

Research Article

Potential of Flavonoid Compounds from *Etlingera elatior* against Estrogen Receptor Alpha (ER+) as an Anti-Breast Cancer in Silico

Nastiti Nur Indriyani^{1,*}

¹STIKes Ibnu Sina Ajibarang, Banyumas, Indonesia, 53163

*Correspondence email : nastitindriyani@stikes-ibnusina.ac.id

Abstract (in English)

Estrogen receptor positive (ER+) subtype breast cancer is one of the most common types of cancer in women and requires targeted therapy to improve the effectiveness of treatment. This study aims to explore the potential of active compounds flavonoid group from *Etlingera elatior* as estrogen receptor alpha (ER α) inhibitors through an in silico approach. Nine compounds were predicted for their pharmacokinetic and toxicity characteristics using SwissADME, then three compounds with the best profiles were selected for molecular docking using AutoDock. The results of the analysis showed that the epicatechin compound had the best binding affinity (-7.57kcal/mol) and a low inhibition constant (K_i $2.80\mu\text{M}$), approaching the positive control value of tamoxifen (-10.49kcal/mol ; K_i $20.32\mu\text{M}$). Epicatechin also showed a good pharmacokinetic profile, was non-toxic, and was conformationally stable in the active pocket of ER+. Thus, epicatechin has the potential as a candidate for natural anticancer agents for the development of ER+ subtype breast cancer therapy based on natural compounds

Keywords: *Etlingera elatior*, breast cancer, docking, estrogen receptor alpha, in silico

Accepted: 22 July 2025

Approved: 20 August 2025

Publication: 1 September 2025

Citation : N.N. Indriyani, "Potential of Flavonoid Compounds from *Etlingera elatior* against Estrogen Receptor Alpha (ER+) as an Anti-Breast Cancer in Silico," Journal of Tropical Pharmacy and Chemistry (JTPC), vol. 9, no. 1, pp. 31–38, Sept. 2025, doi: 10.30872/jtpc.v9i1.289.

Copyright : © year, Journal of Tropical Pharmacy and Chemistry (JTPC). Published by Faculty of Pharmacy, Universitas Mulawarman, Samarinda, Indonesia. This is an Open Access article under the CC-BY-NC License



1 Introduction

Breast cancer continues to be the most commonly diagnosed cancer and a leading cause of cancer-related mortality among women worldwide. According to projections by the International Agency for Research on Cancer (IARC), global cancer cases are expected to rise to 28.4 million by 2040—an alarming 47% increase compared to 2020. This upward trend is largely driven by demographic transitions, aging populations, and increased exposure to carcinogenic risk factors as a result of globalization and economic development [1].

Among the molecular subtypes of breast cancer, estrogen receptor alpha-positive (ER+ or ER α) remains the most prevalent, accounting for approximately 70% of all diagnosed cases [2]. This subtype is characterized by its dependency on estrogen signaling for tumor growth and survival, making the estrogen receptor a key target in therapeutic intervention [3]. Current endocrine therapies, including selective estrogen receptor modulators (SERMs) like tamoxifen and aromatase inhibitors (AIs), have significantly improved patient outcomes. However, these treatments are not without limitations—drug resistance, relapse, and adverse side effects remain major challenges in long-term management [4].

As the need for novel, safe, and targeted anticancer agents grows, natural products have emerged as a promising alternative. Bioactive compounds derived from medicinal plants are increasingly explored for their ability to modulate cancer pathways with reduced toxicity. One such plant of interest is *Etlingera elatior* (commonly known as torch ginger), a member of the Zingiberaceae family, traditionally used in Southeast Asian herbal medicine [5].

Recent pharmacological studies suggest that *E. elatior* exhibits potent anticancer activity through multiple mechanisms, including hormone receptor inhibition, induction of apoptosis, and suppression of inflammation and oxidative stress [6]. These effects are attributed to its rich phytochemical profile, which includes flavonoids, terpenoids, phenolics, and alkaloids. Notably, flavonoids have demonstrated the ability to interfere with estrogen receptor signaling by acting as either partial agonists or antagonists [7] [8]. This selective estrogen receptor modulation (SERM-like activity) presents a compelling opportunity for developing plant-based therapies targeting ER+ breast cancer [6].

