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Research Article

Analysis of Compound Activities in Cinchona Officinalis as Antiaging With a Computational Approach

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ABSTRACT

Several studies on plants that have antiaging properties have been widely published. From these studies, research has not been carried out on compounds in cinchona plants that may provide efficacy as antiaging. Initially, cinchona is a plant that is famous for its antimalarial properties. But the use of cinchona as an antimalarial has now been reduced so research needs to be done to look for another potential of the cinchona plant. This study aims to conduct a computational approach of compounds derived from cinchona as an inhibitor of the elastase, hyaluronidase, collagenase, and tyrosinase enzymes with oleanolic acid, EGCG, and arbutin as comparative compounds. The method used in this study is molecular docking using YASARA, Marvinsketch, PLANTS, VMD, and statistic R software. From the research results, six (6) candidates of active compounds as elastase enzyme inhibitors, twenty one (21) candidates of the active compound as hyaluronidase enzyme inhibitors, four (4) candidates of the active compound as collagenase enzyme inhibitors, and four (4) candidates of the active compound as tyrosinase inhibitors. Two compounds have potential as antiaging, i.e chlorogenic acid and Cyanidol 3-rhamnoglucoside.

1. INTRODUCTION

Aging is a natural process that will be experienced by everyone. This aging process is characterized by the appearance of wrinkles on the face, dry and rough skin, patches of aging/pigmentation, and decreased skin elasticity. In this process, there is a gradual loss of tissue's ability to repair or replace itself and maintain its normal structure and function. Aging can be

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caused by various factors, namely factors that come from within the body, namely intrinsic factors, and factors that come from outside the body, namely extrinsic factors (Mohiuddin AK *et al.*, 2019). Intrinsic factors include the activity or work of certain enzymes. The enzymes involved in the aging process of the skin include elastase, hyaluronidase, collagenase, and tyrosinase. These enzymes have their respective roles in their involvement in the aging process, where the anti-aging effect is related to the inhibition of the activity of these enzymes. While extrinsic factors, such as exposure to sunlight, air temperature, smoking, and free radicals. Free radicals can cause the accumulation of cell damage resulting in the initiation of aging (Tu PTB *et al.*, 2015).

According to Alonso, J, 2004, quinine has antiaging activity due to its secondary metabolite compounds. The secondary metabolites present in quinine include alkaloids, namely quinine, quinidine, synkonin, synconidine, quinamine, 3-epiquinamine, cincophylline, and cincophyllamine, phenolic acids, namely protocateuric acid, quinic acid, caffeic acid, chlorogenic acid, p-coumaric acid, and quinine. quinovinic acid, flavonoids namely epicatechin, kaempferol, quercetin, avicularin, delphinine, cyanidol 3-glucoside, and cyanidol 3-rhamnoglucoside and glycosides namely quinovine (Ernawati T *et al.*, 2018; Keene AT *et al.*, 1983; Ramawat KG *et al.*, 2013). Apart from being antiaging, quinine is an industrial plant that contains alkaloids in the bark where quinine alkaloids have important values and are used in the pharmaceutical industry and beverage industry in tonic water. The four main types of alkaloids that have high economic value are quinine, synconin, quinidine, and synconidine. In the pharmaceutical industry, quinine is used as a malaria drug. In addition to malaria drugs, quinine is also used as a cardiac arrhythmia drug (Hoffman RW *et al.*, 2018). Until now, quinine has only been used in the pharmaceutical and beverage industries and has not been used in the cosmetic industry.

In Indonesia, according to the Ministry of Industry of the Republic of Indonesia, the national cosmetic industry (2019) experienced an increase in growth. Based on data from the Ministry of Industry, the increase in cosmetic sales in 2012 was 14% to Rp 9.76 trillion from the previous Rp 8.5 trillion. Also in 2017, the increase in cosmetic sales increased by 20%, or four times the national economic growth, and is predicted to continue. In Indonesia, there are no antiaging cosmetic preparations that use compounds from the quinine plant as an active ingredient.

