pISSN 2302-1616, eISSN 2580-2909
Vol 12, No. 2, December 2024, pp. 101-109
Available online http://journal.uin-alauddin.ac.id/index.php/biogenesis
DOI https://doi.org/10.24252/bio.v12i2.53561

In vitro and in silico study of kepok banana corm extract as anti-tyrosinase

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ABSTRACT. Tyrosinase is a critical enzyme in melanin synthesis, where its overactivity can result in hyperpigmentation disorders. Despite the availability of synthetic tyrosinase inhibitors, concerns about safety have prompted the search for natural alternatives. The objective of this study is to evaluate the potential of Kepok banana (*Musa acuminata* x *balbisiana*) corm extract as a natural tyrosinase inhibitor, using in vitro and in silico approaches. The extract was prepared by maceration with etanol 96%, followed by sonication and lyophilization. LC-MS analysis was performed on a Shimadzu LCMS 8040 using a Shim Pack FC ODS column with 90% methanol as the mobile phase under isocratic conditions. Samples were ionized via ESI in positive mode and scanned over m/z 10–1000. Peaks were identified based on their m/z values and MS/MS fragmentation patterns. In vitro and in silico analyses were applied, respectively, to study the biological process of kepok banana corm extract as a natural tyrosinase inhibitor. The result of the kepok banana corm extraction process was 12.5% dry powder with bioactive components identified via LC-MS, including flavonoids, phenolics, and terpenoids. The kepok banana corm ethanol extract exhibited strong tyrosinase inhibition with an IC_{50} of 91.074 µg/mL, falling below the 100 µg/mL threshold for strong inhibitors and showing a similar inhibition pattern to the standard kojic acid (IC_{50} = 10.87 µg/mL). Molecular docking revealed that major compounds, particularly flavonoids, exhibited high binding affinity with the tyrosinase enzyme through hydrogen bonding and hydrophobic interactions, similar to kojic acid, a known inhibitor. These findings suggest that kepok banana corm extract may serve as a promising natural tyrosinase inhibitor, with potential applications in hyperpigmentation treatment and cosmetic formulations.

Keywords: flavonoids; hyperpigmentation; in vitro and in silico analysis; kepok banana corm extract; tyrosinase inhibition

Article History: Received 20 December 2025; Received in revised form 1 August 2025; Accepted 4 August 2025; Available online 31 August 2025.
How to Cite This Article: Andini A, Raharjo SJ, Misgiati M, Izza A, Istiana M. 2024. In vitro and in silico study of kepok banana corm extract as anti-tyrosinase. Biogenesis: Jurnal Ilmiah Biologi. vol 12(2): 101-109. doi: https://doi.org/10.24252/bio.v12i2.53561.

INTRODUCTION

Tyrosinase is a key enzyme responsible for the production of melanin, a pigment crucial for skin color and protection against UV radiation (Furi *et al*., 2022). However, excessive melanin production, often triggered by overactive tyrosinase, can lead to hyperpigmentation disorders such as melasma, age spots, and post-inflammatory hyperpigmentation. As such, the search for effective tyrosinase inhibitors has become an important area of dermatological research (Pratiwi *et al*., 2021). Current tyrosinase inhibitors like hydroquinone, arbutin, and kojic acid are commonly used, but they can have adverse effects with long-term use, such as skin irritation or cytotoxicity (Julan *et al*., 2023; Lestari, 2023; Werdiningsih, 2024). Hence, finding safer and more effective natural alternatives is essential.

Banana corms, particularly from the Kepok variety (*Musa acuminata* x *balbisiana*), have been identified as rich sources of bioactive compounds, including polyphenols, flavonoids, and other antioxidant-rich substances (Andini *et al*., 2023; Wenas *et al*., 2020). These compounds have shown potential biological activities, including anti-inflammatory and antioxidant properties, which could contribute to tyrosinase inhibition (Wenas *et al*., 2020). Yet, despite the increasing interest in plant-based tyrosinase inhibitors, the specific potential of Kepok banana corms in this context has not been well-explored. This suggests an opportunity to investigate Kepok banana corm extract's potential role as a natural anti-tyrosinase agent.

