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# The inhibitory activity of peonidin purple sweet potato in human epidermal receptor-2 receptor (her-2) expression by in silico study

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**Abstract.** An acetylated anthocyanin (peonidin) is one of the flavonoid group compounds contained in purple sweet potato (*Ipomoea batatas*) which has anticancer activity. Overexpression of Human Epidermal Receptor-2 receptor (HER-2) could induce spontaneous dimerization and autophosphorylation, and trigger the occurrence of focal adhesion kinase (FAK) activation in order to induce migratory process and breast cancer cell metastasis. Lapatinib is one the drug which used to inhibit over-expression of HER-2. The purpose of this study was to determined the inhibition mechanism of over-expression HER-2 protein of peonidin by using in silico molecular docking method. In silico method such as molecular docking is done through stages such as validation of molecular docking method, optimization of peonidin 3D structure, docking of peonidin with HER-2 protein which refers to the binding energy parameter where the lower binding energy value indicates the stronger and stable bond between peonidin with HER-2 protein. The binding energy of peonidin was compared with native ligand's binding energy and lapatinib's binding energy. The result of this study was peonidin's binding energy with HER-2 protein was -7,54 kcal/mol, while the native ligand's binding energy and lapatinib's binding energy with HER-2 protein were -5,77 kcal/mol and -0,56 kcal/mol. The binding energy indicates peonidin as a purified anthocyanin of purple sweet potato had potential activity as anti-breast cancer because it suppressed the excessive expression of the HER-2 protein.

## 1. Introduction

Breast cancer has relatively high incidence in the worldwide, approximately 20% of all malignancies [1]. Breast cancer in Indonesia got the second rank after cervical cancer. It is estimated that 10 out of 100,000 populations are affected by breast cancer and 70% of patients check themselves at an advanced stage [2].

In 30% of cases of breast cancer is caused by Human Epidermal Receptor-2 (HER-2) overexpression [3]. Invasion of cancer cells can occur due to the overexpression of HER-2 protein. The overexpression of HER-2 protein could induce migratory process and metastasis process of cancer cell through spontaneous dimerization induction, autophosphorylation, and the occurrence of focal adhesion kinase (FAK) activation [4]. Several treatments have been done for breast cancer, but the results have not been satisfactory, even the effects of surgical failure can cause cancer to spread to the other part of body with severe conditions [5]. Because of that, we need to developing a new drug which has a good therapeutic effect by excavating natural compounds derived from plants.



Purple sweet potato (*Ipomoea batatas* L.) is one of the most abundant commodities in Indonesia [6]. One of the phytochemical properties in *Ipomoea batatas* is anthocyanin [7]. Purple sweet potato contains 10 types of anthocyanins with differences in R1, R2, and R3 are: sianidin-3-sophorosid-5-glucosid, peonidin-3-sophorosid-5-glucosid, sianidin-3- (6"-6" - dicoffeoylsophoroside) -5-glucosid, sianidin-3- (6"-caffeoyl-6" - p-hidroxybenzoylsophorosid) -5-glucosid, sianidin-3- (6"-caffeoylsophorosid) -5-glucosid, sianidin-3- (6'-caffeoyl-6" - feruloylsophorosid) -5-glucosid, peonidin-3- (6', 6' - dicoffeoylsophoroside) -5-glucosid, pionidin-3- (6"-caffeoylsophorosid) -5-glucosid, pionidin-3- (6"-caffeoyl-6" - p-hidroxybenzoylsophorosid) -5-glucosid and peonidin-3- (6"-caffeoyl-6" - feruloylsophorosid) -5-glucosid [8]. Anthocyanin has been widely used as a dye, especially beverages, as many synthetic dyes are known to be toxic and carcinogenic. According to JEFCA (Joint FAO / WHO Expert Committee on Food Additives) has stated that extracts containing anthocyanin have low toxicity effects. Attention to intensive anthocyanin pigment in recent years due to its health benefits, including reduce the risk of coronary heart disease, stroke risk, anticancer activity, anti-inflammatory effects, improving eye acuity, and improving cognitive behavior. Attention to intensive anthocyanin pigment in recent years due to its health benefits as anticancer [9]. One type of anthocyanin which can be developed as a new drug is an acetylated anthocyanin (peonidin) which has better stability during storage than the other type of anthocyanin.