In discovering the activity of a compound present in plants, the conventional research method that is usually carried out is to isolate the compound suspected of having activity and then test with enzymes according to their activity until a compound with potential is found. This conventional method has many drawbacks such as requiring a long time and quite large costs. The use of computational methods has recently become an interesting phenomenon as a tool in drug discovery. The exponentially increasing capability of informatics technology is an opportunity to develop simulations and calculations in drug design. A Computational/In silico approach is a method of approaching a real condition or situation into a computer simulation using a certain program. The terminology in silico, analogous to in vitro and in vivo refers to the use of computers in drug discovery studies, as it is known that the drug discovery process takes a very long time and

is expensive, therefore the tendency to use in silico methods in computational chemistry in modeling molecule (*drug design*) has gained significant momentum (Casciuc L. *et al.,* 2019). In computational chemistry modeling or simulation of how the interaction between drug compounds that enter the body and the receptor or enzyme that will be addressed by the molecular docking method can be predicted, where with this method it can be predicted whether a molecule can bind selectively to the receptor or enzyme and provides an overview of the interaction in a specific way. molecules between enzymes and ligands.

This study aims to analyze with a computational approach the compounds in quinine on their use as antiaging at four receptors. Cinchona ledgeriana Moens ex Trimen, Cinchona officinalis L and Cinchona succirubra Pav. ex Klotzsch is a plant that will be tested for its compounds in the study, this is because the three plants are quinine plant species that contain the most alkaloids compared to other types of quinine plants (Ramawat KG *et a.l,* 2013).

2. MATERIALS AND METHODS

Materials

65 The structure of compounds from the quinine plant downloaded from The PubChem Substance and Compound Database include quinine, quinidine, synconin, synconidine, quinamine, 3-epiquinamine, cincophylline, cincophyllamine, protocateuric acid, quinic acid, caffeic acid, chlorogenic acid, p- coumaric acid, quinovinic acid, epicatechin, kaempferol, quercetin, avicularin, delphinine, cyanidol 3-glucoside, and cyanidol 3-rhamnoglucoside and quinovine. The structure of elastase, hyaluronidase, collagenase, and tyrosinase enzymes with PDB codes 5JMY, 2J1E, 5UWK, and 5M8N, respectively. The chemical structure of the comparison compound was EGCG which was used as a comparison compound or positive control of elastase and collagenase enzyme inhibitors, oleanolic acid as a comparison compound, or positive control of hyaluronidase enzyme inhibitor and arbutin as a comparison compound or positive control of a tyrosinase enzyme inhibitor.

Tools

The hardware used is an HP Elite Book 2560p Laptop with specifications Intel® Core™ i7-2620M @ 2.7 GHz, 2701 Mhz, 2 Core(s), 4 Logical Processor(s), Windows 10 Pro, 64-bit Operating System, 8 GB RAM , 128GB SSD. The software used includes PLANTS (Protein-Ligand Ant System) for running docking, YASARA (Yet Another Scientific Artificial Reality Application) for enzyme preparation and validation, and Marvin Sketch for ligand preparation or structure making of comparison compounds and test compounds, VMD (Visual Molecular Dynamics).) for visualization of the bond of comparison compounds and test compounds on enzymes in 3-dimensional (3D) form and R statistics to determine representative compounds through t-test or t-test.

Enzyme Preparation

The crystal structures of the enzymes 5JMY, 2J1E, 5UWK, and 5M8N downloaded from https://www.rcsb.org/ were prepared using YASARA software. From this procedure, 3 files will be obtained, namely protein.mol2, ref_ligand.mol2 and ligand.mol2.

Preparation of Native Ligands, Comparative Ligands, and Test Ligands

The native ligands obtained from the previous procedure, the comparison ligands, and the test ligands downloaded from The PubChem Substance and Compound Database were prepared with Marvin Sketch software at pH 7.4 and stored as ligand_2D.mrv. Look for conformers then save the result as a .mol2 file. This procedure is performed on each ligand.

Enzyme Optimization and Setting RMSD Value

The prepared native ligand was optimized with the crystal structure of the enzyme using PLANTS software to obtain a score, the best score was selected and saved as a mol2 file. then determined the RMSD using the YASARA software. The enzyme can be used if it gives an RMSD value of 2 Å.

Comparison Ligand Docking

The comparison ligand file obtained from the previous procedure was docked with PLANTS software. So that the best score will be obtained which is then used as a comparison for the best test ligand score.