A clear research gap exists in the study of tyrosinase inhibition using Kepok banana corm extract, particularly through both in vitro and in silico approaches. While in vitro assays provide insights into the biological activity of extracts on enzymes or cell models (Wang *et al*., 2019; Fadilah *et al*., 2020), in silico studies allow for molecular-level exploration of potential binding interactions between active compounds and tyrosinase (Pratiwi *et al*., 2021; Azhar *et al*., 2023;). Combining these two

methodologies could offer a comprehensive understanding of the extract's mechanisms and potency in inhibiting tyrosinase.

Therefore, the purpose of this study is to evaluate the potential of Kepok banana corm extract as a natural tyrosinase inhibitor using in vitro and in silico approaches. By assessing the extract's effects on tyrosinase activity in a laboratory setting and simulating its interaction with the enzyme at a molecular level, this study aims to provide a dual perspective on its anti-tyrosinase potential. Ultimately, this research aims to contribute to the growing body of knowledge on plant-based tyrosinase inhibitors, offering insights that could lead to the development of safe, natural, and effective treatments for hyperpigmentation disorders. Should Kepok banana corm extract demonstrate significant tyrosinase inhibition, it could emerge as a promising candidate for skincare and cosmetic applications.

MATERIALS AND METHODS

Extraction and LC-MS analysis. Kepok banana corm simplicia weighing 25 grams was placed in a beaker glass, then 250 mL of solvent was added and stirred. The solvents used was etanol 96%. The maceration was carried out for 3 hours at room temperature, then sonicated (200 W, 40 KHz) for 30 minutes, 70℃. The extract obtained was filtered and the residue was remacerated with each solvent. The remacerated filtrate was combined with the initial filtrate and then concentrated to a thickness of 50 mL using a rotary evaporator under vacuum at 55℃. The concentrated extract was centrifuged for 10 minutes to remove any solids that may have escaped during filtration. The extract was stored in a freezer until frozen, then lyophilized for 62 hours to obtain dry extract in powder form (Andishmand *et al*., 2023).

The Shimadzu LCMS 8040 LC/MS was used to conduct high-resolution MS/MS analysis (Zhao *et al*., 2020). The Shimadzu Shim Pack FC-ODS (2 mm x 150 mm, 3 µm) was used to separate metabolites before analysis. Injection volume: 1 µL (water extract and n-hexane extract), capillary voltage: 3.0 kV, column temperature: 35°C, mobile phase mode: isocratic, flow rate: 0.5 mL/min. Sampling cone voltage is 23.0 V, and the solvent is 90% methanol. MS focused ion mode io type [M]+, Collison energy 5.0 V, desolvation gas flow 60 mL/hour, desolvation temperature 350°C, fragmentation method: low energy CID, ionization: ESI, scanning 0.6 sec/scan (mz: 10-1000), source temperature 100°C, and run time 60 minutes.

In vitro analysis. 1 mg of the sample was dissolved in 1000 µL of 0.15% DMSO. The sample was sonicated for 10 minutes until a homogeneous solution was achieved. Sample dilutions were prepared at concentrations of 10 ppm and 100 ppm for preliminary screening. The diluted samples were incubated for 15 minutes at 37°C, and the maximum absorption wavelength (λmax) for this tyrosinase assay is determined by scanning the reaction mixture of L-DOPA and tyrosinase across the UV-Vis spectrum to identify the peak absorbance of dopachrome, which occurs around wavelength of 485 nm. Perform the same procedure for the tyrosinase enzyme and the L-DOPA substrate, using a phosphate buffer blank at pH 6.8 (Priani & Fakih, 2021; Furi *et al*., 2022).

