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Research Article

In Silico Evaluation of Selected Phytochemicals as Potential HER2 Tyrosine Kinase Inhibitors Against Breast Cancer Using Molecular Docking Analysis

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ABSTRACT

Breast cancer remains one of the leading causes of cancer-associated morbidity and mortality among women worldwide, with human epidermal growth factor receptor 2 (HER2)-positive tumors exhibiting aggressive clinical behavior and poor prognosis. The present study aimed to investigate the inhibitory potential of selected phytochemicals against HER2 kinase using molecular docking approaches. The crystal structure of HER2 in complex with a covalent inhibitor (PDB ID: 7PCD; resolution 1.77 Å) was retrieved from the Protein Data Bank and prepared using AutoDock tools. Eight phytochemicals, namely apigenin, berberine, curcumin, fisetin, genistein, luteolin, piperine, and quercetin, were obtained from the PubChem database and subjected to molecular docking using AutoDock Vina. Docking simulations were performed within the ATP-binding pocket comprising key residues LEU726, LYS753, SER783, LEU796, MET801, CYS805, THR862, ASP863, and PHE864. Among the investigated compounds, genistein exhibited the highest binding affinity (−9.7 kcal/mol), followed by curcumin (−9.1 kcal/mol), both demonstrating stronger binding energies than the reference inhibitor 70I (−8.7 kcal/mol). These phytochemicals established stable hydrogen bonding and hydrophobic interactions with critical catalytic residues involved in HER2 inhibition. The findings suggest that genistein and curcumin possess promising therapeutic potential as natural HER2 inhibitors and warrant further validation through molecular dynamics simulations and experimental studies for the development of novel phytochemical-based therapeutics against HER2-positive breast cancer.

1. Introduction

Breast cancer remains the most frequently diagnosed malignancy among women worldwide and continues to be a major contributor to cancer-related mortality. According to the latest global cancer statistics, breast cancer accounts for approximately 2.3 million new cases annually, emphasizing the urgent need for effective therapeutic interventions. Among the molecular subtypes of breast cancer, human epidermal growth factor receptor 2 (HER2)-positive breast cancer represents nearly 15–20% of all diagnosed cases and is associated with aggressive tumor progression, increased metastatic potential, poor prognosis, and reduced overall survival rates. HER2 is a transmembrane receptor tyrosine kinase belonging to the epidermal growth factor receptor family that regulates cell proliferation, differentiation, angiogenesis, and survival pathways. Aberrant amplification or overexpression of HER2 promotes constitutive activation of downstream signaling cascades, including PI3K/Akt and MAPK pathways, leading to uncontrolled cellular proliferation. Although targeted therapies such as trastuzumab, lapatinib, tucatinib, and neratinib have significantly improved clinical outcomes, the emergence of drug resistance, adverse effects, and therapeutic limitations necessitates the discovery of novel HER2 inhibitors with improved efficacy and safety profiles (Sung et al., 2024; Siegel et al., 2025; Loibl et al., 2024).

Natural products and phytochemicals have emerged as promising sources of anticancer agents owing to their structural diversity, biological activities, and favorable pharmacological properties. Numerous plant-derived compounds exhibit antiproliferative, antioxidant, anti-inflammatory, and apoptosis-inducing effects against various cancer types, including HER2-positive breast cancer. Flavonoids, polyphenols, alkaloids, and curcuminoids have demonstrated the ability to modulate oncogenic pathways, inhibit receptor

tyrosine kinases, suppress angiogenesis, and induce cell cycle arrest. Compounds such as quercetin, genistein, luteolin, curcumin, apigenin, and berberine have been reported to interfere with HER2-mediated signaling mechanisms and exhibit potential kinase inhibitory activities. Recent advances in computational biology have facilitated the systematic investigation of phytochemicals as lead compounds for targeted drug discovery. Molecular docking provides an efficient and cost-effective strategy for evaluating ligand–protein interactions, predicting binding affinities, and identifying potential inhibitors before experimental validation. Consequently, in silico approaches have become indispensable tools for accelerating the development of novel therapeutic candidates targeting HER2-associated breast cancers (Mishra et al., 2024; Khan et al., 2025; Rodrigues et al., 2024).