Docking Ligand Test

In this procedure, the test ligand docking of the enzyme is carried out using the PLANTS software. So that the best score will be obtained which is then compared with the best score for the comparison ligand.

Visualization of Ligand Interaction With Enzymes

The docked file is then made into a .pdb file type using the YASARA software. The file will be visualized using VMD (Visual Molecular Dynamics) software to see the interactions that occur between enzymes and ligands.

3. RESULTS AND DISCUSSIONS

Enzymes Analysis

The first step in the docking method is to determine the RMSD value of the enzyme crystal structure which is downloaded from https://www.rcsb.org/. The determination of the RMSD value of the enzyme was carried out using the YASARA software. The enzyme is good to use if it gives RMSD value 2, and has a good alignment. From the validation results, the enzymes used were Elastase with PDB code: 5JMY RMSD value 1.1172, Hyaluronidase with PDB code: 2J1E RMSD

value 1.8969, Collagenase with PDB code: 5UWK RMSD value of 1.7078 and Tyrosinase with code GDP: 5M8N RMSD value 0.4050.

Docking Result Analysis

Of the 65 compounds in the quinine plant, there were 21 active compounds (the docking score was more negative than the comparison compound/positive control) which were tested by the molecular docking method for the elastase enzyme with PDB code 5JMY, hyaluronidase with PDB code 2J1E, collagenase with PDB code 5UWK and tyrosinase with GDP code 5UWK. PDB code 5M8N using PLANTS software.

Molecular docking is a technique that is commonly used in designing candidate drug molecules through a bioinformatics approach. Molecular docking can be used to determine the interaction of candidate drug molecules with enzymes. Molecular docking can assist in the implementation of virtual screening of candidate drug molecules (ligands) by observing the interaction between ligands and enzymes. The interactions used as parameters are to determine the bond between the ligand and the enzyme, the conformation of the ligand when it binds to the enzyme, and evaluation by looking at the affinity of the ligand to the enzyme. The affinity of the ligand with the enzyme is described by the docking score. The more negative the docking score, the compound requires lower energy to bind or interact so that the potential for the compound to bind or interact with the enzyme or its affinity is greater.

Based on the docking results, obtained 6 test compounds that have a lower docking score than the comparison compound EGCG on the elastase enzyme, namely synconine, synconidine, chlorogenic acid, avicularin, reynoutrin, and cyanidol 3-rhamnoglucoside compounds, 21 test compounds that have a higher docking score. lower than the comparison compound oleanolic acid in the hyaluronidase enzyme, namely quinine, quinidine, synkonin, synconidine, protocatestrong acid, quinic acid, caffeic acid, chlorogenic acid, p-coumaric acid, epicatechin, kaempferol, quercetin, avicularin, reynoutrin, delphinine, cyanidolphinine 3-glucoside, cyanidol 3-rhamnoglucoside, quinamine, 3-epiquinamine, cincophylline and cincophyllamine, 4 test compounds that have a lower docking score than the comparison compound EGCG on the collagenase enzyme, namely chlorogenic acid compounds, cincophylline and 4 test compounds that have a score docking is lower than the comparison compound arbutin on the tyrosinase enzyme, namely se life of chlorogenic acid, epicatechin, cincophyllamine, and cyanidol 3-rhamnoglucoside. The docking results can give different docking scores due to the different affinity of the test compound and the comparison compound on the enzyme. The more negative the docking score, the greater the affinity of the compound to the enzyme.

Of the 21 active compounds, there are 2 compounds that are active in the four enzymes, namely chlorogenic acid and cyanidol 3-rhamnoglucoside, 2 compounds that are active in 3 enzymes, namely cincophylline on elastase enzymes, hyaluronidase, and collagenase and cincophyllamine which is active on hyaluronidase, collagenase and tyrosinase enzymes, 4

compounds namely synkonin, synconidin, avicularin, and reynoutrin are active on 2 enzymes namely elastase and hyaluronidase enzymes, 1 compound that is active on 2 enzymes namely epicatechin namely hyaluronidase and tyrosinase enzymes, 12 compounds that are only active on 1 enzyme namely quinine, quinidine, acid strong protocatechins, quinic acid, caffeic acid, p-coumaric acid, kaempferol, quercetin, delphinine, cyanidol 3-glucoside, quinamine, and 3-epiquinamine, namely the hyaluronidase enzyme.

