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# HKSA Analysis and Docking of Antioxidant Activity of Curcumin Analogues Against Tyrosinase Enzyme

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**Abstract:** The aim of the HKSA and Docking analysis was to determine the potential of curcumin analogues as antioxidants for the activity of the tyrosinase enzyme. Predictor calculations were carried out using the hyperchem application with the CNDO semi-empirical geometric optimization method. Multilinear regression analysis using SPSS to find the relationship between predictors and the activity of curcumin analogue derivative compounds as tyrosinase inhibitors. To see the affinity between the new curcumin analog derivative compound and the tyrosinase enzyme, docking was carried out using Autodock Tools and visualization using Biovia discovery studio. The results of the best HKSA equation model are: $LogIC_{50}$: -3.195 – (1.135 x HOMO) + (1.064 x LUMO) - (0.239 x LogP) + (0.155 x HE). This equation is used to predict new compounds derived from curcumin analogs that can be used as new tyrosinase inhibitors. The parameters for selecting this compound were because it had better activity and $LogIC_{50}$ values compared to the parent compound. The docking results of the test ligand have the same amino acid residues as the original ligand (Tyrosine) with a binding energy of the compound 2,5-bis (4-hydroxy 3-allyl-benzylidene) cyclopentanone, namely -5.92 kcal/mol and a Ki value of 46.03 uM more better compared to the binding energy of the compound (Tyrosine) which is -4.96 kcal/mol and the Ki value which is 231.77 uM. This shows that the compound 2,5-bis (4-hydroxy 3-allyl benzylidene) cyclopentanone has potential inhibitory activity on tyrosinase receptors as an antioxidant activity.

***Keywords:*** *Curcumin, Tyrosinase, Antioxidant, QSAR, Docking*

***Abstrak:*** *Tujuan dari analisa HKSA dan Docking dilakukan untuk menentukan potensi analog kurkumin sebagai antioksidan terhadap aktivitas enzim tirosinase. Perhitungan prediktor dilakukan menggunakan aplikasi hyperchem dengan metode optimasi geometri semi-empirik CNDO. Analisis regresi multilinear menggunakan SPSS untuk mencari hubungan antara prediktor dan aktivitas senyawa turunan analog kurkumin sebagai inhibitor tirosinase. Untuk melihat afinitas antara senyawa turunun analog kurkumin yang baru dengan enzim tirosinase dilakukan docking menggunakan Autodock Tools yang visualisasinya menggunakan Biovia discovery studio. Hasil model persamaan HKSA terbaik yaitu : $LogIC_{50}$: -3.195 – (1.135 x HOMO) + (1.064 x LUMO) - (0.239 x LogP) + (0.155 x HE). Persamaan ini digunakan untuk memprediksi senyawa baru turunan analog kurkumin yang bisa dijadikan sebagai inhibitor tirosinase yang baru. Parameter pemilihan senyawa tersebut karena memiliki aktivitas dan nilai $LogIC_{50}$ yang lebih baik dibandingan senyawa induk. Hasil docking ligan uji memiliki kesamaan residu asam amino dengan ligan asli (Tyrosin) dengan energi ikat senyawa 2,5-bis (4-hidroksi 3-allyl-benzilidena) siklopentanon yaitu -5.92 kcal/mol dan nilai Ki yaitu 46,03 uM lebih baik dibandingkan energi ikat senyawa (Tyrosin) yaitu -4.96 kcal/mol dan nilai Ki yaitu 231,77 uM. Hal ini menunjukkan bahwa senyawa 2,5-bis (4-hidroksi 3-allyl benzilidena)*

*siklopentanon memiliki potensi aktivitas penghambatan pada reseptor tirosinase sebagai aktivitas antioksidan.*

***Kata kunci:** Kurkumn, Trosinase, Antioksidan, HKSA, Docking*

## ▪ INTRODUCTION

Indonesia is a tropical country that receives a significant amount of sunlight. Sunlight plays an essential role in life, such as aiding in the formation of vitamin D. However, it also has negative effects, including premature aging, skin cancer, and hyperpigmentation. The skin, being the outermost part of the human body, plays a crucial role in protecting it. One of the skin's primary functions is to shield the body from UV rays. Excessive exposure to ultraviolet (UV) light increases the production of free radicals known as reactive oxygen species (ROS). These reactive oxygen species enhance pigmentation and damage melanocytes due to oxidative stress. Hyperpigmentation disorder is a condition characterized by patches of skin that are darker than normal, caused by increased melanin synthesis activity (Sholikha and Wulandari, 2022).