Structure-based drug discovery approaches have significantly enhanced the identification of novel kinase inhibitors by enabling the exploration of ligand binding within experimentally validated active sites. The crystal structure of HER2 kinase complexed with a covalent inhibitor (PDB ID: 7PCD) provides a high-resolution framework (1.77 Å) for understanding the molecular architecture of the ATP-binding pocket and assessing ligand interactions. The catalytic region of HER2 comprises important residues including LYS753, LEU726, SER783, MET801, CYS805, LEU796, THR862, ASP863, and PHE864, which contribute to substrate recognition and inhibitor stabilization. Investigating the binding potential of bioactive phytochemicals within this catalytic cleft may facilitate the identification of alternative therapeutic agents with improved pharmacological characteristics. Therefore, the present study aimed to evaluate selected phytochemicals, namely apigenin, berberine, curcumin, fisetin, genistein, luteolin, piperine, and quercetin, against HER2 kinase using molecular docking simulations and compare their binding performance with the co-crystallized inhibitor, thereby identifying potential lead molecules for HER2-targeted breast cancer therapy (Liu et al., 2024; Zhang et al., 2025; RCSB Protein Data Bank, 2025).

1. Materials and Methods

2.1. Protein Selection and Preparation for Docking

The crystal structure of the human epidermal growth factor receptor 2 kinase domain complexed with a covalent inhibitor (PDB ID: 7PCD) was selected as the molecular target for docking investigations owing to its high crystallographic resolution (1.77 Å) and the presence of a co-crystallized ligand occupying the ATP-binding site. The protein structure was retrieved from the RCSB Protein Data Bank (https://www.rcsb.org/structure/7PCD). Prior to docking simulations, protein preparation was performed using AutoDock Tools (ADT 1.5.7) to obtain a receptor model suitable for molecular interaction studies. All crystallographic water molecules, buffer ions, and non-essential heteroatoms were removed from the structure to eliminate interference during ligand binding analysis. Additional chains not involved in the catalytic domain were excluded from the receptor model. Polar hydrogen atoms were subsequently added to account for hydrogen bonding interactions, while Kollman united atom charges and Gasteiger partial charges were assigned to accurately represent electrostatic properties. The prepared receptor was then subjected to energy refinement and converted from PDB format into PDBQT format, which serves as the standard receptor input file for AutoDock Vina. The ATP-binding region comprising LEU726, LYS753, SER783, LEU796, MET801, CYS805, THR862, ASP863, and PHE864 was considered the active site for docking simulations.

2.2. Ligand Selection and Preparation

Eight phytochemicals possessing documented anticancer and kinase inhibitory properties were selected for docking studies. The compounds included apigenin (CID: 5280443), berberine (CID: 2353), curcumin (CID: 969516), fisetin (CID: 5281614), genistein (CID: 5280961), luteolin (CID: 5280445), piperine (CID: 638024), and quercetin (CID: 5280343). The co-crystallized inhibitor 70I (CID: 164575486) was employed as a standard reference compound to validate the docking protocol through redocking analysis. Chemical structures of all phytochemicals were downloaded from the PubChem database in SDF format. Ligand preparation involved optimization of molecular geometry and conversion of file formats using Open Babel utilities. Hydrogen atoms were added to ensure proper protonation states, and Gasteiger charges were assigned for accurate molecular representation. Rotatable bonds were defined to permit conformational flexibility during docking calculations. The ligands were subsequently converted into PDBQT format, which is compatible with AutoDock Vina. Proper ligand preparation is essential to achieve reliable predictions of binding affinities, hydrogen bonding interactions, and hydrophobic contacts within the catalytic cavity of HER2 kinase.

2.3. Molecular Docking Simulation

Molecular docking studies were performed using AutoDock Vina to investigate the binding affinity and interaction profiles of selected phytochemicals within the ATP-binding pocket of HER2 kinase. The docking grid was generated based on the position of the co-crystallized inhibitor present in the 7PCD crystal structure. The search space was centered at x = 9.98 Å, y = −8.69 Å, and z = −13.72 Å, encompassing the catalytic cleft formed by residues LEU726, LYS753, SER783, LEU796, MET801, CYS805, THR862, ASP863, and PHE864. Docking simulations were conducted using prepared receptor and ligand PDBQT files under AutoDock Vina default parameters. Multiple binding conformations were generated for each ligand, and the best docking pose was selected based on the lowest binding free energy value (kcal/mol) and interaction stability within the active site. The docking protocol was validated through redocking of the native inhibitor 70I to assess the reliability of the predicted binding orientation. Protein–ligand interactions, including hydrogen bonds and hydrophobic contacts, were analyzed using visualization tools to identify residues contributing significantly to ligand stabilization and HER2 inhibition.