In silico analysis. In silico analysis consists of several stages, namely: (1) Design: This in silico method used a molecular docking analysis method between the active cinnamon essential oil compounds against the human D4 dopamine receptor dan structure of the D2 dopamine Receptor. In addition, a molecular docking comparison was also carried out the active 20 cinnamon essential oil compounds; (2) Searching for amino acid sequence: Amino acid sequences that make up the human D4 dopamine receptor and the D2 dopamine Receptor were obtained from The Research Collaboratory for Structural Bioinformatics Protein Data Bank database (https://www.rcsb.org). The three-dimension structure of protein was downloaded in the human D4 dopamine receptor (id: 5wiv) and structure of the D2 dopamine Receptor (id: 6cm4); and (3) Preparation of ligand compounds: The ligands in this study were compounds found in 20 cinnamon essential oil compounds. obtained from GCMS results. The ligands were then interacted with a receptor, and their chemical structures were obtained by accessing PubChem. The three-dimensional structure of the 20 compounds 20 cinnamon

essential oil compounds was obtained from the PubChem Open Chemistry Database. The three-structure of various compounds in the smile format was then converted into *.pdb files using LigParGen is a web-based service that provides force field (FF) parameters for organic molecules or ligands (Dodda *et al*., 2017a; Dodda *et al*., 2017b).

Molecular docking of ligand with protein target. Molecular docking of a ligand with its protein target consists of several stages, namely: (1) Protein preparation: The three-dimensional structure of D4 dopamine receptor (id: 5wiv) and D2 dopamine Receptor (id: 6cm4) was prepared separately by removing water molecules, ions and cofactors present in the protein. Furthermore, the protein is edited by adding hydrogen atoms and given a charge by computing the Gasteiger. The grid box is set by focusing on the active site residues of the protein with dimensions (40 × 40 x 40) centered on (-0.311 0.848 2.895) (Ananda *et al*., 2024). Protein preparation was carried out using AutoDock Tools 1.5.7 software. Next, the file is saved in *pdbqt format for use in molecular docking; (2) Ligand preparation: Preparation of the active compounds of 20 compounds of cinnamon essential oil compounds form GC-MS was carried out using the AutoDock Tools 1.5.7 software. Ligand files are saved in *pdbqt format for use in molecular docking; (3) Molecular docking using AutoDock Vina: Docking simulations between the 20 compounds of cinnamon essential oil compounds form GC-MS and target proteins were carried out using AutoDock Vina v1.2.3 software. After receptor and ligand preparation, the docking process was started using the command prompt. Docking results were then visualized with the Discovery Studio 4.1 software (Ananda *et al*., 2024); and (4) Visualization and analysis of docking results protein and ligand interactions from the docking results were then analysed and visualized using BIOVIA Discovery Studio software. The results were analysed by determining the ligand conformation that had the best binding affinity value and analysing binding interactions based on amino acid residues in 2D and 3D form. The binding affinity value was determined based on the most negative value and compare to native ligand.

Data analysist. IC_{50} determination was carried out by preparing five serial concentrations of the sample and kojic acid standard, each measured in triplicate. Each solution was incubated with tyrosinase and L-DOPA in phosphate buffer (pH 6.8) at 37°C for 15 minutes, and absorbance was measured at 485 nm. Percentage inhibition was calculated relative to the control, and the logarithm of concentration was plotted against the probit of % inhibition to generate a linear regression equation ($y = bx + a$). The IC_{50} value, corresponding to 50% inhibition (probit = 5), was calculated from this regression. (Witasari & Nadia Salsabila, 2022).

RESULTS AND DISCUSSION

In this procedure, 25 grams of Kepok banana corm simplicia was weighed and placed in a beaker glass, followed by the addition of 250 mL of solvent to facilitate extraction. Ethanol 96% is used for extraction because it effectively dissolves both polar and non-polar compounds, maximizing the yield of bioactive constituents. Additionally, it is safe, non-toxic, and widely accepted in both pharmaceutical and food industries for its efficiency and compatibility with most compounds (Pandey *et al*., 2014; Huang *et al*., 2019). This solvent selection aims to maximize the range of metabolites extracted from the corm material, capturing both polar and non-polar constituents (Baranowska *et al*., 2021).

The maceration was conducted for 3 hours at room temperature to allow for passive diffusion of the solvents into the plant matrix, gradually extracting the target compounds. After maceration, sonication was applied at 200 W and 40 kHz for 30 minutes at 70°C. Sonication uses ultrasonic waves to create cavitation in the solvent, enhancing the breakdown of plant cell walls and improving the release of bioactive compounds into the solution (Manzoor *et al*., 2021; Kumar *et al*., 2022). This step is essential to increase the efficiency of extraction, particularly for tightly bound intracellular compounds.

