ARTICLE INFO

AUTHOR'S AFFILIATIONS
Faculty of Medicine, Universitas Wijaya Kusuma Surabaya[1], Department of Anatomy, Faculty of Medicine, Universitas Wijaya Kusuma Surabaya[2*], Department of Anatomical Pathology, Faculty of Medicine, Universitas Wijaya Kusuma Surabaya[3]

CORRESPONDING AUTHOR
Candra Rini Hasanah Putri, Department of Anatomy, Faculty of Medicine, Universitas Wijaya Kusuma Surabaya[2]
E-mail: candra.rini.hp@uwks.ac.id

Article history

Received	22-07-2025
Revised	24-02-2026
Accepted	09-03-2026
Available online	31-03-2026

Please cite this article in APA 7th edition style as:
Putra,I. P. W., Putri, C. R. H., & Agusaputra, H. (2026). In Silico Study: Comparison of Binding Affinity of Quercetin and TAK-285 Against HER2 Malignacy Protein. *Jurnal Ilmiah Kedokteran Wijaya Kusuma, 15(1), 17-32*

https://doi.org/10.30742/jikw.v15i1.4735

In Silico Study: Comparison of Binding Affinity of Quercetin and Tak-285 Against HER2 Malignancy Protein

I Putu Widja Putra[1], Candra Rini Hasanah Putri[2], Harman Agusaputra[3]*

Abstract

Background : Cancer is a leading global health challenge, driven by various proteins that promote malignant cell growth—one of which is HER2, a transmembrane receptor tyrosine kinase in the ErbB family. TAK-285 is a well-known HER2 inhibitor. Recently, natural compounds such as quercetin have gained attention for their ability to suppress HER2 overexpression and offer therapeutic potential. **Objective:** This study is to compare the binding affinity between quercetin and the reference inhibitor TAK-285 with the HER2 protein, as well as to analyze the molecular interaction patterns of HER2 using In Silico study. Through this, the study seeks to determine the potential similarity in the inhibition mechanisms of HER2 quercetin and TAK-285. **Methods:** Experimental study using In Silico docking methods, was performed using AutoDock Vina via PyRx 0.8 to evaluate involving docking interactions between quercetin and HER2, as well as TAK-285 and HER2. **Results :** The molecular docking results revealed that Quercetin binds to HER2 with an average binding affinity of –8.04 ± 0.40 kcal/mol, while TAK-285 exhibits a stronger interaction with an average binding affinity of –9.62 ± 0.21 kcal/mol. Despite having a slightly lower binding affinity, quercetin successfully interacts with key residues in the HER2 binding pocket and demonstrates potential as a natural HER2 inhibitor. **Conclusion:** These findings suggest that quercetin may serve as a promising lead compound for HER2-targeted therapy and support further investigation through in vitro and in vivo studies.

Keywords: HER2, In Silico Study, Quercetin, TAK-285.

Original Research Article

INTRODUCTION

Cancer is characterized by uncontrolled cell growth, which allows cells to invade surrounding biological tissues through invasion or migration to distant sites (Aisy et al., 2021). It remains one of the leading causes of death worldwide and represents a major challenge in global health. Hanahan and Weinberg (2011), introduced the concept of the hallmarks of cancer, which describes the fundamental characteristics of malignancy, including sustained proliferative signaling, resistance to growth suppressors, evasion of cell death, as well as the ability to invade tissues and metastasize. According to Sung et al. (2021), there were approximately 19.3 million new cancer cases and nearly 10 million cancer-related deaths globally. In Indonesia, breast cancer ranks first with 65,858 new cases,

accounting for approximately 16.6% of all cancer cases, followed by cervical and lung cancers (Sung et al., 2021).

One critical mechanism involved in malignancy is the activation of receptor tyrosine kinases (RTKs), particularly those in the ErbB family. Among them, the Human Epidermal Growth Factor Receptor-2 (HER2) is a transmembrane tyrosine kinase that shares structural similarities with the Epidermal Growth Factor Receptor (Amtiria & Berawi, 2018). Various studies have been conducted to identify HER2 inhibitors in an effort to suppress malignant cell proliferation. One such inhibitor is TAK-285 (Son et al., 2023).

