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Chemical Profiling of *Scoparia dulcis* L. Leaf Ethanol Extract and In Silico Antiaging 2Y9X Inhibitor Study

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Abstract: The intensity of UV radiation that is quite high in the tropics can make the skin age quickly, such as wrinkles, dry, dull skin, or dark spots. In Indonesia, it turns out that 76% of women experience premature aging in this way. The cause is exposure to UVA and UVB radiation, which triggers the production of Reactive Oxygen Species (ROS). Many local plants have been researched for anti-aging, but no one has discussed the anti-aging activity of *Scoparia dulcis* L. Previous research indicates that Scoparia dulcis L. leaves exhibit antibacterial, antimicrobial, antioxidant, anti-inflammatory, and antidiabetic effects. Therefore, this study aimed to identify potential anti-aging compounds in the ethanol extract of *Scoparia dulcis* L. leaves as inhibitors of tyrosinase enzyme (PDB ID: 2Y9X), which plays a role in melanin production. Plant material was macerated to preserve flavonoid compounds. Chemical profiling of the extract was analyzed using LC-MS, which identified 104 secondary metabolite compounds. Then, use an in silico approach through molecular docking with AutoDock Vina to evaluate anti-aging compounds in the ethanol extract of *Scoparia dulcis* L. leaves. The docking results indicated that six compounds showed promising inhibitory potential, with binding affinities better than that of the positive control (-6.0 kcal/mol). These compounds were vanillic acid (-6.2 kcal/mol), caffeic acid (-6.0 kcal/mol), scopoletin (-6.4 kcal/mol), scoparone (-6.2 kcal/mol), jasmonic acid (-6.2 kcal/mol), and budlein A (-6.2 kcal/mol). The six compounds were also analyzed again using Lipinski's Rule of Five so that they could be used as a reference for further experiments for oral drugs. As a result, all of six compounds met that rule and had a smaller bond affinity value than the positive control.

Keywords: Anti-aging 2Y9X; Inhibitor; In Silico; Molecular Docking; *Scoparia dulcis* L.

Introduction

Indonesia is a tropical country with relatively high UV radiation levels year-round. This condition causes premature aging, which is characterized by the appearance of wrinkles, dry skin, dull skin, and dark spots [1]. Epidemiological research reports that 80% of skin signs of aging are caused by long-term exposure to UV rays [2]. Literature study by [3], reports that 76% of women in their early 30s in Indonesia experience premature aging. The reason is that UVA and UVB rays from sunlight spark the creation of Reactive Oxygen Species (ROS), which then leads to oxidative stress on the skin. If ROS levels exceed the antioxidant defence capacity of skin cells, they can damage collagen and disrupt collagen production. As a result, skin tone becomes uneven, skin cells die without cell regeneration, and hypopigmentation, hyperpigmentation, and skin cancer [4] [5].

Biologically, the color of human skin is influenced by the amount and distribution of melanin pigment produced by melanocyte cells through the process of melanogenesis. Well, in this melanogenesis, the enzyme tyrosinase plays an important role in converting tyrosine into L-DOPA and dopaquinone. [6]. During melanogenesis, an oxidation reaction occurs between copper ions and oxygen. The tyrosinase enzyme works by utilizing two Cu^{2+} ions, each of which is bound by three histidine residues in its active center [7]. One way to prevent premature aging is to inhibit the activity of the enzyme tyrosinase that produces excess melanin [8].

Various inhibition methods have been used to predict antiaging activity by inhibiting the enzyme tyrosinase. One of them is molecular docking. This method is often used as a first step for the discovery or development of drugs with the help of software and is considered efficient because it can evaluate hundreds to thousands of compound candidates before further experimental testing [9] [10].

