Jurnal Ilmiah Ibnu Sina, 10(1), Maret 2025, 166-181
p-ISSN: 2502-647X; e-ISSN: 2503-1902

IN SILICO STUDY: THE POTENTIAL OF KILEMO (*Litsea cubeba*) ENDEMIC PLANT FROM KALIMANTAN AS ANTI-BREAST CANCER THROUGH HER2 INHIBITION

Dwi Utami[1], Tarisha Elmaningtyas Zahro[2], Khairun Nisa[2], Muhammad Farid[3]*

[1] Department of analytical and medicinal chemistry, Faculty of Pharmacy, Ahmad Dahlan University, Yogyakarta, Indonesia
[2] Department of Pharmacy, Faculty of Pharmacy, Ahmad Dahlan University, Yogyakarta, Indonesia
[3]Department of Medicine, Faculty of Medicine, Ahmad Dahlan University, Yogyakarta, Indonesia

*Email: muhammad2100034023@webmail.uad.ac.id

Artikel diterima: 31 Desember 2024; Disetujui: 22 Maret 2025
DOI: https://doi.org/10.36387/jiis.v9i2.2352

ABSTRAK

Kanker payudara merupakan kanker yang paling banyak dijumpai di dunia dengan tingkat komplikasi dan kematian yang tinggi. Salah satu mekanisme terjadinya kanker payudara adalah ekspresi berlebihan reseptor faktor pertumbuhan epidermal manusia-2 (HER2). Tanaman kilemo (*Litsea cubeba*) mengandung senyawa naringenin, asam ellagik, asam kafeat, asam ferulat, dan asam siringat yang dapat menghambat ekspresi berlebihan HER2. Penelitian ini merupakan studi pendahuluan pengembangan tanaman sebagai kandidat obat alami anti kanker payudara melalui studi docking molekuler. Metode yang digunakan dalam docking molekuler senyawa kilemo dengan domain protein kinase HER2 manusia. Pertama-tama dilakukan preparasi protein dan ligan uji, dilanjutkan dengan validasi metode docking dengan redocking. Senyawa yang diuji interaksinya dengan protein dan dilakukan analisis serta visualisasi hasil menggunakan Autodock-4 dan Biovia Discovery Studio, senyawa yang digunakan adalah evaluasi prediksi farmakokinetik. Hasil penelitian menunjukkan bahwa senyawa yang terkandung memiliki afinitas yang baik terhadap domain protein kinase HER2 manusia. Naringenin dan asam ellagik memiliki potensi terbaik dengan energi pengikatan -8,60 kkal/mol dan -7,76 kkal/mol, dengan konstanta penghambatan masing-masing 493,67 µM dan 2,05 µM. Prediksi farmakokinetik keenam senyawa tersebut memenuhi persyaratan kandidat obat oral. Meskipun afinitas pengikatan semua senyawa yang diuji lebih rendah daripada lapatinib, namun berdasarkan prediksi toksisitas, senyawa tersebut tidak bersifat hepatotoksik seperti Lapatinib. Sebagai kesimpulan, tanaman tersebut berpotensi untuk dikembangkan sebagai kandidat obat tradisional untuk obat antikanker payudara alami yang lebih aman daripada lapatinib.

Kata kunci: Kanker Payudara, HER2, *Litsea cubeba, docking molekuler*

Jurnal Ilmiah Ibnu Sina, 10(1), Maret 2025, 166-181
p-ISSN: 2502-647X; e-ISSN: 2503-1902

ABSTRACT

Breast cancer is the most common cancer in the world with high complication and mortality rates. Overexpression of human epidermal growth factor receptor-2 (HER2) is one of the mechanisms of breast cancer. The Kilemo plant (Litsea cubeba) contains compounds such as naringenin, ellagic acid, caffeic acid, ferulic acid, and syringic acid, which can inhibit the overexpression of HER2. This research is a preliminary study of the development of the plant as an anti-breast cancer natural drug candidate through a molecular docking study. The method used in the molecular docking of kilemo compounds with the protein kinase domain of human HER2. Firstly, the preparation of proteins and test ligands, followed by validation of the docking method with redocking. The compound was testing the interaction with proteins and analyzing and visualizing results using Autodock-4 and Biovia Discovery Studio, compounds was the evaluation of pharmacokinetic predictions. The results showed that the compounds contained have good affinity for the protein kinase domain of human HER2. Naringenin and ellagic acid have the best potential with the binding energy of -8.60 kcal/mol and -7.76 kcal/mol, with inhibition constants of 493.67 µM and 2.05 µM. Pharmacokinetic predictions of the six compounds fulfill the requirements of oral drug candidates. Although the binding affinity of all tested compounds were lower than lapatinib, but based on toxicity prediction, the compounds are not as hepatotoxic as Lapatinib. In conclusion, the plant has potential to be developed as a traditional medicine candidate for natural anti-breast cancer drugs that are safer than lapatinib.

