Molecule docking using molegro virtual docker method from ethanol extract of *Bougainvillea spectabilis* Willd Bractea as an inhibitor in tyrosinase for sunscreen

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Abstract: **Background:** Excessive UV exposure can cause immunosuppresion, photoaging and skin cancer. Sunscreen has aphysical protection mechanism throuh scattering sunlight that enters the skin. **Objective:** The flowe ethanol extract B. spectabilis Willd include: 16-Octadien-3-ol 37-dimethyl, 3-cyclohexen-1-old-4-methyl, 5-Hepten-2one-6-methyl, 1 Heptanol 6-methyl, Dimethylsulfoxonium, L-lactidacid, Carbamite, Frrmamide N-methyl, Formamide N-N-dimethyl and p-Trimethylsilyloxyphenyl-(trimethyl silyloxy) trimethylsilyacrylate. **Method:** Molegro Virtual Docker on the ethanil extract of bractea B.spectabilis Willd with method LC-MS. **Result:** The results of docking compounds with the main content of 16-Octadien-3-ol 37-dimethyl, which can be seen from the rerank score, namely -65.5258, -62.9153, -61.7784 Hydrogen bonding and electrostatic bonds in the main content of the ehanol extract of bractea B. spectabilis Willd 16-Octadien-3-ol 37-dimethyl with 4 amino acid tyrosinase namely Asn 378, Ser 394, Gly 360, Phe 362 while in the PABA control with 4 amino acids including His 215, His 192, Ser 394, Gly 389 and Kojic acid standard ligand with 7 amino acids including Gly 389, Ser 394, His 224, His 215, His 192, His 377 and His 404. Conclusion: The interaction of 16-Octadien-3-ol 37-dimethyl towards the tyrosinase enzyme is more harmonious and stable than the positive control PABA and the standard Kojic acid ligand.

Key-Words: Extract ethanol, Bractea Bougainvillea, Tabir surya and Molecular docking.

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1. Introduction

Sunlight contains UV rays that can harm the skin. These UV rays can cause various disorders of the skin ranging from redness (erythema), dark spots (pigmentation), premature aging, dryness, wrinkles, and even cause skin cancer [1]. Of all solar radiation, only 0.2% causes an erythema reaction on the skin, namely the UV-B spectrum (290–320 nm), while the UV-A spectrum that causes pigmentation is light with a wavelength of 320–400 nm. The spectrum of UV-C light with a wavelength of less than 295 nm which is deadly or called the germicidal spectrum does not reach the earth because it is filtered by ozone in the atmosphere [2];[3]. To prevent all the dangers caused by sunlight, it is very important to use sunscreen, namely cosmetic ingredients that can physically or chemically inhibit the penetration of UV rays into the skin. Sunscreen products containing synthetic chemicals have been developed recently, but many people are turning to natural ingredients which are considered safer and more affordable. Based on research by Abarca, 2016., found that B. glabra bractea had an SPF value of 16.96 [4]. The use of substances that are sunscreens can prevent various diseases caused by UV radiation, several classes of active sunscreen compounds such as flavonoids have been reported to have the ability to protect against UV rays [5]; [6]. Phenolic compounds, especially the flavonoid group, have the potential to be used as sunscreens due to the presence of a chromophore group (conjugated single double bond) which is able to absorb UV rays, both UVA and UVB, thus reducing their intensity on the skin [7]; [8]. So that the leaves of Bougainvillea spectabilis Willd allow it to have a potential sunscreen profile as a cosmetic ingredient related to sunscreen [9]. Medicinal computational chemistry can describe compounds in three-dimensional (3D) form, then make comparisons on the basis of similarity and energy with other compounds whose activities are known *pharmacophore query*). This study can predict the activity of hypothetical compounds and at the same time can eliminate compounds that have low activity[10].

2. Problem Formulation

1. How to screen the compound content of ethanol extract of B. spectabilis Willd bractea?
2. Do the compounds resulting from screening for the ethanol extract of B. spectabilis Willd bractea compounds have higher sunscreen activity than the standard ligand kojic acid (KOJ_516) on the tyrosinase receptor (PDB code: 5M8Q) in silico?

3. Problem Solution

The crystalline structure of the tyrosinase enzyme with the code pdb 5M8Q. The struscture of 10 compounds from plants Bougainvillea. Downloaded from The Pub Chem substance data test through the LCMS method. We used Molegro Virtual Docker 6.0 for docking and analysis of amino acids tyrosinase enzyme receptor (PDB code 5M8Q downloaded at www.pdb.org. computer equipment Intel(R) Core TM i5-115G7 2.40 GHz and 2419 MHz Operating System.