Once the extraction was complete, the solution was filtered to separate the liquid extract from solid residues. The remaining solid residue was remacerated with fresh solvent to ensure maximum

extraction yield, and the remacerated filtrate was combined with the initial filtrate. This combined filtrate was then concentrated to a final volume of 50 mL using a rotary evaporator under vacuum at 55°C, a step designed to reduce solvent volume while preserving the heat-sensitive bioactive compounds by avoiding higher temperatures (Rusnedy, 2021). After concentration, the extract was centrifuged for 10 minutes to remove any remaining particulate matter that may have bypassed the filtration step, further purifying the extract.

For storage and preservation, the concentrated extract was frozen and then lyophilized for 62 hours to produce a stable, dry powder form. Lyophilization (freeze-drying) removes water content under low temperature and vacuum, preserving the structural integrity and activity of heat-sensitive compounds (Patel *et al*., 2016). This dry extract was then analyzed for its metabolite profile using a high-resolution mass spectrometry setup, specifically the Shimadzu LCMS 8040 LC/MS, equipped with a Shim Pack FC-ODS column to achieve high-resolution separation of metabolites. The use of isocratic mobile phase conditions with a 90% methanol solvent at a flow rate of 0.5 mL/min ensures consistent elution of compounds for accurate and reliable analysis.

The Shimadzu LCMS 8040 parameters were carefully chosen to optimize ionization and fragmentation of the metabolites (Zhao *et al*., 2020). An injection volume of 1 µL for both water and n-hexane extracts provided sufficient sample quantity for analysis without overloading the column. The capillary voltage of 3.0 kV and sampling cone voltage of 23.0 V facilitated effective ionization of compounds, with a desolvation temperature of 350°C and desolvation gas flow of 60 mL/hour aiding in the removal of solvent vapors. A scanning range of mz 10–1000 was used to detect a wide array of compounds, while a 60-minute run time allowed for a thorough analysis of the extract. This setup ensures comprehensive profiling of the Kepok banana corm metabolites, supporting subsequent analyses of their potential bioactivity.

Based on the results of the extract, a yield of 12.5% was obtained, this result meets the yield requirements in the Indonesian Herbal Pharmacopoeia which explains that the yield of extracts from the musaceae family is >11.2%, the yield of >10% is also categorized as a good yield (Imanullah *et al*., 2024). The results of secondary metabolite analysis showed the presence of 122 components in the ethanol extract of kepok banana corm as can be seen in Figure 1. of the 122 secondary metabolite components contained in kepok banana corm extract include flavonoids, steroids, phenolics, terpenoids, and other components.

