.6 kcal/mol (Table 2). A total of 80 test ligands were added to the NEP enzyme, and only ten tested ligands produced the lowest ΔG which can be seen in Table 2. The 7-deacetoxy-7-oxogedunin test ligands produced the lowest ΔG of -8.5 kcal/mol. Among the best-tested ligands, swielimonoid B and swietenolid ligands produced the highest ΔG of -7.6 kcal/mol. All interactions of the test ligands with the enzyme occurred spontaneously because they produced a negative ΔG. However, none of the tested ligands had better activity than the natural ligands in terms of ΔG values.

Tropolone is a natural ligand added to the PPO3 enzyme. Based on molecular docking results on the PPO3 enzyme, tropolone produces ΔG -6 kcal/mol. As many as 49 of the 80 tested ligands were successfully tethered to the PPO3 enzyme, the rest could not

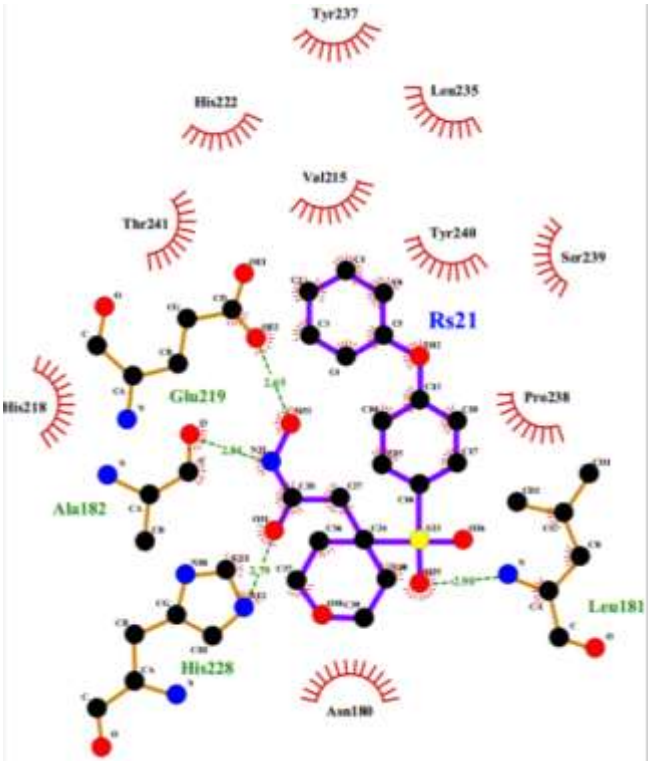
be docked because it has a larger structure than their grid box size. There are five test ligands that produce the lowest ΔG which can be seen in Table 3. Germacrene A ligands produce the lowest ΔG of -6.7 kcal/mol. Among the best-tested ligands, ɤ-himakalene yielded the highest ΔG of -6.3 kcal/mol. Some of the interactions of the test ligands with the PPO3 enzyme were non-spontaneous because they produced a positive ΔG. All of the best-tested ligands had better activity than the natural ligands when viewed from the ΔG value.

Visualization and Physicochemical Analysis

Besides ΔG there are other parameters in molecular docking, viz similarity of the interactions of the amino acid residues with the ligands. The interaction of amino acids with ligands can be seen through 2D visualization of the results of molecular docking using LigPlot+ software. Amino acid residues that interact with natural ligands will be used as a reference for all the best test ligands for each enzyme, then the number of the same amino acid residues is compared to obtain the % Binding Site Similarity (BSS) value.

The physicochemical analysis was evaluated using the online site http://www.swissadme.ch. Physicochemical analysis based on the Lipinski rule of five (Ro5). Ro5 depends on four physicochemical parameters; molecular weight, not more than 500 g/mol; lipophilicity (LogP) not more than 5, or MLogP value not more than 4.15; and the number of hydrogen bond donors and acceptors are not more than 5 and 10. If the ligand used does not meet Ro5, it is likely that the ligand will have problems if swallowed. However, only three of the four parameters that are fundamental to the structure of the ligands are applied (Attique et al. 2019, Lipinski 2016).

