

ORIGINAL ARTICLE

IDENTIFICATION OF COMPOUNDS IN SOURSOP LEAVES (*Annona muricata* L) AS BREAST ANTICANCER AGAINST ALFA ESTROGEN RECEPTORS BY MOLECULAR DOCKING

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Abstract The incidence of breast cancer in Indonesia is steadily rising. Women have the highest incidence of breast cancer. Acetogenins are highly effective inhibitors of mitochondrial complex I or NADH dehydrogenase, making them a promising option for therapeutic creation against breast cancer. The plant known as *Annona muricata*, also referred to as the soursop leaf plant, is purported to possess the ability to suppress the activity of breast cancer. Hence, it is imperative to assess the chemical composition of soursop leaves on receptors by docking experiments. Research utilizing the active site on the alpha estrogen receptor has determined that the *reticulín* molecule, with a free energy of -8.14 kcal/mol, is a potential contender for breast cancer therapeutic medications. Reticulin exhibits the highest affinity for binding to the active site of *estrogen receptor alpha*. This chemical exhibits the capacity to impede the growth of breast cancer.

Keywords: Soursop Leaves · Alpha Estrogen · Breast Cancer · Molecular Docking



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Introduction

Breast cancer is a malignancy that arises from the development of malignant cells in the breast tissue. These cells have the ability to develop into tumors, which can be detected through inspection (Qhoiriyah et al., 2024). Breast cancer has a disproportionately high impact on females. According to the World Health Organization (WHO), 2.3 million women were diagnosed with breast cancer in 2020, with 685,000 losing their lives to the disease. There will be 7.8 million women who have survived a breast cancer diagnosis in the last five years by the end of 2020. This data points to breast cancer as the leading cancer kind (Taqiyah et al., 2022). In 2020, according to Globocan data, there were a total of 396,914 new cancer cases in Indonesia. Out of them, 68,858 cases (16.6%) were specifically related to breast cancer. In addition, the number of fatalities exceeded 22 thousand instances (Apriliani et al., 2024).

Breast cancer risk factors are grouped into definite risk factors and other possible factors. Certain factors include geography, age, family history, menstrual history, pregnancy, and benign breast disease (Pratiwi et al., 2017). Additional potential causes may encompass exogenous estrogen, oral contraceptives, obesity, a diet heavy in fat, alcohol consumption, and smoking (Yulianti et al., 2016).

In general, the work of adjuvant hormone therapy is to suppress the growth and development of cancer, which is believed to be related to the role of the hormone estrogen. causes breast cancer cells to multiply and develop. In patients. ER-positive breast cancer requires

hormonal therapy, which is a type of adjuvant systemic therapy that is often given after definitive treatment of localized breast cancer. Tamoxifen is the most used type of hormone therapy. Tamoxifen is a synthetic non-steroidal antiestrogen that works by competitively binding to estrogen receptors, thereby inhibiting the action of estradiol. Long-term use of tamoxifen has shown side effects in the form of increased endometrial thickness in several studies. Endometrial thickening can be a sign of endometrial polyps, hyperplasia, or cancer (Thayyib et al., 2020).

Treatment of breast cancer includes surgical intervention with or without chemotherapy or radiation therapy, followed by hormonal treatment in hormone receptor positive patients. Tamoxifen is commonly employed as the standard hormonal therapy for patients diagnosed with estrogen receptor positive breast cancer. Research has demonstrated that it enhances the length of time without disease recurrence and the overall length of survival by counteracting the effects of estrogen on breast tissue (Agreno et al., 2022). The main benefits of tamoxifen as adjuvant hormonal therapy for breast cancer are reducing the risk of recurrence (*locoregional* or contralateral), slowing or stopping metastasis, thereby increasing patient life expectancy, and reducing the risk of breast cancer in women at high risk. The most common side effect of treatment is hot flushes, besides vascular disease: stroke and thromboembolism and even endometrial cancer (Fadhil et al., 2019).