Research procedure

a. Receptor

The three-dimensional crystal structure of different receptors taken from Protein Data Bank (PDB) (http://www.rcsb.org/) is as follows tyrosinase PDB code 5M8Q.All the PDB's were loaded in the Molegro virtual docker (MVD) with the removal of all water molecules.

b. Ligand preparation

Structures of ligands were drawn using marvin sketch and energy minimization was done using MMFF94 force field. Energy minimization is done to help the docking

programme for identifying the bioactive conformer from the local minima. One major advantage of MVD is that it helps in assigning the missing bond orders, charges, bonds, and hybridization states of the imported ligands. The 2D structures of 10 ligands are illustrated in Table 1.

c. Docking and Analysis of Amino Acids.

Docking and analysis of amino acids can be carried out using the program *Molegro Virtual Docker,* and all stages use a 3D image. Things that need to be considered in this process is the selection of docking compounds and cavity where the drug will interact (Saifuddin, 2014). The parameters measured in the docking process are the energy values involved, in the form of MolDock Score, Rerank Score, and Hbond as well as the RMSD value. To measure the strength of drug-receptor binding, the parameter that is often used is value Rerank Score [11].

Assessment

Each purely minimized docking uses DockScore, molecular mechanics of the scoring functions used in this study such as Rerank Score, RMSD (Root Mean Standard Deviation) and H Bond [12].

4. Results

After the process is done *docking* by using *Molegro Virtual Docker* the results obtained were between PABA (Rerank score: - 65.5258) and 10 active compounds from *B. spectabilis Willd* have varied *rerank scores* and approach the positive control *rerank score*, namely PABA. *Rerank score* The highest active compound is *1,6-Octadien-3-ol,3,7-dimethyl* (*Rerank score*: - 65,5258). *Rerank score* is a value that reflects the bond energy required to form a bond with the receptor, so that from this value the activity of a compound can be predicted, it can be seen that the lower the value *rerank score*, so that the bond between the ligand and the receptor will also be more stable. Based on simulation results *docking* it can be predicted that Compound *1,6-Octadien-3-ol,3,7-dimethyl* has the highest activity compared to the 9 active compounds of *B. spectabilis Willd*and higher than the positive control, namely PABA and standard ligands

On the interaction between the ligand and the receptor with several amino acid residues from the 5M8Q receptor. Amino acids involved in the process of compound interaction *1,6-Octadien-3-ol,3,7-dimethyl*. Amino acid residues that play a role in the bond between receptors and compounds*1,6-Octadien-3-ol,3,7-dimethyl* is Asn 378 and the amino acid residues that play a role in receptor binding with standard ligand Kojic Acid and PABA positive control are Ser 394 and Gly 389.