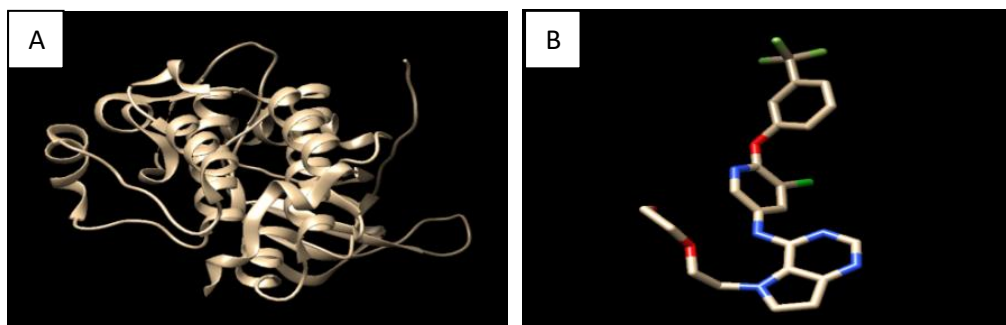
In silico molecular docking techniques can be used to predict how a protein interacts with a ligand, so the activity of the bioactive compound and its synergistic action with other drugs can be known. This method will improve the effectiveness and efficiency of research on new drug development. Therefore, we want to know about the inhibition mechanism of overexpression of HER-2 protein by an acetylated anthocyanin from purple sweet potato through in silico simulation.

## 2. Method

Molecular docking was performed to get the drug-receptor binding energy. The PDB files obtained from Protein Data Bank (PDB) ([www.rcsb.org](http://www.rcsb.org)) is a worldwide repository for processing and distribution of 3D biological macromolecular structure data. The structure of HER-2 (3PP0) proteins were downloaded from PDB and prepared for docking by removing the heteroatoms and water molecules in them. The software used were as follows: Autodock 4.2. for molecular docking, Chimera 1.10.1 for protein and ligand preparation. The three-dimensional structure optimization by using HyperChem 8 by semi-empirical AM1 computation and calculate with a single point and geometry optimization. The downloaded PDB file of HER-2 were first read in Chimera 1.10.1, added waters removed, and polar hydrogens were added. The structure of peonidin was drawn by using Hyper Chem 8. Next running docking protein target and ligand in file Autodock 4.2. The configuration then the ligand's binding energy to target protein score was compared to native ligands.

## 3. Result And Discussion

The result of protein preparation can be seen in Figure 1. The aim of protein preparation is obtaining protein structure without ligand and its native ligand (available space / pocket / cavity) in which chain is selected chain A. At the time of preparation of H<sub>2</sub>O molecule on chain A protein without native ligand is removed so that at the time of docking peonidin can interact perfectly with HER-2 proteins [10].



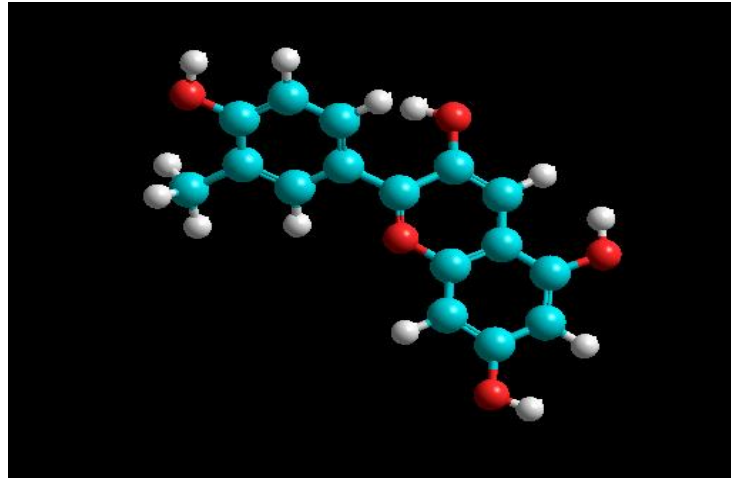
**Figure 1.** Structure of HER-2 protein without Native Ligand (A) and Native Ligand (B)