Previous research has reported on the duration of tamoxifen administration in breast cancer patients and its impact on endometrial pathological abnormalities. Jindal et al. (2015) conducted research to assess the radiographic and microscopic state of the endometrium in women diagnosed with breast cancer who were on tamoxifen therapy. In this study it was discovered that the average use of tamoxifen in the sample was 19.7 months, with the group using tamoxifen for 6 to 12 months being the group with the largest number (44%). Jindal et al. (2015) evaluated endometrial tissue on samples that met the criteria for hysteroscopy and found endometrial abnormalities in the form of endometrial hyperplasia, polyps, changes in tissue pattern and adenocarcinoma. In disorders

such as hyperplasia, samples had used tamoxifen for 24-48 months. In samples with adenocarcinoma findings, tamoxifen had been used for 48 months. In disorders in the form of polyps and changes in tissue patterns, the use of tamoxifen is for 15 months and 7-60 months respectively (Jindal et al., 2015).

Side effects of tamoxifen arise due to the receptor-selective nature of this drug. One tissue is an estrogen antagonist while another tissue is an estrogen agonist. In 3094 breast cancer sufferers with adjuvant tamoxifen treatment, the most frequently complained of side effects were hot flushes (1264 or 40.9%) followed by nausea, vomiting (384 or 12.4%), fatigue (544 or 17.6%), joint pain (911 or 29.4%); Also found were the incidence of stroke (88 or 2.8%), thromboembolism (214 or 6.9%), and endometrial cancer (17 or 0.8%). Other side effects include fractures (237 or 7.7%), cataracts (213 or 6.9%), abnormal vaginal discharge, and dryness of the vaginal mucosa (725 or 23%) (Kusumastuti and Cholisoh, 2024).

Annona muricata is a plant commonly known as the soursop plant in Indonesia. The local name is called daun nangka belanda or sirsak. This plant is widely cultivated in tropical and subtropical areas in Central and South America, Southeast Asia. *Annona muricata* is widely used in traditional medicine to cure various diseases in many countries (Dewi et al., 2023).

Phytochemical studies have been carried out on *Annona muricata* and 212 compounds have been isolated and identified. Extensive research shows that the leaves are a major source of *ethnomedicinal* compounds used to fight tumors and cancer. Much evidence shows that *A. muricata* leaf extract suppresses tumor growth in animal models. Meanwhile, in vitro examination shows that *A. muricata* leaves have a cytotoxic effect on pancreatic cancer cells, breast cancer cells and lung carcinoma cells (Dewayani et al., 2023). The active substance in the soursop plant which functions as an anticancer is *Annonaceous Acetogenins* (Ramandhita et al., 2021).

Acetogenins are potent inhibitors of mitochondrial complex I or NADH dehydrogenase. This substance causes a decrease in ATP production which will cause cancer cell death. Then the apoptotic pathway is activated



and activates p53 which can stop the cell cycle to prevent uncontrolled proliferation. The triterpenoid and flavonoid compounds in soursop leaves also have anticarcinogenesis effects (Muthmainna and Usman, 2024).

This study aims to explore the potential of *Annona muricata* L. leaf compounds as anti-breast cancer agents, focusing on their interaction with estrogen alpha receptors through molecular docking techniques. While various natural compounds have been evaluated for their anti-cancer properties, there is still a lack of understanding regarding the specific mechanisms and binding affinities of *Annona muricata* leaf compounds with estrogen alpha receptors. By employing advanced molecular docking methods, this research seeks to address this gap and provide new insights that could pave the way for the development of more effective and selective plant-based therapies for breast cancer. The successful outcome of this study is expected to enrich the existing literature and offer potentially safer and more effective therapeutic alternatives compared to conventional treatments.

Materials and Methods

Material

The ligand compound used is tamoxifen which is a breast cancer therapy drug. The compounds contained in soursop leaves are *Coreximine*, *Anomuricine*, *Reticulin*, *Anonaine* and *Anomurine* (Mun'iem et al., 2023).