Keywords: Breast Cancer, HER2, *Litsea cubeba, molecular docking*

INTRODUCTION

Breast cancer ranks first with the highest number of new cases, reaching 66,271 cases (41.8%) of a total of 408,661 new cases of cancer in Indonesia, with a mortality rate of 22,598 cases (14.4%) (Bray et al., 2024). This figure shows that breast cancer is still a significant health problem, therefore attention is needed to overcome the emergence of new cases. Cancer cells are formed from normal cells due to modifications or mutations of DNA and RNA that cause cancer cells to be very similar to their original organism cells but not identical. This is why breast cancer is not often detected by the immune system, significantly if it is weakened (Zhou et al., 2022). Cancer cell mutations can occur spontaneously or caused by other factors such as electromagnetic radiation, viruses, bacteria, fungi, parasites, and poor lifestyle that help increase the rate of cancer cell-inducing mutations (Łukasiewicz et al., 2021). Cancer is also called an "Entropic Disease" because it is associated with an increase in the entropy

of the organism to a point where it cannot repair itself (Sung et al., 2021). External intervention is required to allow the organism to return to a stable entropic state. In general, breast cancer treatment uses the drug lapatinib. Lapatinib is a small dual-molecule kinase inhibitor in breast treatment. The proposed mechanism of action includes inhibition of HER2, a signaling protein involved in the pathogenesis of breast cancer by controlling various cellular processes. Lapatinib has toxic effects, including diarrhea, rash, pruritus, nausea, and hepatotoxicity. The prevalence of elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ranges between 37% and 53%, and the onset of hepatotoxicity varies widely from a few days to several months after lapatinib administration (Moon et al., 2019). Treatment using natural medicine can be considered in overcoming the side effects of lapatinib drug use.

Kilemo (Litsea cubeba) has been traditionally used in communities as a herbal remedy to address various health issues, including inflammation, infections, and digestive disorders. This plant is rich in bioactive compounds, particularly polyphenols, which contribute to its therapeutic properties. Numerous studies have evaluated the antioxidant activities, toxicity profiles, and DNA damage protective effects of various solvent extracts from Litsea cubeba fruits. The findings indicate that the methanol extract exhibits significant antioxidant activity and demonstrates potential protection against DNA damage (Seal et al., 2020).

Methanol concentrate of the plant indicated better cell reinforcement exercises when contrasted with other dissolvable concentrates, the quantity of phenolic and polyphenolic compounds in L. cubeba by HPLC were done with the methanol concentrate of the plant. Kilemo (*Litsea cubeba*) is an endemic plant from Central Kalimantan that contains many compounds, including naringenin, ellagic acid, caffeic acid, ferulic acid, and syringic acid, which have the potential as anti-breast cancer through regulation of the HER2 (Human epidermal growth factor receptor-2) oncogene (Seal et al., 2020). Naringenin, ellagic acid, caffeic acid, ferulic acid, and syringic acid exhibit promising anticancer properties against HER2-positive cancers. These compounds have been shown to

inhibit cell growth and induce apoptosis by modulating HER2 expression and signaling pathways. Their combined antioxidant and anti-inflammatory effects highlight their potential as therapeutic agents in cancer treatment.

HER2 is a membrane protein tyrosine kinase (TK) and oncogene that is overexpressed and gene-amplified in about 20% of breast cancers (Zhai et al., 2023). Normal tissues have a low complement of HER2 membrane protein. When activated, it provides cells with strong proliferation and antiapoptotic signals to promote rapid cancer cell growth. In breast cancer, HER2 is the dominant TK receptor, amplified in 20% of cases (Sohrab & Kamal, 2022). HER2 has no ligand and relies on heterodimerization with other receptors or homodimerization with itself when expressed at very high levels to be activated (Ahn et al., 2020). Before further pharmacological activities were carried out, this research was conducted for basic drug development studies. As a foothold for potential drugs that target HER2, it is necessary to tether the compounds contained in the kilemo plant to determine the existing interactions. A computational molecular docking study and ADMET (absorption, distribution, metabolism, excretion, and toxicity) prediction were used in this study. The results of this study will be the basis for drug development from the kilemo plant as an anti-breast cancer candidat.

MATERIAL AND METHODS

The device used in this research was a Lenovo IdeaPad Flex 5 computer with the following specifications: CPU: AMD Ryzen™ 5 5700U (6-Core/12-Thread, up to 4 GHz) 8GB DDR4-3200Mhz RAM. Software used (software): Avogadro, Chem Office Suite 2019 v19.0.0.22, Autodock 4.2.6, Biovia Discovery Studio (BDS), and the pKCSM and SwissADME websites.

The material used in this study was the protein structure of 3PP0, a breast cancer activation protein, obtained from https://www.rcsb.org/. The compounds used as new ligands were obtained from the literature of kilim plant phytochemical journals. The compounds obtained were processed in 3D form from https://pubchem.ncbi.nlm.nih.gov/.