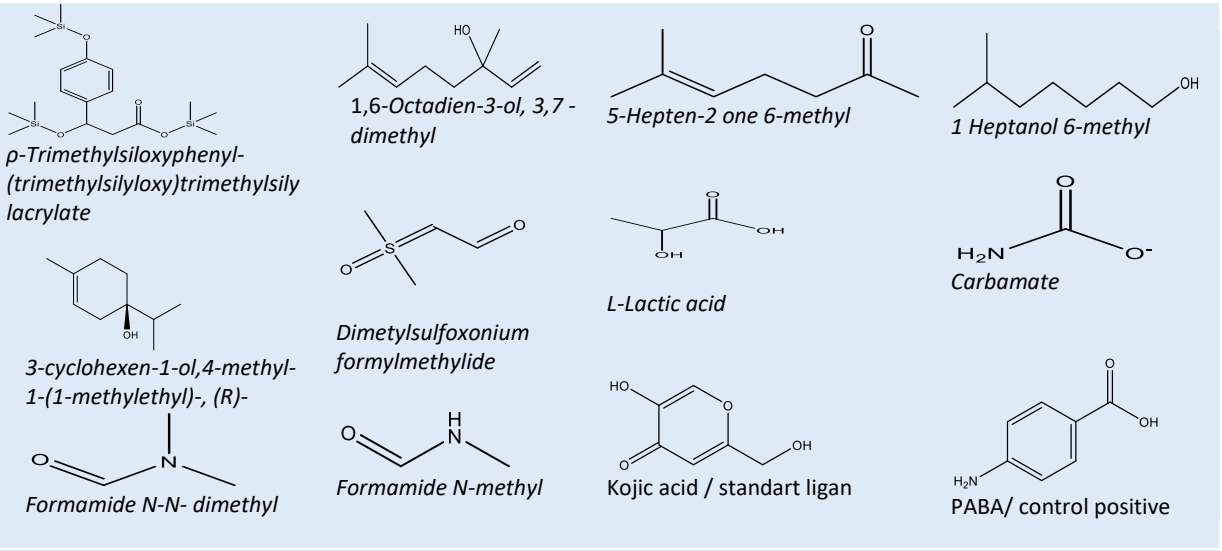


Figure 1: Shows the chemical structure of the ethanol extract of bractea *Bougainvillea spectabilis* Willd, ligan and control positive

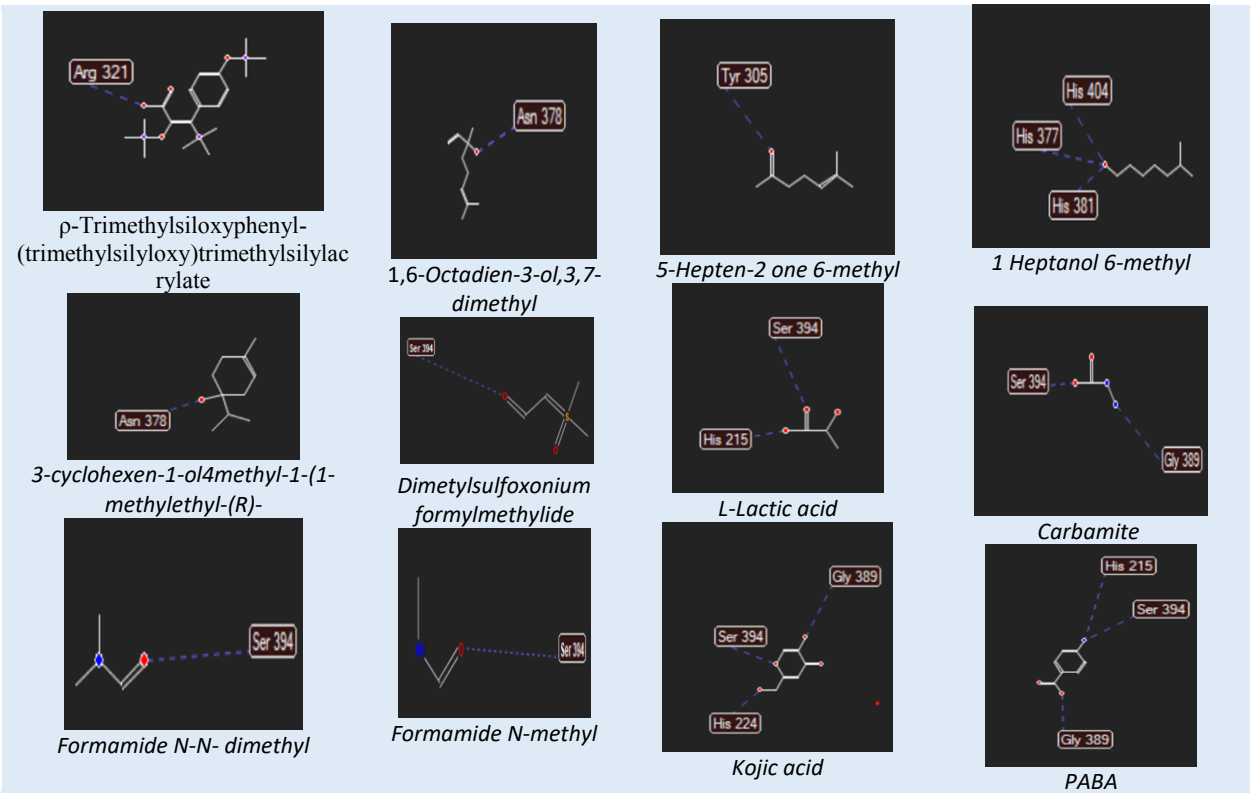
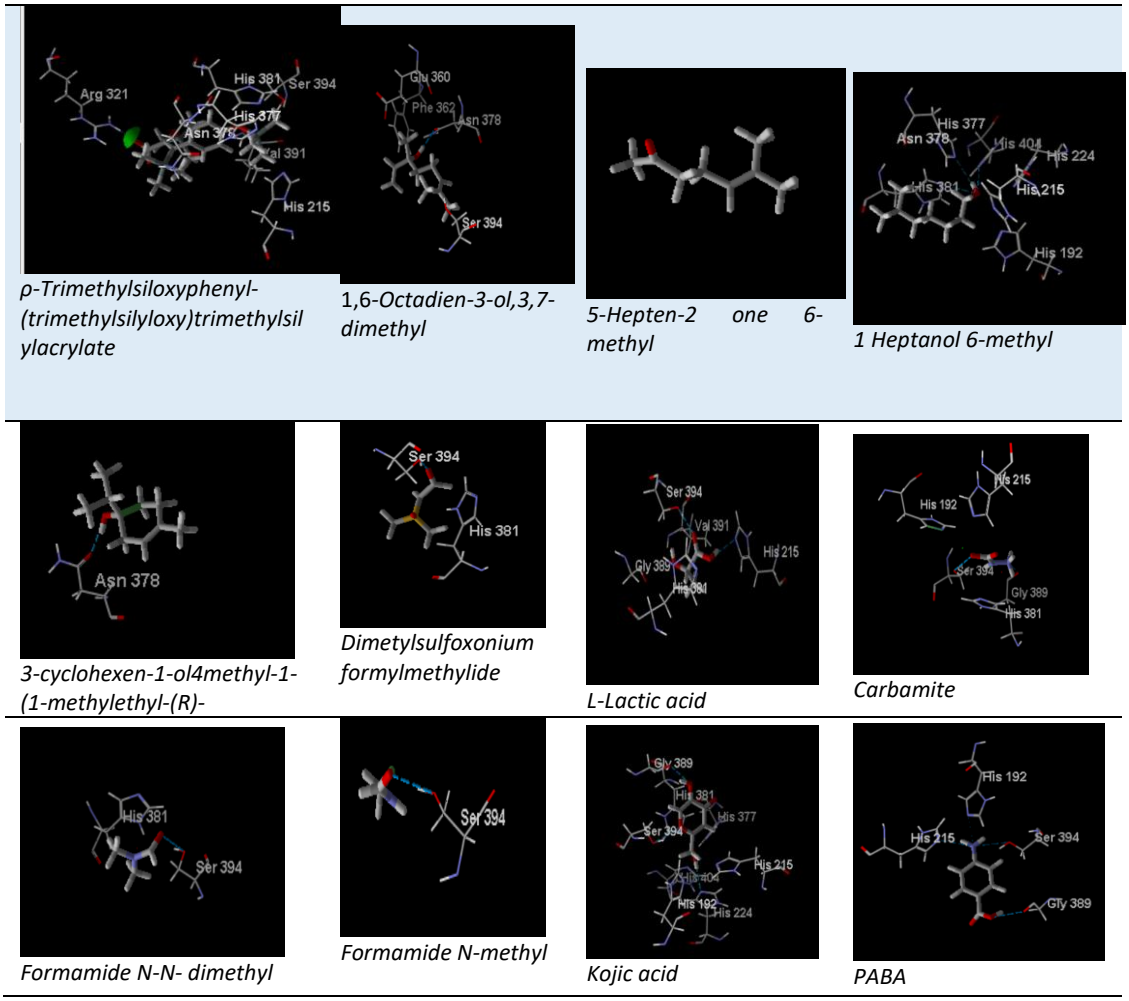