**Table 1:** Molecular Docking Method Validation of HER-2 Protein

Conformation	RMSD (Å)	Energy Binding (kcal/mol)	Hydrogen Bond
1	1.42	-5.77	-
2	1.88	-4.97	-
3	5.41	-4.53	ASP863 THR862
4	5.12	-4.14	-
5	2.68	-3.03	-
6	2.90	-2.33	MET801
7	2.48	-1.57	ARG849 SER728
8	2.58	-1.09	-
9	3.23	-0.90	MET801
10	4.62	-0.25	-

The results and interactions that occur in the validation of the molecular docking method can be seen in table 2. The aim of molecular docking validation is to determine the conformational similarities between native ligand-protein complex in crystallography compared with experimental results [11]. Validation parameter for docking is Root Mean Square Deviation (RMSD) value which shows the ligand irregularity rate experimentally against the crystallographic ligand on the same binding site. The RMSD value  $\leq 3\text{\AA}$  indicates that the method used is valid.

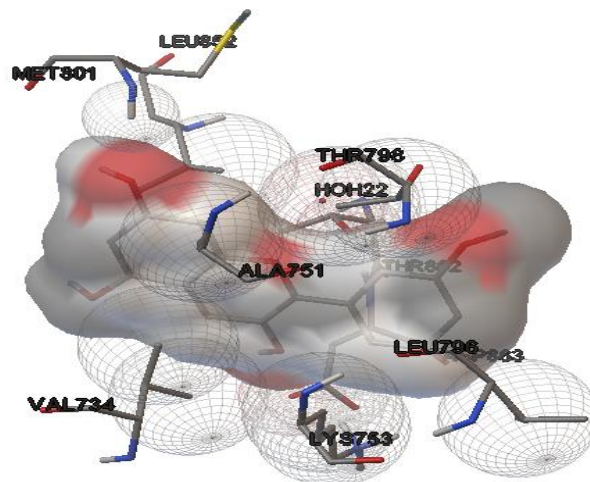
Preparation is done by first drawing the structure of peonidin 3D and then done optimization on HyperChem 8 program to get a stable structure. The energy produced by peonidin compounds after calculating the single point of energy is 3529,799 kcal / mol and decreased to -3634.471 kcal / mol after geometry optimization aimed to minimize the energy to obtain a more stable compound [12].



**Figure 2:** The Structure of Peonidin after Geometry Optimization

**Table 2:** Docking of Peonidin and HER-2 Protein

Conformation	Energy Binding (kcal/mol)	Hydrogen Bond
1	-7,54	-
2	-7,51	-
3	-7,49	-
4	-7,42	MET801
5	-7,31	ASP863
6	-7,29	ASP863
7	-7,29	ASP863
8	-7,23	-
9	-7,20	MET801
10	-7,10	ASP863



**Figure 3:** Interaction Between Peonidin and HER-2 Protein

The results and interactions that occur in docking of peonidin compounds against HER-2 protein can be seen in table 2 and figure 3. Docking of peonidin and HER-2 protein results is energy binding of -7.54 kcal/mol which can be seen in Table 2. When compared with the native ligand and lapatinib as a control to determined how strong and stable the bond, the binding energy of peonidin is lower (more negative) than native ligand's binding energy of -5.77 kcal/mol and lapatinib's energy binding of -0.56 kcal/mol which indicating that peonidin has a stronger and more stable bond compared to the native ligand. In the peonidin docking results no hydrogen bonds are found and it was same with native ligand. The amount of number of hydrogen bonds can determine the strength of the interactions, as can be seen from the physical and chemical properties between H<sub>2</sub>O and HF which are much different even though they have hydrogen bonds. H<sub>2</sub>O has a higher boiling point than HF. This indicates that it takes a higher energy to break the H<sub>2</sub>O molecule bond, the explanation is because the H<sub>2</sub>O molecule has two hydrogen bonds while the HF (Jefrey, 1997). Based on the comparison of binding energy result between peonidin, native ligand, and lapatinib, it can be seen that peonidin as an acetylated anthocyanin in purple sweet potato has anticancer activity by inhibiting the overexpression of the HER-2 protein. Overexpression of HER-2 protein can lead to the process of migration and metastasis of breast cancer cells.

#### 4. Conclusion

Peonidin as an acetylated anthocyanin of purple sweet potato has anti-breast cancer activity through inhibition of overexpression of HER-2 protein with a binding energy of -7.54 kcal / mol.

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