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Original Article

Utilization of Secondary Metabolites in Algae *Kappaphycus alvarezii* as a Breast Cancer Drug with a Computational Method

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ABSTRACT

Breast cancer is one of the worst diseases that affect female people. Long-term treatment with therapy or surgery has a detrimental impact on the patient. The algae *Kappaphycus alvarezii* has gotten a lot of interest as a breast cancer medication because it contains chemicals that are expected to be anti-cancer. The objectives of this paper were to see how secondary metabolites in algae interact with the Nuclear Factor- kappaB protein kinase in breast cancer. The ligands and proteins were obtained from the PubChem and PDB websites, respectively. Swiss ADME was then used to assess the Pharmacokinetics and Drug likeness Properties. The last stage involved using molecular docking with PyRx and molecular dynamics to identify the interaction and visualization between the ligand and the target protein. The findings of the test revealed that the maraniol chemical had a superior binding capacity with NF kB protein kinase because it has a chromone group that controls transport efficiently in preventing breast cancer proliferation.

Key words: Breast cancer, *K. alvarezii*, NF kB protein kinase, Molecular docking.

INTRODUCTION

Cancer is a disease characterized by abnormal cell proliferation caused by mutations, deletions, and a number of other factors which change the processes and signaling channels. This illness is one of the leading causes of mortality worldwide and is widely dreaded by people. Breast cancer is the most common kind of cancer in women, affecting more than 1/4% of the population and increasing every year.[1,2] External and internal factors contribute to the genesis of this illness.[3,4] According to experts who continue to conduct molecular research to find out the cause of this cancer, the types of genes that play a role in breast cancer include breast cancer-associated genes (BRCA1 & BRCA2), human epidermal growth factor receptor 2 (HER2), epidermal growth factor receptor (EGFR), c-Myc and kB kinase protein.[3]

Humans have undergone a variety of therapies to minimize and cure breast cancer, including surgery and therapy. The employment of these two procedures on a regular basis will have a negative effect in the form of a decline in the immune system, making them more susceptible to illness[5]. Furthermore, because these approaches are generally expensive, persons with low incomes are unable to receive appropriate therapy. As a result, it is critical to develop the use of natural materials as an alternative treatment that is effective, safe, and, most importantly, accessible to people at all levels of society.

The magnificent flora and animals of Indonesia are well-known. *Kappaphycus alvarezii* is one form of flora that can be utilized to treat cancer. These marine creatures produce secondary metabolites, such as maraniol or methyl coumarin, fucoxanthin, and saponin compounds, which are known as an anticancer agent for leukemia, colon, breast adenocarcinoma and others.[6] Molecular approaches such as molecular docking are routinely employed to test natural components for therapeutic potential.[7] The contribution of this project was to examine the outcomes of computational methods of secondary metabolites in algae *Kappaphycus alvarezii* with Nuclear Factor-kappaB (NF-kB) inducing kinase protein is involved in the development of breast cancer. Furthermore, this work may be regarded as a material for successfully and efficiently producing anti-cancer treatments, mainly for breast cancer.

MATERIALS AND METHODS

Ligand and protein preparation

Maraniol or methyl coumarin and fucoxanthin are the compounds found in algae *K. alvarezii*.[6] Maraniol (CID: 66595), fucoxanthin (CID: 5281239) and ribociclib (CID: 44631912) are downloaded from the PubChem website (http://pubchem.ncbi.nlm.nih.gov) to obtain the three-dimensional crystal structure of maraniol, fucoxanthin and Ribociclib. Then, the obtained data is opened in Discovery Studio and renamed with PDB format.

The extreme NF-κB-inducing kinase (NIK) amount can cause several diseases like autoimmune and cancer.[8] The NIK kinase protein can be downloaded in the protein data bank website (http://www.rcsb.org//pdb) with PDB ID: 4DN5. The NIK kinase used as a targeted drug in molecular docking and prepared with Discovery Studio to remove the original ligand and water from the protein and saved in PDB format.

Pharmacokinetics and druglikeness properties

Swiss ADME is a tool based on the website (http://www.swissadme.ch) that is used to estimate the ADME, pharmacokinetics and drug-likeness

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properties of maraniol and fucoxanthin. Also to predict the Lipinski Rule of Five violation for the maraniol and fucoxanthin compound.[9] In the web browser (http://www.swissadme.ch), the chemical structure of maraniol is drawn or the list of SMILES of the chemical structure of maraniol and fucoxanthin are written. Then, the operator can press the run button and the website will calculate the parameter value.