Recently, increased attention has been given to natural small-molecule compounds that act as potential HER2 inhibitors. One such compound is quercetin (Qu), a flavonoid derived from phenylbenzopyrone structures, commonly found in fruits, plants, and vegetables (Naushafira et al., 2022). In plants, quercetin is present in various glycoside forms, particularly quercetin-3-rutinoside (Lin et al., 2015). It exhibits anticancer activity through anti-proliferative, pro-apoptotic, and anti-angiogenic effects (Putra et al., 2022). Previous in vitro studies have demonstrated its ability to suppress HER2 overexpression, although the underlying molecular mechanism remains unclear (Seo et al., 2016). Based on this evidence and its structural characteristics that may facilitate interaction within kinase ATP-binding domains, this study was designed as a focused mechanistic comparison with the reference HER2 inhibitor TAK-285 rather than a multi-compound screening analysis.

To date, few studies have directly compared the binding potential of quercetin and TAK-285 to the HER2 protein in the context of HER2 oncogenic activation inhibition using in silico methods. This raises the question of whether quercetin inhibits HER2 activity in a manner similar to the reference inhibitor TAK-285. Consequently, this study employs an in silico approach to explore that hypothesis. In silico methods use computer simulations and specific software to identify compounds with high potency and selectivity through molecular computations (Wang et al., 2015). The aim of this study is to compare the binding affinities and molecular interaction patterns of quercetin and the reference inhibitor TAK-285 with the HER2 protein using in silico analysis, this comparison may provide insight into the potential similarity in HER2 inhibition mechanisms between quercetin and TAK-285.

MATERIALS AND METHODS

This study explores the anticancer potential of quercetin through an experimental approach using molecular docking methods. The primary objective is to compare the binding affinity and amino acid residue interactions between quercetin and the reference inhibitor TAK-285 against the Human Epidermal Growth Factor Receptor-2 (HER2) protein using an in silico method. In silico techniques involve computer-based simulations to identify compounds with high potential and selectivity (Wang et al., 2022). The docking procedures involved two main ligand–protein interactions: quercetin with HER2, and TAK-285 with HER2. The results of these docking simulations were then analyzed to compare binding affinities. Docking itself refers to a method used to determine the optimal interaction between a ligand and its receptor (Setiawan and Irawan, 2017)

Data Collection

The initial procedure that must be carried out is to select and obtain a 3D structure from the quercetin compound obtained from the https://pubchem.ncbi.nlm.nih.gov site with 5280343 code, then converted to PDB format using open babel on PyRx and the structure is optimized and made flexible according to docking needs. The three-dimensional structure of the HER2 complex with TAK-285 was obtained from the RCSB Protein Data Bank (PDB ID: 3RCD) (Ishikawa et al., 2011) . The structure is stored in PDB format and cleaned of water molecules as well as innate ligands (TAK-285) using PyMol and stored in PDB form and then converted to PDBQT in PyRx. Next, a molecular docking process was carried out between quercetin with HER2 and TAK-285 with HER2 through the PyRx application. The grid box is determined according to the active area (Binding Pocket) of HER2. The docking parameters use the default PyRx settings for the prediction of 9 best bond confirmations. The results came out,

then 1 confirmation was selected with the lowest (negative) strength value (Binding Affinity) as the main result. Next, visualization of the results through PyMol. To search for amino acid residues involved in the docking of quercetin compounds with HER2 and TAK-285 with HER2 through the LigPlot+ software. Finally, it compares the bond strength values between quercetin compounds with HER2 and TAK-285 with HER2 and compares the amino acid residues involved.

Schedule and Implementation of Data Collection

The data collection process was carried out from October 2023 to June 2025.