Statistic Analysis

Statistical analysis was carried out on the data from the virtual screening using One Sample T-test. One Sample T-test is one of the t-test methods carried out with the aim of comparing the sample to a reference value through the p-value. If the p-value is more than 0.05, the comparison compound and the test compound are not significantly different, which means that the difference in docking scores between the comparison compound and the test compound does not show a significant difference in activity. However, if the p-value is less than 0.05, the comparison compound and the test compound differ significantly, which means that the difference in docking scores between the comparison compound and the test compound indicates a significant difference in activity.

Bonding Mode Elucidation

After obtaining data from the docking process, compounds that have a docking score that is more negative than the comparison compound or have a stronger affinity than the comparison compound will be elucidated in the bonding mode using Visual Molecular Dynamic (VMD) software which aims to visualize the interaction between ligands and amino acids in binding. The enzyme site is depicted in 3-dimensional (3D) form and measures the bond distance between the test compound and the amino acids present in the enzyme in angstroms (Å).

Based on the bond mode elucidation results, it was found that amino acids that play an important role in the affinity of the test compound on the elastase enzyme (PDB Code: 5JMY), namely ARG222, PHE544, ASN542, HIS711 and ARG110 as well as groups that most play a role in elastase enzyme activity (PDB Code: 5JMY) is a hydroxyl group (-OH), an amino acid that plays an important role in the affinity of the test compound on the hyaluronidase enzyme (PDB Code: 2J1E), namely LEU672, VAL763, LEU741, TRP657, HIS671, ASP742, HIS670, GLU762, TYR687 and ALA760 and the group The most important role in the activity of the hyaluronidase enzyme (PDB Code: 2J1E) is the hydroxyl group (-OH), an amino acid that plays an important role in the affinity of the test compound on the collagenase enzyme (PDB Code: 5UWK), namely HIS187, ALA188, GLU223, ALA199, ALA220 , ALA141, PHE224, HIS222 and ALA221 and the groups that most play a role in collagenase enzyme activity (PDB Code: 5UWK) are hydroxyl groups (-OH) and amino acids that play an important role in the affinity of the test compound on the tyrosinase enzyme. e (PDB

Code: 5M8N), namely PHE188, HIS224, TRP223, and HIS227, and the group that plays the most role in tyrosinase enzyme activity (PDB Code: 5M8N) is the hydroxyl group (-OH).

4. CONCLUSIONS

From the results of docking the compounds contained in the Conchina officinalis, 6 compounds were found to be active in inhibiting the elastase enzyme, 21 compounds were active in inhibiting the hyaluronidase enzyme, 4 compounds were active in inhibiting the collagenase enzyme, 4 compounds were active in inhibiting the tyrosinase enzyme and 2 active compounds inhibited the four enzymes. These compounds are chlorogenic acid and cyanidol 3-rhamnoglucoside.