QSAR and toxtree analysis

QSAR Analysis of the compound from algae *K. alvarezii* was conducted with the PASS server website (http://way2drug.com/passonline/predict.php). Maraniol and fucoxanthin as the drug candidate were analyzed with the PASS server website to evaluate with the breast cancer disease. Toxtree analysis is used to determine the crammer rules, mutagenicty, carcinogenecity and skin corossion of the compounds.[10]

Molecular docking and visualization method of the compounds

In this research, maraniol and fucoxanthin were docked with NIK kinase protein (PDB ID: 4DN5) with the molecular docking method. The molecular docking method was supported with the PyRx application software. In addition, ribociclib is used as a control for the molecular docking method because of ribociclib is used as a therapeutic drug for patients with breast cancer.[11]

The 3dligandsite website (https://www.wass-michaelislab.org/3dlig/) was used to validate the molecular docking method. This website was used to determine the pocket binding of the protein. On this website explained the place where the molecule will bind to the protein.[10]

The visualization of the complex which resulted from molecular docking method was conducted with Discovery Studio Visualizer. In Discovery Studio Visualizer, the second-dimension and three-dimension interaction between the compounds and the amino acid residue from the protein can be completed.[12]

Molecular dynamics simulations

Molecular dynamic simulation is a method to make a model protein and the CABS-flex is a tool to do protein modelling. In CABS-flex, the protein chain structure that required is single and continuous protein. The CABS-flex website can be accessed at (http://biocomp.chem.uw.edu.pl/CABSflex2/submit), the RMSF value and protein modelling simulation will acquire.[13]

RESULTS AND DISCUSSION

Ligand and protein preparation

Maraniol (CID: 66595) and fucoxanthin (CID: 5281239) are the compound in algae *K. alvarezii* which were download from PubChem. Then, ribociclib (CID: 44631912) that usually use as a drug of a cancer therapy were dock with NIK kinase protein (PDB ID: 4DN5). Maraniol, fucoxanthin and ribociclib were downloaded from PubChem website with 3D SDF format. Subsequently, the compounds were opened in Discovery Studio and saved in PDB extension. The NIK kinase protein with PDB code 4DN5 was downloaded from protein data bank website (https://www.rcsb.org/structure/) and opened in Discovery Studio application. In Discovery Studio application, the water and original ligand were removed from the protein and the protein saved in PDB extension. Table 1 described the compounds and protein that were docked with PyRx application.

NF-κB-inducing kinase (NIK) protein regulates some physiological processes, including immune cell function, inflammation and cell death. The extreme amounts of NIK kinase can cause autoimmune disorders, tumors or cancer. NIK kinase protein has two signal pathway, which were classical and alternative pathway that regulates some disease, and NIK kinase has been studied as a key component of the alternative NIK pathway and connected to various diseases.[8] NIK kinase protein contributed in proliferation and metastases of breast cancer, and in previous research NIK kinase protein showed a good interaction with active compound such as Curcumin, Hesperidin, Hesperetin and many more.[5]

The 3dligandsite website was used to analyze the pocket binding of the NF-κB-inducing kinase (NIK) protein. The binding site of the NF-κB-inducing kinase (NIK) protein is located at Arginine number 405, Leusin number 406, Glysine number 407, Arginine number 408, Serine number 410, and Phenilalanine number 411. Figure xx explained the binding site of NF-κB-inducing kinase (NIK) protein and used in docking method.

Pharmacokinetics and druglikeness properties

The pharmacokinetics and drug-likeness properties of Maraniol were conducted with the SwissADME web tool (http://www.swissadme.ch/index.php). The analysis resulted in the molecular weight, Log P-value, number of hydrogen bonds, hydrogen acceptors. And also, the solubility in water, the pharmacokinetics, and the Lipinski Rule of Five. Table 2 explained the result of physicochemical properties of maraniol from algae *K. alvarezii.* and Table 3 described the lipophilicity, water solubility, pharmacokinetics, and druglikeness of maraniol, fucoxanthin and ribociclib as a standard.

The lipophilicity of compounds could be measure with computation method between n-octanol and water. The water solubility value is very important for identification of the formulation of the drug, if the quantity of the water solubility of the drug is adequate, the active compound can deliver greatly in small capacity. Pharmacokinetics method in this research was used to evaluate the ADME performance of the drug candidate. Maraniol has the high value of gastrointestinal absorption and has a blood brain-barrier, meaning that Maraniol has a neurological side effect. Meanwhile, fucoxanthin has a low gastrointestinal absorption and has no blood brain barrier. Then, Ribociclib was used as a standard because it has an activity as a breast cancer drug.[11] Log Kp value was used to determine the skin permeation of the drugs taken in transdermal system. The lower of the log Kp (in cm/s) value means the less skin permeant of the molecule. It means, Maraniol and Ribociclib have a good skin permeation *via* transdermal system. Then, the Lipinski Rule of Five was used to estimate the chemical bond characteristics of a drug molecule. The Lipinski Rule had 0 violation result in Swiss ADME website, which means Maraniol and Ribociclib can consume via oral or transdermal system.[9,15–17] Antineoplastic is a drug that used as a chemotherapy treatment for cancer or solid tumor that consists of one chemical substances or in combination.[18]

Table 1: List of compounds that were docked with NIK kinase protein.

