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ANTI-BREAST CANCER BIOACTIVE COMPOUNDS AND IN-SILICO MOLECULAR PREDICTION OF *Crassostrea angulata* (Lamarck, 1819)

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Abstract

Breast cancer is the second leading cause of death in Indonesia. Bioprospecting bioactive compounds from marine organisms is expected to be one of the solutions for breast cancer prevention. *Crassostrea angulata* is one of the species of sea oysters that is commonly consumed, and it has an ethnomedical history among Indonesian people for decades. The aim of this study is to use in silico analysis to find out how well bioactive compounds from *C. angulata* methanol extract can fight breast cancer. To find compounds that work in *C. angulata*, LC-HRMS and a molecular docking method that mixed KNApSAcK, CLC-Pred, SEA, STRING, PubChem, UniProt, PyMOL, PyRx, and PoseView were used. The result showed at least 12 active anti-cancer compounds in *C. angulata*, but only 2 of them are anti-breast cancer compounds (Flufenamic Acid, FA, and Hymenamide C, HC). Molecular docking results showed a strong binding affinity between the active compound Flufenamic Acid (FA) with its breast cancer target proteins (CSF1R, PLK4, MKNK2, and ABL1) and the Hymenamide-C (HC) compound with its breast cancer target proteins (GRB2 and OXTR). FA bioactive compounds also showed lower RMSD values (close to 0 Å) with native ligands for each target protein. FA has the potential to be a better anti-breast cancer compound than HC. However, these two compounds still hold potential as inhibitors of breast cancer target proteins, and further research on marine bio-natural products for human use is necessary.

Keywords: bioprospecting, molecular docking, oyster, protein, secondary metabolites

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Prediksi senyawa bioaktif antikanker payudara dan molekuler *in-silico Crassostrea angulata* (Lamarck, 1819)

Abstrak

Kanker payudara merupakan penyebab kematian kedua terbanyak di Indonesia. Bioprospeksi senyawa bioaktif dari organisme laut diharapkan dapat menjadi salah satu solusi pencegahan kanker payudara. *Crassostrea angulata* merupakan salah satu spesies tiram laut yang biasa dikonsumsi dan memiliki sejarah etnomedik di kalangan masyarakat Indonesia. Penelitian ini bertujuan untuk mengevaluasi potensi senyawa bioaktif antikanker dari ekstrak metanol *C. angulata* menggunakan analisis *in-silico*. Identifikasi senyawa aktif *C. angulata* menggunakan LC-HRMS melalui pendekatan *molecular docking* dengan mengombinasikan program-program KNApSAcK, CLC-Pred, SEA, STRING, PubChem, UniProt, PyMOL, PyRx, and PoseView. Hasil penelitian menunjukkan 12 senyawa aktif antikanker pada *C. angulata*, namun hanya 2 senyawa antikanker payudara (*Flufenamic Acid*, FA dan *Hymenamide C*, HC). Hasil *molecular docking* menunjukkan bahwa *binding affinity* yang kuat antara senyawa aktif FA dengan protein target kanker payudara (CSF1R, PLK4, MKNK2, dan ABL1) dan senyawa HC dengan protein target kanker payudara (GRB2 dan OXTR). Senyawa bioaktif FA menunjukkan nilai RMSD yang lebih rendah (mendekati 0Å) dengan ligan asli dari masing-masing protein target. FA memiliki potensi sebagai senyawa antikanker payudara yang lebih baik dari HC. Senyawa FA dan HC berpotensi sebagai penghambat protein target kanker payudara, namun masih memerlukan penelitian lebih lanjut terutama untuk penggunaan senyawa tersebut pada manusia.