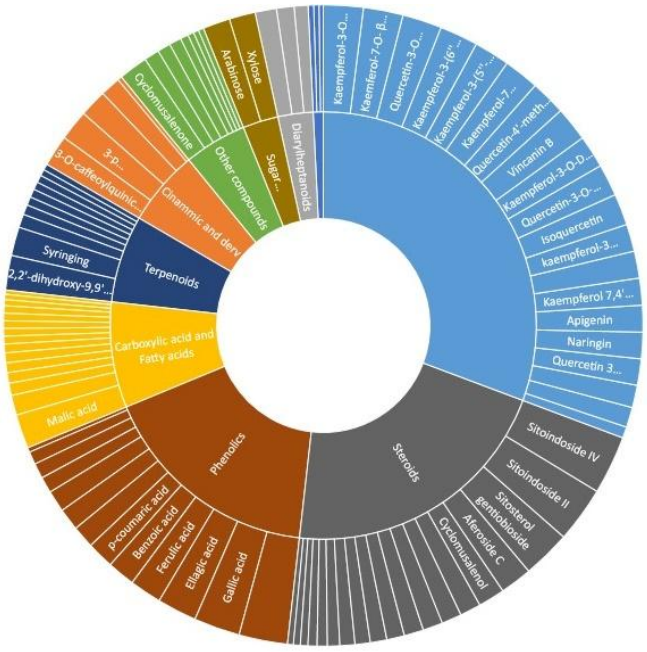


Fig. 1. The 122 secondary metabolite components of kepok banana corm extract

The analysis results show that there are components that make up ethanol extract of kepok banana corm, inculding flavonoid glicosides (25%), i.e.: Kaempferol-3-O-rhamnoside 1.63%, kaemferol-7-O-β-D-glucoside 1.63%, quercetin-3-O-rhamnoside 1.62%, kaempferol-3-(6"-caffeoylglucoside) 1.58%, kaempferol-3-(5"-feruloylapioside) 1.47%, kaempferol-7-rhamnoside 4' glucoside 1.45%, quercetin-4'-methyl ether-3- neohesperidoside 1.45%, vincanin B 1.42%, luteolin-7-glucoside 1.11%, kaempferol-3-O-D-glucoside 1.34%, quercetin-3-O-neohesperidoside 1.31%, isoquercetin 1.29%, kaempferol-3-glucoside-2"-rhamnoside-7-rhamnoside 1.12%, kaempferol 7,4'-dimethyl ether 3-neohesperidoside 1.10%, apigenin 1.09%, naringin 1.08%, quercetin 3-glucoside 1.08%, kaempferol-4'-methyl ether 3-neohesperidoside 0.92%, rutin 0.82%, etc; flavonoids (18%), i.e. quercetin 1.61%, luteolin 1.40%, quercetin 3-rutinoside 1.32%, kaempferide 1.34%, kaempferol 1.34%, catechin 1.12%, 3,5,7-trihydroxyflavone 0.97%, 3,3',5,7-tetrahydroxy-4'-methoxyflavone CID5281699 0.96%, naringenin 0.88%; steroid (17%), ie: sitoindoside IV, 2.40%, sitoindoside II 2.29%, sitosterol gentiobioside 1.98%, aferoside C 1.31%, cyclomusalenone 1.20, cyclomusalenol 1.099%, aferoside B 0.86%, obtusifoliol 0.82%, collettiside III 0.822%, etc.; phenolic (14%), i.e. 4',4"-dihydroxyanigorootin 2.0%, llagic acid 1.63%, gallic acid 1.90%, ferulic acid 1.32%, benzoic acid 1.14%, p-coumaric acid 1.11%, shikimic acid 0.92%, etc.; carboxylic acid-fatty acid (7%), i.e 3-O-caffeoylquinic acid methyl ester 1.28%, 3-p-coumaroylquinic acid 1.26%, 5-O-caffeoylshikimic acid 1.127%, etc.; terpenoid (5%), i.e. syringing 1.18%, 2,2'-dihydroxy-9,9'-bis-(4-hydroxyl phenyl)-[3,3'-bi-1H-phenalene]-1,1'–dione 1.42%, 3-epicycloeucalenol 0.41%, etc.; Cinnamic acids and derivative (5%), i.e.: malic acid 1.40%, fumaric acid 0.82%, isobutyl acetate 0.50%, etc.; diarylheptanoids (2%); sugar (2%); alkaloids (0.5%); and other compounds (2,5%), as shown Figure 2.