Compounds	Types	PDB ID
Ribociclib	Positive Control	4DN5
Maraniol	Flavonoid Derivative	4DN5
Fucoxanthin	Epoxycarotenol	4DN5

Table 2: The physicochemical properties of Maraniol, Fucoxanthin and Ribociclib.

Compounds	Physicochemical Properties				
	Formula	Molecular Weight (g/mol)	Hydrogen Bond Donors	Hydrogen Bond Acceptors	Number of Heavy Atoms
Maraniol	$C_{12}H_{12}O_3$	204.22	0	3	10
Fucoxanthin	$C_{42}H_{58}O_6$	658.91	2	6	0
Ribociclib	$C_{23}H_{30}N_8O$	434.54	2	5	15

Table 3: The pharmacokinetics and druglikeness of Maraniol, Fucoxanthin and Ribociclib.

Compounds	Lipophilicity	Water Solubility	Pharmacokinetics			Druglikeness
	Log $P_{o/w}$	Solubility (mol/L)	GI Absorption	Blood Brain Barrier	Log Kp (Skin permeation (cm/s))	Lipinski Rule
Maraniol	2.54	7.96e-04	High	Yes	-5.71	Yes, 0 violation
Fucoxanthin	7.51	1.26e-06	Low	No	-4.60	No, 2 violations
Ribociclib	2.00	3.06e-06	High	No	-7.40	Yes, 0 violation

Table 4: QSAR analysis result with PASS server website.

Ligand	Protein Kinase Inhibitor	Cancer Probability Activity
Maraniol	Yes	Breast cancer, cervical cancer, renal cancer, and small cell lung cancer (antineoplastic)
Fucoxanthin	Yes	Antineoplastic
Ribociclib	Yes	Antineoplastic

Table 5: Toxtree toxicity analysis of Maraniol, Fucoxanthin and Ribociclib.

Compound Name	The Crammer Rules	Carcinogenecity	Mutagenecity	Skin Corossion
Maraniol	High (Class III)	Negative for nongenotoxic carcinogenicity	Structural alert for *S. typhimurium*	Corrosive to skin
Fucoxanthin	High (Class III)	Negative for nongenotoxic carcinogenicity	Structural alert for *S. typhimurium*	Not corrosive to skin

Table 6: Molecular docking result.

Compound	Protein Target	Binding energy (kcal/mol)	RMSD (Å)
Ribociclib	NIK kinase	-7.4	0
Maraniol	NIK kinase	-7.5	0
Fucoxanthin	NIK kinase	-6.4	0

