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Evaluating quercetin analogs from Indonesian bioflavonoids for breast cancer: Insights from *in silico* and cytotoxicity assays

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ABSTRACT

Introduction: Breast cancer remains a leading cause of cancer-related mortality, with HER2-positive and triple-negative breast cancer presenting major therapeutic challenges. Natural bioactive compounds, particularly flavonoids, have gained attention for their anticancer properties. Among them, quercetin and its analogs have exhibited cytotoxic and apoptotic effects against various cancer cell lines. This study explores the anticancer potential of quercetin-derived bioflavonoids from Indonesian plants through bioinformatics and cytotoxicity assays.

Methods: Fifteen quercetin-derived bioflavonoids from Indonesian plants (MarkHerb database) were analyzed *in silico* using AutoDock and GROMACS to predict interactions with the HER2 receptor. Cytotoxicity against T47D breast cancer cells was assessed using the MTT assay to determine IC_{50} values.

Results: The in silico analysis revealed strong receptor interactions, with tiliroside exhibiting a binding energy of -8.51 kcal/mol, which is close to that of the native ligand (-10.54 kcal/mol). Tiliroside demonstrated similar amino acid interactions and post-MD stability (100 ns) to the native ligand, outperforming quercetin. Additionally, the MTT assay indicated a moderate cytotoxic effect with an IC_{50} value of 166.32 µg/mL.

Conclusion: Tiliroside shows promise as a breast cancer therapeutic candidate, supporting further exploration of bioflavonoid-based therapies. This study highlights the potential of natural bioflavonoids in anticancer research through bioinformatics and in vitro analysis.

Implication for health policy/practice/research/medical education:
The findings of this study highlight the potential of quercetin-derived bioflavonoids, particularly tiliroside, as a promising candidate for breast cancer therapy. These insights contribute to the development of bioflavonoid-based alternatives for breast cancer treatment and emphasizes the need for continued investigation into natural anticancer agents.

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Introduction

Breast cancer remains one of the most common types of cancer and the leading cause of cancer-related deaths among women. According to the Global Cancer Observatory (GLOBOCAN) 2022, it is estimated that there will be 2.3 million new cases of breast cancer and 666,000 breast cancer-related deaths worldwide. These figures represent 23.8% of all new cancer cases and 15.4% of cancer deaths among women, respectively. Regionally, East Asia reported the highest number of cases (480,019; ASIR: 37.54 per 100,000), while South-Central Asia recorded the highest number of deaths (135,348; ASMR: 13.41 per 100,000). The incidence rate is still increasing in women aged between 40-45 years, early diagnosis and therapy carried out quickly and precisely is the main approach to the arrangement of breast cancer patients (1).

Human epidermal growth factor receptor 2 (HER2), also known as ErbB2, is a transmembrane tyrosine kinase receptor that plays a critical role in cell growth, differentiation, and survival. HER2 is overexpressed in

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approximately 15%-20% of breast cancer cases, making it a significant biomarker and therapeutic target. The overexpression of HER2 is associated with aggressive tumor behavior, poor prognosis, and increased resistance to standard therapies, emphasizing its critical role in breast cancer pathophysiology (2). HER2-driven cancers are characterized by rapid cell proliferation, enhanced tumor invasiveness, and resistance to apoptosis. These attributes arise from HER2's ability to activate multiple downstream signaling pathways, including the PI3K/AKT/mTOR and RAS/RAF/MEK/ERK pathways. These pathways promote survival, angiogenesis, and metastasis in breast cancer cells, making HER2 a central focus in cancer research and drug development (3).

Targeting HER2 has been a cornerstone in the management of HER2-positive breast cancer. Therapeutic agents such as trastuzumab and pertuzumab (4), monoclonal antibodies that block HER2 signaling, and small molecule tyrosine kinase inhibitors like lapatinib, have significantly improved outcomes for patients with HER2-positive breast cancer. However, challenges remain, such as the emergence of resistance to these therapies and off-target effects, highlighting the need for novel therapeutic approaches (5,6).