Despite its therapeutic promise, research on the specific interaction between *E. elatior* bioactive compounds and ER α remains limited. To address this gap, in silico approaches such as molecular docking offer an efficient and cost-effective strategy for early-stage drug discovery. Molecular docking simulates the binding affinity and interaction between ligands (plant compounds) and target proteins (such as ER α), providing valuable insight before proceeding to in vitro or in vivo validation [9].

Given the growing burden of ER+ breast cancer and the limitations of current treatment modalities, this study aims to systematically explore the potential of *E. elatior* compounds in modulating the estrogen receptor alpha through molecular docking analysis. This empirical investigation serves as a critical first step in identifying promising candidates for future development of safer and more effective plant-derived therapeutics.

2 Method

Tools

In silico analysis was conducted using a Lenovo ThinkPad L470 laptop running Windows 10 Pro 64-bit, powered by an Intel® Celeron® CPU 3955U @ 2.00 GHz processor. The compound structures were retrieved from the PubChem database (<https://pubchem.ncbi.nlm.nih.gov>), while the protein target structures were obtained from the Protein Data Bank (PDB) via www.rcsb.org.

To assess drug-likeness, pharmacokinetic properties, and toxicity profiles, several online predictive tools were utilized. Lipinski's Rule of Five and pharmacokinetic predictions were performed using

SwissADME (<https://www.swissadme.ch>), while toxicity predictions were carried out using ProTox-II (<https://tox.charite.de>). Relevant protein targets were identified using SwissTargetPrediction (<https://www.swisstargetprediction.ch>), and protein-protein interaction networks were explored using the STRING database (<https://string-db.org>).

For compound visualization and preparation, ChemDraw Professional 16.0 and Chem3D 16.0 were used. Protein and ligand preparation, as well as docking simulations, were performed using AutoDock Tools version 1.5.6, and the results were further analyzed and visualized using BIOVIA Discovery Studio Visualizer.

Lipinski's Rule of Five Screening

A literature review was conducted to identify the chemical constituents present in the ethanol extract of *E. elatior* flower. The selected compounds were then subjected to physicochemical screening using Lipinski's Rule of Five (RO5) to predict their drug-likeness. This prediction was performed using the SwissADME web server (<https://www.swissadme.ch>).

Pharmacokinetics and Toxicity Analysis

The pharmacokinetic properties and toxicity profiles of the identified bioactive compounds were also assessed using SwissADME. Canonical SMILES (Simplified Molecular Input Line Entry System) notations for each compound were retrieved from the PubChem database and input into SwissADME for absorption, distribution, metabolism, and excretion (ADME) predictions.

Toxicological evaluation was carried out using the ProTox-II platform (<https://tox.charite.de>), assessing parameters such as carcinogenicity, mutagenicity, hepatotoxicity, immunotoxicity, and cytotoxicity [10].

Ligand and Protein Preparation

The research began with ligand and protein preparation. The target protein used was the Estrogen Receptor Alpha (ER α), with PDB ID: 3ERT, obtained from the RCSB Protein Data Bank. The protein structure was determined using X-ray diffraction at a resolution of 1.90 Å, derived from *Homo sapiens*, and without any mutations.

The test ligands consisted of flavonoid compounds identified from LC-MS analysis of the ethanol extract of *E. elatior* flower: Pyrocatechol, Procyanidin B2, ($\pm$)-Catechin, Kaempferol-7-O-glucoside, Astragalin, Fisetin, Epicatechin, Quercetin-3-galactoside, and Isoquercitrin [11]. These compound structures were downloaded from PubChem in .pdb format.

The native ligand, 4-hydroxytamoxifen, which naturally binds to the target protein, was used for validation purposes. Unnecessary components such as water molecules and non-essential ligands were removed from the protein structure using BIOVIA Discovery Studio Visualizer.

Molecular Docking Validation

Validation of the docking protocol was conducted using AutoDock by re-docking the native ligand into the prepared target protein. The method was considered valid if the resulting Root Mean Square Deviation (RMSD) value was less than 2 Å. During this step, the grid box was also defined to localize the active site where the ligand interacts with amino acid residues of the receptor.