Kata kunci: bioprospeksi, metabolit sekunder, molecular docking, protein, tiram

INTRODUCTION

Cancer is one of the most common causes of patient death in hospitals (Wu *et al*., 2012). Cancer is characterized by abnormal cellular growth that leads to malignancy (Maharani, 2012). The number of cancer cases in Indonesia is 136.2 per 100,000 people (Budhy 2019). The Global Cancer Observatory (2020) fact sheet of the International Agency for Research on Cancer (IARC) WHO showed that the number of new cancer cases in the world in 2020 was 19,292,789 cases, 11.7% (2,261,419 cases) of which were breast cancer cases. Breast cancer is the most common cancer in Indonesia and the second leading cause of death worldwide (Suryani, 2020). WHO stated that 8-9% of women have breast cancer, which is comparable to that of cervical cancer. WHO stated that approximately 0.5–1% of breast cancers occur in men. The American Cancer Society's estimates for breast cancer in the United States for 2024 are 310,720 new cases of invasive breast cancer diagnosed in women. The American Cancer Society estimates for breast cancer in men in the United States for 2024 are approximately 2,790 new cases of invasive breast cancer diagnosed, and approximately 530 men will die from breast cancer.

Indonesia is a country with abundant natural resources (Haryanto, 2015), one of which is oysters (Haeruddin *et al*., 2022; Handayani & Syahputra, 2017). Ministry of Marine Affairs and Fisheries of the Republic of Indonesia (2023) showed that *Crassostrea angulate* is one of Indonesia's trending coastal biodiversity commodities for the export market. *Indonesian coastal waters widely distribute C. angulate.* The unique habitat for this Portuguese oyster is the Ngambur estuarine water in Pesisir Barat Regency, Lampung, Indonesia. The Portuguese oyster has been explored and exploited by local people for many purposes, such as consumption, aesthetics, other daily, and even ethnomedical use for decades (Qurani *et al*., 2020; Yulianda, 2020). Therefore, there is a lack of information on bioactive compounds related to their ethnomedical use.

Wu *et al. (2012)* and Ayodele *et al.* (2023) said that a new idea called "clinical medicine systems" needs to be introduced so that bioactive compound information can be better explored. According to this concept, a better exploration of Portuguese oysters will connect with various research fields, such as biological systems, clinical science, omics-based technologies, bioinformatics,

and computational science, to improve diagnosis, therapy, and prognosis of diseases, including those involving bioactive anticancer compounds. Bioinformatics is a combination of biology and information engineering. In general, bioinformatics refers to the use of computer technology and analysis software to store and display biological data, supported by internet availability (Fatchiyah, 2015). Bioinformatics provides an integrative analysis of cost-effectiveness. One of the research methods that use the concept of databases and applications contained in bioinformatics is the in-silico method (Pannindriya *et al.*, 2021).

Research using computers or computer simulations is known as in silico (Khaerunnisa *et al.*, 2020). In-silico testing often finds new drug compounds that improve the activity of the parent compound (Hardjono, 2013). The in-silico method that is often used is the molecular docking method (Diana *et al.*, 2024). Using this method, we can guess whether the active compounds found in certain organisms could be used to fight cancer by comparing them to compounds that are already known to fight cancer (Yusransyah *et al.*, 2016; Ayodele *et al.*, 2023). These things might help with the research goals, like finding and testing bioactive compounds that could help fight breast cancer and studying how these compounds work at the molecular level. We discovered these compounds in *C. angulata* in Ngambur, Pesisir Barat Regency, Indonesia. The goal of this study is to use in silico analysis to find out how well bioactive compounds from *C. angulata* methanol extract can fight breast cancer. The result may propose specific compounds for further research on potential marine bio-natural products for human use.

MATERIALS AND METHODS

Sample Collection

C. angulata were collected from the Ngambur coastal waters from July to October 2019 (Figure 1). The C. angulata was taken using tools (mask, snorkel, fins, ziplock, and knife) and then placed into ziplocks. The ziplocks were stored in a cool box containing ice cubes and not directly exposed to sunlight. The samples were then transported to the Oceanography Laboratory, Department of Fisheries and Marine Sciences, Faculty of Agriculture, University of Lampung.