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Supplemementaries

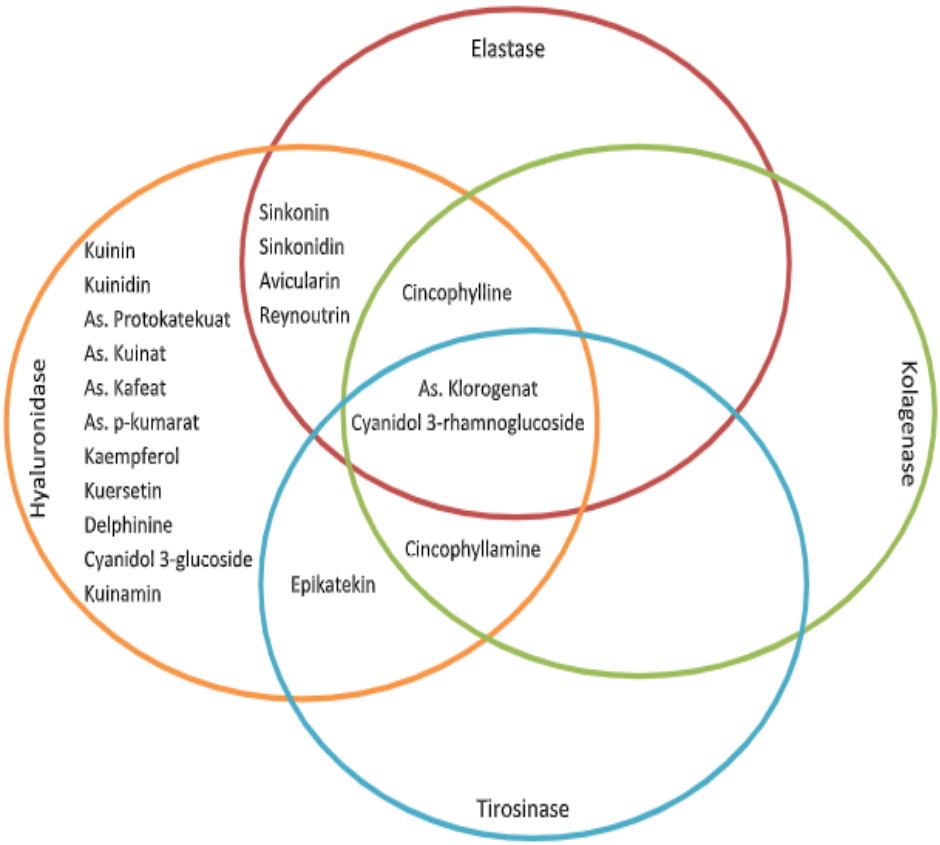

Figure 1. Diagram Venn of active compounds in Conchina officinalis on antiaging receptor

Table 1. Score Docking Active Compounds on Enzim Elastase (Kode PDB: 5JMY)

No.		***Score Docking***
	Comparison Compound (EGCG)	-85,5480
	Active Compounds	

1	Sinkonin atau (S)-[(2R,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl]-quinolin-4-ylmethanol	-95,0483
2	Sinkonidin atau (R)-[(2S,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl]-quinolin-4-ylmethanol	-95,5348
3	Asam Klorogenat atau (1S,3R,4R,5R)-3-[(E)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxy-1,4,5-trihydroxy cyclohexane-1-carboxylic acid	-93,6276
4	Avicularin atau 3-[(2S,3R,4R,5S)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]oxy-2-(3,4-dihydroxyphenyl)-5,7-dihydroxychromen-4-one	-87,5508
5	Reynoutrin atau 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(3R,4S,5R)-3,4,5-trihydroxyoxan-2-yl]oxychromen-4-one	-86,9655
6	Cyanidol 3-rhamnoglucoside atau (2R,3R,4R,5R,6S)-2-[[(2R,3S,4S,5R,6S)-6-[2-(3,4-dihydroxyphenyl)-5,7-dihydroxychromenylium-3-yl]oxy-3,4,5-trihydroxyoxan-2-yl]methoxy]-6-methyloxane-3,4,5-triol;chloride	-94,3675

Table 2. Score Docking Active Compounds on Enzim Hyaluronidase (Kode PDB: 2J1E)

No.		***Score Docking***
	Comparison Compound (Oleanolic Acid)	-55,7905
	Active Compounds	
1	Kuinin atau (R)-[(2S,4S,5R)-5-ethenyl-1-azabicyclo [2.2.2]octan-2-yl]-(6-methoxyquinolin-4-yl) methanol	-71,0126
2	Kuinidin atau (S)-[(2R,4S,5R)-5-ethenyl-1-azabicyclo [2.2.2]octan-2-yl]-(6-methoxyquinolin-4-yl) methanol	-73,6219
3	Sinkonin atau (S)-[(2R,4S,5R)-5-ethenyl-1-azabicyclo [2.2.2]octan-2-yl]-quinolin-4-ylmethanol	-72,6596
4	Sinkonidin atau (R)-[(2S,4S,5R)-5-ethenyl-1-azabicyclo [2.2.2]octan-2-yl]-quinolin-4-ylmethanol	-71,1457
5	Asam protokatekuat atau 3,4-dihydroxybenzoic acid	-67,7342
6	Asam Kuinat atau (3R,5R)-1,3,4,5-tetrahydroxycyclohexane -1-carboxylic acid	-67,1636
7	Asam Kafeat atau (E)-3-(3,4-dihydroxyphenyl)prop-2-enoic acid	-66,5951