2. Results and Discussion

3.1. Molecular Docking Simulation:

Molecular docking simulations were performed to evaluate the binding potential of eight selected phytochemicals against the ATP-binding domain of HER2 kinase (PDB ID: 7PCD) and compare their interactions with the co-crystallized inhibitor (70I). The docking analysis revealed considerable variation in binding affinities among the investigated compounds, with binding energies ranging from −8.2 to −9.7 kcal/mol. Among all phytochemicals, genistein exhibited the strongest binding affinity with a docking score of −9.7 kcal/mol, surpassing the reference inhibitor (−8.7 kcal/mol). The 2D interaction analysis (Figure-1) revealed that genistein forms three conventional

Table 1. Molecular Docking Scores, Hydrogen Bonding, and Hydrophobic Interactions of Selected Phytochemicals with HER2 Kinase (PDB ID: 7PCD)

Sl.No	Phytochemical name (PubChem ID)	Binding energy (kcal/mol)	No. of H bonds	H Bond interactive AAs	Hydrophobic interactive AAs
1	Apigenin CID: 5280443)	-8.4	3	Ile767, Lys753, Ala751	Glu770, Ala771, Phe864, Val734, Leu796, Ile752, Val797, Thr798, Thr862, Asp863
2	Barberine (CID: 2353)	-8.3	0	0	Gly804, Gly727, Asp863, Lys753, Leu796, Thr862, Val734, Ala751, Thr798, Leu785, Leu852, Met801, Ser783, Leu800, Leu726
3	Curcumin (CID: 969516)	-9.1	2	Lys753, Thr862	Asp863, Phe864, Thr798, Ile752, Ser783, Val734, Cys805, Gly804, Leu800, Pro802, Leu726, Met801, Ala751, Leu852, Ala771, Leu785, Leu796, Glu770, Ile767
4	Fisetin (CID: 5281614)	-8.4	1	Asp863	Ser783, Leu785, Leu796, Thr798, Lys753, Ala751, Val734, Leu852, Leu726, Leu800, Met801, Gly804, Thr862
5	Genistein (CID: 5280961)	-9.7	3	Asp863, Lys753, Glu770	Leu852, Val734, Phe864, Ile767, Ala771, Ser783, Thr862, Thr798, Ala751
6	Luteolin (CID: 5280445)	-8.5	2	Ile767	Ile797, Ile752, Thr798, Leu796, Lys753, Val734, Ala771, Glu766, Glu770, Phe864, Asp863, Thr862, Ala751, Lys753
7	Piperine (CID: 638024)	-8.5	0	0	Lys753, Ser783, Leu785, Thr798, Thr862, Ala751, Leu852, Val734, Leu726, Gly804, Met801, Leu800
8	Quercetin (CID: 5280343)	-8.2	0	0	Cys805, Gly804, Leu726, Leu800, Met801, Leu852, Val734, Ala751, Lys753, Thr798, Asp863, Thr862, Ser783
9	70I (CID: 164575486) Standard Inhibitor	-8.7	1	Asp863	Pro885, Arg849, Asp845, Asn850, Gly727, Leu726, Val734, Leu852, Ala751, Lys753, Thr798, Leu785, Ser783, Ala771, Phe864, Met774, Arg784, Leu796, Thr862, Ser728, Gly729

hydrogen bonds with LYS753, ASP863, and GLU770, contributing to binding stability. Additional π–π T-shaped, π–alkyl, and π–sigma interactions with PHE864, ILE767, and VAL734, along with van der Waals contacts, enhance ligand accommodation within the HER2 ATP-binding pocket.

Curcumin also demonstrate d notable binding efficiency with a binding energy of −9.1 kcal/mol, whereas luteolin and piperine exhibited docking scores of −8.5 kcal/mol, followed by apigenin and fisetin with −8.4 kcal/mol. The two-dimensional interaction analysis illustrates the binding mode of curcumin within the ATP-binding pocket of HER2 kinase (PDB ID: 7PCD) (Figure-2). Curcumin establishes two conventional hydrogen bonds with the crucial catalytic residues LYS753 and THR862, contributing significantly to ligand stabilization. A carbon hydrogen bond interaction is observed with PHE864, further supporting complex stability. Additionally, several π–sigma and π–alkyl interactions are formed with residues LEU796, LEU852, LEU726, ALA751, and ALA771, enhancing hydrophobic complementarity within the binding cavity. Van der Waals interactions involving SER783, ILE752, VAL734, CYS805, GLY804, LEU800, PRO802, LEU785, ILE767, GLU770, and ASP863 further stabilize curcumin, indicating its favorable accommodation and strong binding affinity toward the HER2 active site.