C. angulata Extraction

Extraction of *C. angulata* refers to research (Cahyaningrum *et al.*, 2015; Handayani *et al.*, 2016; Verdiana *et al.*, 2018). The 500 g of *C. angulata* sample was cut into small pieces, 500 mL of 96% methanol was added, and then crushed in a blender for 5 min. *C. angulata* slurry was transferred to a 3 L glass jar macerator, and then 96% methanol was added as much as 1.5 L. After two days of *C. angulata* soaking, sonication was carried out using an ultrasonic bath at 40 kHz for 60

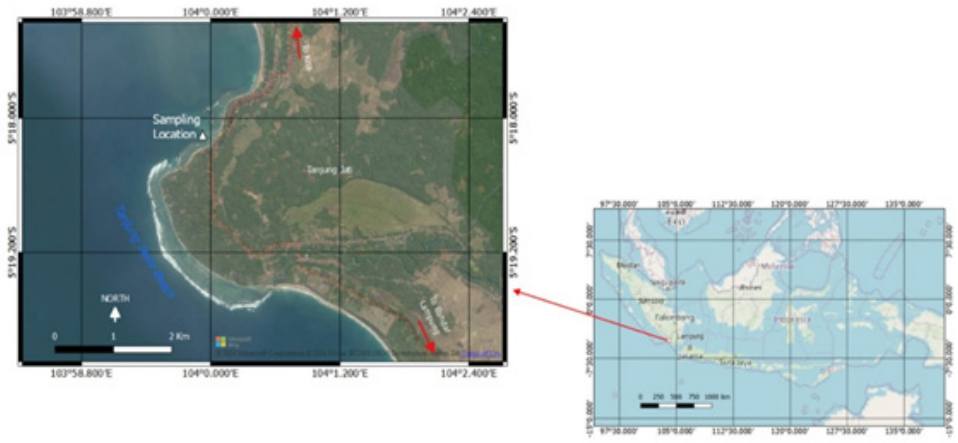

Figure 1 Sampling location of *C. angulata*
Gambar 1 Lokasi pengambilan *C. angulata*

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minutes and then filtered using Whatman No. 1 filter paper. Furthermore, the sample extract filtrate was evaporated using a rotary vacuum evaporator at a temperature of 35-400°C until the crude extract was obtained and poured into a 250 mL vial bottle. The crude extract was weighed and then the yield was calculated.

Characterization of Active Compounds in *C. angulata*

Isolation of active compounds is carried out in two stages, namely data mining and chromatographic analysis using LC-HRMS. IPB University's Advanced Research Laboratory carried out the LC-HRMS analysis. In silico analysis supervised by the Indonesian Institute of Bioinformatics (INBIO). Data mining for active C. angulata compounds is done by accessing the database from the KNApSAcK site. Afendi et al. (2012) say that the KNApSAcK site is a database project that lets you look at mass spectrum data sets and get information about metabolites by entering their names, the names of the compounds that make them up, their molecular weights, or their molecular formulas.

Evaluation of *C. angulata* Potential Compounds

The stage in evaluating the potential of compounds is the screening of compound activity using the CLC-Pred program. There is a website called CLC-Pred that lets you use structural formulas to guess how chemicals will kill nontransformed cells and cancer cells. CLC-Pred predicts how harmful a chemical compound will be to cells so that researchers can decide if it should be included in experiments (Lagunin *et al.*, 2018). The research used an experimental quantitative approach. In experimental research, one or more independent variables are changed while other relevant variables stay the same. Then, the researchers watch how the changes affect the dependent variable (Rukminingsih *et al.*, 2020).

Target Protein Prediction

In the target prediction method, SEA Search Server was used. SEA Search Server is such a program for linking proteins based on chemical similarities between ligands. As Ayodele *et al.* (2023) and Keiser *et al.* (2007) say, the ligand's off-target activity can be used to test the expected and unexpected similarities that SEA finds. Furthermore, protein-protein interaction analysis was carried out using STRING, which aims to find out how the interaction between proteins occurs on several targets that have been obtained.