Method

Protein Preparation and Docking Method Validation

Protein Preparation and Docking Method Validation Protein preparation is a process to separate the receptor and native ligand that was required before the molecular docking. The target protein was obtained through the Protein Data Bank (PDB). The separation between native ligands, macromolecules, and some other molecules, such as water and cofactors, from the receptor was done using BDS software. The receptor was found after separating macromolecules with native ligands and water. Meanwhile, the native ligand was obtained after separating the ligand, macromolecule, and water.

Redocking was performed after the native ligand was obtained from separating protein components. This process required forming a grid box with a center point to obtain the coordinates of the native ligand that will later be used in molecular docking. This validation process was needed to obtain the root mean square deviation (RMSD) value; a value of less than 3 indicates that the method results were close to the experimental. A small RMSD value indicated that the position of the native ligand was close to the crystallographic results (Syahputra et al., 2022).

Ligand Molecular Docking Test Process

The test ligands found in PubChem were geometry-optimized using Avogadro software. ChemDraw software was used to minimize the energy of the test ligands and obtain a more stable ligands structure. Thus, the ligands were ready for molecular docking using Autodock-4 software. Molecular docking used the native ligand coordinates on the redocking results with grid box coordinates X, Y, and Z. The docking was done by tethering the optimized test ligand to the receptor.

Visualization and Analysis of Docking Results

The best-appearing result with the lowest binding energy of molecular docking between the test ligand and receptor was then visualized. The docking result analysis parameters used include the amount of binding energy (AG), inhibition constant (IC), the number of binding interactions, and amino acid residues.

Pharmacokinetic Profile Prediction with ADMET Parameters

ADMET analysis is the main prediction that affects drug kinetics (Guan et al., 2018), and it is predicted on the pKCSM and SwissADME websites. The prediction of absorption parameters is based on intestinal absorption and P-glycoprotein substrate values. Distribution parameters were observed through BBB (Blood-brain barrier) and CNS (Central nervous system) permeability values. Metabolism was analyzed through substrates of CYP2D6 and CYP3A4. Excretion parameters observed were total clearance (CLtotal) and renal substrate OCT2 (Ramadhan et al., 2024). AMES toxicity and hepatotoxicity were used as parameters of toxicity

RESULTS AND DISCUSSION

Protein Preparation and Docking Method Validation

The docking of a test ligand or compound to a protein receptor was the principle of molecular docking to predict the orientation and position of the test ligand when it binds to the protein receptor. The test ligand was the lowest energy ligand to achieve the best interaction. The crystal structure of the kinase domain of human HER2 (PDB code: 3PP0) has been prepared by removing native ligands, water molecules, and cofactors (Figure 1).

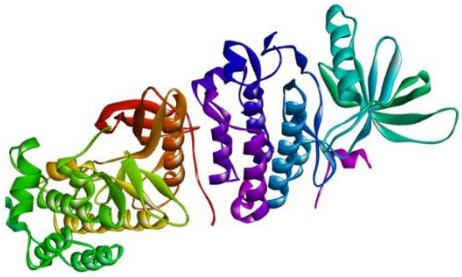

Figure 1. Crystal Structure of the Kinase Domain of Human HER2

The crystal kinase domain of human HER2 was a complex human structure with high resolution. The selective HER2 kinase domain is a protein's activation and inhibition functions at the molecular level. Aetgeerts et al. (2011) showed that interactions in the glycine-rich region prevent intrinsic catalytic interactions in HER2. This suggests that the HER2 kinase domain was an essential functional site in developing breast cancer drugs with better specificity (Aertgeerts et al., 2011).

The redocking process was performed to validate the docking method using Autodock-4 software. The native ligand 1, as the active side,

was found after the protein preparation process and has been optimized for geometry and energy minimization. The result of grid box formation with the centre point, as shown in Table 1, showed the number of grid points 40 with coordinates (X:16,387; Y:17,394; Z:26,218) and grid distance 0.375 A (strong). The RSMD value obtained was 0.693 A; this showed that the redocking results have no significant difference from the crystallographic results, as shown in Figure 2. RSMD value >3 indicates a significant difference in native ligands (Syahputra et al., 2022).