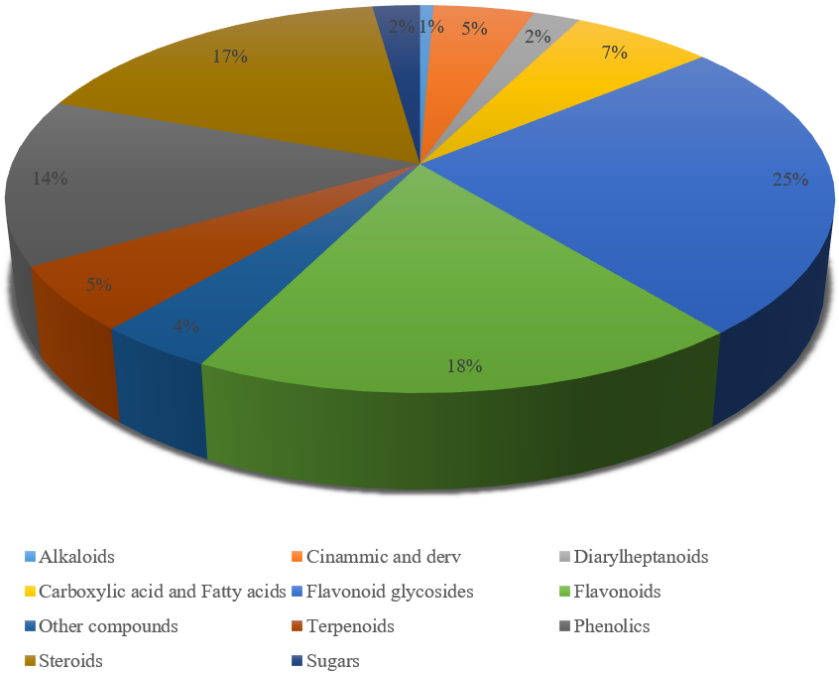


Fig. 2. The compotition of the 122 secondary metabolite components of kepok banana corm extract

In vitro study. Melanin production can be reduced by inhibiting the tyrosinase enzyme. To achieve this, a compound that acts as a tyrosinase inhibitor is necessary. If the extract contains such an inhibitor, it will effectively block melanin formation, leading to a reduction in the brown coloration. The absorbance measured during the test reflects the sample's ability to inhibit the tyrosinase enzyme. This absorbance data can be used to calculate the percentage inhibition, which indicates how effectively the sample inhibits tyrosinase at various concentrations. A higher percentage of inhibition correlates with stronger inhibition of the tyrosinase enzyme, thereby reducing melanin formation, which is also visually evident in the fading brown color. The inhibitory effect on

tyrosinase can be quantified by the IC50 value, which represents the concentration of an inhibitor that reduces enzyme activity by 50%. A lower IC50 value indicates more potent inhibition, as it takes a smaller concentration of the sample to achieve 50% inhibition of tyrosinase activity.

The tyrosinase enzyme used in the assay is an enzyme stored at low temperature. Optimal storage of tyrosinase enzymes is carried out at 20℃ so that the enzyme catalytic reaction is stopped. Tyrosinase enzyme reactivates in the temperature range of 35-37℃. The samples were then incubated at 37℃ for 30 minutes. The temperature of 37℃ was chosen as the sample treatment because the temperature is in accordance with body temperature and the optimal temperature for enzymes to work, while 30 minutes is enough time for the tyrosinase enzyme, substrate and extract to react with each other.