Molecular Docking

Ramadhani *et al.* (2021) and Ayodele *et al.* (2023) both said that molecular docking has three steps: preparing the ligand, preparing the receptor, and docking the molecules. Ligand preparation was performed by searching the 3D structure of chemical compounds using PubChem. Compounds obtained from the results of LC-HRMS analysis were written in the search engine at the PubChem site. The 3D conformation file of the compound has been downloaded in sdf format. Receptor preparation began with protein screening by downloading a 3D target protein file using the UniProt database. UniProt is a protein database that contains amino acid sequences, motifs, domains, functions, mutations, and 3D structural information about proteins. The protein target is downloaded in .pdb format. Then the target protein file is opened in PyMOL software to remove the water molecule, and the native ligand is taken. The native ligand was selected and saved in .pdb format as a control ligand for the docking process. The.pdb format stores the target protein as a receptor. The molecular docking process was performed using PyRx 0.8 software by selecting the Vina Wizard feature. The molecular tethering process is done by inputting the target protein or receptor and the target ligand. Then the binding side is determined by adjusting the position of the grid box. Analysis of the molecular tethering results is done by selecting the ligand conformation that has the lowest binding affinity. The ligand-receptor complex formed is visualized with the help of PyMOL software and the PoseView site.

The docking results were visualized by overlaying ligand-ligand and ligand-receptor. Visualization was performed using PyMOL

software. The ligand-ligand overlay shows the RMSD value and where the atoms are on the ligand based on the docking result with ligand control (LC). RMSD shows the comparison of the docking result ligand conformation with LC conformation. The ligand-ligand overlay combines the drug candidate compound and the native ligand into a single graphical display for easy comparison. This is done by obtaining the superposition or stacking of two or more molecular structures so that the compounds are located in the same position in three-dimensional space (Saputri *et al*., 2016).

RESULTS AND DISCUSSION

Diversity of *C. angulata* Bioactive Compounds

The LC-HRMS test on *C. angulata* samples found 100 compounds with a retention time (RT) of less than 30 minutes. The test used a C18 column, a flow rate of 0.2 mL/min, and an injection volume of 2 µL. The LC-HRMS analysis results provide the compound name, molecular formula, molecular weight, retention time, and sample area of the detected compound. There are seven compound names (Table 1) and 57 molecular formulas identified by LC-HRMS (Figure 2). Table 2 displays the five compounds found during the KNApSAcK database search for compounds from *C. angulata*. They are Hymenin, Oroidin, 10E-Hymenialdisine, 2-Bromoaldisine, and Aldisine (Afendi *et al*., 2012). The 57 molecular formulas were then searched using the Simplified Molecular Input Line Entry System (SMILES) on the PubChem website. This found 24 compounds that could be identified by their compound name, molecular formula, and SMILES or simple compound structure notation.

Table 1 *C. angulata* compound from the KNApSAcK database
Tabel 1 Senyawa *C. angulata* dari pangkalan data KNApSAck

Maltodextrin (%)	Yield (%)
Hymenin	$C_{15}H_{18}O_4$
Oroidin	$C_{11}H_{11}Br_2N_5O$
10 E-Hymenialdisine	$C_{11}H_{10}BrN_5O_2$
2-Bromoaldisine	$C_8H_7BrN_2O_2$
Aldisine	$C_8H_8N_2O_2$