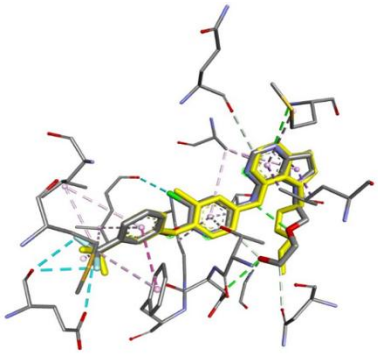

Figure 2. The Results of Redocking Validation between Native Ligand (native ligand: grey color ; redocking native ligand: yellow color)

Visualization and Analysis of Docking Results

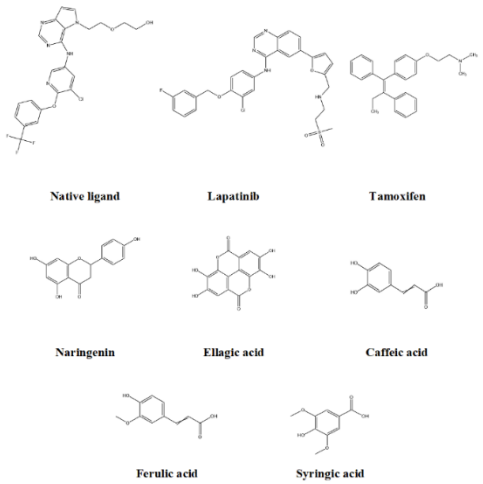

Figure 3. Structure of *Litsea cubeba* compounds, native ligand, and control

The native and test ligands were visualized in 2D using the ChemDraw software. The test ligands used in this research were naringenin, ellagic acid, caffeic acid, ferulic acid, and syringic acid, which were the main active compounds in *Litsea cubeba* from ethanolic extract of High Performance Liquid Chromatography (HPLC) results (Seal et al., 2020). The optimized test ligands obtained a stable and better molecular structure (Figure 3).

The results of molecular docking of Litsea cubeba compounds with HER2 kinase domain conducted using grid

coordinates during the validation of the docking method showed significant activity. Observation of affinity binding energy (ΔG) and inhibition constant (IC) were obtained using the best conformational model (lowest energy). Amino acid bond elucidation was performed to identify hydrogen bonds and non-hydrogen bonds. The potentials of the kilemo plant compounds as a suitable HER2 inhibitor are shown in Table 2..

Table 1. The Redocking Validation

Native Ligand	Number of Grid			Grid Coordinate			Grid Spacing	RMSD
	X	Y	Z	X	Y	Z		
2-{2-[4-({5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol	40	40	40	16.387	17.394	26.218	0.375 A	0.693 A

Table 2. Results of Molecular Docking Analysis between Native Ligands, Test Ligands, and Controls for the Protein Kinase Domain of Human HER2

Compound/Ligand	Binding Affinity Energy (ΔG) (kcal/mol)	Inhibition Constant (IC) (μM)	Binding and Amino Acid Residues	
			Hydrogen Bonds	Non-Hydrogen Bonds
Native ligand	-10.13	37.28	MET^{801,} ASN^{850,} ARG^{849}, GLN^{799} THR^{862}	MET^{774,801} GLU^{770,} LEU^{726,785,796,852}, PHE^{864}, ALA^{751}, VAL^{734}, LYS^{753}
Lapatinib (control)	-9,20	180,09	ARG^{849}, THR^{862}, GLN^{799}	ASP^{863}, ALA^{751}, LEU^{726,785,} ^{796,852}, LYS^{753}, VAL^{734}, CYS^{805}
Tamoxifen (control)	-9,97	49,41	SER^{783}, THR^{862}	ALA^{751}, LEU^{726,852}, VAL^{734}, LYS^{753}
Naringenin	-8.60	493.67	SER^{783}, THR^{862}, ARG^{849}, ASN^{850}, LYS^{753}, ALA^{751}, LEU^{796}	LEU^{852}, VAL^{734}
Ellagic acid	-7.76	2.05	GLN^{799}, MET^{801}, ARG^{849}, ASN^{850}, GYL^{729}	LEU^{729,852}, ALA^{751}, VAL^{734}, LYS^{753}
Caffeic acid	-6.40	20.46	THR^{862,798}, SER^{783}, ASP^{863}, LYS^{753}, GLU^{770}, GYL^{865}	PHE^{864}, MET^{774}, LEU^{785,796}
Ferulic acid	-5.65	72.38	ASP^{863}, MET^{801}, GLN^{799}, THR^{862}, LEU^{800}	LEU^{796}, VAL^{734}, ALA^{751}, LYS^{753}
Syringic acid	-5.53	88.75	ASP^{863}, ARG^{784}, SER^{783}, GLU^{770}	PHE^{864}

The molecular docking results of naringenin found an energy affinity of -8.60 kcal/mol with an inhibition constant of 493.67 µM. Naringenin interacts with hydrogen bonds through residues SER783, THR862, ARG849, ASN850, LYS753, ALA751, LEU796, and LEU852. In addition to interacting with hydrogen bonds, Figure 4 shows that naringenin interacts with alkyl bonds through residue VAL734. In the research of Salehi et al. (2019), naringenin inhibits breast cancer cell migration through inflammatory and apoptotic cell signaling pathways. Naringenin-induced cell death was associated with cell cycle changes and promoting cellular apoptosis (Salehi et al., 2019).