Berberine and quercetin showed comparatively lower affinities of −8.3 kcal/mol and −8.2 kcal/mol, respectively. The superior binding performance of genistein and curcumin suggests their enhanced compatibility within the HER2 catalytic cavity and their ability to establish stable intermolecular interactions with critical residues. Interestingly, several phytochemicals displayed docking energies comparable to or exceeding that of the standard inhibitor, indicating their potential as alternative HER2-targeted therapeutic agents. The observed docking scores are consistent with previous studies reporting flavonoids and polyphenolic compounds as promising inhibitors of receptor tyrosine kinases due to their planar aromatic structures, hydrogen bond donor–acceptor characteristics, and favorable hydrophobic interactions within kinase active sites. These findings indicate that naturally occurring phytochemicals may serve as valuable lead molecules for the development of novel HER2 inhibitors against HER2-positive breast cancer.

Analysis of hydrogen bonding patterns revealed that hydrogen bond formation played a crucial role in stabilizing ligand conformations within the HER2 active pocket. Genistein established three hydrogen bonds involving ASP863, LYS753, and GLU770, suggesting strong anchoring within the ATP-binding cleft and contributing to its highest docking affinity. Similarly, apigenin formed three hydrogen bonds with ILE767, LYS753, and ALA751, while curcumin interacted through two hydrogen bonds involving LYS753 and THR862, residues known to participate in inhibitor recognition and catalytic stabilization. Luteolin exhibited two hydrogen bond interactions with ILE767, whereas fisetin formed a single hydrogen bond with ASP863. In contrast, berberine, piperine, and quercetin did not exhibit hydrogen bond formation but maintained favorable binding energies through extensive hydrophobic interactions.

The reference inhibitor established one hydrogen bond with ASP863, confirming the importance of this residue in ligand

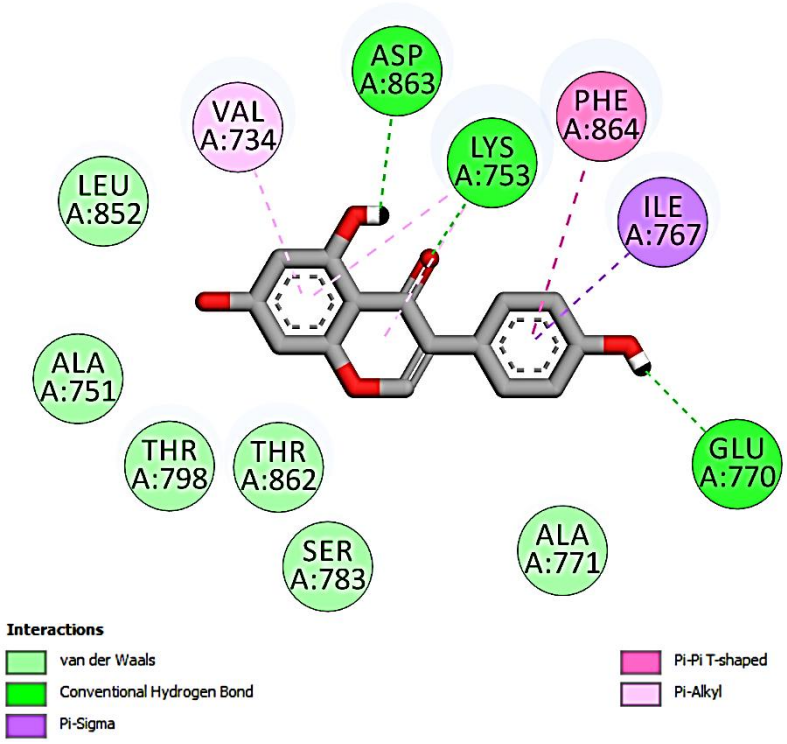

Fig 1. Two-Dimensional Interaction Diagram of Genistein Bound to the HER2 Kinase Active Site (PDB ID: 7PCD) Waals interactions between oleanolic acid and key BCL-2 residues.

stabilization within the HER2 kinase domain. Notably, residues LYS753, ASP863, THR862, SER783, and GLU770 appeared repeatedly among the interacting amino acids, highlighting their significance in mediating ligand recognition and binding specificity. Previous structural studies have identified these residues as essential componen ts of the HER2 catalytic region responsible for ATP coordination and kinase inhibition. Therefore, the ability of phytochemicals such as genistein and curcumin to mimic the interaction pattern of the co-crystallized inhibitor suggests their potential capacity to competitively inhibit HER2 signaling pathways involved in breast cancer progression.