Molecular weight plays a role in drug development. Kelutur et al. (2020) stated that compounds with a molecular weight above 500 g/mol are difficult to penetrate through the membrane, both in the skin and in digestion. The LogP value indicates the solubility coefficient in fat or water with a range of -0.4 to -5. The large value of LogP causes the hydrophilic properties of the compound to decrease and has the potential to be retained in the lipid bilayer. This increases the toxicity of the compound and makes it difficult to be excreted. However, if the LogP value is too small, it can make it difficult for the compound to pass through the lipid bilayer (Syahputra et al. 2014). The number of hydrogen bond donors and acceptors indicates the capacity of hydrogen bonds, therefore, the more the hydrogen bond, the lower the absorption rate (Prasetiawati et al. 2021, Rachmania et al. 2015).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His218
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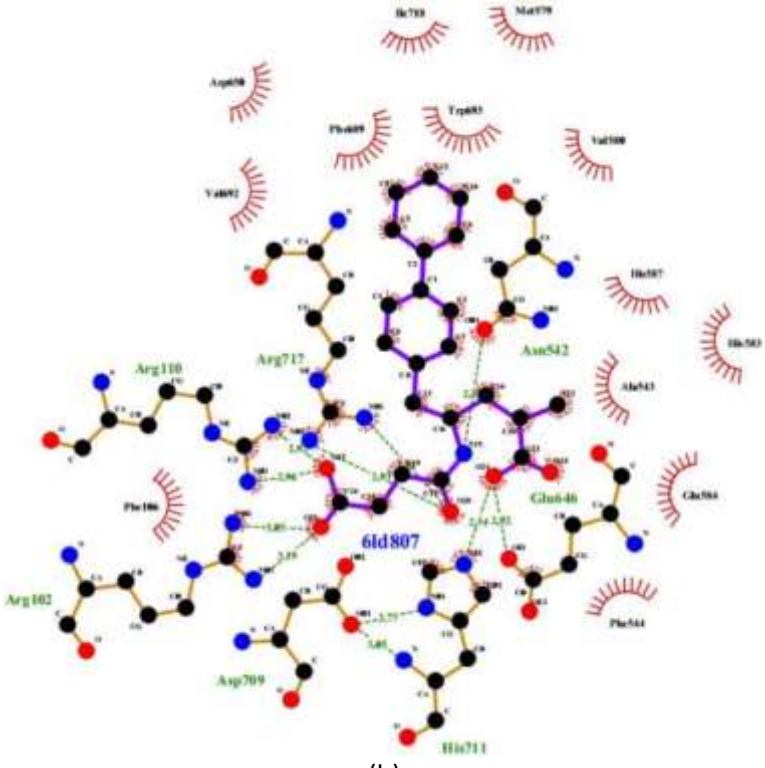
Asn180

(a)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His711

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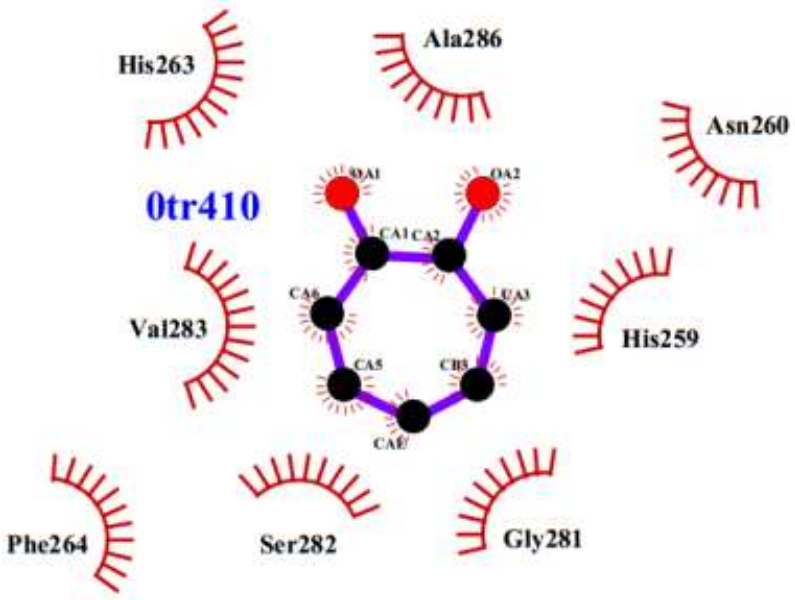