With the increasing interest in natural medicine, natural compounds such as flavonols found in various plants have been investigated for their potential to treat cancer (7,8). One of the flavonol group compounds is quercetin which is known as one of the most widely distributed and extensively studied flavonoids (9,10). Its strong antioxidant and anti-inflammatory activities are thought to play a role in treating and protecting against diseases such as cancer. Quercetin is reported to have breast cancer cell death induction activity with a high degree of selectivity. Differences in quercetin preparation may affect the anti-breast cancer effect against T47D cells, which overexpress HER2 (11).

The application of quercetin in the pharmaceutical field is limited due to its poor bioavailability resulting from poor water solubility and poor permeability (12). Some quercetin derivatives such as rutin, isoquercetin and other derivatives that have glucose functional groups have good water solubility and water permeability, but there are still very few studies on their efficacy against breast cancer (13).

Testing the efficacy of a drug candidate can be done by several methods, including *in vitro* and *in silico* tests (14). *In silico* testing is done with computer simulation methods. *In silico* testing is done through the virtual screening technique (15), molecular docking, and molecular dynamics (MD) (16). This technique has become an integral part of the new drug design and development process. The *in vitro* assay used is the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) cytotoxicity method, which is one of the methods used to measure the toxicity of compounds on living cells. This method is based on the conversion of MTT, a pale yellow colored compound, into purplish blue formazan by the mitochondrial enzymes of active living cells. The intensity of the formazan color reflects the number of living cells that are still active (17,18). Based on this, the researchers are interested in using the database of natural ingredient compounds available on the MarkHerb website, which is a provider of native isolates in Indonesia, then testing the activity of flavonols class compounds which are quercetin analogs *in silico* bioinformatics against breast cancer targeting HER2 receptors and *in vitro* tests with the MTT cytotoxic method. This study explores the anticancer potential of quercetin-derived bioflavonoids from Indonesian plants through bioinformatics and cytotoxicity assays.

Materials and Methods

Ligand preparation

The ligands were chosen from 15 flavonol group isolates derived from Indonesian plants, listed and purchasable in the MarkHerb database. The selected flavonoids were those available in sufficient quantities and could be obtained from Indonesian biological sources, such as tiliroside, quercetin, as well as other derivative compounds, which had clear isolation and identification records in the MarkHerb database. Their 3D structures were sourced from the PubChem website. These structures were then optimized using GaussView 6.0 and Gaussian software, employing various parameters, including the Density Functional Theory (DFT) or Hartree-Fock calculation methods, the 3-21G basis set, and vacuum simulation conditions (19).

Receptor preparation

The 3D structure of HER2 was obtained from the Protein Data Bank (PDB) via the Research Collaboratory for Structural Bioinformatics website using PDB code 3PP0. Native ligands/inhibitors and water molecules were removed. The native ligand here was the ligand crystallized on the 3PP0 receptor in PDB with ligand code 03Q and name 2-{2-[4-({5-chloro-6-[3-(trifluoromethyl)phenoxy] pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol, which was recorded to have an IC_{50} against HER2 of 11 nM. The protein was partially charged using a Kollman charge force field and polar hydrogen was added. All steps for protein preparation were performed using AutoDock 4.2 software (20-22).

Molecular docking simulation

To validate the molecular docking, the native ligand-inhibitor complex was separated from the 3PP0 protein. Next, the ligand was docked back to the active site by AutoDock 4.2 software, using the flexible method. The native ligand conformation from the docking process

was compared with the conformation before docking by overlap analysis. Validation was assessed using the root-mean-square deviation (RMSD) parameter, where an RMSD value of less than 2.0 Å indicated the reliability of the method (23)

Molecular docking simulations were performed using the parameters previously validated with native ligands. The 3D structures of quercetin compounds and their analogs were fitted to the active sites of the native ligands. Binding energies and amino acid interactions were analyzed, and the docking results were further examined using Discovery Studio v17 (1,15,24).