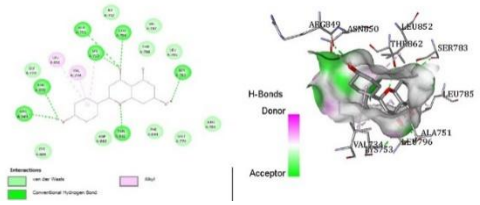

Figure 4. Amino Acid Interaction and Visualization of Molecular Docking Results of Naringenin

The ellagic acid compound shows molecular docking results with an energy affinity of -7.76 kcal/mol with an inhibition constant of 2.05 µM. Figure 5 shows the amino acid interactions in hydrogen bonds on residues GLN799, MET801, ARG849, ASN850, and GYL729. Other interactions form pi-alkyl hydrophobic bonds on residues LEU729, LEU852, ALA51, VAL734, and LYS753. These results align with previous research that Ellagic acid compounds have potential as proliferation inhibitors, encourage apoptosis, inhibit metastasis, and tumor cell invasion through different molecular mechanisms, especially malignant tumors such as breast cancer (Jafari Karegar et al., 2023).

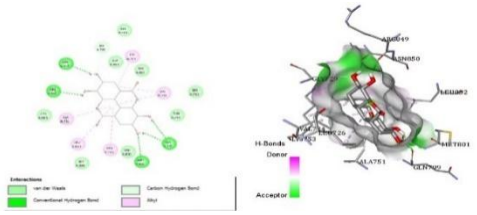

Figure 5. Amino Acid Interaction and Visualization of Molecular Docking Results of Ellagic Acid

Based on the docking results, Figure 6 shows that caffeic acid has hydrogen bond interactions with residues THR862, THR798, SER783, ASP863, LYS753, GLU770, and GYL865. In addition, this compound also has pi-alkyl bond hydrophobic interactions with residues PHE864, MET774, LEU785, and LEU796. This compound has an affinity of -6.40 kcal/mol with an inhibition constant of 20.46 µM. Caffeic acid has vigorous antiradical activity in

breast tumors. This compound induces inflammatory mediators that result in apoptosis by inhibiting the TRIF, TLR4, and IRAK4 pathways (Alam et al., 2022).

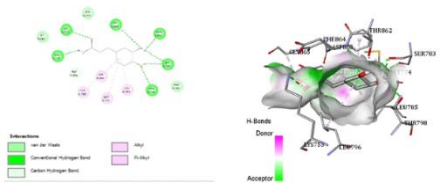

Figure 6. Amino Acid Interaction and Visualization of Molecular Docking Results of Caffeic Acid

The molecular docking results in Figure 7 show an affinity energy of -5.65 kcal/mol with an inhibition constant of 72.38 µM. The interactions formed are hydrogen bonds ASP863, MET801, GLN799, THR862, and LEU800. This compound found pi-alkyl hydrophobic bonds through residues LEU796, VAL734, ALA751, and LYS753. In their research, Zhai et al. (2023) showed that ferulic acid had antioxidant, anti-inflammatory, antifibrosis, and anti-cancer properties. The anti-cancer activity of ferulic acid is in the form of induction of apoptosis by p53 and ROS pathways, inhibition of proliferation through cell cycle blockade and protein kinase B pathways, and inhibition of tumor cell metastasis through vascular endothelial growth factor (VEGF) (Bao et al., 2023; Cao et al., 2022; Zhai et al., 2023).

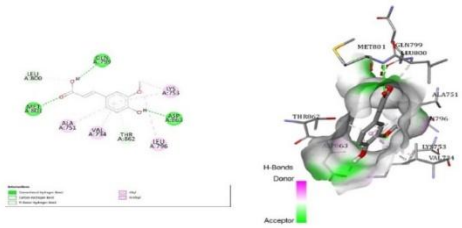

Figure 7. Amino Acid Interaction and Visualization of Molecular Docking Results of Ferulic Acid

The molecular docking syringic acid results found an affinity energy of -5.53 kcal/mol with an inhibition constant of 88.75 µM. This compound has hydrogen bond interactions through residues ASP863, ARG784, SER783, and GLU770. Figure 8 shows the formation of hydrophobic bonds through pi-alkyl bonds through residue PHE864. Syringic acid has been shown to have antioxidant, anti-inflammatory, antimicrobial, and anti-cancer activities and is a hepato-protective agent (Adeyi et al., 2023; Pei et al., 2021). Anti-cancer activation through increasing ROS, regulating mTOR as a selective induction of apoptosis, and increasing DNA damage to significant proliferative genes in cancer (Mihanfar et al., 2021). In vivo, tests conducted by Adeyi et al. (2023) showed better effectiveness of syringic

acid than ascorbic acid as a hepatoprotection (Adeyi et al., 2023).