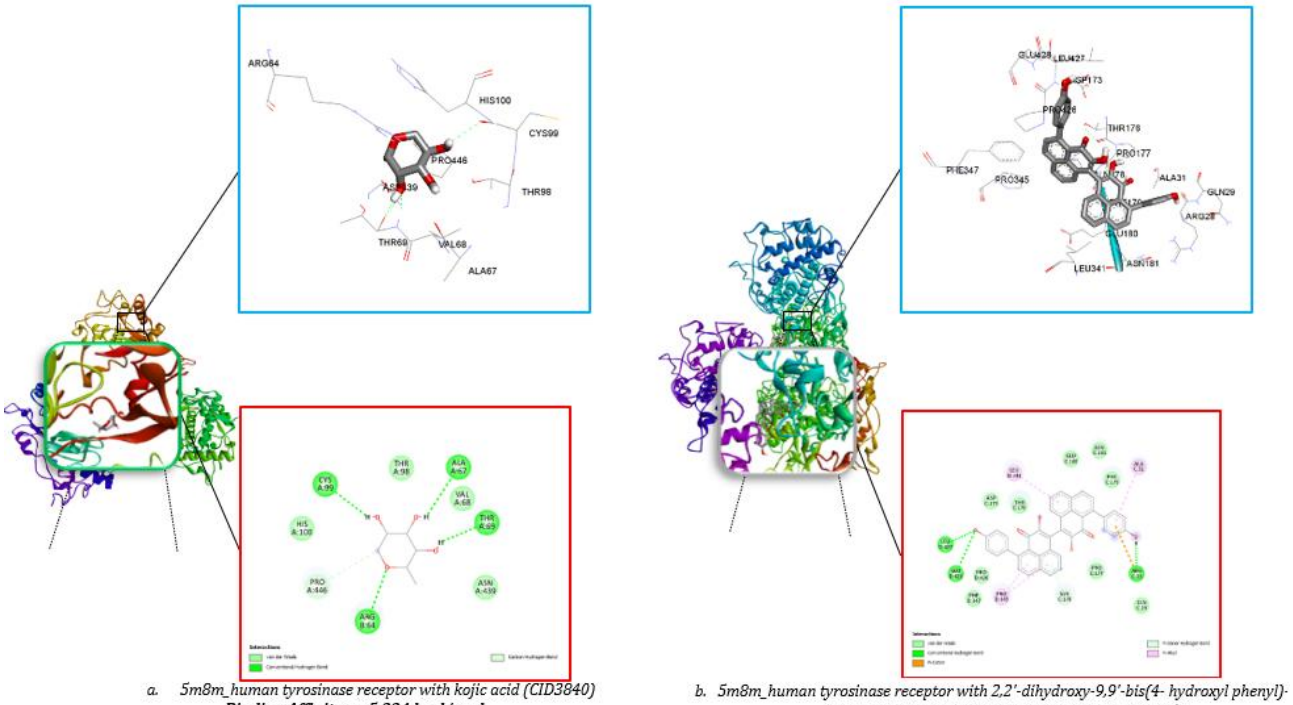
The test results of tyrosinase enzyme inhibitor activity obtained IC50 value of kojic acid of 10.87 µg/mL with the value of y = 3.8295x + 8.8844 and R2 = 0.9902. The IC50 value of kepok banana corm ethanol extract is 91.074 µg/mL with y=0.5x + 3.3113 and R2=0.9753. The absorbance values for kojic acid, ethanol extracts decrease as the concentration increases. Higher concentrations of the sample solution result in lower absorbance and reduced intensity of the brown color. This suggests that at higher concentrations, the test samples have an enhanced ability to inhibit tyrosinase activity, preventing melanin formation, which leads to lower absorbance values associated with melanin's brown color. Consequently, lower absorbance indicates a higher percentage of inhibition, meaning the sample solution exhibits stronger inhibitory power at higher concentrations. According to the classification for tyrosinase inhibition potency, the results indicated that the ethanol extract display strong inhibitory activity against the tyrosinase enzyme.

The strong inhibitory activity against the tyrosinase enzyme is likely due to the presence of flavonoids. LC/MS analysis showed that the sample contains flavonoid compounds, which constitute approximately 43% of its composition. Flavonoids are known to inhibit tyrosinase activity, reducing skin pigmentation by directly blocking this enzyme in the melanogenesis process. They achieve this through a competitive inhibition mechanism with the enzyme’s substrate. The effectiveness of flavonoids in inhibiting tyrosinase is influenced by the position and number of hydroxyl (OH) groups on their benzene rings; a higher number of OH groups enhances their inhibitory effect. In contrast, the presence of sugar conjugates on the benzene ring can decrease this inhibitory activity.

In silico study. Tyrosinase-related protein 1 (TYRP1) is one of three tyrosinase-like glycoenzymes in human melanocytes that are key to the production of melanin, the compound responsible for the pigmentation of skin, eye, and hair. Difficulties with producing these enzymes in pure form have hampered the understanding of their activity and the effect of mutations that cause albinism and pigmentation disorders (Lai *et al*., 2017). Kojic acid and its derivatives are compounds conjugated with a pyridine amino group that were designed and synthesized to explore their inhibitory activity against tyrosinase. Docking analysis and molecular dynamics simulations showed considerable binding affinity and significant interactions with the tyrosinase enzyme to target the melanogenesis pathway, making it a strong candidate for controlling hyperpigmentation in the future (Niri *et al*., 2023). In this study, kojic acid was used as a native ligand and 43 (major components) of the 122 extracted compounds were analyzed by LC-MS, then docked with the target protein 5m8m_human tyrosinase receptor. This research succeeded in showing a comparison of the potential of natural bioactive compounds from ethanol extract of kepok banana corm, i.e. 2,2'-dihydroxy-9,9'-bis-(4-hydroxyl phenyl)-[3,3'-bi-1H- phenalene]-1,1'–dione (CID136703905) and several other bioactive compounds, with 5m8m_human tyrosinase receptor.