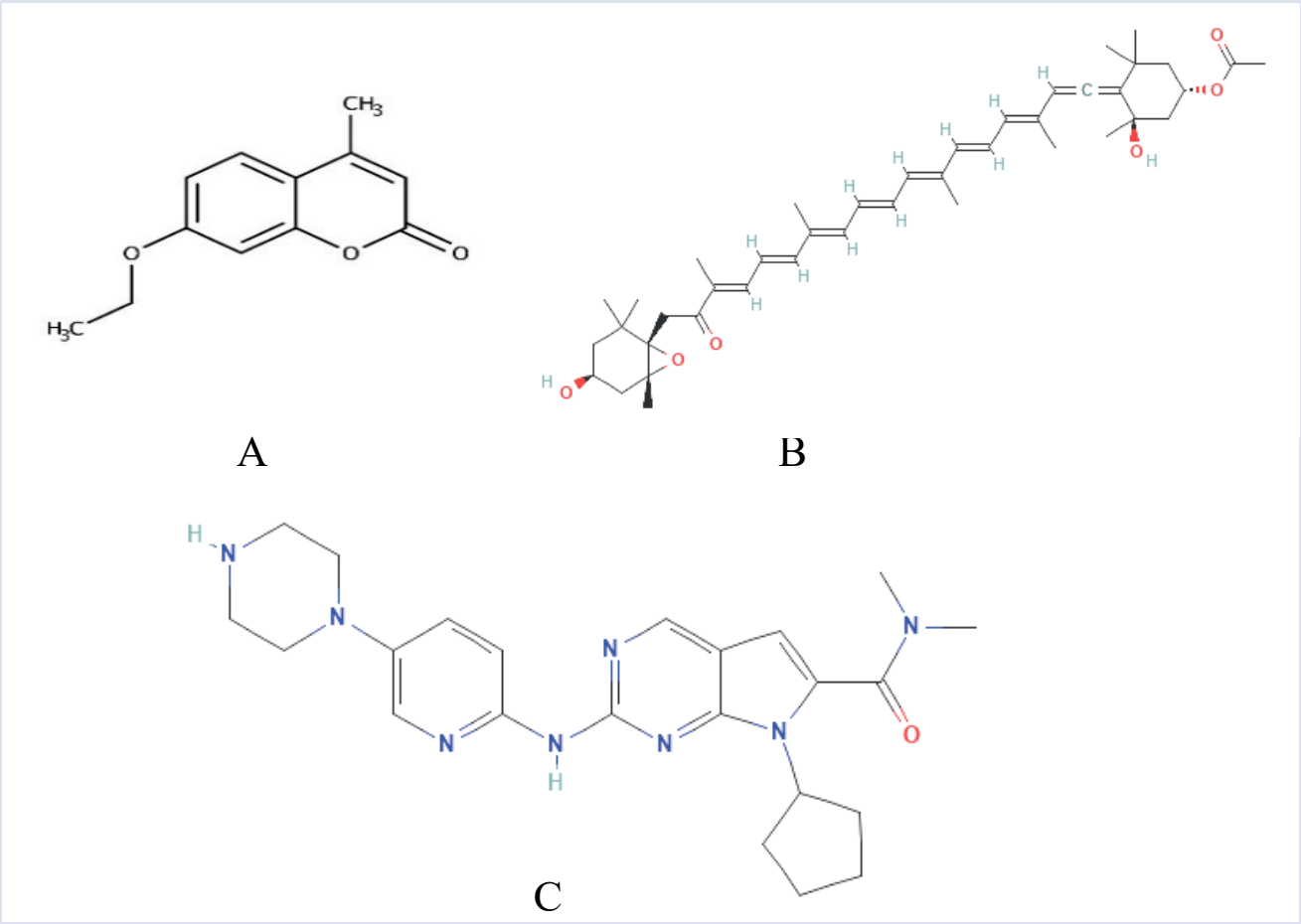

Figure 1: The structure of A. Maraniol, B. Fucoxanthin, C. Ribociclib.

