

## *In Silico* Study of Compounds in Bawang Dayak (*Eleutherine palmifolia* (L) Merr.) Bulbs on Alpha Estrogen Receptors

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### Abstract

Breast cancer is an uncontrolled malignancy of the breast that originates from glandular cells, gland ducts, and the supporting tissues of the breast. The development of herbal-based anticancer drugs is progressing, one of which is derived from the natural ingredients of *Eleutherine palmifolia* tubers. The aim of this study was to determine the activity of compounds derived from *Eleutherine palmifolia* tubers on the alpha-estrogen receptor (ER $\alpha$ ) using an *in silico* study. The crystal structure of the enzyme used was 3ERT which was obtained from the Protein Data Bank (PDB). The applications used in this journal are Chem3D (initial preparation of ligands and receptors), AutoDock4 (redocking and calculation of root mean square deviation (RMSD)), and Biovia (visualization of redocking results). Tamoxifen was used as a reference ligand. Based on the results of the *in silico* study, the best compound that has the potential to be developed as a candidate for anticancer drug is Eleutherine because the results of the *in silico* test on Eleutherine have a value of  $G = -7.56$  kkal/mol and the smallest  $KI = 2.89$  nM, so it can be concluded that eleutherine is one of potential drug candidate for anti cancer.

**Keywords:** *Breast cancer, eleutherine, estrogen receptor  $\alpha$ .*

### INTRODUCTION

According to the World Health Organization (WHO), cancer is the leading cause of death in the world, with around 10 million people dying from cancer in 2020 (Sung, *et al.*, 2021). In 2020, the most common new cases of cancer were breast cancer with 2.26 million cases, followed by lung cancer and colon cancer (World Health Organization, 2021).

Empirical testing resulted in data that the onion bulbs (*Eleutherine sp.*) can be used as a

treatment for wounds, coughs, bloody diarrhea, jaundice, abdominal pain, inflammation of the intestinal axis, dysentery, colon cancer, breast cancer, ulcer drugs, and vomiting stimulants (Muti'ah, *et al.*, 2020). Preclinically, the *Eleutherine palmifolia*

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plant can be used as an anticancer by inhibiting the proliferation process of T47D breast cancer cells. This test was carried out *in vitro*, *in vivo*, and *in silico* (Muti'ah, *et al.*, 2020)

In the human body, there are several receptors that can be expressed, one of which is estrogen receptor (ER) which consists of core ER, extra-nuclear ER, and ER paired G protein (GPER). ER $\alpha$  includes core ER that in human tissue is widely expressed including the breast, prostate, uterus, liver, and bones. Overall, alpha-estrogen receptor (ER $\alpha$ ) has an important role in the development of breast cancer in inhibiting tumor progression, maintaining the luminal phenotype, and restoring breast cancer sensitivity to hormone therapy (Liu, *et al.*, 2020).

According to Liao, *et al.* (2014), high expression of ER $\alpha$  is closely correlated with breast cancer cell proliferation. The proximity of this correlation makes ER $\alpha$  a potential target for breast cancer therapy. Therefore, it is necessary to develop a natural compound that has the potential to inhibit the activity of ER $\alpha$ . The naphthoquinone derivative compound, Eleutherinol, has an affinity for ER $\alpha$  and can be found in *Eleutherine palmifolia* (Narko, *et al.*, 2017; Ha, *et al.*, 2013). So the purpose of this study is to determine the activity of compounds derived from *Eleutherine palmifolia* bulbs against ER $\alpha$  using *in silico* studies that are expected to obtain natural compounds that have the potential to inhibit ER $\alpha$  activity.

## METHODS

### Hardware

Laptop with specifications Intel® Core i3-2430M CPU@ 2.40GHz (4 CPUs) and 4096 MB RAM. The software used is the Windows 10 Ultimate E 64-bit Operating System equipped with the AutoDockTools program (version 4.2), ChemDraw 2D and 3D free trial versions, Discovery Studio Visualizer, Protein Data Bank via the <http://www.rcsb.org/pdb/>, pharmacokinetic and toxicity testing via <https://preadmet.bmdrc.kr/>.

### Materials

Using Human Estrogen Receptor Alpha protein (3ERT) downloaded from website <https://www.rcsb.org/> and 10 the ligands is Eleutherol, Eleutherine, Anthraquinone, Methylanthraquinone, Glucopyranoside, Oxyresveratrol, Isoliquiritigenin, Naphthoquinone, Quinone, Naphthalene.