Identification of potential 5m8m_human tyrosinase receptor inhibitors was carried out using in silico analysis, namely by comparing the activity of 2,2'-dihydroxy-9,9'-bis-(4-hydroxyl phenyl)-[3,3'-bi-1H - phenalene]-1 ,1' –dione (CID136703905) with kojic acid (Niri *et al*., 2023). Virtual analysis via in silico is a dynamic screening for new therapeutic agents (Raharjo & Kikuchi, 2016). The potential of the bioactive compound against the tyrosinase receptor was investigated based on binding affinity and binding site (Raharjo *et al*., 2014, 2015). This study revealed the highest activity

of 2,2'-dihydroxy-9,9'-bis-(4-hydroxylphenyl)-[3,3'-bi-1H-phenalene]-1,1'–dione (CID136703905) compared to bioactive compounds others in ethanol extract of kepok banana corm, against 5m8m_human tyrosinase receptor, as presented in Figure 4 and Table 1. In vitro analysis, shows the value of tyrosinase enzyme inhibitor activity obtained IC50 value of kojic acid of 10.87 µg/mL and IC50 value of kepok banana corm ethanol extract is 91.074 µg/mL, this is of course in line with the binding affinity of kojic acid is -5,324 kcal/mol and binding affinity is 2,2'-dihydroxy-9,9'-bis-(4-hydroxyl phenyl)-[3,3'-bi-1H-phenalene]-1,1'–dione and other bioactive in ethanol extract of kepok banana corm. However, of course it is necessary to follow up with subsequent in-vivo analysis and clinical trials, in order to confirm the potential of 2,2'-dihydroxy-9,9'-bis-(4- hydroxyl phenyl)-[3,3'-bi-1H-phenalene]-1,1'–dione and other bioactive in ethanol extract of kepok banana corm against human tyrosinase receptor.



a. 5m8m_human tyrosinase receptor with kojic acid (CID3840)
Binding Affinity = -5.324 kcal/ mol

b. 5m8m_human tyrosinase receptor with 2,2'-dihydroxy-9,9'-bis(4- hydroxyl phenyl)-[3,3'-bi-1H- phenalene]-1,1' –dione (CID136703905)
Binding Affinity = -10.55 kcal/mol

Fig. 3. Interaction 3D and 2D of [a] 5m8m_human tyrosinase receptor receptor with native_kojic acid (CID3840); [b] 5m8m_human tyrosinase receptor receptor with 2,2'-dihydroxy-9,9'-bis(4- hydroxyl phenyl)-[3,3'-bi-1H- phenalene]-1,1' –dione (CID136703905)

CONCLUSION

This study demonstrates that ethanol extract from the Kepok banana corm holds significant potential as a natural tyrosinase inhibitor. The dual in vitro and in silico approach provided a comprehensive evaluation of the extract's ability to inhibit tyrosinase activity, which is crucial in melanin synthesis and hyperpigmentation control. The LC-MS analysis revealed that flavonoids, which comprised approximately 43% of the extract, likely play a key role in this inhibition due to their known ability to competitively inhibit tyrosinase by interacting with its active site. In the in vitro tests, the extract showed a strong inhibitory effect on tyrosinase, indicated by its IC50 value (91.074 µg/mL). In silico docking further confirmed the binding potential of the major components in the extract, particularly flavonoid glycosides, which showed favorable interactions with tyrosinase's active sites. These findings indicate that the Kepok banana corm extract, rich in flavonoids and other bioactive compounds, may offer a promising natural alternative to synthetic tyrosinase inhibitors like kojic acid. This study adds valuable insights to the field of natural anti-tyrosinase agents, highlighting

Kepok banana corm extract's potential for development into safe and effective treatments for hyperpigmentation disorders in cosmetic and dermatological applications.

ACKNOWLEDGEMENTS

This research was funded by Directoreate General of Higher Education, Misnistry of Education and Culture, Republic of Indonesia which has provided research grants for novice lecturers in Letter of Agreement of Assigment of Research Program Implementation Number: 421/SPK/D.D4/PPK.01.APTV/VIII/2024. The authors declare that they have no conflict of interest.

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