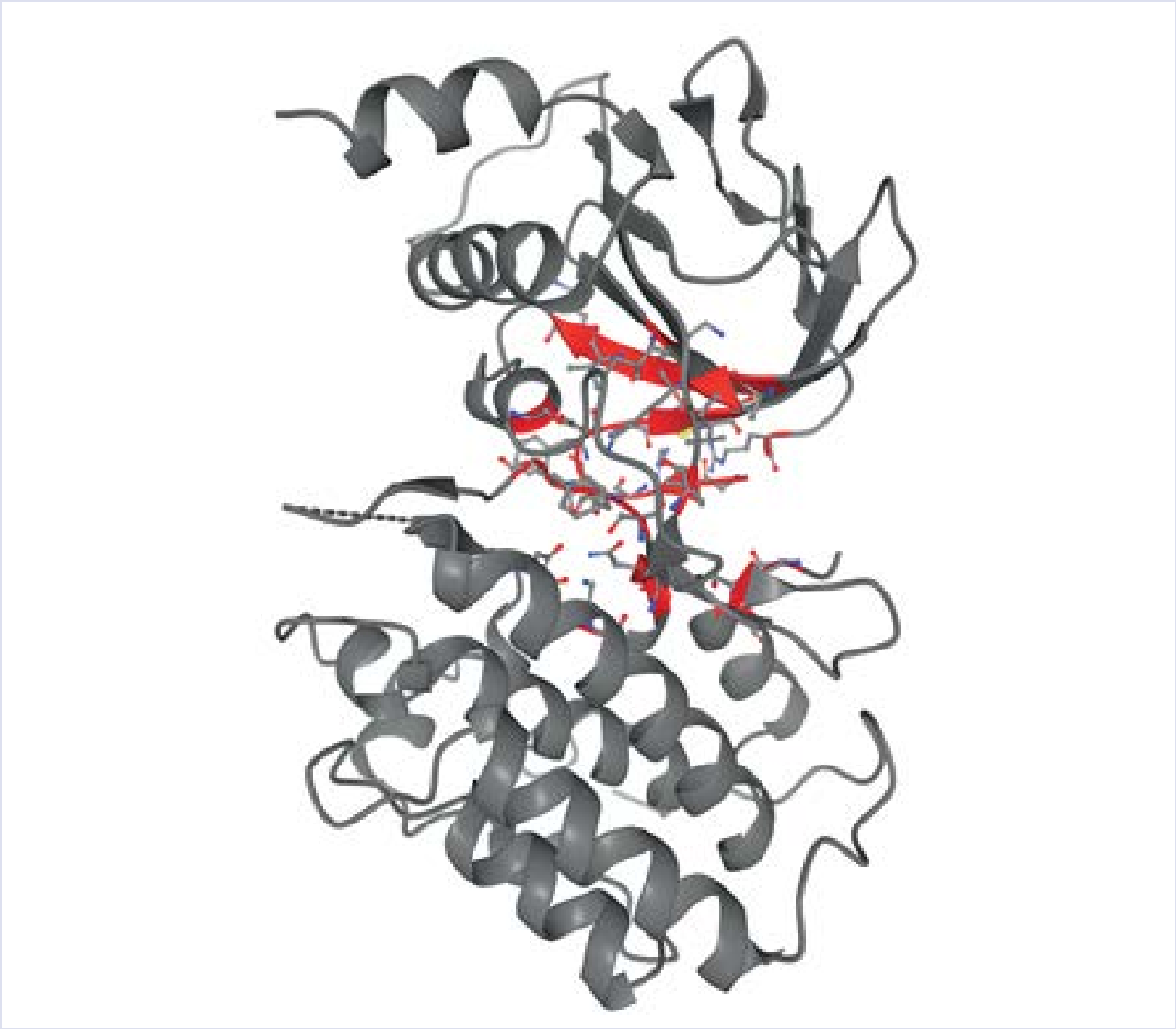

Figure 2: The binding site of the NIK kinase protein was coloured in red.

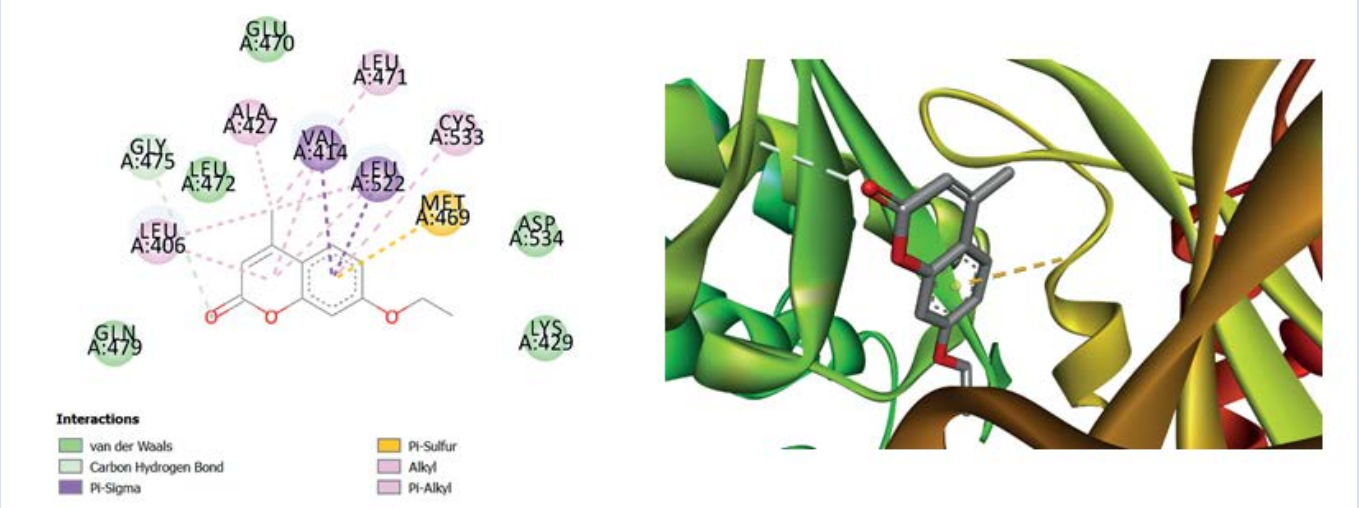

Figure 3: 2D and 3D images of molecular docking result between maraniol and 4DN5.