Receptor

The 3D receptor crystal structure data utilized for molecular docking research was acquired from the Protein Data Bank (PDB) via the website <http://www.rcsb.org/pdb/>. The receptor used to predict activity is the ACE2 receptor PDB code 3ERT (Fauzi and Muchtaridi, 2020).

Tools

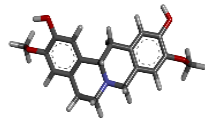
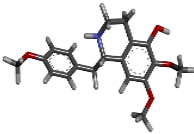
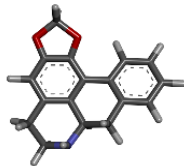
Hard Traps using an Acer Aspire laptop type A314-22. Soft Traps using windows 10 Enterprise Pro 64-bit operating system, x64 based processor, equipped with the MGL-Tools program consisting of Autodocks (The Scripps Research Institute, Inc.), Chem Office 12, Discovery Studio 2016 Client® and PreADMET software.

For the compounds contained in soursop leaves in this study, tests were carried out using *Autodock* 4.2 software. As comparative data, ligand data, namely *remdesivir*, was prepared using a 3D structure in PDF format which was downloaded via an application. <https://pubchem.ncbi.nlm.nih.gov/>. This site provides a database of compound structures for *virtual screening* purposes. the five compounds are shown in Table 1.

Target protein preparation and simulation

The 3ERT receptor is employed in this receptor preparation, and it can be obtained from the Protein Data Bank website (<http://www.rcsb.org/pdb>). Subsequently, the receptors were viewed utilizing the Discovery Studio 2016 Client® software. This program prepares the downloaded receptors by eliminating water molecules and their inherent ligands. The outcome will be a pristine receptor that is then stored in Protein Data Bank (.pdb) format (Fauzi et al., 2021).

Table 1. Medicinal compounds from soursop leaf (*Annona muricata* L).

No	Molecule Name	Molecular Structure
1.	Coreximine	
2.	Anomuricine	
3.	Reticulin	
4.	Anonaine	

5. Anomurine



chemical structure of the compound is drawn or uploaded in Molfile (mol) format. The program automatically calculates the predicted values of the selected parameters, namely: Absorption, Distribution, Metabolism, Excretion and Toxicity (Fauzi et al., 2021).

Analysis Molecular Docking

The study results depict the spatial relationships of the five chemicals with the protein by showing the sites of their chemical bonds. Gibbs free energy values (ΔG) are used to represent bond strengths. This value represents a metric that indicates the degree of affinity between the substance and the receptor. A ligand's binding to a receptor is more stable when the ΔG value is smaller. Apart from that, the inhibition constant (K_i) is also displayed to determine the binding affinity (Fauzi et al., 2021).

ADMET Prediction

ADMET parameters are calculated using the preADMET® program accessed through the website (<https://preadmetbmdrc.kr/adme/>). The

Results and Discussion

The process of binding *reticulín* molecules and medicinal compounds to the receptor aims to achieve the most energetically favorable interaction with the receptor. The findings indicated that one molecule exhibited the highest binding affinity, leading to a free energy of -8.14 kcal/mol. The study utilized *reticulín* as the positive control, a medication known for its ability to suppress the growth of breast cancer. The outcomes of the molecular docking simulation, which involved the interaction between chemicals found in soursop leaves and pharmaceutical substances, with the *Alpha Estrogen receptor*, are presented in Table 2.