Melanin is the primary pigment responsible for determining the color of skin, hair, and eyes in humans. It is produced by melanocytes through the process of melanogenesis. Both melanogenesis and skin pigmentation are crucial for protecting against damage caused by ultraviolet radiation from the sun and for preventing skin cancer. However, excessive melanin production can lead to depigmentation, posing significant aesthetic and dermatological issues. Although melanogenesis involves a complex series of enzymatic and chemical reactions, enzymes like tyrosinase are essential in regulating melanin formation by inhibiting its activity (Zolghadri et al., 2019).

Tyrosinase is an enzyme involved in the formation of skin pigment through the process of melanogenesis. During melanogenesis, tyrosinase regulates melanin biosynthesis by hydroxylating L-tyrosine into L-DOPA and then oxidizing L-DOPA into dopaquinone. The activity of tyrosinase is influenced by the intensity of incoming UV light. Increased UV exposure accelerates the activity of tyrosinase, resulting in more melanin production. Melanin formation can be inhibited in various ways, including by inhibiting the activity of the tyrosinase enzyme, thereby reducing melanin production and preventing hyperpigmentation (Furi et al., 2022).

Tyrosinase activity can be reduced either by binding copper (Cu) at the enzyme's active site using a direct tyrosinase inhibitor or by reducing the dopaquinone product with antioxidants. Antioxidants prevent the oxidation process by neutralizing free radicals, thus becoming oxidized themselves. They work by breaking the chains of radical molecules. By cleaning up initial radicals, antioxidants can prevent oxidation reactions from continuing and can stabilize transition metal radicals like copper and iron, thus inhibiting oxidation (Denny and Asep, 2018).

There is growing interest in using natural ingredients from herbal plants for the development of modern medicinal and cosmetic products due to their relatively low side effects. Natural antioxidants capable of inhibiting the tyrosinase enzyme include curcuminoid compounds. Curcuminoids are a type of potent natural antioxidant polyphenol found in the rhizomes of plants from the Zingiberaceae family, such as Curcuma longa L. The main component of curcuminoids in this plant is curcumin, which has been shown to possess various biological activities, including antioxidant,

anti-inflammatory, anticancer, antibacterial, and antiviral properties. Recently, several curcuminoids and their analogs have been developed and used as oral supplements for various medical conditions. Additionally, there is substantial evidence confirming that curcumin and its derivatives are safe for topical application and are used in commercially available cosmetic products and for wound healing. Consequently, the beneficial properties of curcumin and its analogs have spurred significant efforts in cosmetic development for their use as safe therapeutic agents (Athipornchai et al., 2021).

During its development, modifications continue to be made to these compounds to produce compounds that are more potent, stable, safe and have more specific activity. Therefore, research was carried out on this curcumin analogue with the aim of conducting virtual screening to look for potential drug candidates based on their inhibitory interaction ability with the tyrosinase enzyme which is related to antioxidant activity. This study used an in silico approach to curcumin analogues, which were chosen because they have advantages compared to in vivo and in vitro approaches. These advantages include significant time and cost savings. Traditional synthesis of new drugs through a combination of chemistry and massive screening requires large costs and time, while molecular database screening of model compounds can be an alternative in more efficient drug design (Adelin et al., 2013).

In silico testing can be conducted through molecular docking, which aims to predict the interaction between molecules and the predetermined target cells. In this process, docking is used to predict the orientation between two molecules when certain forces act between them, thereby forming a stable bond. This technique predicts whether a molecule can bind to receptors, proteins, DNA, and perform ligand docking by placing it in a specific area. The goal of molecular docking simulation is to understand and predict molecular recognition by finding the stability of the bond between the ligand and receptor at minimum energy conditions. This docking simulation can be used to study the mechanism of action of a chemical compound or macromolecule such as proteins and peptides at the molecular level, ultimately enabling the development of structure-based drugs (Khairah et al., 2019).