### Lipinski Predictions

Lipinski predictions were made to analyze drug-like properties using the Chemdraw application. Based on Lipinski's rule of five, a compound has similar properties to drugs if the molecular weight (BM) of the compound is less than 500 Daltons, the log *P* partition coefficient value is less than 5, the number of hydrogen bond donors (HBD) less than 5, and the number of hydrogen bond acceptors (HBA) is less than 10.

### ADMET Predictions

Analysis to predict the absorption, distribution, metabolism, excretion, and toxicity profile of the test compound was carried out by redrawing the structure of the test compound, then clicking on 'submit' to display the results of ADME information. After that, download the file into the desired format (excel, CSV, PDF, SDF) to save the prediction results, to see the toxicity profile, press the "Toxicity" task in the upper right corner of the page, then the next step is the same as the ADME test. Prediction of the ADMET profile shows a variety of absorption data including human intense absorption (HIA) and cell permeability of CaCO<sub>2</sub>, then distribution that includes plasma protein binding (PPB) and blood brain barrier distribution (BBB), as well as toxicity data which includes mutagenic and carcinogenic.

### Molecular Docking Simulation

Molecular docking begins by preparing receptors that will be used and can be downloaded from Brookhaven Protein Data Bank (GDP) on the website <https://www.rcsb.org/>.

In this journal, the receptor that will be used is the ER $\alpha$  with PDB code 3ERT found in humans (*Homo sapiens*). These macromolecules were obtained from the research with methods that used the X-Ray method Diffraction and resolution 1.90Å tethered 4-Hydroxytamoxifen (Shiau, *et al.*, 1998). Next process is the separation process files of macromolecules and ligands using Biovia Discovery Studio software to ensure the structure that will used has an active side. Water molecules and residues present in the protein structure must be removed by deletion, so that the water molecules do not interfere with the docking simulation process and ensure that only ligands and receptors can interact. This process of removing water molecules is also known as desolvation. Receptors and ligands are stored separately in the .pdb file format on the desktop. The preparation of the receptor begins with the addition of a hydrogen atom which aims to adjust the docking atmosphere, approach pH 7 and automatically set to polar only, then add a Kollman charge. The next process is to save the receptor in pdbqt. format, then the preparation of the 4-Hydroxytamoxifen ligand by adding hydrogen atoms arranged to merge nonpolar, so that only polar hydrogen atoms will interact with protein residues then add gasteiger charge and the file is saved in pdbqt file format. The ligand is then continued with the molecular docking process using the Autodock program (Sari, *et al.*, 2020).

Validation method was carried out by redocking the innate ligand of the target receptor with 2 parameters namely the grid parameter (Grid Parameter File/Grid Box) and the anchoring parameter (Docking Parameter File/Grid Coordinate) with the help of the Autodock Tools software by opening the receptor file and ligands in .pdbqt format. The grid parameters include determining the coordinates and determining the volume. Function of Gridbox in determining the receptor area to be anchored based on the x, y, and z coordinates of the comparison compound in order to determine the lowest energy conformation of the ligand. The

coordinates used in the anchoring of the molecule to the 3ERT receptor, with the coordinate centers, that are x 30.01, y -19.113, and z 24.207. Meanwhile, the volume of the mooring grid used in this study is 40x40x40 with spacing of 0.375. The mooring parameters are carried out using the Lamarckian Genetic Algorithm method and the conformational search is 100 times. Validation of this method is carried out in order to find out whether the program used is in accordance with the requirements for use. The analysis was carried out by evaluating the results of the RMSD. If the RMSD results are obtained 2 then the parameters used are considered valid (Suherman, *et al.*, 2020).

After the method validation is done, then running docking can be done using Autodock4 and Autogrid4. After the running process is complete, the file in .dlg format can be opened with the help of the Notepad++ program. The results obtained from running docking in the form of bond energies, inhibition constants of all tested ligands and the number of clusters. These results are used to compare to each other results.