8	Asam Klorogenat atau (1S,3R,4R,5R)-3-[(E)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxy-1,4,5-trihydroxycy clohexane-1-carboxylic acid	-78,5183
9	Asam p-kumarat atau (E)-3-(4-hydroxyphenyl)prop-2-enoic acid	-65,4881
10	Epikatekin atau (2R,3R)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol	-75,5197
11	Kaempferol atau 3,5,7-trihydroxy-2-(4-hydroxyphenyl) chromen-4-one	-72,2368
12	Kuersetin atau 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy chromen-4-one	-74,7252
13	Avicularin atau 3-[(2S,3R,4R,5S)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]oxy-2-(3,4-dihydroxyphenyl)-5,7-dihydroxychromen-4-one	-78,2985
14	Reynoutrin atau 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(3R,4S,5R)-3,4,5-trihydroxyoxan-2-yl]oxychromen-4-one	-84,7443
15	Delphinine atau [(1S,2R,3R,4R,5S,6S,8R,9R,13S,16S, 17R,18R)-8-acetyloxy-5-hydroxy-6,16,18-trimethoxy-13-(methoxymethyl)-11-methyl-11-azahexacyclo [7.7.2.12,5.01,10.03,8.013,17]nonadecan-4-yl] benzoate	-66,9012
16	Cyanidol 3-glucoside atau (2S,3R,4S,5S,6R)-2-[2-(3,4-dihydroxyphenyl)-5,7-dihydroxychromenylium-3-yl]oxy-6-(hydroxymethyl)oxane-3,4,5-triol;chloride	-79,9629
17	Cyanidol 3-rhamnoglucoside atau (2R,3R,4R,5R,6S)-2-[[(2R,3S,4S,5R,6S)-6-[2-(3,4-dihydroxyphenyl)-5,7-dihydroxychromenylium-3-yl]oxy-3,4,5-trihydroxyoxan-2-yl]methoxy]-6-methyloxane-3,4,5-triol;chloride	-84,3490
18	Kuinamin atau 3a-(5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl)-2,4-dihydro-1H-furo[2,3-b]indol-8b-ol	-68,6974
19	3-epiquinamine atau (3aS,8bR)-3a-[(2R,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl]-2,4-dihydro-1H-furo[2,3-b]indol-8b-ol	-74,4776
20	Cincophylline atau 3-ethenyl-9-methoxy-2-[(6-methoxy-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl]-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine	-73,0278
21	Cincophyllamine atau (2R,3R,12bR)-3-ethenyl-9-methoxy-2-[[(1R)-6-methoxy-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]methyl]-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine	-73,8445

Table 3. Score Docking Active Compounds on Enzim Kolagenase (Kode PDB: 5UWK)

No.		***Score Docking***
	Comparison Compound (EGCG)	-97,4707
	Active Compounds	
1	Asam Klorogenat atau (1S,3R,4R,5R)-3-[(E)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxy-1,4,5-trihydroxy cyclohexane-1-carboxylic acid	-107,2970
2	Cyanidol 3-rhamnoglucoside atau (2R,3R,4R,5R,6S)-2-[[(2R,3S,4S,5R,6S)-6-[2-(3,4-dihydroxyphenyl)-5,7-dihydroxychromenylium-3-yl]oxy-3,4,5-trihydroxyoxan-2-yl]methoxy]-6-methyloxane-3,4,5-triol;chloride	-110,2660
3	Cincophylline atau 3-ethenyl-9-methoxy-2-[(6-methoxy-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl]-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine	-109,6470
4	Cincophyllamine atau (2R,3R,12bR)-3-ethenyl-9-methoxy-2-[[(1R)-6-methoxy-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]methyl]-1,2,3,4,6,7,12,12b-octahydroindolo [2,3-a]quinolizine	-106,2030

Table 4. Score Docking Active Compounds on Enzim Tirosinase (Kode PDB: 5M8N)