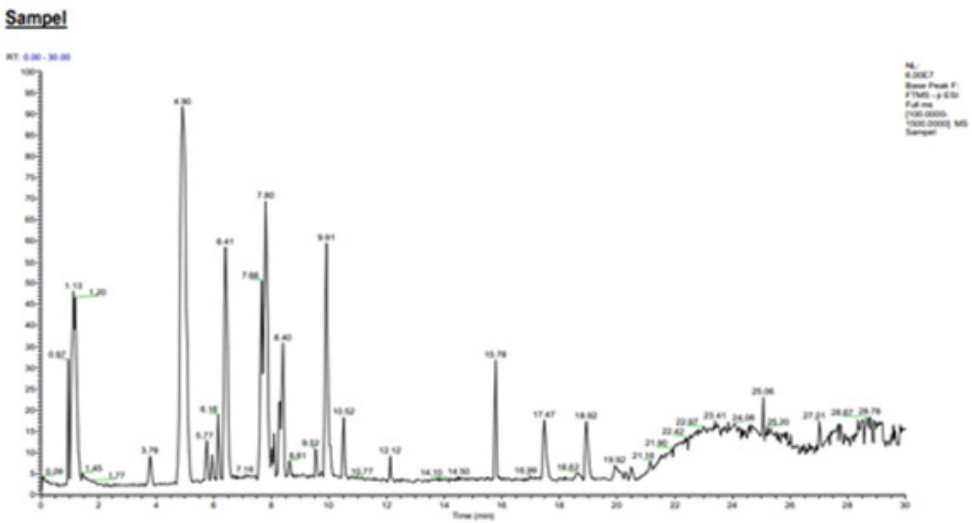

Figure 2 LC-HRMS chromatogram of *C. angulata* extract
Gambar 2 Kromatogram LC-HRMS ekstrak *C. angulata*

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Potential *C. angulata* Compounds

As part of the search for possible compounds, the anticancer activity of the 24 compounds was predicted using the CLC-Pred site. Twelve of the compounds were already known to have anticancer activity. Furthermore, target protein screening was carried out on the 12 compounds using the SEA Search Server (SEA) site and produced 388 target proteins. Then, a search for breast cancer target proteins from the Therapeutic Target Database (TTD) with the keyword "breast cancer" was conducted, and 60 target proteins were found. The screening results from SEA and TTD were compared using the Venny 2.1.0 software. This showed that 8 target proteins were linked to 5 compounds (Table 2).

SEA displays the *p*-value and MaxTC. These numbers are used together to guess how biologically active the tested compound might be against the protein target. Additionally, the compound is more likely to have biological activity against the protein target if the *p*-value is smaller and the MaxTC value is higher. The *p*-value is the probability that the similarity between the protein target and the chemical compound found is random or the probability that the similarity is not statistically significant. The smaller the *p*-value, the more significant the similarity between the protein target and the chemical compound. MaxTC is a way to find out how similar a compound's molecular structure is to a reference molecular structure that is linked to biological activity. Tanimoto Coefficient (TC) values range from 0 to 1 (Keiser *et al.*, 2007).

Breast Cancer Protein Interactions

Protein-protein interaction (PPI) analysis using the Search Tool for Retrieval of Interacting Genes/Proteins (STRING) website on 388 target proteins (nodes) resulted in 2426 interactions (edges) with PPI enrichment *p*-value < 1.0e-16 shown in Table 3. The expected number of edges represents the number that would result from randomly selecting the nodes. A small PPI enrichment *p*-value indicates that the nodes are not random and the number of edges observed is significant. The nodes on the graph represent the protein itself, while the edges of the graph represent the interactions. An edge connecting two nodes indicates the presence of an interaction between the two proteins (Faroby *et al.*, 2022). By understanding a protein's position in a PPI network, we can use PPI to define its function. Identification of significant proteins can be useful in various studies, one of which is for the discovery of new drugs (Abdullah *et al.*, 2022).