The compound used for molecular docking research is obtained from the ethanol extract of Scoparia dulcis L. leaves. This plant belongs to the *Plantaginaceae* family, which usually grows in low-lying areas in tropical and subtropical regions [11]. This plant has pharmacological activity as an antibacterial, antimicrobial, antioxidant, anti-inflammatory, and antidiabetic [12]. In addition, another study found that the chloroform extract of *Scoparia dulcis* L. contains terpenoids, flavonoids, steroids, saponins, and polyphenols [13]. Recent studies have shown that natural compounds derived from Lycopodium japonicum exhibit significant tyrosinase inhibitory activity, supported by molecular docking analyses of ligand–protein interactions [14]. However, studies specifically investigating the antiaging potential of compounds from *Scoparia dulcis* L. through tyrosinase inhibition remain limited. In addition, there is a lack of research integrating LC-MS-based chemical profiling with molecular docking targeting the tyrosinase enzyme structure (PDB ID: 2Y9X). This gap highlights the need for a comprehensive approach that combines compound

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identification and computational screening. Therefore, this study aims to evaluate the inhibitory potential of compounds identified from the ethanol extract of *Scoparia dulcis* L. leaves against the tyrosinase enzyme using an in silico molecular docking approach.

Research Methods

Tools and Materials

The material used was Scoparia dulcis L. leaves obtained from Nganjuk, East Java, Indonesia (7.3779749° N, 112.6343752° E), 90% ethanol, and filter paper. The equipment used includes a 500 mL glass cup, blender, glass funnel, Buchner funnel, vacuum pump, rotary evaporator (BUCHI R-80 System), Erlenmeyer side pipe 1000 mL, plastic hose, 1000 mL evaporator flask, analytical scale (OHAUS Pioneer), digital scale (KOBE SF-400), and LC-MS instrument (SHIMADZU).

Hardware and Software

The Lenovo IdeaPad 3 14ITL6 laptop comes equipped with an 11th-generation Intel Core i3-1115G4 processor, PyRx Virtual Screening Tool software, BIOVIA Discovery Studio Visualizer 2024 Client, PDB web server, and PubChem.

Procedure

Extraction of Scoparia dulcis L. leaves

Scoparia dulcis L. leaves obtained from Nganjuk, East Java, located at 7.3779749° N and 112.6343752° E, Indonesia, were dried, mashed, and macerated using 90% ethanol solvent for 3 × 24 hours. In the maceration process, the extract is stirred, filtered, and collected every 1x24 hours. The macerated extract is then evaporated using the BUCHI R-80 System rotary evaporator to obtain a thick extract. respectively; *A* and *B* are constants.

Identification of secondary metabolites using LC-MS

After the extract was evaporated, we analyzed it using the LC-MS Shimadzu Pack FC-ODS instrument, which has a capillary column (inner diameter 2 mm x 150 mm, particle size 3 µm), and an injection volume of only 1 µL. Well, the parameters for the ESI include a capillary voltage of 3.0 kV, chromatography column temperature of 35 °C, flow rate of 0.5 mL/min, use of ethanol as a solvent, focus ion MS mode [M]+, ionization of ESI, retention time of up to 80 minutes, plus an isocratic motion phase. We identified the compound content in this ethanol extract based on literature data from NIST, its retention time, and the molecular mass spectrum that came out of the chromatogram [15].

In silico study

This study employed a computational-experimental approach using molecular docking to evaluate the antiaging potential of compounds identified from the ethanol extract of *Scoparia dulcis* L. leaves. The overall workflow consisted of compound identification, protein and ligand preparation, molecular docking and result evaluation. The three-dimensional (3D) crystal structure of the tyrosinase enzyme from *Agaricus bisporus* (PDB ID: 2Y9X) was obtained from the RCSB Protein Data Bank and used as the target protein [16]. Simultaneously, all compounds identified through LC-MS analysis were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov). The three-dimensional (3D) structure of the 2Y9X protein is presented in Figure 1.

Protein preparation was carried out using BIOVIA Discovery Studio Visualizer 2024 Client by removing water molecules and native ligands to obtain a clean protein structure. The native ligand, 2-Hydroxycyclohepta-2,4,6-trien-1-one, was isolated and re-prepared as a positive control for docking validation.