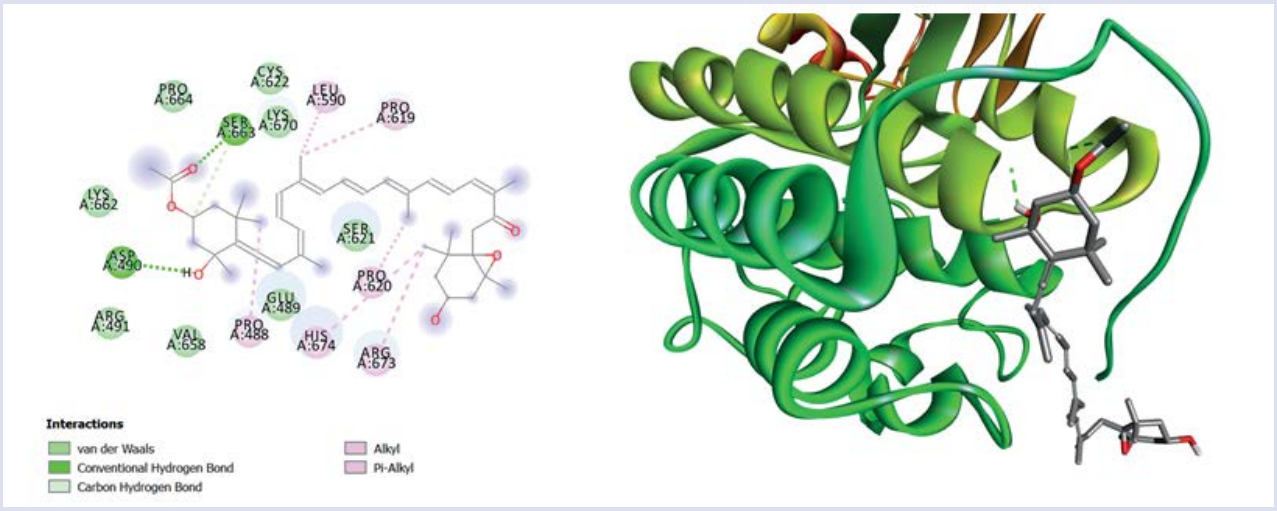

Figure 4: 2D and 3D images of molecular docking result between fucoxanthin and 4DN5.

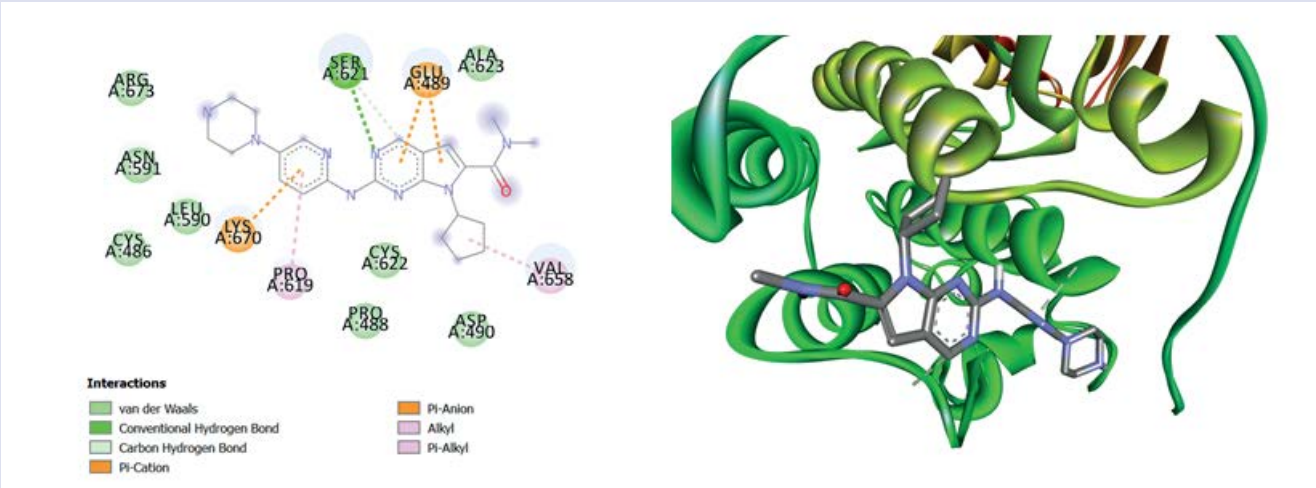

Figure 5: 2D and 3D images of molecular docking result between ribociclib and 4DN5.