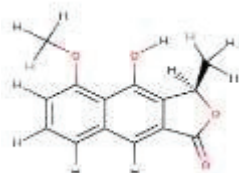
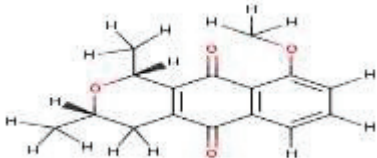
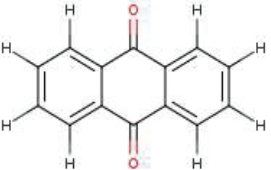
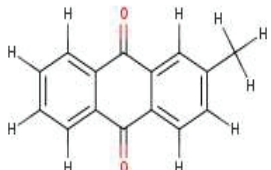
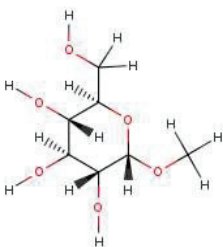
## RESULTS

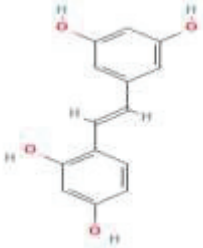
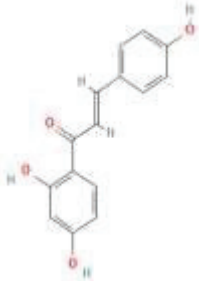
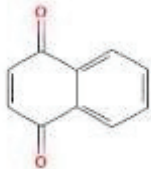

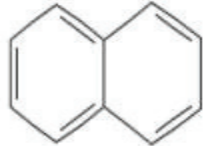
Lipinski prediction results can be seen in Table 1, ADMETOX prediction results can be seen in Table 2, and the molecular docking simulation results can be seen in Table 3.

## DISCUSSION

In Table 1 all compounds have a small relative molecular mass of <500 Da, this is in accordance with the theory which states that the relative molecular mass value shows its relation to the distribution process of the drug. In the distribution process, the drug will penetrate the biological membrane. Drugs that have a relatively small molecular mass, the drug will easily penetrate biological membranes. The results of the Log *P* value of all compounds <5. This Log *P* value

Tabel 1. Lipinski prediction results of the *Eleutherine palmifolia* compounds.

No	Name of Compound	Molecular Weight (<500 Da)	Log P (<5)	Hydrogen Bond		Description
				Donor (<5)	Acceptor (<10)	
1	Eleutherol	244.24 g/mol	2.45	1	4	Qualify
						
2	Eleutherine	272.30 g/mol	2.58	0	4	Qualify
						
3	Anthraquinone	208.21 g/mol	1.94	0	2	Qualify
						
4	Methylantraquinone	222.24 g/mol	2.20	0	2	Qualify
						
5	Glucopyranoside	194.18 g/mol	0.80	4	6	Qualify
						

No	Name of Compound	Molecular Weight (<500 Da)	Log P (<5)	Hydrogen Bond		Description
				Donor (<5)	Acceptor (<10)	
6	Oxyresveratrol	244.24 g/mol	1.41	4	4	Qualify
						
7	Isoliquiritigenin	256.25 g/mol	2.02	4	3	Qualify
						
8	Naphthoquinone	158.15 g/mol	1.33	0	2	Qualify
						
9	Quinone	108.09 g/mol	0.94	0	2	Qualify
						
10	Naphthalene	128.17 g/mol	1.99	0	2	Qualify
						

indicates a relationship with hydrophobicity or lipophilicity. In terms of pharmacokinetics, drugs that are absorbed orally must be able to cross the lipid bilayer in the intestinal epithelium. This is useful so that the transport system is efficient so that the drug must be ensured to be lipophilic to be able to penetrate into the lipid bilayer, but not too lipophilic because once the drug has entered the lipid bilayer, the drug cannot penetrate out again and is retained in the body. so the drug can be toxic. The hydrogen bonds of all the compounds studied had <5 donor hydrogen bonds and <10 acceptor hydrogen bonds. The donor and acceptor values of these hydrogen bonds show their relation to the biological activity of a drug molecule (Liao, *et al.*, 2014). Based on the results obtained, it shows that the 10 compounds from the *Eleutherine palmifolia* have met the rules of Lipinski's Rule of Five. Therefore, 10 compounds from *Eleutherine palmifolia* bulbs have good absorption so that they are suitable for use as oral preparations.

In Table 2. HIA (%) in all compounds is included in the low category (0-20%) (Nursamsiar, *et al.*, 2016). HIA is the sum of bioavailability and absorption evaluated from the ratio of excretion through urine, bile and feces. This HIA parameter aims to predict the process of drug absorption that occurs in the intestine. In addition, the permeability ability of CaCO<sub>2</sub> cells was also studied where in the results all compounds were in-

cluded in the low category (<4 nm/sec) (Cheng, *et al.*, 2013). CaCO<sub>2</sub> cells are an *in vitro* model to determine drug transport through intestinal epithelium derived from human colonic adenocarcinoma which has multiple transport pathways. From the distribution parameters that were predicted based on the binding to plasma proteins, namely the PPB parameter, all compounds had a strong attachment of >90% except for Glucopyranoside and Quinone compounds (Kumar, *et al.*, 2018; Purwaniati, 2020). PPB is a drug fraction that is available in free form for distribution to various tissues (Kleywegt and Jones, 1997). Toxicity prediction is carried out to predict and assess the possible risks that arise from the test compound that can affect humans. The test compound as a drug candidate in addition to having good biological activity, requires a low toxicity value (Lipinski, *et al.*, 1997). Of the 10 compounds that were tested, it was found that two test compounds, namely Glucopyranoside and Oxyresveratrol, had no results on mutagens and carcinogens, indicating that these compounds met the requirements of not causing toxicity.