Table 2. Results of molecular docking of medicinal compounds and soursop leaf compounds against the *Alpha Estrogen receptor*

No	Compound Name	Bond Interactions	
		Inhibition Constant (K_i)	Free Energy (ΔG Gibbs)
1.	Tamoxifen	3.13 μM	-11.60 kcal/mol
2.	<i>Reticulin</i>	1.07 μM	-8.14 kcal/mol
3.	Anomuricine	1.40 μM	-7.99 kcal/mol
4.	Anonaine	1.65 μM	-7.89 kcal/mol
5.	Anomurine	1.82 μM	-7.83 kcal/mol
6.	Coreximine	2.28 μM	-7.70 kcal/mol

Validation tests were conducted to verify the docking parameters that will be employed in screening compounds from soursop leaves. Picking the most dense cluster finds the best spot for docking compounds. The next thing to think about is the kind of interaction that takes place between the receptor and ligand molecules. Finding the spot with the lowest binding energy finishes the docking search. The simulation findings indicate that the structural deviation, as

measured by the root mean square deviation (RMSD) value, is 2.0 Å. Establishing the box layout entails defining parameters and selecting a grid box with dimensions of 40x40. In the *Estrogen receptor Alpha* receptor, the resulting grid box as the active site has coordinates: center x = 30.010, y = -1.913, z = 24.207 with a distance of 0.375 Å. Preparation of the *Alpha Estrogen receptor* with Autodock 4.2 is seen in Figure 1.

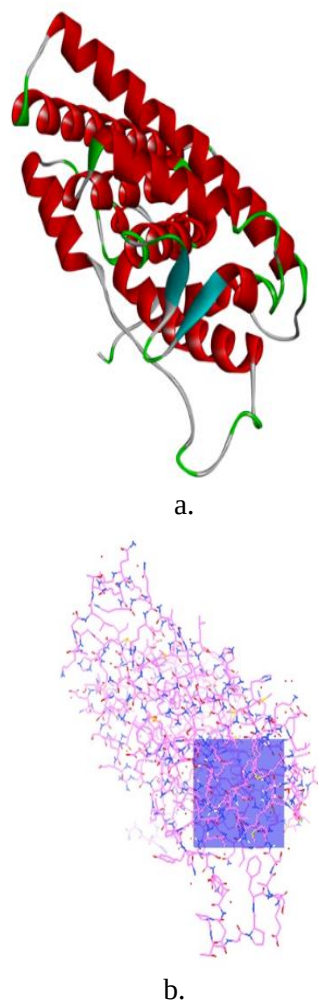


Figure 1. a. Reseptor *Main protease*, b. The active site of the 3ERT receptor

The evaluation of validation data is conducted using the root mean square deviation (RMSD) value, along with the examination of the binding site and the parameters employed. The results are considered genuine if the root mean square deviation (RMSD) is less than or equal to 3 Å. Docking is considered successful if the predictions fall within an RMSD of 2 Å, and failed if the values exceed 3 Å (Ding et al., 2016). The parameters can be utilized for molecular docking simulations because the RMSD value, which was 2.0 Å, passes the validation standards, according to the validation results.

The drug tamoxifen has been tested for breast cancer so it is the best in treating breast cancer. The results obtained from the molecular prediction of tamoxifen are free energy -11.60

kcal/mol and an inhibition constant of 3.13 μ M. However, based on molecular docking predictions, *reticulin* also has great potential to be developed as a breast cancer drug candidate because the results obtained are the best among the 4 other compounds. The docking results for *reticulin* with the Alpha Estrogen receptor are free energy -8.14 kcal/mol, and an inhibition constant of 1.07 μ M. The hydrogen bonds formed between *reticulin* and the Alpha Estrogen receptor can be seen in the visualization in Figure 2.

Based on the results of this analysis, soursop leaf compounds are able to interact with the alpha estrogen receptor binding pocket. The potential compound of soursop leaves, namely *reticulin*, has the best results in k_i and free energy.

The interactions between ligands compounds from *Annona muricata* and amino acids within the active site of a protein estrogen alpha receptor) significantly influence the system's free energy. These interactions include various types of non-covalent bonds such as hydrogen bonds, hydrophobic interactions, ionic bonds, and van der Waals forces.