The results of the protein-protein interactions (PPI) analysis of the 388 target proteins based on functional enrichment

Table 2 *C. angulata* compounds associated with breast cancer target proteins from SEA search server

Tabel 2 Senyawa *C. angulata* yang berhubungan dengan target protein kanker payudara dari SEA *search server*

Bioactive compound	Target protein	*p*-value	MaxTC
Hymenin	ERN1	1.702×10^{-6}	0.41
	MAP4K2	3.303×10^{-9}	0.50
	CSF1R	1.325×10^{-8}	0.49
Oroidin	SETD7	2.72×10^{-9}	0.29
	PLK4	1.40×10^{-5}	0.45
	MKNK2	3.42×10^{-3}	0.45
10 E-Hymenialdisine	BRS3	1.02×10^{-6}	0.36
2-Bromoaldisine	GSR	2.00×10^{-6}	0.38
Aldisine	GSR	4.44×10^{-13}	0.36

show that there are 50 nodes (proteins) and 137 edges that interact with each other and are involved in various biological processes related to breast cancer. The study looks at three things: KEGG pathways (for breast cancer), WikiPathways (for integrated breast cancer pathways), and tissue expression (for breast cancer cells and breasts). The 50 target proteins belong to 6 compounds. The PPI enrichment p-value in STRING shows how likely it is that a protein interaction will happen by chance

Anti-Breast Cancer Activity

By using the CLC-Pred site, it was possible to guess that FA compounds might be able to kill breast cancer cells. The Pa value of 0.634 against the BT-549 cell line indicates this. The BT-549 cell line is a type of breast cancer known as ductal carcinoma. According to Lee *et al*. (2012), ductal carcinoma in situ (DCIS) of the breast is a complicated disease in which cancerous cells grow and show up in the breast milk ducts. The p-value for the HC compound prediction was 0.608, which means that the MDA-MB-231 cell strain is a type of adenocarcinoma breast cancer. An adenocarcinoma is a subtype of carcinoma that begins and grows in glandular cells lining the inside of an organ (LUNGevity, 2016). In CLC-Pred, the "Pa" value (probability "to be active") tells us how likely it is that the compound will kill cancer cells. The higher the Pa value, the more likely it is that the compound will kill cancer cells (Lagunin *et al*., 2018). The expected results for breast cancer activity showed two possible active compounds: Hymenamide C (HC) and Flufenamic Acid (FA). FA is characterized by a Pa value of 0.634, a cell line (BT-549), and breast tissue. HC is characterized by a Pa value of 0.608, along with the cell line MDA-MB-231 and breast tissue.

Screening results through SEA found 5 breast cancer target proteins for FA compounds, while STRING-DB found 42 target proteins. Then 3 target proteins were selected from these results to be tested, with consideration based on the availability of native ligands in the target protein. Furthermore, for the compound HC, 1 target protein was found from SEA and 4 target proteins from STRING-DB. Then, 3 target proteins were selected for testing, with the same considerations as for the FA compound. Table 3 presents the breast cancer target proteins for both compounds.

Molecular Docking

Molecular docking was performed on FA and HC compounds using PyMOL and PyRx software. The compounds were docked as ligands with target proteins as receptors and native ligands as ligand control (LC). A native ligand is a crystallographic compound or ligand bound to a receptor, according to experimental results. The position of the grid box adjusts the conformation of the ligand and receptor. The docking result showed the binding affinity value between the compound and the protein. To validate the docking process, dock RMSD is used to get the RMSD (Root Mean Square Deviation) value, and

Table 3 Selected breast cancer target proteins
Tabel 3 Protein target kanker payudara terpilih

Compounds	Target protein	Description	p-value	MaxTC
Hymenin	CSF1R	Macrophage colony-stimulating factor 1 receptor	1.33×10^{-8}	0.49
	PLK4	Serine/threonine-protein kinase PLK4	1.40×10^{-5}	0.45
	MKNK2	MAP kinase-interacting serine/ threonine-protein kinase 2	3.42×10^{-3}	0.45
Aldisine	ABL1	Tyrosine-protein kinase ABL1	6.14×10^{-3}	0.49
	GRB2	Growth factor receptor-bound protein 2	5.79×10^{-27}	0.38
	OXTR	Oxytocin receptor	1.53×10^{-11}	0.51

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PyMOL and PoseView are used to show the docking results. Grid box in docking was a 3D area defined around the receptor that wants to be docked based on x, y, and z coordinates (Sari *et al.*, 2020). A study by Huda *et al.* (2020) used a grid box to find the shape or center coordinate value of the protein that the ligand would most likely bind to. This helped to narrow the search. Table 4 displays the coordinates of docking positioning using the grid box.