The best receptor selected was <2.5 resolution. The target receptor structure used in this journal has a resolution value of 1.90 so that it meets the criteria (Liu, *et al.*, 2020). In addition, the criteria used in selecting the target receptor is to look at the value of R-factor and R-free. The recommended R-factor and R-free values are <0.25 and lower and

Table 2. ADMET prediction results of the *Eleutherine palmifolia* compounds.

No	Name of Compound	Absorption		Distribution		Toxicity	
		HIA (%)	CaCO-2 (nm/sec)	PPB (%)	BBB	Mutagen	Carcinogen
1	Eleutherol	0.005	-4.807	95.212	0.436	No	Yes
2	Eleutherine	0.027	-5.028	94.58	0.165	Yes	Yes
3	Anthraquinone	0.005	-4.631	98.453	0.145	Yes	Yes
4	Methylanthraquin one	0.004	-4.673	99.28	0.139	Yes	Yes
5	Glucopyranoside	0.718	-5.362	11.03	0.296	No	No
6	Oxyresveratrol	0.004	-4.755	97.72	0.059	No	No
7	Isoliquiritigenin	0.006	-4.732	99.32	0.065	Yes	Yes
8	Naphthoquinone	0.006	-4.529	91.81	0.309	Yes	Yes
9	Quinone	0.957	-5.0	82.13	0.074	No	Yes
10	Naphthalene	0.004	-4.237	95.68	0.652	No	Yes

Table 3. Molecular docking simulation results.

No	Compound	Cluster	Binding energy (kcal/mol)	Ki (nM)	Interactions with amino acids		
					Hydrogen bond	Van der waals bond	Etc
1	Reference drug (Tamoxifen)	0.0	-10.54	18.94	Carbon Hydrogen Bond THR A:347	-	Interactions Alkyl and Pi-Alkyl LEU A:428 LEU A:387 LEU A:346 LEU A:525 MET A:388 MET A:421 ALA A:350 PHE A:404
2	Eleutherol	0.0	-6.44	18.91	Conventional Hydrogen Bond ARG A:394	-	Interactions Pi-Alkyl LEU A:346 LEU A:391 MET A:388
3	Eleutherine	0.0	-7.56	2.89	Carbon Hydrogen Bond GLU A:353 LEU A:387	-	Interactions Alkyl dan Pi-Alkyl LEU A:391 LEU A:428 LEU A:384 ILE A:424 MET A:388 LEU A:346 LEU A:349 ALA A:350 GLU A:353
4	Quinone	0.0	-4.16	888.27	-	-	GLU A:353 LEU A:387 ALA A:350 LEU A:391 LEU A:349 Pi-Anion Pi-Alkyl
5	Naphthalene	0.0	-5.17	161.5	-	-	GLU A:353 ALA A:350 LEU A:387 LEU A:349 LEU A:346 LEU A:391 MET A:388 Pi -Anion Pi -Alkyl

No	Compound	Cluster	Binding energy (kcal/mol)	Ki (nM)	Interactions with amino acids		
					Hydrogen bond	Van der waals bond	Etc
6	Glucopyranoside	0.0	-0.89	222.53	Conventional Hydrogen Bond ALA A:551 Carbon Hydrogen Bond ARG A:548	-	-
7	Oxyresveratrol	0.0	-2.3	20.71	Conventional Hydrogen Bond LEU A:549 ALA A:651 ARG A:548	-	Pi-Alkyl Pi-Sigma
8	Anthraquinone	0.0	-2.81	8.64	Carbon Hydrogen Bond ARG A:548	-	Pi-Sigma ALA A:551 Pi-Alkyl LEU A:549 Pi-Lone Pair
9	Methylantraquinone	0.0	-3.17	4.77	Carbon Hydrogen Bond ARG A:548	-	Pi-Alkyl ALA A:551
10	Isoliquiritigenine	0.0	-2.71	10.3	Carbon Hydrogen Bond LEU A:549	-	Pi-Alkyl ARG A:548 ALA A:551
11	Naphthoquinone	0.0	-2.16	26.01	-	-	Pi-Lone Pair ARG A:548 Pi-Alkyl ALA A:551