Materials of Tools and Instruments Used

The material used in this study is a chemical element data of quercetin compounds and HER2 proteins with reference inhibitors TAK-285. The molecular docking process uses the Autodock Vina PyRx 0.8 software downloaded from the https://sourceforge.net/projects/pyrx/ and visualization using the PyMol application.

Data Processing Techniques

After the bond strength data was collected, the next process was to compare the binding strength of quercetin with HER2 and HER2 with TAK-285. In addition, a comparison of amino acid residues involved in the bond was carried out.

Statistical Analysis

To assess the consistency and reliability of the docking results, each ligand–protein interaction (Quercetin–HER2 and TAK-285–HER2) was subjected to 10 independent docking runs using AutoDock Vina via PyRx. The binding affinity values from each run were recorded and analyzed using Microsoft Excel. The mean (average) and standard deviation of binding affinity values were calculated using the AVERAGE and STDEV.S functions, respectively, to represent central tendency and variability. This approach allows for a comparative evaluation of the binding strength and stability between the two ligands. Additionally, the binding affinity values were interpreted using a threshold-based classification, where values below –6.0 kcal/mol are considered indicative of biologically significant interactions (Chun et al., 2023; Morris et al., 2009)

RESULTS

The separation of the HER2 protein from its native ligand was performed to provide a binding pocket for the test compounds to interact with the target protein. The visualization result (Figure 1) shows the 3D structure of the HER2 protein without its native ligand (TAK-285), where image A represents the ribbon model and image B represents the surface model of the protein chain.

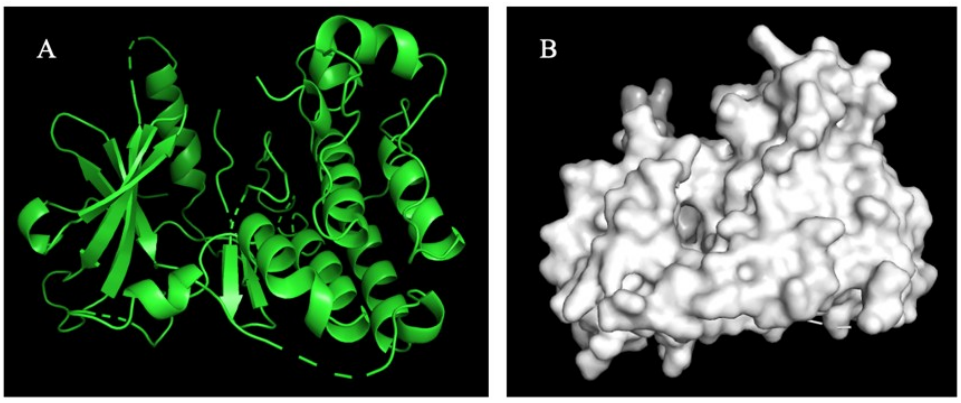

Figure 1. 3D Structure of HER2 Protein Chain in ribbon(A) and surface (B) Form Without Ligand Retrieved from http://www.rcsb.org.

Subsequently, validation was performed using a grid box to assist in aligning the ligand and protein for each docking algorithm (Table 1). The dimensions and center of mass values were obtained during the grid box setup process (Table 2).

Table 1. Grid Box Dimension Values for Molecular Docking

Ligand	X	Y	Z
Quercetin	13	14	12
TAK-285	50	50	50

Source: Research Findings, 2025

Table 2. Center of Mass Values of the Ligand

Ligand	X	Y	Z
Quercetin	-38,1130	-28,5143	-75,2757
TAK-285	-32.409	-33,601	-67,903

Source: Research Findings, 2025

The docking results shown in Figure 2 demonstrate that the quercetin molecule binds to HER2 at the exact same position where the reference inhibitor TAK-285 interacts with HER2, indicating a potential similarity in their binding sites.