Molecular dynamics simulation

Molecular dynamics simulations were performed using GROMACS 2016 software to study the stability and structural fluctuations of quercetin-derived bioflavonoid compounds against breast cancer targets. The simulation started with the preparation of the initial structure, which involved creating topology and parameter files using GROMACS (25), as well as setting up the system with appropriate solvents and ionization i.e. by surrounding the receptor-ligand combination with sodium (Na+) and chloride (Cl-) ions;the system neutralization was accomplished. The Transferable Intermolecular Potentials 3-Point (TIP3P) water model, which describes the interactions between atoms in a water molecule through hydrogen, oxygen, and hydrogen bonds, was used to solve the problem (26). Simulations were performed for 100 ns using the md integrator with a time step of 2 fs and a total simulation step of 50 million steps. Warm-up and equilibration procedures were performed first to ensure the stability of the system temperature and pressure. After the production simulation was completed, post-MD analysis was performed to evaluate the stability and dynamics of the molecules. RMSD analysis was used to monitor the molecular structure changes during the simulation, by checking the conformity of the atomic positions to the reference structure (27). In addition, root mean square fluctuation (RMSF) analysis was used to evaluate the conformational fluctuations of individual residues in the molecule, which provided information regarding the stability and flexibility of certain parts of the molecule. The results of the RMSD and RMSF analyses were extracted using the gmx rms and gmx rmsf commands, and then visualized to gain insight into the MD and potential interactions relevant to cancer inhibition (28).

Cytotoxicity assay

Cytotoxicity testing of sample compounds against T47D breast cancer cells using the MTT assay method was carried out through several stages. First, T47D cells were cultured in RPMI-1640 or DMEM media containing 10% FBS and 1% antibiotics (penicillin-streptomycin), then incubated at 37 °C with 5% CO_2 until they reached 70-80% confluence. Afterwards, the cells were harvested using trypsin-EDTA, counted, and grown in 96-well plates at a density of approximately 5×10^4 cells per well in a volume of 100 µL. The plate was then incubated for 24 hours to allow the cells to adapt and adhere. Next, sample solutions in various concentrations (250, 125, 62.5, 31.25, 15.625, 7.8125, and 3.9 µg/mL) were added to each well, replacing the culture medium, and the cells were again incubated at 37°C with 5% CO_2 for 48 hours (29).

After the incubation period, 10 µL of MTT solution (5 mg/mL in PBS) was added to each well and the plate was re-incubated for 3-4 hours to allow formazan crystals to form. The media in each well was then carefully removed, and 100 µL of DMSO was added to dissolve the formazan crystals, with gentle stirring until the purple color was evenly distributed. Absorbance was measured at a wavelength of 570 nm using a microplate reader, with a reference wavelength of 630 nm. This absorbance data was used to calculate the percentage of cell viability using the cell viability formula (The ratio of sample absorbance to control absorbance multiplied by 100%). Based on the graph of the relationship between sample concentration and percentage of cell viability, the IC_{50} value could be determined, which was the concentration of sample that reduced cell viability by 50%. Each concentration was tested in 4 replicates to ensure the accuracy of the data, and the entire procedure was performed using aseptic technique to avoid contamination (30).

Results

Validation

The native ligand inhibitor crystallized at the HER2 active site (PDB: 3PP0) is a type of HER2 inhibitor. Therefore, we adjusted the amount of torsion of the native ligand to limit its flexibility. The validation showed good results with an RMSD value of 1.12 Å. This shows the strength of this docking method can be used to predict the affinity to HER2 protein (3PP0). The validation results can be seen in Figure 1.

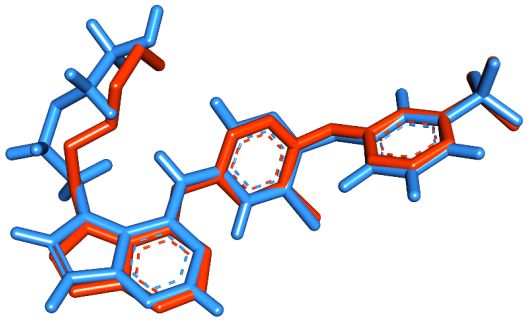

Figure 1. The overlay conformation of native ligand before (blue) and after (read) docking process, with validation results of root mean square deviation.