These FA compounds had binding strengths of -8.4, -8.8, -8.4, and -10 kcal/mol for the target proteins 7MFC (1), 4JXF (2), 6CK3 (3), and 2FO0 (4), in that order. When the FA compounds were docked to the LC of each target protein, the RMSD values were 0.327, 1.49, and 2.47, in that order. It was able to bind to 2AOA (5) and 6TPK (6) proteins with binding strengths of -7.9 and -10.4 kcal/mol. It also had RMSD values of 3.16 Å and 10.92 Å against the LC of the target proteins. In RMSD, there were two parts: the structure that was tested and the structure that was docked or predicted. The difference in atomic position between the two parts was looked at. If the RMSD value is less than 2.0 Å, it means that the position of the ligand closely matches its original conformation (Suvannang *et al.*, 2011). Table 5 presented molecular docking compounds and breast cancer target proteins.

Visualization of Molecular Docking Results

The ligand-receptor overlay shows the "ligand-receptor complex" and where the binding site is located based on the docking point found by adjusting the grid box. The ligand appears in pink in the ligand-ligand overlay image, while the LC appears in blue. In the ligand-receptor overlay image, the ligand is shown in pink, while the receptor is shown in teal. Table 6 displays the docking results and visual overlay.

PoseView visualizations revealed molecular mechanisms by illustrating compound interactions with amino acids. It was possible to see how ligands interact

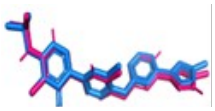
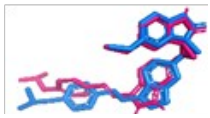
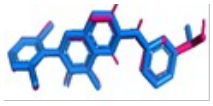
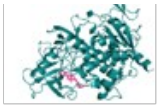
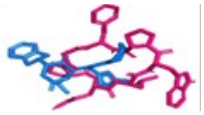
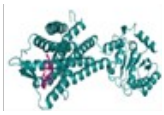
Table 4 Grid box for target protein
Tabel 4 *Grid box* protein target

Target protein	Grid box (Å)					
	Center			Dimension		
	X	Y	Z	X	Y	Z
7MFC	26.793	-13.2918	-17.0384	23.0762	10.7297	11.9035
4JXF	27.2884	-23.4199	-48.9334	17.6885	18.4088	14.4029
6CK3	50.2124	-19.9832	-0.4820	10.7716	16.8615	12.3174
2FO0	0.0804	12.3194	17.4618	15.9552	13.0792	18.2068
2AOA	43.5107	16.4160	6.7961	19.6064	20.5213	19.4319
6TPK	-8.2148	-0.2268	124.8194	14.3534	16.8044	21.9681

Table 5 Molecular docking of breast cancer target compounds and proteins
Tabel 5 Penambatan molekuler protein dan senyawa target kanker payudara

Compounds	Target protein	Docking result
23.0762	CSF1R (PDB: 7MFC)	11.9035
	PLK4 (PDB: 4JXF)	14.4029
	MKNK2 (PDB: 6CK3)	12.3174
	ABL1 (PDB: 2FO0)	18.2068
14.3534	GRB2 (PDB: 2AOA)	19.4319
	OXTR (PDB: 6TPK)	21.9681

Table 6 Docking and overlay results of ligan and receptor protein
Tabel 6 Hasil penambatan dan penumpukan protein ligan dan reseptor

No	Overlay ligan-ligan	Overlay ligan-reseptor	RMSD (Å)	Binding Af-finity (kkal/mol)
1			0.327	-8.4
2			1.434	-8.8
3			1.49	-8.4
4			2.47	-10
5			3.16	-7.9
6			10.92	-10.4