Molecular Docking Procedure

Following validation, molecular docking was carried out for each test ligand and a standard breast cancer drug (acetylcysteine as a control) against the ER α protein. The docking procedure followed the

validated protocol. Binding affinities and key amino acid interactions were recorded for all compounds. The docking results were further visualized and analyzed using BIOVIA Discovery Studio Visualizer [12].

3 Result and Discussion

Based on the analysis presented in Table 1, three compounds ($\pm$)-Catechin, Fisetin, and Epicatechin—were found to fully comply with Lipinski's Rule of Five, indicating favorable drug-likeness profiles. In contrast, six other compounds—Pyrocatechol, Procyanidin B2, Kaempferol-7-O-glucoside, Astragalin, Quercetin-3-galactoside, and Isoquercitrin—did not meet the criteria, suggesting limited oral bioavailability or pharmacokinetic suitability. The full results of the Lipinski screening are detailed in Table 1.

Table 1. Analysis Results Based on Lipinski's Rule of Five

No	Compound Name	Parameter				
		Molecular Weight (g/mol)	H-Bond Donors	H-Bond Acceptors	Log P	Molar Refractivity
		<500 g/mol	<5	<10	<5	40-130
1	Pyrocatechol	110,11	2	2	0,97	30,49
2	Procyanidin B2	578,52	10	12	1,35	146,71
3	($\pm$)-Catechin	290,27	5	6	0,83	74,33
4	Kaempferol-7-o-glucoside	447,37	6	11	1,96	106,24
5	Astragalin	448,38	7	11	-0,09	108,13
6	Fisetin	286,24	4	6	1,55	76,01
7	Epicatechin	290,27	5	6	0,85	74,33
8	Quercetine 3-galactoside	610.52	10	16	-1.30	141.12
9	Isoquercitrin	464,38	8	12	-0,48	110,16

Additional pharmacokinetic parameters, including Caco-2 permeability, Human Intestinal Absorption (HIA), and Plasma Protein Binding (PPB), were evaluated for each flavonoid compound derived from *Etlingera elatior* flower extract. According to the results, the Caco-2 permeability values of ($\pm$)-Catechin and Epicatechin were classified as low, indicating limited intestinal permeability. Meanwhile, Pyrocatechol, Procyanidin B2, Kaempferol-7-O-glucoside, Astragalin, Quercetin-3-galactoside, and Isoquercitrin fell into the moderate category.

For HIA predictions, Quercetin-3-galactoside and Isoquercitrin were categorized as having poor absorption, while the remaining compounds showed moderate intestinal absorption potential. In terms of PPB analysis, Pyrocatechol and Procyanidin B2 exhibited weak binding to plasma proteins, whereas the other compounds demonstrated strong binding affinity. These predicted pharmacokinetic parameters are summarized in Table 2.

Table 2. Predicted Pharmacokinetic and Toxicity Profiles

No	Compound Name	Pharmacokinetic Predictions			Toxicity Prediction				
		Caco2	HIA	PPB	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity
1	Pyrocatechol	16.5456	87.4128	97.3235	Inactive	active	inactive	Inactive	Inactive
2	Procyanidin B2	16.7426	27.6407	100.000	Inactive	Inactive	active	Inactive	Inactive
3	(±)-Catechin	0.6616	63.6272	82.5469	Inactive	Inactive	inactive	Inactive	Inactive
4	Kaempferol-7-o-glucoside	5.6320	21.7433	38.3410	Inactive	Inactive	inactive	Inactive	Inactive
5	Astragalin	15.1755	30.0748	39.7219	Inactive	Inactive	inactive	Inactive	Inactive
6	Fisetin	9.5515	77.4196	59.9807	Inactive	active	inactive	Inactive	Inactive
7	Epicatechin	0.6615	63.6272	82.5469	Inactive	Inactive	inactive	Inactive	Inactive
8	Quercetine 3-galactoside	6.0565	2.8893	37.6074	Inactive	Inactive	active	Inactive	Inactive
9	Isoquercitrin	11.9675	16.5556	65.7652	Inactive	Inactive	active	Inactive	Inactive

Molecular docking simulations further evaluated the interaction between selected ligands and the Estrogen Receptor Alpha (ER α). Among the tested compounds, (±)-Catechin and Epicatechin yielded negative binding affinity values, indicating spontaneous binding interactions with the receptor. Specifically, (±)-Catechin showed a binding affinity of -6.25 kcal/mol, while Epicatechin exhibited a stronger interaction at -7.57 kcal/mol. For comparison, the standard control ligand, Tamoxifen, produced a binding affinity of -10.49 kcal/mol. Although both test compounds displayed lower binding affinity than Tamoxifen, the results suggest potential for further investigation as ER α modulators. The detailed energy components for each ligand, including the control and test compounds, are shown in Table 3.