Molecular docking of ligands against HER2

Quercetin compounds and their analogs include astragalin, tiliroside, hyperoside, nicotiflorin, galangin, casticin, quercitrin, isoquercetin, kaempferol, rutin, fisetin, narcissin, myricetin 3-O-rutinoside, and kumatakenin. The selected analogs were quercetin analogs that could be obtained commercially through the MarkHerb website. Molecular docking of quercetin analogs on HER2 protein showed varying binding energies (Table 1). The lowest binding energy was shown by tiliroside (-8.51 kcal/mol) and quercetin was -6.60 kcal/mol. While the native ligand as a reference showed a binding energy of -10.54 kcal/mol. The conformations produced by each compound show similar amino acid interactions at the active site compared to the native ligand. The native ligand formed 3 hydrogen bonds, while quercetin formed 1 hydrogen bond, and tiliroside formed 2 hydrogen bonds. From the total interactions, it can be seen that the native compound, quercetin, and tiliroside formed interactions with a total of 27, 19, and 23, respectively. Details of ligand-receptor residue interactions can be seen in Table 2 and 2D and 3D visualization of amino acid residue interactions at HER2 active site with native ligand, quercetin (B), and tiliroside in Figure 2.

Table 1. Binding energy of native ligand and quercetin derivatives against the target receptor

Ligand	Binding energy (kcal/mol)
Native	-10.54
Tiliroside	-8.51
Narcissin	-8.07
Myricetin 3-O-rutinoside	-7.98
Nicotiflorin	-7.81
Rutin	-7.06
Quercetin	-6.6
Casticin	-6.51
Fisetin	-6.51
Astragalin	-6.28
Galangin	-6.21
Kumatakenin	-6.21
Isoquercetin	-6.2
Hyperoside	-6.17
Quercitrin	-6
Kaempferol	-5.63

Molecular dynamics simulation

RMSD and RMSF analysis of ligand-receptor complexes

The stability of the ligand complexes was analyzed by MD simulation and compared with the binding of the original ligand as a reference. The tiliroside-HER2 complex was continued for MD analysis, as this is the compound that binds closest to the original ligand value. The stability of the system was measured through RMSD and RMSF at 100 ns simulation (Figures 3A and 3B). For the tiliroside-HER2 complex, the graph shows fluctuations similar to the original ligand. However, the average value of the fluctuation showed similar fluctuations between the two ligands, which was 0.3074 Å in the native ligand-HER2 complex and 0.3071 Å in the tiliroside-HER2 complex. In the RMSF graph, both the native ligand and tiliroside showed very similar fluctuations. Furthermore, the highest fluctuations were shown by residues 706 and 993, responsible for the loop region.

Cytotoxicity test of ligands to T47D cells

Cytotoxicity test of ligands to T47D breast cancer cells was conducted. Figure 4 shows the morphological observations of T47D cells that were still alive and cells that experienced death (dead) after treatment with tiliroside compounds at various dilution levels. T47D cells are one of the breast cancer cell lines often used to evaluate the cytotoxic potential of anticancer compounds. Tiliroside, tested in this study, is one of the bioflavonoid derivatives known to have potential activity against cancer cells.

In Figure 4A (dilution 250), it can be seen that most of the cells appear clearer and more concentrated, indicating the presence of a larger number of live cells. At this dilution, the concentration of tiliroside may not be high enough to induce significant death in T47D cancer cells, so most cells retain their living morphology. Meanwhile, in Figure 4B (dilution 3.9), there is a more significant change in cell morphology, where cell density appears to be reduced, indicating increased cell death. In this dilution, the lower concentration of tiliroside was effective in triggering programmed cell death, so that more cells experienced morphological death. This indicates that tiliroside is capable of exerting cytotoxic effects on T47D cells at certain concentrations, supporting its potential as an effective candidate anticancer compound against HER2+ breast cancer.