## ▪ METHOD

1. Data Sources

The compounds that are the subject of this research are eleven analogues of curcumin compounds mentioned in the journal (Jiang et al., 2013).

2. Compound optimization and descriptor calculation

Eleven compounds underwent geometric optimization using Hyperchem 8.0 software with the semiempirical CNDO (Complete Neglect of Differential Overlap) method, employing the Plaque-Ribière algorithm and an RMS gradient of 0.01 kcal/mol. The results of the descriptor calculations, including hydration energy, molecular polarizability, total energy, bond energy, electronic energy, isolated atomic energy, and nuclear interactions, were obtained from the log file during geometry optimization. HOMO and LUMO energies were retrieved from the orbitals menu, while dipole moment, LogP, surface area, lattice surface area, volume, molar refractivity, molecular mass, and heat of formation were obtained from the QSAR properties menu.

The selected descriptors represent electronic, steric, and hydrophobic characteristics (Siregar and Roza, 2021).

3. Building the HKSA Model

Multiple linear regression analysis was conducted to derive the HKSA equation using SPSS software with the backward and enter methods. The independent variables were the compound descriptors, while the dependent variable was the tyrosinase inhibitor activity of the curcumin analog compound, expressed as $LogIC_{50}$. The HKSA equation was selected based on statistical criteria, including the correlation coefficient (R), coefficient of determination ($R^2$), adjusted $R^2$, F-value, standard error (SE), and significance (sign) (Widiyanti et al, 2021).

4. Designing New Compounds

Based on the best HKSA equation, structural modifications are carried out to obtain new curcumin analogue compounds which have tyrosinase inhibitor activity as better antioxidants. Modifications were made to substituents $R_2$, $R_3$, $R_4$, $R_5$, and $R_6$ as listed in Table 2.1.

**Table 2.1.** New structural data of the compound 2-(2,4-Dihydroxybenzylidene)-5-(4-hydroxybenzylidene)cyclopentanone

| No | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ |
|---|---|---|---|---|---|
| Modification 1 | H | $C_3H_6$ (allyl) | OH | H | H |
| Modification 1 | H | $C_6H_6N_2$ | OH | H | H |
| Modification 1 | H | $CH_3$ | OH | $CH_3$ | H |
| Modification 1 | H | $OCH_3$ | OH | H | H |
| Modification 1 | H | $C_3H_7$ | OH | $C_3H_7$ | H |
| Modification 1 | H | $CH_3$ | OH | H | H |
| Modification 1 | H | $OCH_3$ | OH | $OCH_3$ | H |
| Modification 1 | H | $NO_2$ | OH | $NO_2$ | H |

After modification, the new compound undergoes geometric optimization and descriptor value calculations again until a $LogIC_{50}$ value is obtained which is lower than the parent compound.

5. Molecular Docking and Visualization of Docking Results

To explore the potential mechanism of antioxidant activity of curcumin analogs, in silico molecular docking was performed on the modified compounds with the best $LogIC_{50}$ values. Molecular docking was conducted between the modified compounds and the protein receptor. The enzyme receptor was obtained from the Protein Data Bank (PDB) (www.rcsb.org) with PDB ID: 6JU7. The 3D structure of the protein enzyme was prepared using BIOVIA Discovery Studio Visualizer 2021 software. In BIOVIA Discovery Studio Visualizer 2021, the receptors were separated from their original ligands, and both files were saved in *.pdb format. Modified curcumin analog compounds were used as test ligands. The structure of the curcumin analogs was prepared using Hyperchem 8 software. These test ligands were prepared in the same manner as the original ligands and saved in *.pdb format for the molecular docking process (Guinessha et al, 2021).