Figure 2: Interaction of hydrogen bonds from arylhydrocarbons enzymes that bind to the main constituent compounds of the ethanol extract of bractea *Bougainvillea spectabilis* Willd.

Table I: Interaction of hydrogen bonds between ligands (the main constituents of ethanol extract and tyrosinase enzyme receptors.

Nama Senyawa/ligan	Arg 321	Asn 378	Tyr 305	His 404	His 377	His 381	Leu 307	Tyr 336
ρ-Trimethylsiloxyphenyl-(trimethylsilyloxy)trimethylsilylacrylate	+	-	-	-	-	-	-	-
1,6-Octadien-3-ol,3,7-dimethyl	-_	+	-	-	-	-	-	-
5-Hepten-2 one, 6-methyl	-	-	+	-	-	-	-	-
1 Heptanol,6-methyl	-	-	-	+	+	+	-	-
3-cyclohexen-1-ol,4-methyl-1-(1-methylethyl-,(R)-	-	+	-	-	-	-	-	-
Dimethylsulfoxonium formylmethylide	-	-	-	-	-	-	-	-
L-Lactic acid	-	-	-	-	-	-	-	-
Carbamite	-	-	-	-	-	-	-	-
Formamide, N-N-dimethyl	-	-	-	-	-	-	-	-
Formamide, N- methyl	-	-	-	-	+	+	+	-
Kojic Acid (ligan standart)	-	-	-	-	-	-	-	-
PABA(control positive)	-	+	+	-	+	+	+	-