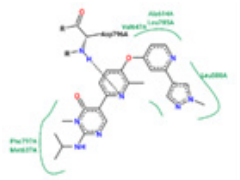
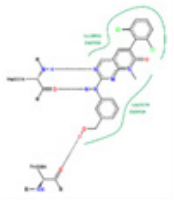
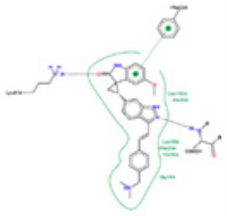
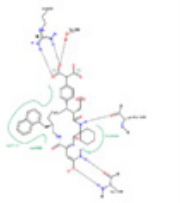
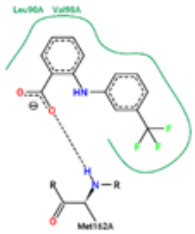
with protein residues in PoseView. This included hydrogen bonds, π-π and π-cation interactions, metal interactions, and indirect hydrophobic contacts. Black dotted lines of ligand to protein indicated hydrogen bonding and metal interactions. Green residues indicate hydrophobic interactions toward the ligand. The spline segment showed the hydrophobic contact area of the ligand. Green dashed lines indicate π-π or π-cation interactions. According to Wulandari & Hendarmin (2010) and Rena *et al.* (2022), the number of amino acids in the binding site showed where the amino acids were in the area where the protein and the ligand hooked up. Table 7 visualizes the ligand-receptor interaction using PoseView and amino acid residues.

The 7MFC receptor was one of the proteins of CSF1R. The 7MFC receptor has a natural ligand called Z6V: Vimseltinib that works as a flufenamic acid ligand docking process. Vimseltinib is a custom-made control tyrosine kinase inhibitor that gets to CSF1R and blocks it very strongly (Smith *et al.*, 2021). The 4JXF receptor was made up of the crystal structure of PLK4 kinase with 100631 as a natural ligand against it. Inhibitor 400631 is bound to PLK4 through hydrogen and van der Waals interactions. The inhibitor binds to the binding site of the kinase enzyme activity. Qiu *et al.* (2014) say that inhibitor 400631 can bind to the binding site of the PLK4 enzyme and stop it from working.

Reid *et al.* (2018) found that the F67 inhibitor can naturally connect to the 6CK3 receptor, which is a co-crystal structure of MNK2. A study by Nagar *et al.* (2006) says that the 2FO0 receptor is the crystal structure of ABL1, which is also called c-Abl. It is naturally linked to P16, which stops PD166326. Phan

http://dx.doi.org/10.17844/jphpi.v28i1.57937

Table 7 Visualization of ligand-receptor interaction with PoseView and amino acid residues
Tabel 7 Visualisasi interaksi ligan dan reseptor dengan PoseView dan residu asam amino

PoseView	Amino acid residues	PoseView	Amino acid residues
	Asp796 Phe797 Met637 Val647 Leu785 Leu588		Thr338 Met337 Leu389 Ala288 Leu267 Gly340
	Lys41 Cys92 Gly19 Leu18 Leu143 Phe23 Val26 Ala39		Arg86 Ser96 His107 Lys109 Phe108 Lys109 Leu111
	Leu90 Val98 Met162		

et al. (2005) say that the 2AOA receptor is a crystal structure that is naturally linked to the S1S inhibitor and the GRB2 SH2 domain. A study by Waldenspühl *et al.* (2020) says that the human oxytocin receptor (OXTR) has a part called the 6TPK receptor that connects to NU2 and stops OXTR from going to work.

CONCLUSIONS

At least 12 bioactive compounds found in *C. angulata* from Ngambur help fight cancer, and two of them, flufenamic acid and hymenamide C, work against breast cancer. Based on the RMSD and binding affinity values, FA from *C. angulata* collected in Ngambur shows more promise as a breast cancer treatment than HC. The utilization of FA as a potential breast cancer agent should be validated with biochemical research such as in vitro, in vivo, bioactivity, biotoxicity, and exploration of another bioactive compounds research.

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