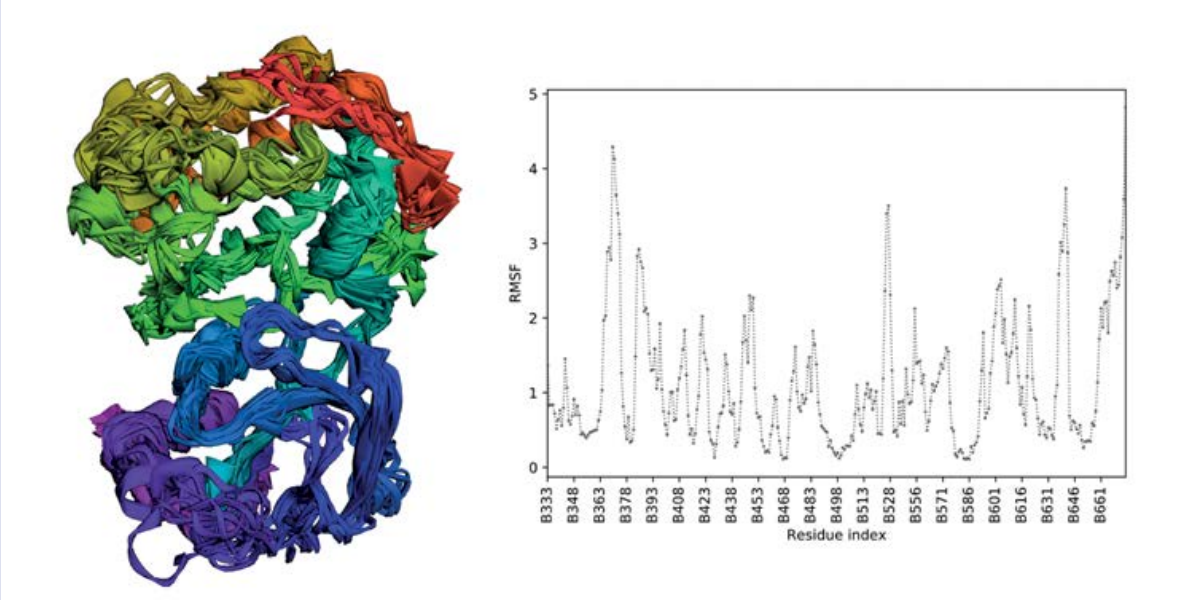

Figure 6: A. The three-dimensional of NIK kinase (PDB ID: 4DN5); B. The RMSF value of NIK kinase protein.

QSAR Analysis and toxtree analysis result

Maraniol, fucoxanthin, and also ribociclib were observed with the PASS server website and resulted in Table 4. Maraniol has an activity with many cancer diseases, such as breast cancer, cervical cancer, renal cancer and small cell lung cancer with Antineoplastic types. Maraniol has a probability active with transcription factor NF kappa B inhibitor. And also, fucoxanthin has a protein kinase inhibitor from the PASS server website, this is evidenced by research conducted by Zhao *et al.*, 2017 that fucoxanthin also has activity as a protein kinase inhibitor.[19]

Molecular docking analysis

Maraniol and fucoxanthin were the compound found in algae *K. alvarezii* and used as a ligand in the molecular docking method. In this research, molecular docking was conducted with PyRx application software. NIK kinase protein was opened in PyRx and defined as macromolecules. Maraniol was opened and the energy was minimized with the OpenBabel menu option in PyRx software. Then, the grid box was setted into X= -26.284, Y= 12.5976, Z= 58.9679 with dimensions was set by X= 25.000 Å, Y= 25.000 Å, Z= 25.000 Å. Table 4 explained the result of energy binding between maraniol and fucoxanthin in algae *K. alvarezii* and the NIK kinase protein. Maraniol had a lower energy binding than ribociclib, which mean the maraniol has the higher capability to attach with NIK kinase and resulted in a high stable of complex.[20] Maraniol are the flavonoid derivative compound and have a chromone group which the formula $C_9H_6O_2$. Chromone group or chromone derivative has a good interaction with breast cancer protein because chromone group could modulate the transportation efficiently.[21]

Ribociclib was used as a control positive in this molecular docking research, because ribociclib is used as a breast cancer drug.[22] Hydrogen bond interaction between the compound and NIK kinase protein in molecular docking method is very important. Because of hydrogend bond interaction showed the specificity between receptor and the drug. Hydrophobicity and another polar interaction is very useful to determine the specificity of drug and protein interaction. Because of that, the drug candidate has to have the equitability between the hydrogen bond interaction and another interaction to make a good solubility and lipophilicity.[23]

Molecular dynamic simulation result with CABS-flex

The molecular dynamic simulation was conducted with the CABS-flex web tool and it is commonly used for protein modeling. From the analysis of protein modeling with the CABS-flex web tool, NIK kinase protein had a variety of RMSF results from 1-3 Å which is the same as the RMSF criteria that has value 1-3 Å.[24]

CONCLUSION

Breast cancer is caused by unregulated cell growth and has a high death rate. Many researchers are working to develop treatments that are effective, efficient, safe and available to everyone. One method is to use secondary metabolite chemicals found in plants. The effects of secondary metabolites in K. *alvarezii* confirmed that maraniol had greater pharmacokinetics and drug-likeness than fucoxanthin. Besides that, QSAR analysis revealed that maraniol has a diverse variety of anti-cancer properties, not only in breast cancer but also in a variation of certain other cancers. Because it possesses a chromone group, the test results reveal that maraniol has a pretty high effectiveness as an anti-breast cancer agent, with a binding energy of -7.5 kcal/mol.

DISCLOSURE STATEMENT

The authors have declared that no competing interests exist.