The results of the IC_{50} tiliroside test against T47D breast cancer cells showed that this compound had moderate cytotoxic potential. Based on IC_{50}. the value

Table 2. Hydrogen bond and hydrophobic interactions formed between selected ligands and the target protein

Ligand	H-Bond	Hydrophobic	Number of interactions formed
Native	MET801, ASP863, ASN850	LEU725	27
Quercetin	LEU726	VAL734	19
Tiliroside	ASP862, LEU726	-	23

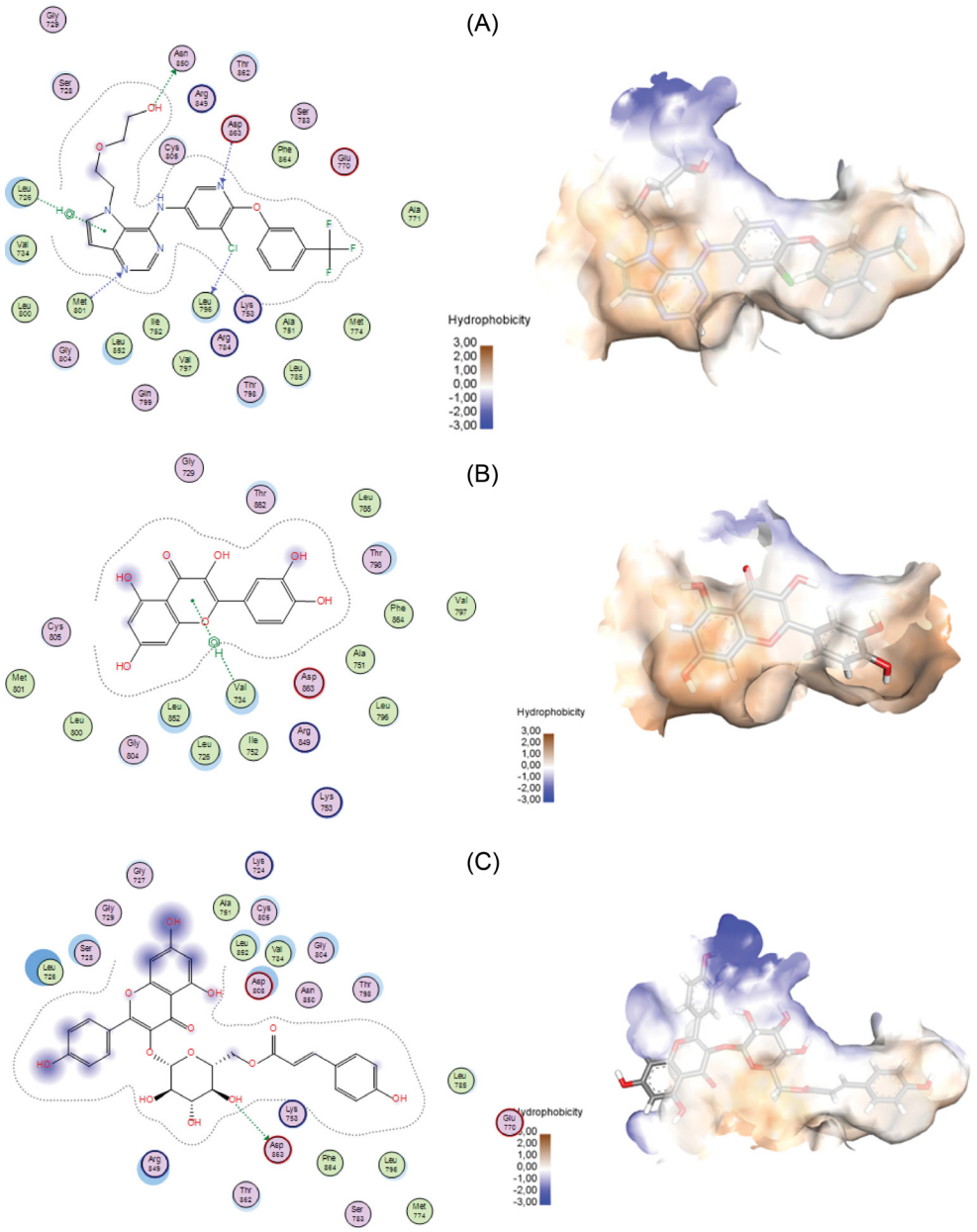

Figure 2. 2D and 3D visualization of HER2 active site interactions with native ligand (A), quercetin (B), and tiliroside (C). Hydrogen bonds and hydrophobic contacts with key residues are highlighted, showing that tiliroside establishes more extensive interactions compared to quercetin.

of tiliroside was obtained from four replicates with a range between 149.37 µg/mL to 181.08 µg/mL, with an average IC_{50} of 166.32 µg/mL and a standard deviation of 13.37. The relatively small standard deviation indicates consistency between replicates. Based on the viability graph (Figure 5), the percentage of T47D cell viability decreased as the concentration of tiliroside increased. At high concentration (250 µg/mL), the cell viability decreased significantly, indicating a strong cytotoxic effect of tiliroside. In contrast with high concentration, at low concentration (3.9 µg/mL), cell viability was still high, indicating that tiliroside had not yet exerted a significant cytotoxic effect at that concentration.

Discussion