6. Molecular Docking Process

In silico molecular docking of curcumin analogs against protein receptors was conducted using Autodock v1.5.7 software. The initial step involved docking the protein receptor with the original ligand. First, the two files in *.pdb format were converted to *.pdbqt format using Autodock v1.5.7. These *.pdbqt files were then imported into the Autodock program, and a grid file was created by selecting the grid option. Subsequently, a docking file was created for the molecular docking process. With the grid and dock files ready, they were docked using the CMD program by typing "Autogrid4 –p grid.gpf –l grid.glg", resulting in a file in *.glg format. Next, the compound docking process was initiated by typing "Autodock4 –p dock.dpf –l dock.dlg". This process produced a dock file in *.dlg format. The molecular docking process for the test ligand against the protein receptor followed the same procedure as for the original ligand. The resulting dock file in *.dlg format contained information such as binding energy, grid coordinates, inhibition constants, and other relevant data (Guinessha et al, 2021).

## ▪ RESULTS AND DISCUSSION

### Analysis of HKSA Result

HKSA began by optimizing the geometry of eleven curcumin analog compounds using Hyperchem software to obtain descriptors for these compounds. Determination of the HKSA equation was carried out using the multiple linear regression analysis method. Multiple linear regression analysis was carried out using SPSS software with descriptors as independent variables and $LogIC_{50}$ as the dependent variable.

The HKSA equation obtained is then selected based on statistical parameters such as the R value, $R^2$ , $adjR^2$ , F, SE, and sign. The descriptors involved in the selected equation model include: electronic descriptors such as HOMO Energy, LUMO Energy, Hydration Energy, and hydrophobic descriptors represented by Log P. The selected HKSA equation model using the CNDO method can be written in full as follows:

$LogIC_{50}$ : -3.195 – (1.135 x HOMO) + (1.064 x LUMO) - (0.239 x LogP) + (0.155 x HE), With a value of R = 0.984; R2 = 0.969; Adj R2 = 0.948; SE = 0.183; $F_{count}$ = 10.209; Sign = 0.000

According to the HKSA model, electronic descriptors are the most influential factors on the antioxidant activity of curcumin analog compounds in relation to tyrosinase. This aligns with Santoso's (2022) assertion that electronic descriptors can affect a drug's ability to penetrate cell membranes and its binding strength to receptors. Additionally, electronic descriptors are important in the drug distribution process and its penetration through biological membranes, which are significantly influenced by the drug's solubility in fat or water. They also help explain the structure-activity relationship and the strength of the interaction between the drug and the receptor.

A high HOMO energy value indicates a greater likelihood of donating electrons, as antioxidants function by donating electrons to neutralize free radicals, thereby preventing oxidative damage to cells and tissues. A high HOMO energy is usually desirable because it indicates that the molecule can shed electrons more easily and act as an effective electron donor. Molecules with low LUMO energy values have good abilities as electron acceptors compared to molecules that have higher LUMO energy values. According to Mulatsari et al. (2019) hydration energy shows the ability of a compound to interact with water molecules. A compound will be more hydrophilic if

the hydration energy is higher. According to Rakhman et al. (2019), the LogP value that is considered good for biological activity is in the range of 0 to 3, where the compound has good water solubility and difficulty penetrating lipid membranes. Therefore, the best $LogIC_{50}$ value obtained from the selected equation model is the compound 2-(2,4-Dihydroxybenzylidene)-5-(4-hydroxybenzylidene)cyclopentanone with a $LogIC_{50}$ of 0.16 µg/mL which can be seen in Figure 3.1.

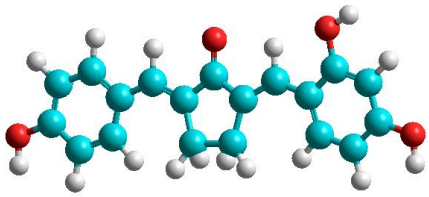


**Figure 3.1.** Basic structure of modified compounds

**Compound Modification**

Of the eight new compounds resulting from structural modifications to the substituents, the compound that had antioxidant activity was the first modification, namely the compound 2,5-bis (4-hydroxy-3-allyl-benzylidene) cyclopentanone with the best $LogIC_{50}$ value, namely -0.13 µg/mL, because this compound has a hydroxyl group and conjugated double bonds which allows electron delocalization to occur. The allyl group is a substituent that has a conjugated double bond (such as -C=C-). According to (He et al., 2015) the conjugation effect refers to the process where adjacent ÿ orbitals on atoms in a molecule overlap, which allows electron delocalization. This delocalization means that the electrons are not tightly bound to one atom or bond in the molecule, but are spread out along several atoms or bonds, thereby increasing interactions with free radicals and making the molecule more reactive as an antioxidant. The structure of the compound is presented in Figure 3.2.