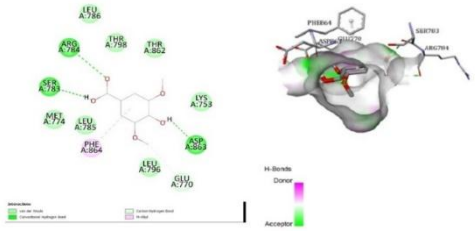

Figure 8. Amino Acid Interaction and Visualization of Molecular Docking Results of Syringic Acid

Through molecular docking analysis, it was found that two amino acid bonds play an active role in the breast cancer treatment process by inhibiting the overexpression of HER2. The threonine (THR) hydrogen bond is active in cancer cell proliferation (Colleti et al., 2019). The non-hydrogen amino acid bond, valine (VAL) at residue 734, can help the compound interact with HER2 (Sanger et al., 2023). However, due to more parameters meeting the requirements, the further development of its potency is recommended.

Pharmacokinetic Profile Prediction with ADMET Parameters

Pharmacokinetic analysis was performed using ADMET parameters. Abdullah et al. (2021) said if a drug is absorbed through the intestine with a value <30%, it has poor absorption (Abdullah et al., 2021). The compound that has low absorption is ellagic acid. BBB permeability was measured as log BB. If the value is >0.3, it will be easier to cross the blood-brain barrier. BBB permeability will be said to be poor if log BB <-1. The CNS distribution parameter was measured as log PS, which can penetrate the CNS if log PS >-2 (Abdullah et al., 2021). The compounds have poor blood-brain barrier permeability (Table 3). All compounds showed that they can penetrate the CNS with a p>-2 value. CYP2D6 and CYP3A4 enzymes cannot metabolize all compounds so it will take longer to be digested. Total clearance (CLtotal) indicates the combination of hepatic and renal clearance. The higher the CL total value, the faster the compound is excreted from the body. Organic cation transporter 2 (OCT2) substrate describes the displacement and clearance of the drug in the body. However, it also depicts potential contraindications. The analysis proved that all compounds were not OCT2 substrates (Abdul-Hammed et al., 2022; Abdullah et al., 2021).

AMES Toxicity describes mutagenic toxicity; both controls (lapatinib and tamoxifen) were not mutagenically toxic.

The results of the compound analysis also showed the absence of mutagenic toxic potential. Further toxicity was observed through its hepatic damaging properties. Lapatinib is one of the anti-cancer drugs that damage the liver. Based on the analysis, all active compounds in the kilemo plant do not damage the liver. This is one of the opportunities to develop a safe anti-cancer through compounds in the kilemo plant. The incidence of hepatotoxicity was reported to begin after the use of lapatinib in a few days to several months (Moon et al., 2019).

In addition, some rules must be met to determine the feasibility of a drug candidate, namely the Lipinski rule. A drug candidate must have a molecular mass requirement ≤500 g/mol, log P ≤5, have a hydrogen donor ≤5, and have a hydrogen acceptor ≤10 (Bojarska et al., 2020). All compounds have met the Lipinski rule except for ellagic acid, which has excess hydrogen donors (Table 4). However, this does not make an obstacle for further development, considering that more parameters have met the requirements.

Table 3. Pharmacokinetic and Toxicity Prediction

Compounds	**Intestinal Absorption (%)**	**P-glycoprotein substrate**	**BBB Permeability**	**CNS Permeability**	**CYP2D6 Substrate**	**CYP3A4 Substrate**	**Total Clearance (log ml/min/kg)**	**Renal OCT2 Substrate**	**AMES Toxicity**	**Hepatotoxicity**
Lapatinib	100	Yes	-1,11	-3,213	No	Yes	0,614	No	No	Yes
Tamoxifen	93,55	No	0,888	-2,165	No	Yes	0,546	No	No	No
Naringenin	54,782	No	-0,706	-3,848	No	No	1,221	No	No	No
Ellagic acid	36,68	Yes	-0,744	-4,031	No	No	1,108	No	No	No
Caffeic acid	43,958	No	-0,742	-3,855	No	No	1,347	No	No	No
Ferulic acid	93,178	Yes	-0,284	-2,534	No	No	0,591	No	No	No
Syringic acid	68,78	No	-0,754	-3,512	No	No	0,627	No	No	No
Requirement	**>30%**	-	**≥0,3**	**≥-2**	-	-	**Higher is better**	-	-	-

Table 4. Lipinski Rule Evaluation

Compounds	Hydrogen Donor	Hydrogen acceptor	Molecular weight (g/mol)	Log P
Lapatinib	2	8	581,069	6,1391
Tamoxifen	0	2	391,684	6,9264
Naringenin	4	5	286,368	0,1877
Ellagic acid	6	8	318,322	-2,8634
Caffeic acid	4	4	190,239	-0,4008
Ferulic acid	2	4	194,186	1,4986
Syringic acid	3	5	206,238	-0,902

CONCLUSION

Based on in silico studies of the main active compounds of Litsea cubeba, two compounds with the best energy affinity to the protein kinase domain of human HER2 were obtained, namely naringenin and ellagic acid. Docking results showed that two amino acid interactions played an active role in the delivery of compounds to the receptor, namely THR862 and VAL734. The pharmacokinetics of the six test compounds gave results that met the requirements. Toxicity prediction shows that the chemical compounds in the kilemo plant are not hepatotoxic as occurs in the anti-cancer drug lapatinib.