HER2 is a tyrosine kinase receptor that plays an important role in the proliferation and development of breast cancer. HER2 overexpression is found in approximately 20-30% of breast cancer cases, which is associated with poor prognosis and resistance to conventional therapy. Targeting HER2 with small molecules such as bioflavonoids is an attractive approach, given the potential of bioflavonoids as safe and affordable anticancer agents. In this study, *in silico* analysis showed that most of the quercetin derivatives isolated from Indonesian biological sources had the ability to interact with the active domain of HER2. The novelty of this research lies in the exploration of

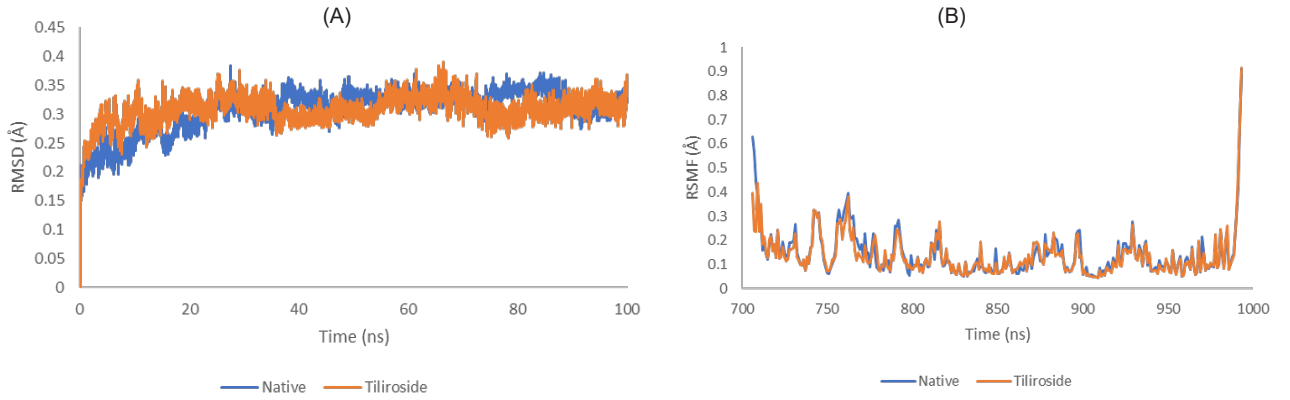

Figure 3. Molecular dynamic simulation analyses of the ligand-protein complexes. (A) RMSD (Root mean square deviation) profiles of the native ligand and tiliroside complex with the target protein over 100 ns simulation showing structural stability; (B) RMSF (Root mean square fluctuation) profiles representing the flexibility of protein residues, indicating comparable fluctuation patterns with slight variations at the C-terminal region.

tiliroside compounds, quercetin derivatives isolated from Indonesian plants, which have not been widely reported in the literature as breast cancer therapeutic candidates with specific HER2 receptor targets. This research combines bioinformatics approach using molecular docking method and MD simulation with experimental validation through cytotoxicity test.