Molecular docking was conducted using PyRx Virtual Screening Tool with the AutoDock Vina engine. All ligand compounds were converted and optimized using Open Babel prior to docking. The docking process was performed by defining grid box coordinates at X: -10.021222, Y: -28.823111, and Z: -43.596111, with an exhaustiveness value of 10. The screening process involved docking all compounds to the target protein and ranking them by binding affinity. Compounds were considered potential inhibitors if they exhibited binding affinity equal to or lower (more negative) than that of the positive control. The docking method was validated by re-docking the native ligand to determine its three-dimensional conformation within the receptor, using grid box coordinates that correspond to the binding site pocket [17] [18].

Results and Discussion

Extraction of Scoparia dulcis L. leaves

Scoparia dulcis L. leaves powder obtained after drying weighed up to 70 grams. Meanwhile, the condensed ethanol extract of *Scoparia dulcis* L. leaves weighed 6.31 grams. Condensed ethanol extracts of *Scoparia dulcis* L. leaves are obtained from the evaporation process using a Rotary Evaporator BUCHI R-80 System. Ethanol solvents are used for compound extraction because ethanol has polar properties that can penetrate cell wall materials and attract secondary metabolite compounds in *Scoparia dulcis* L. faster [19]. To isolate the secondary metabolite compounds present in the ethanol extract derived from *Scoparia dulcis* L. leaves, the solvent is eliminated through the utilization of a rotary evaporator for the evaporation process. In addition, rotary evaporators have the working principle of lowering the pressure so that the boiling point is reduced, expanding the surface area by rotating the extract sample, and providing appropriate heating to the solution [20].

Identification of secondary metabolites using LC-MS

Phytochemicals were pinpointed utilizing LC-MS based on the provided segments. In the ethanol extract derived from *Scoparia dulcis* L. leaves, a total of 104 secondary metabolite compounds were found and recognized through LC-MS analysis.

It is known that, in the identification, 7 compounds have the highest composition above 2%, as shown in Table 1. From the 7 compounds in the composition, there are 6 flavonoid compounds, including compounds number 2, 3, 4,

5, 6, and 7 in Table 1. In addition, there is also 1 compound of the terpenoid group. This shows that ethanol solvents can attract polar compounds, consistent with the like dissolves like theory [21]. Within an ethanol solution, the (-OH) functional group forms connections with the hydrogen bond present in the (-OH) functional group of flavonoid molecules [22]. Phenolics are a category of naturally occurring compounds frequently found in plants [23]. Watkins and colleagues' experiment in 2025 [24] indicates that flavonoid substances may possess properties that combat aging, as they can reduce the likelihood of developing long-term illnesses resulting from pressure, oxidative damage, and swelling.

Table 1. Major compounds identified by LC-MS analysis of secondary metabolites (> 2.00%)

No.	Compound	Composition (%)
1.	(1R,4aS,5S,6R,7R,8S,8aR)-7-acetyloxy-8-benzoyloxy-5-[(E)-5-hydroxy-3-methylpent-3-enyl]-1,4a-dimethylspiro[3,4,5,7,8,8a-hexahydro-2H-naphthalene-6,2'-oxirane]-1-carboxylic acid	2.06
2.	2-(4-methoxyphenyl)-7-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-[[(2S,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl]oxan-2-yl]oxychromen-4-one	2.14
3.	[(2S,3S,4R,5R,6R)-3,5-dihydroxy-2-methyl-6-[[(2R,3S,4S,5R,6S)-3,4,5-trihydroxy-6-[5-hydroxy-2-(4-hydroxyphenyl)-4-oxochromen-7-yl]oxyoxan-2-yl]methoxy]oxan-4-yl] acetate	2.08
4.	Pectolinaroside	2.22
5.	[(2R,3S,4S,5R,6S)-6-[2-(3,4-dimethoxyphenyl)-5,7-dihydroxy-4-oxochromen-3-yl]oxy-3,4,5-trihydroxyoxan-2-yl]methyl (E)-3-(4-hydroxyphenyl)prop-2-enoate	2.15
6.	[(2R,3R,4R,5S,6S)-3-acetyloxy-2-[[(2R,3S,4S,5R,6S)-6-[5,6-dihydroxy-2-(4-hydroxyphenyl)-4-oxochromen-7-yl]oxy-3,4,5-trihydroxyoxan-2-yl]methoxy]-5-hydroxy-6-methyloxan-4-yl]acetate	2.03
7.	Procyanidin C1	2.53