(c)

Figure 1. Visualization of the interaction between **(a)** A-MMP-1, **(b)** LBQ657-NEP, **(c)** Tropolone-PPO3

N-hydroxy-2-[4-(4-phenoxy-benzensulfonyl)-tetrahydropyran-4-yl]-acetamide docked to the MMP-1 and interacted with 14 amino acids, which four hydrogen bonds with the amino acids Leu181, Ala182, Glu219, and His228, as well as forming ten hydrophobic bonds with the amino acid Asn180, Val215, His218, His222, Leu235, Tyr237, Pro238, Ser239, Tyr240, Thr241 (Figure 1a). The β-cytostenone ligand has the lowest ΔG value forming 13 hydrophobic bonds, but only 11 are bound to the same amino acid residues as the natural MMP-1 ligand, resulting in a BSS of 79%. Among the best-tested ligands, the 3β-hydroxystigmast-5-en-7-one ligand has the highest BSS, forming 14 hydrophobic bonds, but only 13 bind to the same amino acid residue as the natural ligand MMP-1, resulting in a BSS of 93 %. The best test ligand that has the lowest BSS, namely 3-O-propionylproseranolid, forms one hydrogen bond with the same amino acid residue as the natural MMP-1 ligand, and eight hydrophobic bonds, but only six bonds with the same amino acid residue as the natural ligand MMP-1, resulting in a BSS of 50%.

LBQ657 docked to the NEP and interacted with 20 amino acids, of which seven hydrogen bonds with the amino acids Arg102, Arg110, Asn542, Glu646, Asp709, His711, Arg717, and 13 hydrophobic bonds with Phe106, Ala543, Phe544, Met579, Val580, His583, Glu584, His587, Asp650, Phe689, Val692, Trp693, Ile718 (Figure 1b). The 7-deacetoxy-7-oxogedunine had the lowest ΔG value forming ten hydrophobic bonds, but only five of them bind to the same amino acid residues as the natural NEP ligand, resulting in a 25% BSS. Among the best-tested ligands, 3β-hydroxystigmast-5-en-7-one had the highest BSS, forming 16 hydrophobic bonds, but only 14 bounds to the same amino acid residue as the natural NEP ligand, resulting in a BSS of 70%. The best test ligand that has the lowest BSS is swietenolide, forming one hydrogen bond with a different amino acid residue from the natural NEP ligand, and ten hydrophobic bonds, but only two of which bind to the same amino acid residue as the natural NEP ligand, resulting in a BSS of 10%. All of the best-tested ligands had a BSS of <50% except for the 3β-hydroxystigmast-5-en-7-on. It can be concluded that all of the best-tested ligands were weak inhibitors except for

the 3β-hydroxystigmast-5-en-7-on. The 3β-hydroxystigmast-5-en-7-one belongs to the group of steroid compounds.