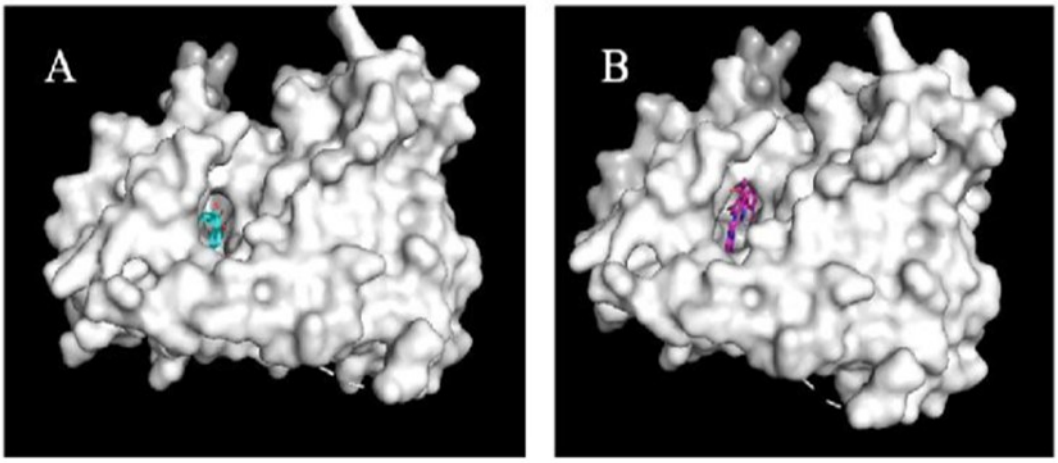

Figure 2. : 3D Surface Structure of Docking Results Between Quercetin and HER2 (A. Light Blue), and HER2 With Reference Inhibitor TAK-285 (B. Magenta) (Source: PyMol Visualization, 2025)

Figure 2 illustrates that both ligands (quercetin and TAK-285) occupy the same binding pocket in HER2, suggesting a potential overlap in their binding mechanisms.
Further validation was performed using LigPlot+ to analyze the ligand–protein interactions (Figure 3 and Figure 4). The results confirmed the binding positions and interaction types, including hydrogen bonds and hydrophobic contacts. Both quercetin and TAK-285 were found to form hydrogen bonds with MET801 and hydrophobic interactions with residues such as Leu852, Leu800, Phe1004, and Gly804.

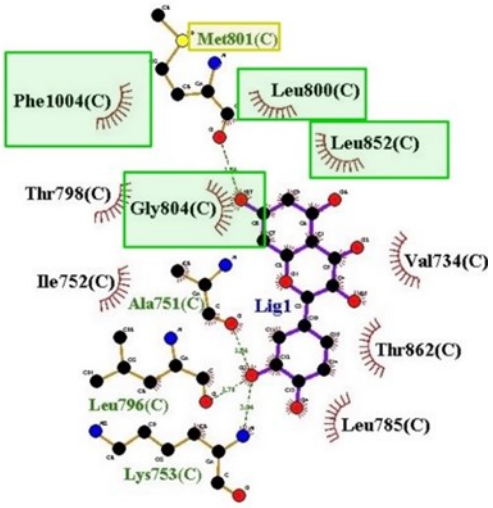

Figure 3. Visualization of HER2 Docking With Quercetin Using LigPlot+
(Source: Research Findings, 2025)

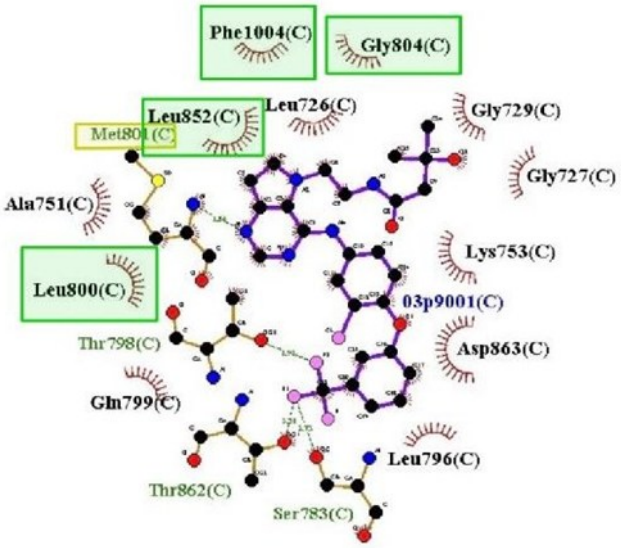

Figure 4. Visualization of HER2 Docking With Reference Inhibitor TAK-285 Using LigPlot+
(Source: Research Findings, 2025)

The comparison of binding affinities between quercetin and TAK-285 to the HER2 protein is shown in Table 3.