Table 3. Binding Energy Calculations of Ligand–Receptor Complexes

Komponen Energi (kkal/mol)	Senyawa			
	Validasi	(±)-Catechin	Epicatechin	Tamoxifen
<i>Final Intermolecular Energy</i>	-14.57	-8.04	-9.36	-12.88
<i>vdW + Hbond + desolv Energy</i>	-13.20	-7.77	-8.94	-11.76
<i>Electrostatic Energy</i>	-1.37	-0.27	-0.43	-1.12
<i>Final Total Internal Energy</i>	-2.13	-1.99	-1.29	-2.22
<i>Torsional Free Energy</i>	+2.68	+1.79	+1.79	+2.39
<i>Unbound System's Energy [= (2)]</i>	-2.13	-1.99	-1.29	-2.22
<i>Binding Affinity</i>	-11.88	-6.25	-7.57	-10.49
<i>Inhibition Constant, Ki</i>	1.95 nM	26.33 μ M	2.80 μ M	20.32 μ M

Discussion

One commonly applied method in early drug discovery is Lipinski's Rule of Five (Ro5) [13]. This rule states that a compound is likely to exhibit good oral bioavailability if it does not violate the following criteria: molecular weight less than 500 Daltons, Log P value less than 5, no more than 5 hydrogen bond donors, no more than 10 hydrogen bond acceptors, and a molar refractivity between 40 and 130. If a test compound meets these criteria, it is more likely to possess favorable pharmacokinetic properties when administered orally and can thus proceed to further in vitro and in vivo evaluations [14].

As shown in Table 1, three compounds ($\pm$)-Catechin, Fisetin, and Epicatechin—fulfilled the Lipinski criteria, indicating their potential as orally bioavailable agents. Beyond Ro5 screening, these compounds were also evaluated for absorption, distribution, metabolism, and excretion (ADME) parameters, which are critical determinants in drug development [15].

According to the pharmacokinetic and toxicity predictions, compounds were selected for molecular docking based on favorable absorption (high Caco-2 permeability and Human Intestinal Absorption), reasonable plasma protein binding (PPB), and minimal toxicity (classified as inactive in all toxicity categories). Based on these criteria, ($\pm$)-Catechin and Epicatechin were considered suitable for further molecular docking studies.

Validation of the docking protocol was conducted to ensure the reliability of the docking method used. In docking studies, validation is considered successful if the Root Mean Square Deviation (RMSD) between the redocked native ligand and its original conformation is less than 2 Å [16]. The validation analysis yielded an RMSD value of 1.022 Å, indicating that the method is valid and acceptable. The overlay of the validated ligand and the original native ligand can be seen in Figure 1.

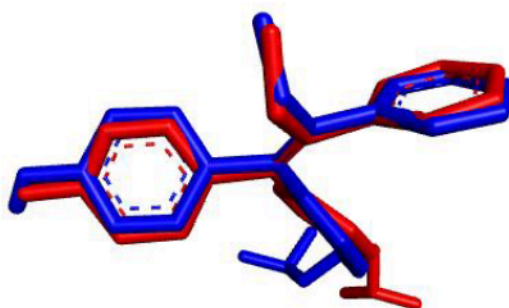


Figure 1. Ligand Overlay (Red: Before Docking, Blue: After Docking)

Based on Figure 1, the aromatic ring of the ligand remained relatively aligned and exhibited only minor changes in orientation after docking. This indicates that the ligand's conformation within the receptor's active site maintained its original structure with minimal rotation at the binding site [13]. Such behavior suggests favorable conformational flexibility and a good fit between the ligand and the receptor. The stability of the aromatic ring orientation post-docking may also imply the presence of non-covalent interactions such as π - π stacking or π -alkyl interactions with aromatic or hydrophobic residues in the receptor's active site [17].