ρ-Trimethylsiloxyphenyl-(trimethylsilyloxy)trimethylsilylacrylate

1,6-*Octadien-3-ol,3,7-dimethyl*

5-Hepten-2 one 6-methyl

1 Heptanol 6-methyl

3-cyclohexen-1-ol4methyl-1-(1-methylethyl-(R)-

Dimetylsulfoxonium formylmethylide

L-Lactic acid

Carbamite

Formamide N-N- dimethyl

Formamide N-methyl

Kojic acid

PABA

Figure 3: Interaction of bonds in organized positions (organized poses) between tirosinase enzymes that bind to the main compounds of the ethanol extract *Bougainvillea spectabilis* Willd.

Table II: Parameters of docking Ligands (compounds in ethanol extract of bractea *Bougainvillea spectabilis* Willd on the active site of the tyrosinase enzyme

Nama Senyawa/ligan	*Moldock score*	*Rerank Score*	*HBond*
1,6-Octadien-3-ol,3,7-dimethyl	- 78,0483	- 65,5258	- 3,6737
Kojic acid (ligan standar)	- 72,4	- 62,9153	- 7,14638
PABA (control positive)	- 72,0372	- 61,7784	- 5,7096
3-cyclohexen-1-ol,4-methyl-1-(1-methylethyl-,(R)-	- 68,2096	- 60,8135	- 2,5
1 Heptanol,6-methyl	- 74,6586	- 59,9818	- 4,18919
5-Hepten-2 one, 6-methyl	- 70,163	- 57,9025	0
Dimethylsulfoxonium formylmethylide	- 55,1276	- 48,2163	- 1,99244
L-Lactic acid	- 44,3703	- 41,0492	- 4,16925
Carbamite	- 43,4832	- 39,8544	- 2,63797
Formamide, N-N-dimethyl	- 40,6825	- 36,4104	- 2,20027
Formamide, N- methyl	- 38,1721	- 32,6054	- 2,13008
ρ-Trimethylsiloxyphenyl-(trimethylsilyloxy)trimethylsilylacrylate	- 97,3286	- 7,10326	- 1,90206

5. Discussion

1. Ligand preparation.

The results of making a two-dimensional structure using the *ChemDraw* program 18.1 is shown in Figure

2. Method validation docking.

To ensurethat the orientation of the ligand, the ligand, the behavior in the ligand-receptor binding model using the Molegro Virtual Docker program, the parameters of this docking method must first be validated by the structure of the receptor used, namely PDB CODE 7VNH, replicated 10 times each [13], [14].

Up to now the structure of several crystals PABA and B. spectabilis Willd ethanol extract compounds Willd's classification of tyrosinase receptors provides information about the location and composition of the inhibitor binding space using the protein in its functional conformation. This research uses X-ray structure in complex with the substrate Tyrosinase (PDB code 5M8Q) for test docking. Ligands and positions obtained from the study docking and to look at the behavior in a model of binding of an inhibitor with a ligand using the program *Molegro Virtual Docker* then the parameter should be first validated on the crystal structure used (PDB code 5M8Q) ligand KOJ_516 (A) for tyrosinase in the conformation found in the structure complex crystals with their ligands, extracted and inserted into the corresponding active sites observed on the crystal structure that with the program *Molegro Virtual Docker* the optimal orientation of the inhibitor can be determined which is complexly bound with active KOJ_516 (A), namely in cavity 5 (volume 58.88) on the protein tyrosinase (PDB code 5M8Q)[15].

2. Docking and Analysis of Amino acids.

The 5M8Q receptor was downloaded from the protein databank site (www.pdb.org) and imported into the program *Molegro Virtual Docker*. The MVD program will automatically correct imported proteins and will directly add H atoms and correct if there are soma wrong amino acids residues in the protein. Results of the detection of sites of interaction between the ligand and the receptor *(cavity)* on the 5M8Q receptor is shown in Figure 4.

6. Conclusion

B. spectabilis Willd *Rerank score* The highest active compound is *1,6-Octadien-3-ol,3,7-dimethyl* (Rerank score: - 65.5258) compared to standard ligands Kojic acid (Rerank score:

- 62.9153) and PABA (- 61.7784) have sunscreen activity.

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Conflict of Interest

There is no conflict of interest between the researchers.

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