Table 3. Comparison of Binding Affinity Affinity (kcal/mol)

Protein targets	Ligand	Binding Affinity (kcal/mol)
HER2	Quercetin	–8.04 ± 0.40
	TAK-285	–9.62 ± 0.21

Source: Research Findings, 2025

Table 3 shows that quercetin has a weaker potential to bind to the active site of HER2 than the reference inhibitor TAK-285, but has the ability to bind. The binding affinity of the reference inhibitors TAK-285 and quercetin on the HER2 target protein are –9.62 ± 0.21 kcal/mol and –8.04 ± 0.40 kcal/mol, respectively, based on 10 independent docking runs for each compound. Both Quercetin and TAK-285

exhibited binding affinities below the commonly accepted threshold of –6.0 kcal/mol, indicating biologically significant interactions (Chun et al., 2023; Morris et al., 2009). This suggests that both compounds have potential inhibitory effects on HER2.

DISCUSSION

This study utilized the HER2 protein structure obtained from the RCSB Protein Data Bank https://www.rcsb.org in 3D (PDB) format, which was subsequently visualized as ribbon and surface models using PyMol. Ribbon representation aids in understanding secondary conformations such as α-helices and β-sheets, whereas the surface view provides a tangible depiction of the ligand-binding topology. The HER2 structure employed in this study was in its unbound form (Figure 1), allowing a free binding pocket for ligand docking.

Previous studies have shown that HER2 can be inhibited by various mechanisms using different inhibitors. For instance, trastuzumab functions as a monoclonal antibody that binds to the extracellular domain of HER2. This inhibitor does not compete with ATP or endogenous ligands at the catalytic domain of HER2, making it a non-competitive inhibitor. Furthermore, it does not bind to allosteric sites to induce conformational changes in HER2, and therefore cannot be categorized as an allosteric inhibitor (Zou et al., 2024; Jaques et al., 2020; Chakrabarty et al., 2013). Another example is zuclopenthixol, which was found to mimic moesin-HER2 interaction and bind to the juxtamembrane region of HER2, stabilizing it in an inactive state. This renders zuclopenthixol an effective allosteric inhibitor of HER2 (Faure et al., 2021). Similar to zuclopenthixol, ebselen oxide functions as an allosteric inhibitor of HER2 by mimicking the endogenous interaction with moesin and stabilizing the receptor in a catalytically inactive conformation (Blasquez et al., 2023).

Another HER2 inhibitor, TAK-285, is a selective tyrosine kinase inhibitor of HER2 and EGFR that acts through competitive inhibition (Martiniano, 2021; Takagi et al., 2014). Crystallographic analysis revealed that TAK-285 binds competitively at the ATP-binding pocket of HER2 (Nakayama et al., 2013). In this study, TAK-285 was used as a reference inhibitor to compare with quercetin.

Validation and grid box configuration were performed to define the three-dimensional space in which docking simulations were conducted. The grid sizes and center coordinates varied between ligands, as shown in Table 1 and Table 2. TAK-285 was docked using a larger grid box (50x50x50) compared to quercetin (13x14x12), adjusted based on molecular size and anticipated interaction space to ensure docking accuracy.