REFERENCES

Abdul-Hammed, M., Adedotun, I. O., Olajide, M., Irabor, C. O., Afolabi, T. I., Gbadebo, I. O., Rhyman, L., & Ramasami, P. (2022). Virtual screening, ADMET profiling, PASS prediction, and bioactivity studies of potential inhibitory roles of alkaloids, phytosterols, and flavonoids against COVID-19 main protease (Mpro). *Natural Product Research*, *36*(12), 3110–3116. https://doi.org/10.1080/14786419.2021.1935933

Abdullah, S. S., Putra, P. P., Antasionasti, I., Rundengan, G., Suoth, E. J., Abdullah, R. P. I., & Abdullah, F. (2021). Analisis Sifat Fisikokimia, Farmakokinetik Dan Toksikologi Pada Pericarpium Pala (*Myristica Fragransa*) Secara Artificial Intelligence. *CHEMISTRY PROGRESS*, *14*(2), 81. https://doi.org/10.35799/cp.14.2.2021.37112

Adeyi, O. E., Somade, O. T., Ajayi, B. O., James, A. S., Adeyi, A. O., Olayemi, Z. M., & Tella, N. B. (2023). Syringic acid demonstrates better anti-apoptotic, anti-inflammatory

and antioxidative effects than ascorbic acid via maintenance of the endogenous antioxidants and downregulation of pro-inflammatory and apoptotic markers in DMN-induced hepatotoxicity in rats. *Biochemistry and Biophysics Reports*, *33*. https://doi.org/10.1016/j.bbrep.2023.101428

Aertgeerts, K., Skene, R., Yano, J., Sang, B. C., Zou, H., Snell, G., Jennings, A., Iwamoto, K., Habuka, N., Hirokawa, A., Ishikawa, T., Tanaka, T., Miki, H., Ohta, Y., & Sogabe, S. (2011). Structural analysis of the mechanism of inhibition and allosteric activation of the kinase domain of HER2 protein. *Journal of Biological Chemistry*, *286*(21), 18756–18765. https://doi.org/10.1074/jbc.M110.206193

Ahn, S., Woo, J. W., Lee, K., & Park, S. Y. (2020). HER2 status in breast cancer: Changes in guidelines and complicating factors for interpretation. In *Journal of Pathology and Translational Medicine* (Vol. 54, Issue 1, pp. 34–44). Seoul National University. https://doi.org/10.4132/jptm.2019.11.03

Bao, X., Li, W., Jia, R., Meng, D., Zhang, H., & Xia, L. (2023). Molecular mechanism of ferulic acid and its derivatives in tumor progression. In *Pharmacological Reports* (Vol. 75, Issue 4, pp. 891–906). Springer Science and Business Media Deutschland GmbH. https://doi.org/10.1007/s43440-023-00494-0

Bojarska, J., Remko, M., Breza, M., Madura, I. D., Kaczmarek, K., Zabrocki, J., & Wolf, W. M. (2020). A supramolecular approach to structure-based design with a focus on synthons hierarchy in ornithine-derived ligands: Review, synthesis, experimental and in silico studies. *Molecules*, *25*(5). https://doi.org/10.3390/molecules25051135

Bray, F., Laversanne, M., Sung, H., Ferlay, J., Siegel, R. L., Soerjomataram, I., & Jemal, A. (2024). Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, *74*(3), 229–263. https://doi.org/10.3322/caac.21834

Cao, Y., Zhang, H., Tang, J., & Wang, R. (2022). Ferulic Acid Mitigates Growth and Invasion of Esophageal Squamous Cell Carcinoma through Inducing Ferroptotic Cell Death. *Disease Markers*, *2022*. https://doi.org/10.1155/2022/4607966

Colleti, C., Melo-Hanchuk, T. D., Silva, F. R. M. da, Saito, Â., & Kobarg, J. (2019). Complex interactomes and post-translational modifications of the regulatory proteins HABP4 and SERBP1 suggest pleiotropic cellular functions. *World Journal of Biological Chemistry*,

10(3), 44–64. https://doi.org/10.4331/wjbc.v10.i3.44

Guan, L., Yang, H., Cai, Y., Sun, L., Di, P., Li, W., & Liu, G. (2018). ADMET-score – a comprehensive scoring function for evaluation of chemical drug-likeness. *Medchemcomm*.