Hydrophobic interaction analysis further supported the stability of the docked complexes and demonstrated extensive ligand accommodation within the hydrophobic subpockets of HER2. Genistein displayed interactions with LEU852, VAL734, PHE864, ILE767, ALA771, SER783, THR862, THR798, and ALA751, providing additional stabilization and contributing to its superior docking score. Curcumin exhibited the highest number of hydrophobic contacts, involving residues ASP863, PHE864, THR798, ILE752, SER783, VAL734, CYS805, GLY804, LEU800, PRO802, LEU726, MET801, ALA751, LEU852, ALA771, LEU785, LEU796, GLU770, and ILE767, suggesting a broad interaction network within the ATP-binding cavity. Berberine, despite lacking hydrogen bonds, formed numerous hydrophobic interactions with residues including MET801, LEU800, LEU726, SER783, LEU796, THR862, and LYS753, indicating that hydrophobic stabilization substantially contributed to its binding affinity. Likewise, piperine and quercetin demonstrated stable occupancy of the catalytic cleft through multiple nonpolar contacts.

The frequent involvement of LEU726, LYS753, SER783, MET801, CYS805, THR862, ASP863, and PHE864 confirms the importance of these residues in ligand accommodation and HER2 inhibition. Overall, the docking results identified genistein and curcumin as the most promising phytochemical candidates, exhibiting stronger binding affinities than the standard inhibitor and forming extensive hydrogen bonding and hydrophobic interaction networks. These findings provide a molecular basis for future investigations involving molecular dynamics simulations, free energy calculations, and experimental validation to explore their potential as novel HER2-targeted therapeutics for breast cancer management.

The present study demonstrated the promising inhibitory potential of selected phytochemicals against the HER2 kinase domain through molecular docking analysis. Among the investigated compounds, genistein exhibited the highest binding affinity (−9.7 kcal/mol), followed by curcumin (−9.1 kcal/mol), both surpassing the co-crystallized inhibitor 70I (−8.7 kcal/mol). These findings suggest that naturally occurring flavonoids and polyphenolic compounds may effectively occupy the ATP-binding cleft of HER2 and interfere with kinase-mediated signaling pathways involved in breast cancer progression. The enhanced binding affinity observed for genistein can be attributed to its ability to establish multiple hydrogen bonds with catalytically important residues, including ASP863, LYS753, and GLU770, in addition to several stabilizing hydrophobic contacts. Similarly, curcumin formed strong interactions with LYS753 and THR862, residues known to play critical roles in ATP recognition and inhibitor stabilization within the kinase domain. Previous investigations have reported that genistein suppresses HER2-mediated downstream signaling by inhibiting PI3K/Akt and MAPK pathways, whereas curcumin has been shown to induce apoptosis, inhibit cellular proliferation, and reduce metastatic potential in HER2-overexpressing breast cancer cells. Recent studies have further emphasized that flavonoid scaffolds possess favorable physicochemical characteristics for receptor tyrosine kinase inhibition, making them attractive candidates for targeted anticancer drug development (Loibl et al., 2024; Harbeck and Gnant, 2024; Khan et al., 2025; Zhang et al., 2025).