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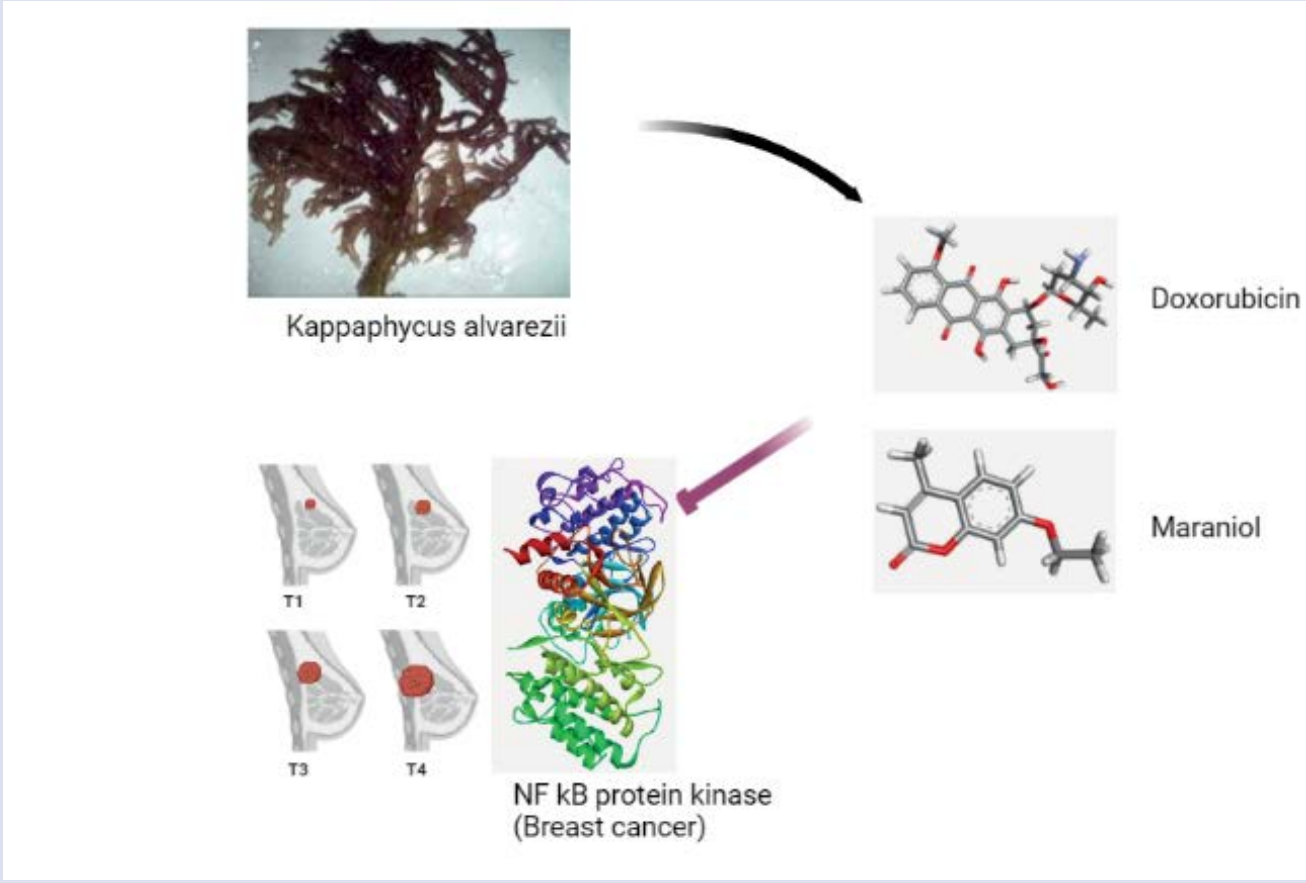
GRAPHICAL ABSTRACT



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Alyaa Farrah Dibha has completed her bachelor's degree program at Brawijaya University, Malang, Indonesia majoring in chemistry. Currently, she is studying for her master program at Brawijaya University, Malang, Indonesia majoring in chemistry. Her research project is focused on natural product organic chemistry and anything related to molecular docking projects.

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Rahadian Zainul has completed a Bachelor of Educational Chemistry in IKIP Padang, then continued his studies and obtained a Master of Chemistry at Universitas Andalas, and earned a Doctoral Chemistry degree at Universitas Andalas. He is a researcher on the design and modification of copper oxide for inactivation SARS-CoV-2 by stimulated indoor lights and a researcher on the design and modification of copper oxide by computation approach with DFTB+. He is also the Head of Cambiotics Research Center, Universitas Negeri Padang. The author has published 41 manuscripts in Scopus-indexed journals and also 8 h-index.

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