From the binding energy calculations, epicatechin demonstrated the strongest potential among the tested compounds as a candidate inhibitor of estrogen receptor alpha (ER α). Epicatechin showed a total binding affinity of -7.57 kcal/mol with an inhibition constant (K_i) of 2.80 μ M, which is comparable to the positive control, tamoxifen (-10.49 kcal/mol; K_i = 20.32 μ M). The intermolecular energy, as well as the van der Waals and hydrogen bond contributions of epicatechin, were more stable than those of catechin. Moreover, epicatechin exhibited low torsional energy, indicating a stable conformation when interacting with the receptor. Given its favorable binding profile, along with safe pharmacokinetic and toxicity predictions, epicatechin stands out as a promising natural anticancer agent. While catechin also shows potential, it demonstrated lower binding affinity and inhibitory effectiveness. Tamoxifen remains superior as a positive control, but natural compounds such as epicatechin may offer an effective and less toxic alternative.

The molecular interaction visualizations revealed that the three ligands exhibited distinct binding affinities to the Estrogen Receptor Alpha (ER+) depending on the type and number of interactions

formed. In Figure A, the ligand formed three conventional hydrogen bonds with residues Glu A:419, Gly A:521, and Thr A:347, along with multiple hydrophobic interactions involving residues such as Ile, Met, Leu, and Ala—indicating a balanced combination of polar and nonpolar interactions. Figure B showed the ligand forming three key hydrogen bonds with Thr A:347, Glu A:353, and Arg A:394, in addition to Pi-alkyl interactions with hydrophobic residues like Leu and Ala, suggesting strong, specific binding in polar regions as well as stabilization via nonpolar contacts. In **contrast, Figure C** was dominated by hydrophobic interactions, with only one conventional hydrogen bond (Thr A:347) and one carbon-hydrogen bond (Leu A:525), along with extensive Pi-alkyl interactions involving nonpolar residues such as Leu, Met, Phe, and Ala. The detailed protein–ligand interaction diagrams are presented in Figure 2.