This study successfully explored the potential of quercetin-derived bioflavonoid compounds derived from Indonesian plants against breast cancer, especially those targeting the HER2 receptor. Based on bioinformatics results, tiliroside compounds showed strong molecular interactions with HER2 receptors, as indicated by binding energy values close to native ligands (-8.51 kcal/mol vs. -10.54 kcal/mol). The amino acid interaction of tiliroside was very similar to the native ligand and its broader coverage compared to quercetin as a comparator, indicating a more stable and specific binding potential. This was also confirmed through the results of post-MD analysis for 100 ns, which showed stability similar to the native ligand. The *in-silico* results of this study showed differences in the number and type of interactions formed between native ligands, quercetin, and tiliroside with their target receptors. Based on the data obtained, the native ligand formed three hydrogen bonds with the receptor, while quercetin formed only one hydrogen bond, and tiliroside formed two hydrogen bonds. In addition, the total interactions formed between the three compounds and the receptors were also different, namely 27 interactions for the native ligand, 19 interactions for quercetin, and 23 interactions for tiliroside. The number of hydrogen bonds and total interactions indicate the affinity and stability of the complexes formed between the compounds and the receptor. Hydrogen bonding is one type of interaction important in determining the affinity of a compound to a receptor because it can contribute significantly to the stability of the complex (15,27). The native ligand, which has three hydrogen bonds, showed a stronger ability to form stable interactions with the receptor compared to quercetin and tiliroside. Tiliroside formed two hydrogen bonds and a total of 23 interactions with the receptor, indicating that tiliroside had a higher affinity than quercetin but was still below the native ligand. This can be explained by the number and type of hydrogen bonds and other interactions that occur at the active site of the receptor. The results of MD simulations

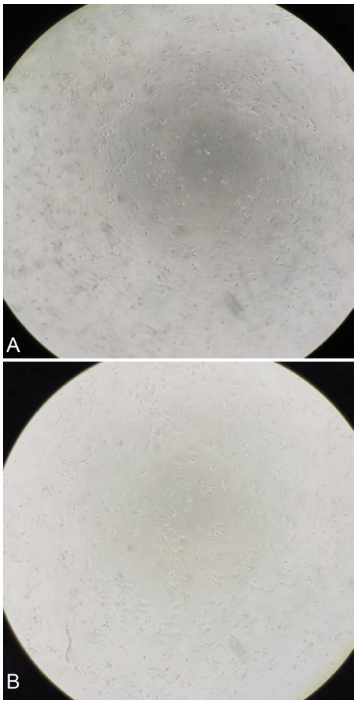

Figure 4. Microscopic observation of T47D breast cancer cells treated with tiliroside at high (250 µg/mL; A) and low (3.9 µg/mL; B) concentrations for 48 hours. The images were taken using an inverted light microscope under ×100 magnification. Reduced cell density and morphological changes such as cell shrinkage and detachment were observed at higher concentrations, indicating cytotoxic effects.