Tropolone docked to the PPO3 enzyme interacts with eight amino acids to form hydrophobic bonds with His259, Asn260, His263, Phe264, Gly281, Ser282, Val283, and Ala286 (Figure 1c). The germacrene A has the lowest ΔG forming nine hydrophobic bonds, but only six of them bind to the same amino acid residues as the natural PPO3 ligand, resulting in a BSS of 75%. Among the best-tested ligands, germacrene D and scopoletin ligands had the highest BSS. The D germacrene ligand forms 12 hydrophobic bonds, while the scopoletin ligand forms ten hydrophobic bonds. The two ligands contain the same eight amino acid residues as the PPO3 natural ligand, resulting in a 100% BSS. The ligands with the lowest BSS were germacrene A and ɤ-himakalene. The ɤ-hymacalene formed eight hydrophobic bonds, but only six of them bind to the same amino acid residues as the PPO3 natural ligand, resulting in a 75% BSS. All of the best-tested ligands had a BSS of >50%, so all of the best-tested ligands were strong inhibitors. The best-tested ligands belong to coumarin and terpenoid compounds.

Table 3. Physicochemical properties of compounds in *S. Macrophylla*

Ligand	Physicochemical Parameters			
	Molecular Weight (g/mol)	Mlo gP	Hydrogen Bond Donor	Hydrogen Bond Acceptor
3-hydroxy-4-(1-oxopropyl)-phenyl acetate	208,21	1,3	1	4
3-O propionylproseranolide	526,62	2,89	0	8
3β,6-dihydroxydihydrocarapin	486,55	1,57	2	8
3β-hydroxystigmast-5-en-7-one	428,69	5,7	1	2
6-O-acetylswietenin B	584,65	2,46	0	10
7-deacetoxy-7- oxogedunin	438,51	2,15	0	6
Febrifugin	552,66	3,19	0	8
Germacrene A	204,35	4,53	0	0
Germacrene D	204,35	4,53	0	0
Granatumin H	526,66	3,14	0	7
α-himakalene	204,35	4,63	0	0
ɤ-himakalene	204,35	4,63	0	0
Khayasin T	552,66	3,19	0	8
Scopoletin	192,17	0,76	1	4
Stigmasterol	412,69	6,62	1	1
Swielimonoid A	566,64	2,34	1	9
Swielimonoid B	586,67	1,8	1	10
Swielimonoid Ca	586,67	1,8	1	10
Swietemahonin E	584,65	1,72	1	10
Swietemahonin G	600,65	0,96	2	11

Swietenolid	486,55	1,57	2	8
β-cytostenone	412,69	6,62	0	1
β-sitosterol	414,71	6,73	1	1

The best test ligands were analyzed for their physicochemical properties to predict whether these ligands could be applied as drugs orally. The swietemahonin G was the only ligand that had more than two deviations from the Lipinski rule, namely the molecular weight of 600 g/mol, and the number of acceptors for hydrogen molecules was 11. Apart from the swietemahonin G ligand, some of the other best-tested ligands have deviations from Lipinski's rule but the number was not more than two. Based on the analysis that was carried out in this study, the compounds in *S. macrophylla* that have the potential as skin antiaging agents are β-cytostenone, 3β-hydroxystigmast-5-en-7-one, germacrene A, and germacrene D. These compounds belong to the steroids and terpenoids.

The test ligands in this study can be predicted for their activities if used by smearing and also docked on other enzymes that play a role in the aging process. In addition, the tested ligand has the potential compound to be an inhibitor against the PPO3 enzyme and can be analyzed for its structure and activity relationship and examined experimentally in vitro.

CONCLUSIONS

There were 14 compounds that had the lowest ΔG potential as anti-skin aging and comply with the Lipinski rule for the MMP-1. These compounds were limonoids, steroids, esters, and coumarins with the two best compounds being β-cytostenone and 3β-hydroxystigmast-5-en-7-one which are steroid compounds. Among the ten compounds with the lowest ΔG that were docked on the NEP, only one compound had anti-skin aging potential and fulfilled the Lipinski rule, namely 3β-hydroxystigmast-5-en-7-one. A total of five compounds interacted spontaneously with PPO3 had the potential for anti-skin aging, and fulfilled the Lipinski rule from the coumarin and terpenoid classes. The two best compounds that had the potential as strong inhibitors of the PPO3 enzyme were germacrene A and germacrene D. Only compounds that bind to PPO3 had better activity than their natural ligands.

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