In silico study

Although 7 compounds had the highest composition as determined by LC-MS analysis, the in silico study identified 104 secondary metabolite compounds that interact with the target protein. This is done to look for potential compounds that have anti-aging activities. All of these compounds were then studied in silico using a molecular docking approach with the PyRx Virtual Screening Tool, using the target protein (PDB ID: 2Y9X) from Agaricus bisporus, which had been downloaded previously (Figure 2).

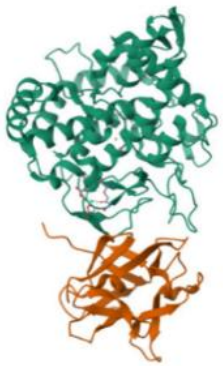


Figure 1. 3D structure of tyrosinase enzyme 2Y9X

This protein was chosen because it can inhibit the activity of tyrannose enzymes. In addition, the 2Y9X protein has a resolution of 2.78 Å, indicating that the protein structure is stable for subsequent molecular docking. The recommended protein resolution value is in the range of 1.5-3 Å [25].

Additionally, support the choice of proteins, as it has been demonstrated that 2Y9X enhances the probability of metal coordination and the development of salt bridges connecting Cu and hydroxyl groups, ultimately impeding the functionality of the tyrosinase enzyme [26]. The molecular docking results are interpreted using the Binding Affinity value (kcal/mol), as shown in Table 2. From the molecular docking results, 6 compounds had binding affinities lower than that of the positive control. These compounds include Vanilic acid, Caffeic acid, Scopoletin, Scoparone, Jasmonic acid, and Budlein A. A lower binding affinity measurement, expressed in kcal/mol, signifies a more robust connection between the ligand and the protein targets [27]. It can also be seen that 4 of the 6 compounds belong to the polyphenol group, including Vanilic acid, Caffeic acid, Scopoletin, and Scoparone. This is because compounds of the polyphenol group are easily extracted in ethanol solvents [28].

Table 2. Molecular Docking Results Through 2Y9X Target Protein

Potential Compound	Binding Affinity (kcal/mol)
2-Hydroxycyclohepta-2,4,6-trien-1-one (positive control)	-6.0
Vanillic acid	-6.2
Caffeic acid	-6.0
Scopoletin	-6.4
Scoparone	-6.2
Jasmonic acid	-6.2
Budlein A	-6.2

The 6 compounds were then further analyzed using Lipinski's Five of Rules (RO5) on the https://scfbio-iitd.res.in/ website with the following parameters: (1) Donor hydrogen bond <5, (2) acceptor hydrogen bond <10, (3) Molecular weight <500 Da, (4) P log value ≤5, and (5) Molar refractivity in the range of 80-130. This rule is used to estimate the potential of secondary metabolite compounds that have the potential to be anti-aging activities. Computational methods can be used to identify candidates for oral drugs that are absorbed by the human body. The compound must meet 4 of the 5 RO5 parameters [29] [30].

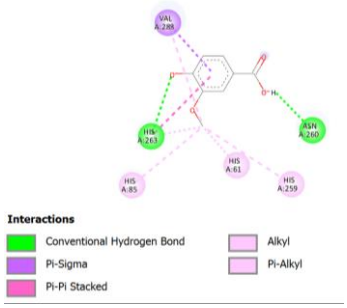
Table 3. Results of RO5 Analysis on 6 Potential Anti-Aging Compounds

Potential Compound	Lipinski's Rule of Five				
	MW[a]	HBD[b]	HBA[c]	Log P[d]	MR[e]
Vanillic acid	162.0	2	4	-0.2	33.6
Caffeic acid	175.0	3	4	-1.0	39.3
Scopoletin	185.0	1	4	-0.3	39.8
Scoparone	196.0	0	4	0.4	41.9
Jasmonic acid	193.0	1	3	-0.3	47.0
Budlein A	353.0	1	7	-0.9	77.5