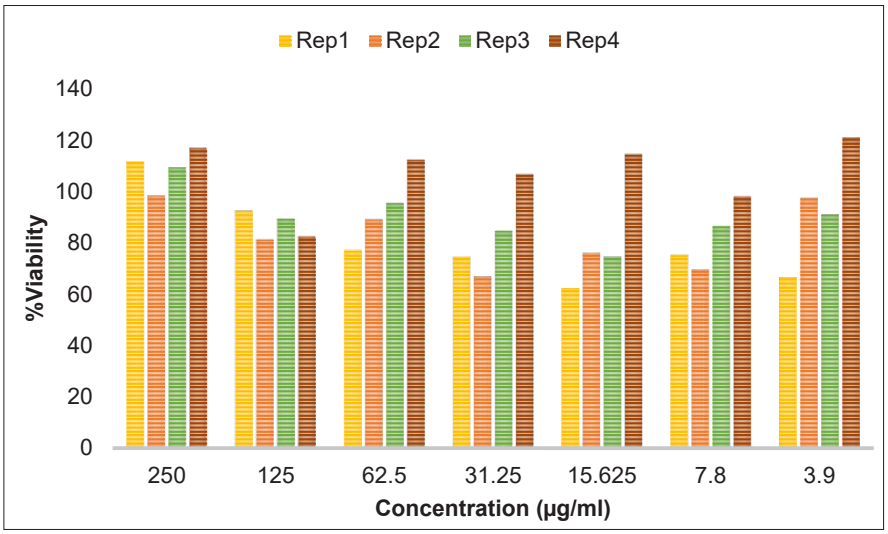

Figure 5. Cytotoxicity profile of the tested compound at various concentrations (250–3.9 µg/mL) against T47D human breast cancer cells. Each concentration was tested in four replicates (Rep1–Rep4). Cell viability was measured after 48 hours of treatment and expressed as a percentage compared to untreated controls.

for 100 ns also confirmed that tiliroside had high stability in interaction with HER2, with stable RMSD values and consistent hydrophobic interactions. This stability is comparable to that of the native ligand, thus strengthening the potential of tiliroside as a candidate HER2 inhibitor.

The cytotoxic assay performed in this study using the MTT method revealed the potential of tiliroside as an anti-breast cancer agent. The cytotoxic assay results also aligned with docking and MD analysis, highlighting the potential of bioflavonoids as anticancer agents due to their mechanisms of action in binding to HER2. From the average IC_{50} (166.32 µg/mL) tiliroside can be categorized as having moderate cytotoxic activity against T47D cells, in accordance with the American National Cancer Institute, where the classification of compound toxicity is based on the IC_{50} value as follows: compounds are categorized as highly toxic if the IC_{50} value is ≤ 20 µg/mL, moderately active or cytotoxic if the IC_{50} value is in the range of 21-200 µg/mL, weak cytotoxic if the IC_{50} value ranges from 201 to 500 µg/mL, and non-toxic if the IC_{50} value is ≥ 500 µg/mL (11,31,32). These results indicate that tiliroside has potential as an anticancer agent. This study supports the hypothesis that quercetin-derived compounds, such as tiliroside, can increase ROS levels in cancer cells to toxic levels, trigger apoptosis, and stop proliferation (33).

Conclusions

The contribution of this research is to reveal the potential of Indonesia's biological resources as a producer of promising active compounds and offer a new approach in evaluating bioactive compounds *in silico* and *in vitro* to support the development of bioflavonoid-based anticancer drugs. This study successfully identified quercetin-derived bioflavonoid compounds from Indonesian plant isolates that have potential anti-cancer activity against breast cancer. Through a bioinformatics approach, interaction modeling between these compounds and breast cancer receptor targets was carried out, as well as cytotoxicity analysis using the IC_{50} test to measure the antiproliferation effect on breast cancer cells. From the analysis, tiliroside showed stronger anticancer activity than other quercetin-derived compounds. These compounds not only have strong interaction potential with relevant molecular targets, but also show lower IC_{50} values, indicating their effectiveness in inhibiting cancer cell growth.

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Visualization: Taufik Muhammad Fakih and Rusdiaman Rusdiaman.
Writing–original draft: Rusli Rusli.
Writing–review & editing: All authors.

Conflict of interests

The authors declare that they have no known conflicts of interest that could have influenced the work reported in this paper.

Ethical considerations

This research did not involve any human or animal participants. Regarding duplication and plagiarism, the research was conducted with academic integrity, ensuring originality and compliance with ethical publishing standards. Furthermore, no part of this study has been submitted or published elsewhere to maintain its novelty and originality.

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