Molecular docking of quercetin and TAK-285 with HER2 was performed using AutoDock Vina integrated in PyRx 0.8. A total of 8 binding conformations for quercetin-HER2 interaction were generated in each docking run. The conformation with the lowest binding energy (most negative value), indicating the most stable interaction, was selected for further analysis. The binding affinity of quercetin to HER2 was –8.04 ± 0.40 kcal/mol, suggesting a stable interaction. The docking of the reference inhibitor TAK-285 with HER2 yielded 6 to 8 binding conformations per run, with the most stable conformation exhibiting a binding energy of –9.62 ± 0.21 kcal/mol. This lower energy compared to quercetin indicates stronger and more stable interaction between TAK-285 and HER2. A binding affinity below -6 kcal/mol is generally considered active and indicative of a strong ligand-target interaction, while values below -9 kcal/mol suggest very strong binding (Chun et al., 2023; Morris et al., 2009) .

In this study, TAK-285 exhibited very strong binding, while quercetin also showed a potentially strong interaction with HER2, particularly at sufficient concentrations. Visualization using LigPlot+ revealed that quercetin and TAK-285 share several amino acid residues and interaction types with HER2. Only one identical hydrogen bond interaction was observed for both ligands, involving Met801. For hydrophobic interactions, four common residues were identified: Leu800, Leu852, Gly804, and Phe1004. In total, 10 out of 13 amino acid residues (76.9%) involved in HER2 binding were shared between quercetin and TAK-285, albeit with different types of interactions. This suggests that both ligands occupy the same binding pocket within HER2. This is further evidenced by the overlapping

ligand positions shown in Figure 2. This binding site is critical as it serves as the phosphorylation activation site, which initiates carcinogenic signaling pathways.

Literature reports highlight the importance of specific interactions with Asp863 and Lys753 in kinase inhibition. Particularly, Asp863 participates in key hydrogen bonding interactions within the ATP-binding pocket of HER2, as observed in molecular docking studies (Soliman et al., 2019; Li et al., 2016). Previous studies have also highlighted the importance of Lys753 interactions in the structural biology of HER-2, suggesting that mutations in this amino acid residue may affect the effectiveness of kinase inhibitors (Gaibar et al., 2020; Verma et al., 2018). In this study, TAK-285 was found to interact with both Asp863 and Lys753 through hydrophobic interactions. In contrast, quercetin formed a hydrogen bond with Lys753 only. Given that hydrogen bonds are generally stronger than hydrophobic interactions, this suggests that even though quercetin only binds to one critical residue, it may still effectively inhibit HER2 kinase activity through this interaction.

These findings complement the in vitro study by Seo et al. (2016), which reported that quercetin reduced proliferation in HER2-overexpressing BT-474 breast cancer cells, with an IC50 of approximately 40–60 µM after 72 hours. Although the inhibitory effect was demonstrated experimentally, the molecular basis of HER2 suppression remained unclear. The present in silico analysis suggests that quercetin may inhibit HER2 through competitive binding at the ATP-binding pocket, similar to TAK-285. For this reason, the analysis was limited to HER2 to allow closer examination of its binding interactions.

CONCLUSION

Quercetin exhibited a binding affinity of –8.04 ± 0.40 kcal/mol to the HER2 protein. This value is slightly lower than that of the reference inhibitor TAK-285, which demonstrated a stronger binding affinity of –9.62 ± 0.21 kcal/mol. Amino acid interaction analysis revealed that 76.9% of the interacting residues in HER2 were shared between quercetin and TAK-285, although the types of interactions differed. This overlap indicates that both compounds are capable of binding to the same active site (binding pocket) on the HER2 protein. Based on these observations, quercetin is presumed to inhibit HER2 through a mechanism similar to that of TAK-285, likely acting as an ATP-competitive inhibitor at the ATP-binding pocket of the HER2 tyrosine kinase domain.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest in this study. All research and writing processes were conducted independently without any intervention from external parties that could influence the results.

ACKNOWLEDGEMENTS

The author expresses sincere gratitude to the Faculty of Medicine, Wijaya Kusuma University Surabaya, for providing the facilities and support throughout the course of this research. Appreciation is also extended to the academic advisors for their guidance and direction, as well as to all parties who contributed to the completion of this study.

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