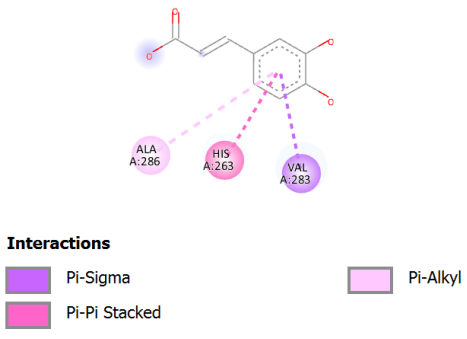
[a] Molecular Weight, [b] Hydrogen Bond Donor, [c] Hydrogen Bond Acceptor, [d] Log P, and [e] Molar Refractivity.

The results of the analysis using the RO5 rule as a reference are shown in Table 3. From these results, 6 potential compounds as anti-aging molecular docking have also met the RO5 rule. This shows that these 6 potential compounds can also be used as oral drug candidates. The six compounds are also predicted to be able to penetrate the digestive membrane and cell membrane, and can reach the target protein easily because they have met the RO5 rule [31]. In addition to their pharmacokinetic properties, the molecular docking results revealed that several of these compounds exhibited strong binding affinity toward the tyrosinase enzyme, suggesting their potential as tyrosinase inhibitors. Consistent with previous studies from Liang (2024), polyphenols and flavonoids exhibit significant inhibitory activity by interacting with the active site of tyrosinase and coordinating with copper ions (Cu^{2+}), which play a critical role in the catalytic mechanism of the enzyme [32].

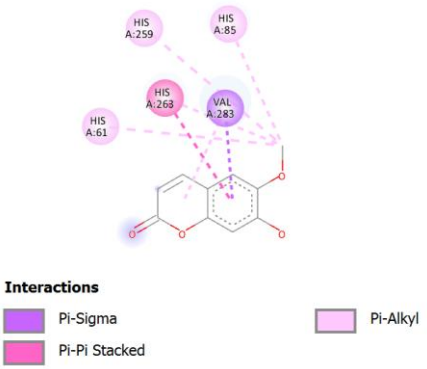
a) Vanillic Acid



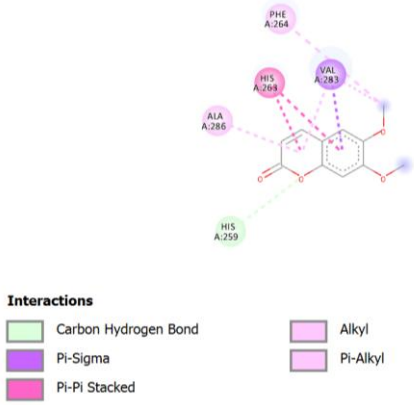
b) Caffeic Acid



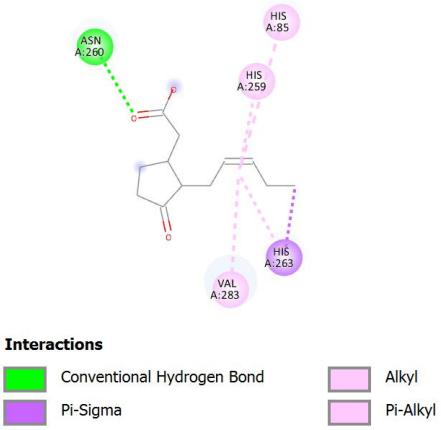
c) Scopoletin



d) Scoparone



e) Jasmonic Acid



f) Budlein A

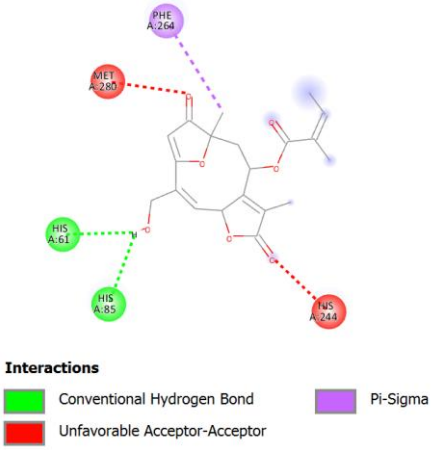


Figure 2. Visualization of Interaction Between Ligands and Tyrosinase Enzyme (2Y9X)