No.		***Score Docking***
	Comparison Compound (Arbutin)	-75,6829
	Active Compounds	
1	Asam Klorogenat atau (1S,3R,4R,5R)-3-[(E)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxy-1,4,5-trihydroxycyclohexane-1-carboxylic acid	-85,1456
2	Epikatekin atau (2R,3R)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol	-82,3561
3	Cyanidol 3-rhamnoglucoside atau (2R,3R,4R,5R,6S)-2-[[(2R,3S,4S,5R,6S)-6-[2-(3,4-dihydroxyphenyl)-5,7-dihydroxychromenylium-3-yl]oxy-3,4,5-trihydroxyoxan-2-yl]methoxy]-6-methyloxane-3,4,5-triol;chloride	-84,7251
4	Cincophyllamine atau (2R,3R,12bR)-3-ethenyl-9-methoxy-2-[[(1R)-6-methoxy-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indo -1-yl]methyl]-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine	-79,1336

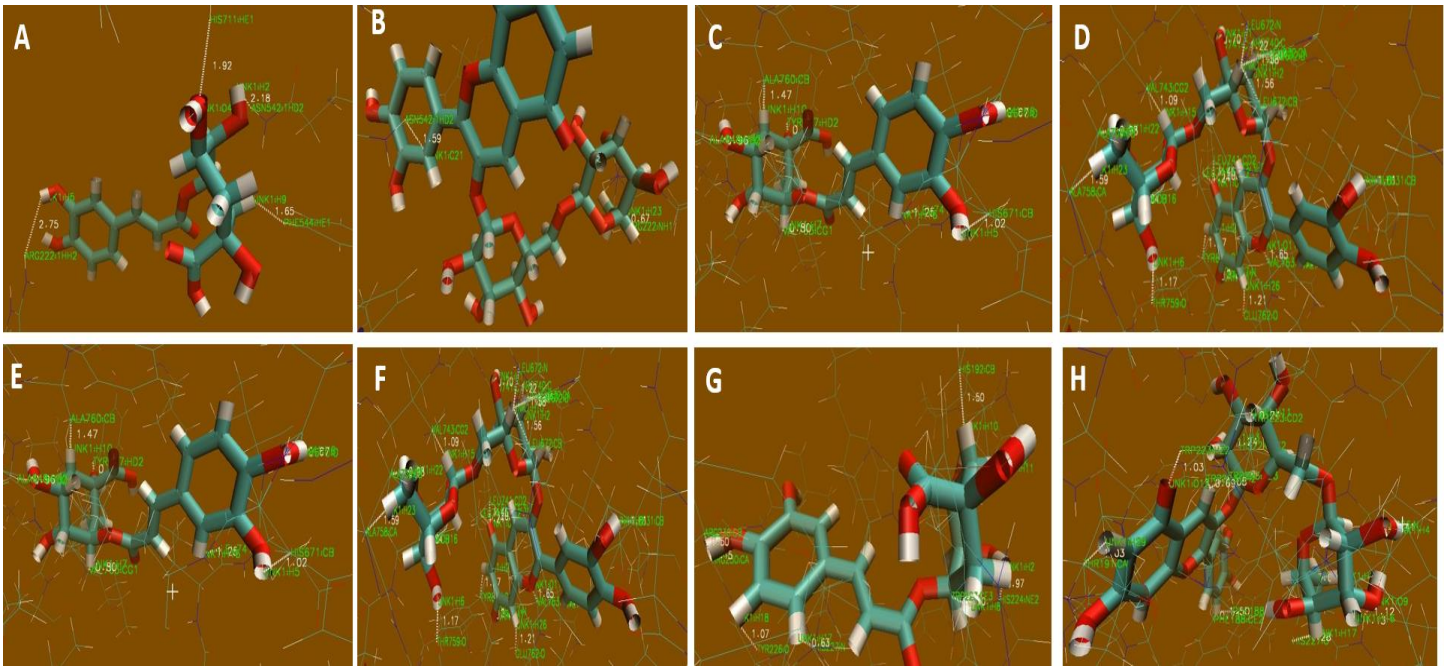

Figure 2. Interaction of Active Compounds with Protein Amino Acids

A) Chlorogenic Acid-5JMY; **B)** Cyanidol 3-rhamnoglucoside-5JMY; **C)** Chlorogenic Acid-2JIE ; **D)** Cyanidol 3-rhamnoglucoside-2JIE ; **E)** Chlorogenic Acid-5UWK ; **F)** Cyanidol 3-rhamnoglucoside-5UWK ; **G)** Chlorogenic Acid-5M8N ; **H)** Cyanidol 3-rhamnoglucoside-5M8N