Hydrogen bonds stabilize the ligand-receptor complex by forming specific and directional interactions between hydrogen donors and acceptors. Ionic bonds are formed between charged residues and contribute to the stability of the complex. Van der Waals forces arise from transient dipole interactions and further stabilize the bond. The change in the total free energy of binding ($\Delta G_{\text{binding}}$) is an important factor that reflects the stability and strength of the ligand-receptor interaction. Lower free energy indicates a more stable and stronger bond, which is essential for effective biological activity. Molecular docking techniques allow prediction and optimization of ligand binding, which can lead to the development of more therapeutic agents. The bonds formed from the best results are visualized in Figure 2.



Figure 2. Visualization results formed between *Reticulin* and the *Alpha Estrogen receptor*

ADMET PREDICTIONS

The ADMET predictions for five chemicals found in soursop leaves, using pkCSM, are displayed in Table 3. Based on absorption predictions, it is evident that *Reticulin* has high permeability in Caco-2 cells. Additionally, the five compounds have favorable absorption in the intestine. Consequently, these compounds have the potential to be absorbed through the intestinal membrane. Anomurine exhibits decreased dermal permeability compared to *Anonaine*, suggesting its limited suitability for topical administration. However, it can be effectively utilized for oral delivery purposes.

The predictive distribution process of High VDss, *Anonaine* and *Coreximine* can penetrate with high distribution in these high lipophilicity areas, and this helps to reduce side effects and toxicity or improve the pharmacological activity of the drug.

Most of the metabolic reactions primarily found in the liver are Cytochrome P450, which has several key enzymes that drive initial drug activation or detoxification by converting high polarity drugs into excreted molecules.

The results showed that all compounds were predicted to be CYP3A4 enzyme substrates. Both are easily metabolized and excreted from the body, thereby preventing toxicity. Cytochrome P450 3A4 (CYP3A4) is the main cytochrome because CYP3A4 can metabolize most types of drugs.

Based on excretion predictions, *Reticulin* and *Coreximine* are not renal OTC2 substrates that cause interactions when given together with OCT2 Inhibitors. The results of the toxicity prediction showed that Anomurine and *Coreximine* did not show any mutagenicity in the predicted toxicity of AMES and hERG inhibitors, which can cause heart problems. Based on the toxicity of T.Pyriformis, all compounds can cause toxicity to protozoa. Hepatotoxicity tests show that Anomurine and *Coreximine* are not toxic, while the predicted Skin Sensitization of all compounds does not show any effect on the skin. ADMET prediction using pkCSM of the top five docking scores showed that *Reticulin* had better values in the ADMET study. These results can be proven by comparing in test tube and in life studies.

Table 3. ADMET predicts that there are 5 docking compounds in soursop leaves using the pkCSM online server