Interaction between ligands and tyrosinase enzyme was visualized using BIOVIA Discovery Studio Visualizer 2024 Client in Figure 2. Hydrogen bonds, π-interactions (π- π stacked, π-sigma, and π-alkyl), as well as unfavorable interactions can be clearly identified. However, other interactions, such as van der Waals forces and certain hydrophobic effects, are not fully visualized. Although they still contribute significantly to the overall binding energy of the ligand within the active site of tyrosinase. The selected compound in Table 4 revealed that the hydrogen bond has an important role in stabilizing the ligand-protein complex. In this case, Vanillic acid formed a conventional hydrogen bond with ASN260 and HIS263 amino acid residues, and Jasmonic acid formed a conventional hydrogen bond with ASN260 amino acid residues. These residues are located near the active sites of the tyrosinase enzyme, which means that the ligand has a catalytically relevant region. In addition to hydrogen bonding, π-interactions were observed, particularly involving histidine residues such as HIS61, HIS85, HIS259, and HIS263, as well as hydrophobic residues such as VAL283 and PHE264. In contrast, Caffeic acid and Scopoletin exhibit π-π stacking and π-σ interactions. In this case, Caffeic acid and Scopoletin exhibit binding stability influenced by hydrophobic and aromatic interactions. On the other side, Budlein A exhibits both stabilizing and destabilizing interactions. Although hydrogen bonds with HIS61 and HIS65 residues, unfavorable acceptor-acceptor interactions with residues such as ASN260 and HIS244 were also detected. These unfavorable interactions may introduce steric hindrance or electrostatic repulsion, thereby weakening the binding stability despite the presence of favorable interactions. The involvement of histidine residues, such as HIS61, HIS85, HIS259, and HIS263, is particularly significant. It causes the residues to be associated with the coordination of Cu^{2+} ions in the catalytic center of tyrosinase enzyme [33]. Research similar [34], were polyphenols and flavonoids inhibit tyrosinase enzyme by interacting active sites residues, forming hydrogen bond and π-interactions. The hydroxyl (-OH) groups that are compounds, such as phenolic groups, tend to exhibit stronger inhibitory activity due to their ability to form stable hydrogen bonds within active sites.

Overall, the molecular docking analysis suggests that compounds capable of forming hydrogen bonds and interacting with amino acid residues in the active site, particularly histidine residues, have greater potential to inhibit tyrosinase activity. This inhibition mechanism may disrupt melanogenesis, thereby contributing to antiaging effects.

Conclusion

This study demonstrated the effectiveness of integrating LC-MS-based chemical profiling with in silico molecular docking as a comprehensive approach to identify potential antiaging compounds from *Scoparia dulcis* L. leaves. The LC-MS analysis enabled the identification of bioactive compounds, which were subsequently screened against the tyrosinase enzyme (PDB ID: 2Y9X), providing an efficient strategy to link chemical composition with predicted biological activity. Several compounds exhibited promising potential based on their favorable binding affinity, compliance with Lipinski's Rule of Five, and their ability to interact with key active site residues, particularly histidine residues associated with Cu^{2+} coordination. The presence of hydrogen bonds and π-interactions further stabiliszd the ligand–protein complexes, suggesting their role in inhibiting tyrosinase activity and melanogenesis. These findings highlight the scientific contribution of combining chemical profiling and computational screening in accelerating the discovery of natural antiaging agents. However, further validation is required through in vitro tyrosinase inhibition assays and ADMET analyses to evaluate pharmacokinetic and toxicity profiles. In addition, formulation studies are necessary to optimize the stability and bioavailability of the identified compounds for potential pharmaceutical or cosmetic applications.

Author's Contribution

A.F. Putri: responsible for the implementation of research, data collection and the preparation of manuscript drafts. Tukiran: contributes to data validation and provides guidance and direction in manuscript preparation.

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