Jafari Karegar, S., Aryaeian, N., Hajiluian, G., Suzuki, K., Shidfar, F., Salehi, M., Ashtiani, B. H., Farhangnia, P., & Delbandi, A. A. (2023). Ellagic acid effects on disease severity, levels of cytokines and T-bet, RORγt, and GATA3 genes expression in multiple sclerosis patients: a multicentral-triple blind randomized clinical trial. *Frontiers in Nutrition*, *10*. https://doi.org/10.3389/fnut.2023.1238846

Łukasiewicz, S., Czeczelewski, M., Forma, A., Baj, J., Sitarz, R., & Stanisławek, A. (2021). Breast cancer—epidemiology, risk factors, classification, prognostic markers, and current treatment strategies—An updated review. In *Cancers* (Vol. 13, Issue 17). MDPI. https://doi.org/10.3390/cancers13174287

Mihanfar, A., Darband, S. G., Sadighparvar, S., Kaviani, M., Mirza-Aghazadeh-Attari, M., Yousefi, B., & Majidinia, M. (2021). In vitro and in vivo anticancer effects of syringic acid on colorectal cancer: Possible mechanistic view. *Chemico-Biological Interactions*, *337*. https://doi.org/10.1016/j.cbi.2020.109337

Moon, J. Y., Han, J. M., Seo, I., & Gwak, H. S. (2019). Risk factors associated with the incidence and time to onset of lapatinib-induced hepatotoxicity. *Breast Cancer Research and Treatment*, *178*(1), 239–244. https://doi.org/10.1007/s10549-019-05382-x

Pei, J., Velu, P., Zareian, M., Feng, Z., & Vijayalakshmi, A. (2021). Effects of Syringic Acid on Apoptosis, Inflammation, and AKT/mTOR Signaling Pathway in Gastric Cancer Cells. *Frontiers in Nutrition*, *8*. https://doi.org/10.3389/fnut.2021.788929

Ramadhan, M. M., Utami, D., & Yuliani, S. (2024). In Silico Study of Purple Yam Anthocyanin Compounds (Dioscorea alata L.) As MAO-B and COMT Inhibitors in Parkinson's Disease. In *Journal of Pharmaceutical Science* (Vol. 20, Issue 1). http://journal.uad.ac.id/index.php/Media-Farmasi/indexmediafarmasi@pharm.uad.ac.id

Salehi, B., Fokou, P. V. T., Sharifi-Rad, M., Zucca, P., Pezzani, R., Martins, N., & Sharifi-Rad, J. (2019). The therapeutic potential of naringenin: A review of clinical trials. In *Pharmaceuticals* (Vol. 12, Issue 1). MDPI AG. https://doi.org/10.3390/ph12010011

Sanger, G., Wonggo, D., Taher, N., Dotulong, V., Setiawan, A. A., Permatasari, H. K., Maulana, S., Nurkolis, F., Tsopmo, A., & Kim, B. (2023). Green seaweed Caulerpa racemosa - Chemical constituents, cytotoxicity in breast cancer cells and molecular docking simulation. *Journal of Agriculture and Food Research*, *12*. https://doi.org/10.1016/j.jafr.2023.100621

Seal, T., Chaudhuri, K., Pillai, B., Chakrabarti, S., Mondal, T., & Auddy, B. (2020). Evaluation of antioxidant activities, toxicity studies and the DNA damage protective effect of various solvent extracts of Litsea cubeba fruits. *Heliyon*, *6*(3). https://doi.org/10.1016/j.heliyon.2020.e03637

Sohrab, S. S., & Kamal, M. A. (2022). Screening, Docking, and Molecular Dynamics Study of Natural Compounds as an Anti-HER2 for the Management of Breast Cancer. *Life*, *12*(11). https://doi.org/10.3390/life12111729

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians*, *71*(3), 209–249. https://doi.org/10.3322/caac.21660

Syahputra, R., Utami, D., Widyaningsih, W., Dahlan, A., Soepomo, J., Janturan, S., Farmakologi dan FarmasiKlinik, D., & Ahmad Dahlan, U. (2022). Studi Docking Molekuler Aktivitas Penghambatan Enzim Tirosinase Ubi Jalar (Ipomoea batatas L. Lam). In *Pharmacon: JurnalFarmasi Indonesia* (Vol. 19, Issue 1). http://pubchem.ncbi.n

Zhai, Y., Wang, T., Fu, Y., Yu, T., Ding, Y., & Nie, H. (2023). Ferulic Acid: A Review of Pharmacology, Toxicology, and Therapeutic Effects on Pulmonary Diseases. In *International Journal of Molecular Sciences* (Vol. 24, Issue 9). Multidisciplinary Digital Publishing Institute (MDPI). https://doi.org/10.3390/ijms24098011

Zhou, S., Liu, S., Zhao, L., & Sun, H. X. (2022). A Comprehensive Survey of Genomic Mutations in Breast Cancer Reveals Recurrent Neoantigens as Potential Therapeutic Targets. *Frontiers in Oncology*, *12*. https://doi.org/10.3389/fonc.2022.786438