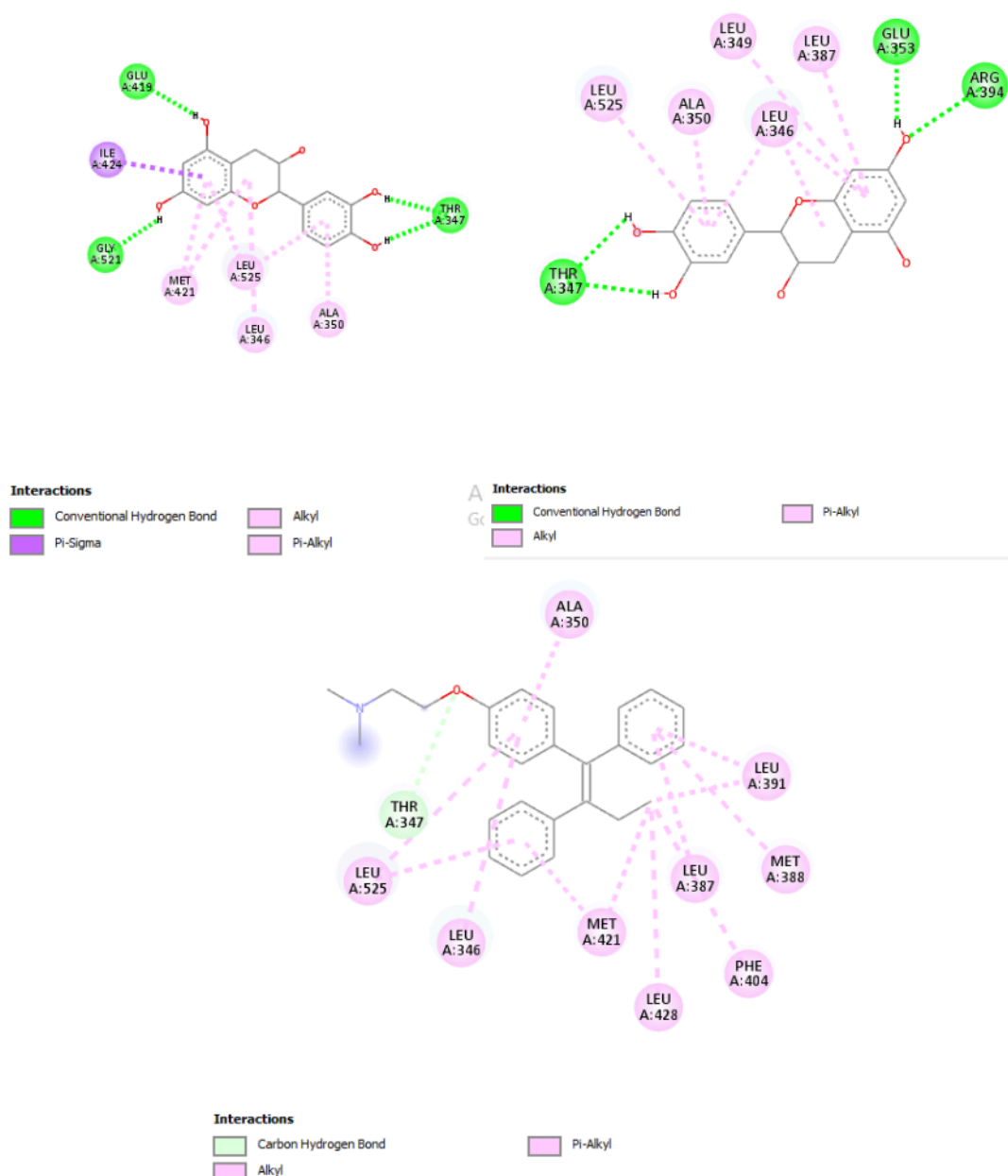


Figure 2. Amino Acid Residues Interacting with (A) Catechin, (B) Epicatechin, and (C) Tamoxifen

4. Conclusion

Based on the predicted pharmacokinetic properties, toxicity profiles, and molecular docking results, epicatechin emerged as the most promising candidate inhibitor of estrogen receptor alpha (ER α) in ER-positive (ER+) breast cancer. Epicatechin demonstrated a favorable pharmacokinetic profile, showed no indications of toxicity, and exhibited strong binding affinity with a binding energy of -7.57 kcal/mol and an inhibition constant (K_i) of 2.80 μ M.

Compared to the other tested compounds, epicatechin offered the most optimal balance between safety and binding effectiveness. These results suggest that epicatechin holds significant potential as a natural lead compound for the development of anticancer agents targeting ER α , particularly from the bioactive constituents of *Etlingera elatior*.

5. Declarations

5.1 Acknowledgements (Optional)

The author would like to express sincere gratitude to STIKes Ibnu Sina Ajibarang for supporting this research.

5.2 Author contributions

NNI was responsible for conceptualization, methodology design, data curation, formal analysis, molecular docking simulations, interpretation of results, and manuscript writing.

5.3 Ethics

No conflict of interest.

5.4 Conflict of Interest

No conflict of interest.

5.5 Funding Statement

This research was fully supported by STIKes Ibnu Sina Ajibarang through internal research funding. The institution had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