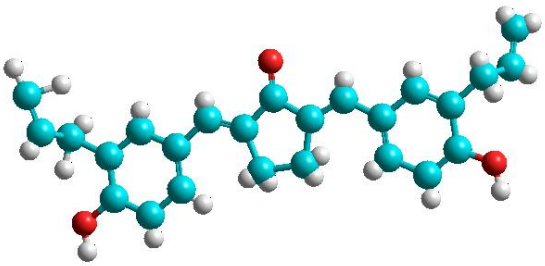


**Figure 3.2.** Structure of the best modified compound

**Analysis of Docking Results and Visualization of Docking Results**

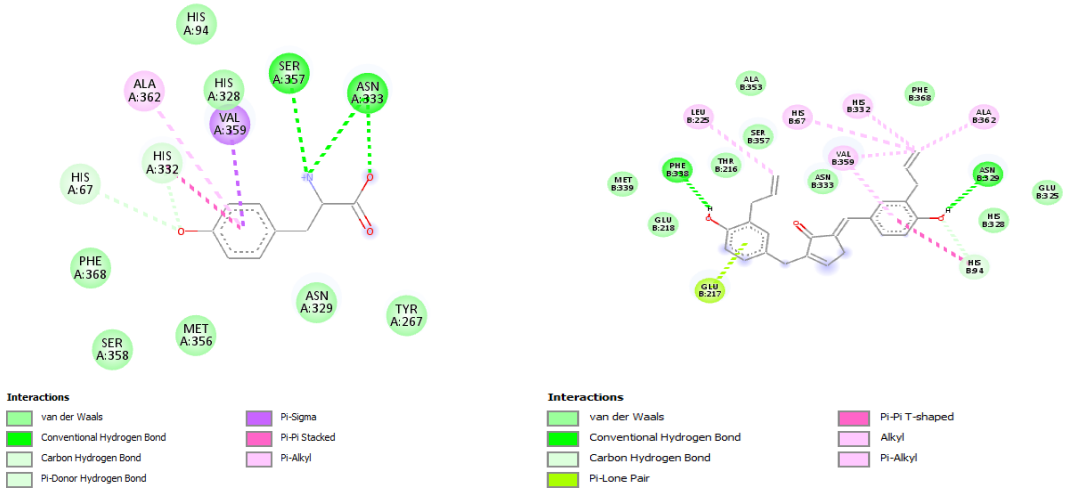
The results of setting the grid box from the molecular docking process on the original ligand are x-dimension = 40, y-dimension = 40, z-dimension = 40, with x-center = 15,736, y-center = 22,402, z-center = -14,790, and grid point spacing of 0.375 Å. These values are used as a guide for docking the tyrosinase receptor on the test ligand. This is done to ensure consistency in treatment between the docking of the original ligand and the test ligand, so that the possibility of differences in results due to

differences in treatment can be avoided. In this study, the test ligand anchored was the compound 2,5-bis (4-hydroxy-3- allyl benzylidene) cyclopentanone. The docking process was carried out using the same grid boxes as in the original ligand validation process.

The analysis of docking results was performed by examining the RMSD (Root Mean Square Deviation) value. RMSD measures how much the interaction between the protein and ligand deviates from the crystal structure before and after the docking process. It helps assess the degree of deviation between the docked structure and the original crystallographic structure. A docking method is considered valid if the RMSD value is less than 2 Å, indicating that the docking parameters used have been validated for the docking of test compounds (Sari et al., 2020). The validation results for the tyrosinase receptor show an RMSD value of 0.575 Å, confirming that the docking method employed is valid.