close to 0.28. The R-factor and R-Free values of the receptor targets used in this paper are 0.229 and 0.262 (Arba, 2019). Molecular anchoring methods are said to be reliable/valid if the RMSD value is 2Å, which means the smaller the RMSD value, the closer the natural ligands from docking are to the natural ligands from crystallography so that the molecular anchoring method can be used to anchor the test compound. From the results of the mooring validation, the smallest RMSD reference value is 0.77. (Results are not included in this journal).

Lower energy binding affinity values for natural ligands have a greater potential to

interact with target proteins (Pangastuti, *et al.*, 2016). Meanwhile, the value of the inhibition constant indicates the strength of the compound in inhibiting the work of the receptor, the smaller the value, the greater the inhibition (Umamaheswari, *et al.*, 2013). Based on the results obtained in Table 3. there are no test compounds that have lower bond energy values or inhibition constants than natural ligands, with natural ligands 3ERT -11.88 kcal/mol and 1.97 nM, respectively. comparison (Tamoxifen) were -10.4 kcal/mol and 18.94 nM. However, the Eleutherine compound had a lower bond energy value and inhibition constant than the other test

compounds with values of -7.56 kkal/mol and 2.89 nM, respectively. These results indicate the ability of Eleutherine compounds to bind to the active site of the 3ERT receptor is weaker than natural ligands. However, this compound still has the possibility to bind to the active site of the 3ERT receptor and has a fairly good inhibitory potential. In addition, the value of the bond energy and the inhibition constant of the Eleutherine compound showed lower results than the comparison ligand. Thus, the compound is predicted to have a better interaction with the 3ERT receptor than the comparison ligand and is the best test compound in this study so that it can be used as a candidate for breast anticancer drugs. In addition, observations were made and compared the results of tethering visualization by looking at the amino acid residues and the number of hydrogen bonds formed from the interaction with each test compound and target receptor (Muti'ah, *et al.*, 2020). Based on the data that has been produced in Table 3. The best test compound for the 3ERT receptor has 2 hydrogen bonds with amino acid residues GLU A:353 and LEU A:357.

In the interaction between the natural ligand of the 3ERT receptor with amino acid residues, there are 2 hydrogen bonds with amino acid residues GLU A:353 and THR A:347, while the reference drug ligand for the 3ERT receptor has 1 hydrogen bond with amino acid residues THR A:347.

Based on pre-clinical studies *in silico*, according to research by Amelia, *et al* (2015), eleutherinol compounds in *Eleutherine americana* can inhibit ER $\alpha$  breast cancer. This is because the eleutherinol compound has a binding energy value of -6.43 kkal/mol to the 3ERT receptor and has two hydrogen bonds with GLU A:353 and ARG A:394 amino acids that can inhibit ER. Eleutherinol is a derivative of eleutherine. Meanwhile, in this study, eleutherine was found as the best compound that has the potential to be developed as a candidate for breast cancer drugs. The eleutherine compound also has a GLU A:353 amino bond which is thought to play an important role in the compound's affinity

for ER $\alpha$ . In addition, the compound eleutherine was chosen because the results of the *in silico* test on eleutherine obtained the value of  $G=-7.56$  kkal/mol and the smallest  $KI=2.89$  nM.

## CONCLUSION

Based on the results of the *in silico* test, it can be concluded that the best compound because bond with amino acid residues THR A:347, so has the potential to be developed as one of candidate for breast anticancer drug candidates is Eleutherine because the results of the *in silico* test on Eleutherine obtained the value of  $G=-7.56$  kkal/mol and the smallest  $KI=2.89$  nM. ADMET prediction results for Eleutherine compounds have a poor absorption value in the intestine (HIA) of 0.027% and a low permeability value (CaCO<sub>2</sub>) of -5.028, but these results are better than other compounds found in *Eleutherine palmifolia*. In addition, the Eleutherine compound has results that meet the requirements according to Lipinski's rule, namely the molecular weight is not more than 500 daltons with the results obtained 272.30 g/mol, has a high lipophilicity with  $\log P < 5$  with the results obtained 2.58, the value of hydrogen bond donors is not more than 5 with an eleutherine yield of 0 hydrogen bonds, and no more than 10 hydrogen bond acceptors with an eleutherine yield of 4.

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