Process	Model	Unit	Compound				
			<i>Reticulin</i>	<i>Anomuricine</i>	<i>Anonaine</i>	<i>Anomurine</i>	<i>Coreximine</i>
Absorption	Water solubility	1708 Molecule	-3.612 log mol/L	-3.286 log mol/L	-3.006 log mol/L	-3.498 log mol/L	-3.43 log mol/L
	Caco-2 Permeability	> 0,90	1.112 log Papp in 10 ⁻⁶ cm/s	1.328 log Papp in 10 ⁻⁶ cm/s	1.79 log Papp in 10 ⁻⁶ cm/s	0,865 log Papp in 10 ⁻⁶ cm/s	1.232 log Papp in 10 ⁻⁶ cm/s
	Intestinal absorption (human)	> 30%	91 %	92.868 %	93.626 %	93.81 %	93.178 %
	Skin permeability	Log Kp > -2,5	-2.823 log Kp	-2.767 log Kp	-2.64 log Kp	-2.846 log Kp	-2.838 log Kp
	P-glycoprotein substrate	Substrate Pgp/No	Yes	No	Yes	Yes	Yes
	Inhibition of P-glycoprotein I	Yes/No	No	Yes	No	Yes	No
	Inhibition of P-glycoprotein II	Yes/No	No	Yes	Yes	Yes	No
Distribution	VDss (human)	Low (log VDss < -0,15) High (log VDss > 0,45)	0,79 log L/kg	0,801 log L/kg	1.532 log L/kg	0,883 log L/kg	1.25 log L/kg
	Unbound fractions (human)	552 Fu	0,242 Fu	0,09 Fu	0,209 Fu	0,143 Fu	0,323 Fu
	BBB Permeability	logBB > 0.3 (Easily crosses the blood brain barrier) logBB < -1 (bad for the brain)	-0,27 log BB	-0,7 log BB	0,486 log BB	-0,288 log BB	-0,105 log BB
	CNS permeability	logPS > -2 (Able to penetrate the CNS Central Nervous System) logPS < -3 (No Capable of penetrating the CNS Central Nervous System)	-2.274 log PS	-2.39 log PS	-1.708 log PS	-1.319 log PS	-2.2 log PS
Metabolism	CYP2D6 substrate	Yes/No	No	No	Yes	Yes	No
	CYP3A4 substrate	Yes/No	Yes	Yes	Yes	Yes	Yes
	CYP1A2 inhibitor	Yes/No	Yes	Yes	Yes	No	Yes
	CYP2C19 inhibitor	Yes/No	No	No	Yes	No	No
	CYP2C9 inhibitor	Yes/No	No	No	No	No	No
	CYP2D6 inhibitor	Yes/No	Yes	No	Yes	Yes	No
	CYP3A4 inhibitor	Yes/No	No	Yes	No	No	No



Process	Model	Unit	Compound				
			<i>Reticulin</i>	<i>Anomuricine</i>	<i>Anonaine</i>	<i>Anomurine</i>	<i>Coreximine</i>
Excretion	Total Permissions	Log ml/minute/kg	1.072 log ml/minute/kg	1.047 log ml/minute/kg	1.031 log ml/minute/kg	1.06 log ml/minute/kg	1.136 log ml/minute/kg
	Renal OCT2 substrate	Yes/No	No	Yes	Yes	Yes	No
Toxicity Process Absorption	AMES Toxicity	Yes/No	No	No	No	Ya	No
	Max. Tolerable dose (human)	≤ 0.477 is considered low ≥ 0.477 is considered high	-0,137 log mg/kg/day	0,115 log mg/kg/day	-0,168 log mg/kg/day	0,062 log mg/kg/day	-0,469 log mg/kg/day
	Herg I inhibitor	Yes/No	No	No	No	No	No
	Herg inhibitor II	Yes/No	Ya	Ya	Ya	Ya	Ya
	Oral Rat Acute Toxicity (LD50)		2.645 mol/kg	2.282 mol/kg	2.553 mol/kg	2.758 mol/kg	2.579 mol/kg
	Chronic Rat Oral Toxicity (LOAEL)		1.067 log mg/kg_bw/day	1.351 log mg/kg_bw/day	1.229 log mg/kg_bw/day	1.444 log mg/kg_bw/day	0.949 log mg/kg_bw/day
	Hepatotoxicity	Yes/No	Ya	No	Ya	Ya	No
	Skin Sensitization	Yes/No	No	No	No	No	No
	T. Pyriformis toxicity	> -0.5 log ug/L is considered toxic	0,735 log ug/L	1.298 log ug/L	0,53 log ug/L	1.459 log ug/L	0,732 log ug/L
	Small Fish Toxicity	< 0.5 mM (log LC50 < -0.3) is considered high acute toxicity	0,644 log mM	0 log mM	0,719 log mM	0,818 log Mm	0,679 log mM



Conclusion

Several soursop leaf compounds have activity in inhibiting breast cancer, namely *reticulin*, the compound from soursop leaves *reticulin* has better potential in inhibiting breast cancer with the best binding affinity on the active site of the *alpha estrogen receptor*.

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Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

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