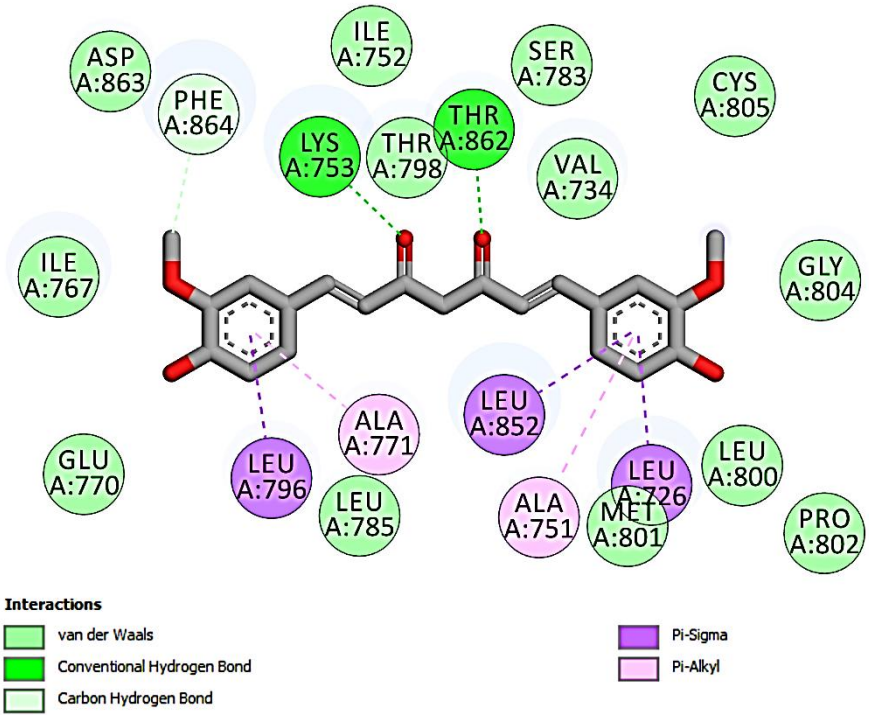

Fig 2. Two-Dimensional Interaction Diagram of Curcumin Bound to the HER2 Kinase Active Site (PDB ID: 7PCD)

Hydrogen bonding and hydrophobic interactions constitute the primary determinants governing ligand stability and specificity within protein active sites. In the present investigation, residues LYS753, SER783, THR862, ASP863, PHE864, MET801, and CYS805 were repeatedly involved in ligand interactions, highlighting their importance in maintaining the structural integrity of the HER2 catalytic pocket. The recurrence of ASP863 and LYS753 in both phytochemical and inhibitor complexes indicates their significance as conserved binding residues and potential hotspots for inhibitor design. Interestingly, berberine, piperine, and quercetin exhibited relatively lower binding affinities despite forming extensive hydrophobic interactions, suggesting that hydrogen bond formation contributes substantially to enhancing ligand–receptor stability (Lunavath et al., 2010; Namthabad et al., 2014). The observed interaction profiles are in agreement with recent computational studies identifying flavonoids and plant-derived metabolites as potent HER2-targeted agents capable of mimicking the binding orientation of clinically relevant kinase inhibitors. Furthermore, the docking results indicate that genistein and curcumin may possess comparable or superior inhibitory potential relative to the standard inhibitor, thereby warranting further validation through molecular dynamics simulations, MM-PBSA free-energy calculations, *in vitro* cytotoxicity assays, and kinase inhibition studies (Porika et al., 2014; Swapna et al., 2024; Ameen et al., 202). Collectively, these findings provide a strong computational foundation for exploring phytochemical-based therapeutics as safer and cost-effective alternatives for the management of HER2-positive breast cancer (Sung et al., 2024; Siegel et al., 2025; Rodrigues et al., 2024; Liu et al., 2025; Gujjeti et al., 2014).

3. Conclusion

The present study highlights the potential of selected phytochemicals as promising inhibitors of HER2 kinase implicated in HER2-positive breast cancer. Molecular docking analysis demonstrated that **genistein** exhibited the highest binding affinity (−9.7 kcal/mol), followed by **curcumin** (−9.1 kcal/mol), both showing stronger interactions than the reference inhibitor 70I (−8.7 kcal/mol). These compounds established stable hydrogen bonding and hydrophobic interactions with critical catalytic residues, particularly LYS753, SER783, THR862, ASP863, and PHE864, indicating their favorable accommodation within the ATP-binding pocket of HER2. The observed interaction patterns suggest that flavonoid and polyphenolic phytochemicals possess considerable potential to interfere with HER2-mediated signaling pathways involved in breast cancer progression. Overall, the findings provide valuable insights into the therapeutic relevance of natural compounds as HER2-targeted agents and establish a strong computational basis for further investigations through molecular dynamics simulations, free-energy calculations, and experimental validation to support the development of novel phytochemical-based therapeutics for breast cancer management.

Conflicting Interests

The authors have declared that no conflicting interests exist.

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