In addition to RMSD, the parameters evaluated from the molecular docking process in this study include binding energy values, inhibition constants, and interactions between ligands and protein residues. Binding energy measures the strength of the interaction between a compound and a receptor. This value reflects the application of the third law of thermodynamics, where $\Delta G < 0$ indicates a spontaneous reaction towards the product, $\Delta G = 0$ signifies a reversible reaction, and $\Delta G > 0$ suggests that the reaction does not occur (towards the reactants) (Pradiana, 2019). The molecular docking results between curcumin analogs and tyrosinase receptors show that both the test ligand and the original ligand have $\Delta G < 0$, with the test ligand achieving the best binding energy value of -5.92 kcal/mol, compared to -4.96 kcal/mol for the original ligand. A lower binding energy value indicates a stronger bond between the ligand and receptor, and a more stable reaction. These results suggest that curcumin analogs have a higher affinity for tyrosinase compared to the native ligand.

According to Pillaiyar et al. (2017), the Ki value reflects the binding affinity of a ligand to an enzyme. A lower Ki value indicates higher binding affinity, while a higher Ki value signifies lower binding affinity. The best Ki value for the original ligand was 231.77 µM, whereas the test ligand achieved a Ki value of 46.03 µM. This suggests that the test ligand has a higher affinity for the tyrosinase receptor (6JU7) compared to the original ligand. Additionally, the Ki value in docking is influenced by the number of rotatable bonds in the molecule. The original ligand structure contains 6 aromatic carbon rings and 3 rotatable bonds. The more flexible the molecule is, due to increased rotational freedom, the easier it is for the molecule to bind effectively to the receptor.




(A) (B)

**Figure 3.3.** Visualization of Native Ligand and Test Ligand

Visualization results in Figure 3.3. showed several similarities in amino acid residues, including HIS94, HIS328, SER357, ASN333, HIS332, HIS67, PHE368, ASN329, VAL359, and ALA362. These amino acid residues indicate that the compound 2,5-bis (4-hydroxy-3-allyl benzylidene) cyclopentanone has an inhibitory position that is almost similar to the original ligand of the tyrosinase inhibitor, namely the compound 2-Amino-3- (4hydroxyphenyl) propanoate. Even though only a small portion of the amino acids interact within the binding site, this suggests that the test compound might have potential inhibitory activity against the tyrosinase receptor. Herdiawan et al. (2018) note that an amino acid residue is a component of a polypeptide chain. The greater the similarity in amino acid residues between alternative medicinal ingredients and clinically tested drugs, the higher the likelihood that these alternative ingredients will be effective in treatment.

Curcumin analog compounds inhibit skin pigmentation by directly targeting and inhibiting the tyrosinase enzyme involved in the melanogenesis process. For instance, the compound 2,5-bis(4-hydroxy-3-allyl-benzylidene)cyclopentanone inhibits tyrosinase through a competitive inhibition mechanism with its substrate. The position and number of hydroxyl groups in this compound are crucial for its inhibitory effectiveness. The more OH groups present on the benzene ring, the more effective the compound is at inhibiting the tyrosinase enzyme (Dwi et al., 2022).

## ▪ CONCLUSION

According to the HKSA analysis results, the factors influencing the antioxidant activity of curcumin analogs include HOMO energy, LUMO energy, hydration energy, and LogP, as represented by the equation model: $LogIC_{50}$ = -3.195 – (1.135 × HOMO) + (1.064 × LUMO) - (0.239 × LogP) + (0.155 × HE). The modification of curcumin analogs indicates that the compound 2,5-bis(4-hydroxy-3-allyl-benzylidene)cyclopentanone exhibits superior antioxidant activity with a $LogIC_{50}$ value of -0.13 µM, compared to 2-(2,4-dihydroxybenzylidene)-5-(4-hydroxybenzylidene)cyclopentanone, which has a $LogIC_{50}$ value of 0.16 µM. Docking test results revealed that 2,5-bis(4-hydroxy-3-allyl-benzylidene)cyclopentanone demonstrates better inhibitory potential on the tyrosinase receptor, indicating stronger antioxidant activity. This is attributed to its similarity in amino acid residues to the

original ligand, 2-Amino-3-(4-hydroxyphenyl)propanoate. The binding energy of 2,5-bis(4-hydroxy-3-allyl-benzylidene)cyclopentanone is -5.92 kcal/mol with a Ki value of 46.03 µM, which is more favorable compared to the binding energy of 2-Amino-3-(4-hydroxyphenyl)propanoate, which is -4.96 kcal/mol with a Ki value of 231.77 µM.

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