6. Bibliography

- [1] H. Sung *et al.*, "Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries," *CA. Cancer J. Clin.*, vol. 71, no. 3, pp. 209–249, 2021, doi: 10.3322/caac.21660.
- [2] C. M. Perou *et al.*, "Molecular portraits of human breast tumours," *Nature*, vol. 406, no. 6797, pp. 747–752, 2000, doi: 10.1038/35021093.
- [3] P. M. Afladhanti, H. A. Hamzah, M. D. Romadhan, S. N. Putri, E. C. Angelica, and T. Theodorus, "Etlingera elatior Compounds as Anticancer Agents of Breast Cancer Through Inhibition of Progesterone Receptor: An In Silico Study," *Indones. J. Cancer Chemoprevention*, vol. 14, no. 2, p. 94, 2023, doi: 10.14499/indonesianjcanchemprev14iss2pp94-104.
- [4] R. K. Rej, J. E. I. I. Thomas, R. K. Acharyya, J. M. Rae, and S. Wang, "Targeting the Estrogen Receptor for the Treatment of Breast Cancer: Recent Advances and Challenges," *J. Med. Chem.*, vol. 66, no. 13, pp. 8339–8381, Jul. 2023, doi: 10.1021/acs.jmedchem.3c00136.
- [5] Ni Wayan Bogoriani, Sri Wahjuni, and Maria Krissanti Ema, "Antioxidant activity of kecombrang flower (*Etlingera elatior*) methanol extract and identification of its compounds using LC-MS/MS," *Indones. J. Biomed. Sci.*, vol. 17, no. 2, pp. 172–177, 2023, doi: 10.15562/ijbs.v17i2.480.
- [6] D. S. F. Ramadhan, T. M. Fakhri, and A. Arfan, "Activity Prediction of Bioactive Compounds Contained in *Etlingera elatior* Against the SARS-CoV-2 Main Protease: An In Silico Approach," *Borneo J. Pharm.*, vol. 3, no. 4, pp. 235–242, 2020, doi: 10.33084/bjop.v3i4.1634.
- [7] J. Long *et al.*, "Research progress of flavonoids targeting estrogen receptor in the treatment of breast cancer," *Bioorg. Med. Chem.*, vol. 120, p. 118106, 2025, doi: <https://doi.org/10.1016/j.bmc.2025.118106>.
- [8] M. Farhan, A. Rizvi, M. Aatif, and A. Ahmad, "Current Understanding of Flavonoids in Cancer Therapy and Prevention," *Metabolites*, vol. 13, no. 4, 2023, doi: 10.3390/metabo13040481.
- [9] G. Anastasya, L. Wensa, S. Permata, A. Amatulloh, Z. T. A. Fath, and A. Zuhrotun, "In Silico Study of Klabet Seed Compounds (*Trigonella foenum-gracum* L.) as Alpha Estrogen Inhibitors In Breast Cancer," *Indones. J. Biol. Pharm.*, vol. 3, no. 3, pp. 183–193, 2023.
- [10] M. S. Amrilah and R. Hilman, "In Silico Studies for Anti-Breast Cancer *Acmella Oleracea* (L.) Flowers," *J. Farm. Sains dan Prakt.*, vol. 10, no. 1, pp. 12–24, 2024.
- [11] M. Mutmainah, Y. Mayangsari, U. Santoso, W. Chansuwan, and N. Sirinupong, "Phytochemical profile and antioxidant activity of torch ginger (*Etlingera elatior*) inflorescence extract after in vitro simulated digestion," *Funct. Foods Heal. Dis.*, vol. 14, no. 7, pp. 528–545, 2024, doi: 10.31989/ffhd.v14i7.1382.
- [12] J. Usmani *et al.*, "Molecular Docking of Bacterial Protein Modulators and Pharmacotherapeutics of *Carica papaya* Leaves as a Promising Therapy for Sepsis : Synchronising In Silico and In Vitro Studies," 2023.
- [13] G. Widiyarti, A. Sundowo, M. Megawati, and T. Ernawati, "Synthesis, Characterization, Anticancer and In Silico ADME Properties of Caproic Acid Derivatives against P388 Cancer Cell Lines," *Indones. J. Pharm. Sci. Technol.*, vol. 1, no. 2, p. 1, 2019, doi: 10.24198/ijpst.v1i2.20192.
- [14] A. S. Salsabila *et al.*, "In Silico Study of Moringa leaves Compound (*Moringa oleifera* L .) as Protein Kinase C Alpha Inhibitor in Breast Cancer," *Indones. J. Biol. Pharm.*, vol. 3, no. 3, pp. 154–173, 2023.
- [15] N. A. Durán-Iturbide, B. I. Díaz-Eufracio, and J. L. Medina-Franco, "In Silico ADME/Tox Profiling of Natural Products: A Focus on BIOFACQUIM," *ACS Omega*, vol. 5, no. 26, pp.

- 16076–16084, 2020, doi: [10.1021/acsomega.0c01581](https://doi.org/10.1021/acsomega.0c01581).
- [16] R. Lelita, R. Gunawan, and W. Astuti, “Molecular Docking Studies Quercetin, Chalcone and its Derivate Inhibitor to Breast Cancer Cells Mcf-7 (Michigan Cancer Foundation-7),” *J. At.*, vol. 1, no. 2, pp. 190–196, 2017.
- [17] P. Wu *et al.*, “DROEG: a method for cancer drug response prediction based on omics and essential genes integration,” *Brief. Bioinform.*, vol. 24, no. 2, pp. 1–12, 2023, doi: [10.1093/bib/bbad003](https://doi.org/10.1093/bib/bbad003).