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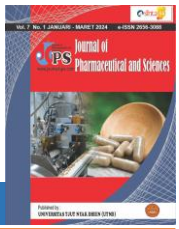

Molecular Docking Study of Luteolin and its Derivatives for Identifying Potential ER-α Inhibitors in Breast Cancer

Studi Molecular Docking Luteolin dan Turunannya untuk Mengidentifikasi Potensi Inhibitor ER-α pada Kanker Payudara

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Abstract

Breast cancer remains one of the leading causes of cancer-related mortality worldwide, with estrogen receptor alpha (ER-α) serving as a primary therapeutic target in hormone-dependent subtypes. Resistance to current endocrine therapies underscores the need for alternative compounds with improved efficacy and safety. Luteolin, a naturally occurring flavonoid, has gained attention as a potential anticancer agent, but its structural modifications may alter biological activity. This study evaluated the binding affinity and interaction profiles of luteolin and its glycosylated derivatives (luteolin 7-glucuronide and luteolin 7-O-glucoside) against ER-α using molecular docking (PDB ID: 7UJ8). The results revealed that luteolin consistently exhibited stronger binding affinity (−7.2 to −8.0 kcal/mol) and stable RMSD values compared to its derivatives, though it remained significantly weaker than the reference drug 4-hydroxytamoxifen (−8.9 to −9.4 kcal/mol). Structural analysis demonstrated that luteolin's superiority arises from its ability to maintain extensive hydrophobic and π–π stacking interactions within the ER-α binding pocket. In contrast, glycosylation introduced bulky polar substituents that disrupted hydrophobic contacts and reduced binding affinity. These findings highlight luteolin as the most promising scaffold among the tested compounds and underscore the structural basis for why glycoside derivatization diminishes ER-α binding. Future work should focus on enhancing luteolin's bioavailability without compromising its key hydrophobic interactions to advance its potential as a lead candidate for breast cancer therapy.

***Keywords*: Breast cancer, Luteolin, Molecular docking, Estrogen receptor alpha, Flavonoid.**

Abstrak

Kanker payudara tetap menjadi salah satu penyebab utama kematian terkait kanker di seluruh dunia, dengan *estrogen receptor alpha* (ER-α) sebagai target terapeutik utama pada subtipe yang bergantung pada hormon. Resistensi terhadap terapi endokrin yang ada menekankan perlunya senyawa alternatif dengan efektivitas dan keamanan yang lebih baik. Luteolin, suatu flavonoid alami, telah mendapat perhatian sebagai agen antikanker potensial, namun modifikasi strukturnya dapat memengaruhi aktivitas biologis. Penelitian ini mengevaluasi afinitas pengikatan dan profil interaksi luteolin serta turunan glikosidasinya (luteolin 7-glukuronida dan luteolin 7-O-glukosida) terhadap ER-α menggunakan pendekatan molecular docking (PDB ID: 7UJ8). Hasil menunjukkan bahwa luteolin secara konsisten memiliki afinitas pengikatan yang lebih kuat (−7,2 hingga −8,0 kcal/mol) dan nilai RMSD yang stabil dibandingkan turunannya, meskipun masih secara signifikan lebih lemah dibandingkan obat referensi 4-hidroksitamoksifen (−8,9 hingga −9,4 kcal/mol). Analisis struktural menunjukkan bahwa keunggulan luteolin terutama disebabkan oleh kemampuannya mempertahankan interaksi hidrofobik dan π–π stacking yang luas di dalam kantung pengikatan ER-α. Sebaliknya, glikosilasi menghasilkan substituen polar yang besar sehingga mengganggu kontak hidrofobik dan menurunkan afinitas pengikatan. Temuan ini menegaskan luteolin sebagai kerangka (scaffold) paling

menjanjikan di antara senyawa yang diuji serta menyoroti dasar struktural mengapa derivatisasi glikosida justru menurunkan kemampuan pengikatan ER-α. Penelitian lanjutan sebaiknya difokuskan pada peningkatan bioavailabilitas luteolin tanpa mengorbankan interaksi hidrofobik kunci untuk mengembangkan potensinya sebagai kandidat utama terapi kanker payudara.

Kata Kunci: Kanker Payudara, Luteolin, Molecular docking, Estrogen receptor alpha, Flavonoid.

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Introduction

Breast cancer is one of the world's leading health problems, with the second highest global incidence (11.6%) after lung cancer, and accounts for 6.9% of all cancer deaths worldwide [1]. In Indonesia, breast cancer is the most common cancer (18.6%), with more than 80% of cases detected at an advanced stage [2]. Biologically, this cancer is caused by genetic mutations that trigger abnormal cell proliferation and is classified based on the expression of estrogen (ER), progesterone (PR), and HER2 receptors, which determine the direction of therapy and prognosis [3].

Estrogen receptor alpha (ER-α) is the primary target for hormone therapy, especially in patients with ER-positive status. Selective Estrogen Receptor Modulators (SERMs) such as tamoxifen and toremifene are first-line therapies, although they often face resistance (e.g., patients with certain CYP2D6 genotypes respond better to toremifene than tamoxifen) and serious side effects [4]. Besides SERMs, aromatase inhibitors, Selective Estrogen Receptor Degraders (SERDs), and CDK4/6 inhibitors such as palbociclib are also used to inhibit cancer cell proliferation, though resistance and cross-resistance remain major challenges [5].

Natural compounds like luteolin have received considerable attention in the development of more effective and minimally toxic anticancer agents. Luteolin is a flavonoid commonly found in vegetables and medicinal plants such as Sophora japonica and Ginkgo biloba, and has shown anticancer activity through the induction of apoptosis, inhibition of proliferation and angiogenesis, and modulation of various signaling pathways [6–8]. Additionally, luteolin has also been reported to enhance the sensitivity of cancer cells to conventional chemotherapy [7]. Its chemical structure, rich in hydroxyl groups, supports its antioxidant activity, but luteolin's bioavailability is low due to poor water solubility and rapid metabolism. This makes formulation approaches such as nanoparticles and derivatization crucial to enhance its stability and effectiveness [6,8].

From an ADME perspective, in silico profiling using SwissADME indicates that luteolin possesses a favorable lipophilicity (consensus Log P 1.73) and is predicted to be moderately soluble in water (Log S ESOL –3.71). Based on Lipinski's rule of five, luteolin meets all criteria without any violation, suggesting good oral drug-likeness [9]. The bioavailability score of 0.55 indicates moderate oral absorption potential, which is in line with previous pharmacokinetic studies reporting that luteolin has limited oral bioavailability due to poor solubility and rapid metabolism [10–12]. SwissADME also predicts high gastrointestinal absorption, but potential inhibition of CYP1A2, CYP2D6, and CYP3A4 enzymes was observed, indicating possible drug–drug interactions [9,13]. These pharmacokinetic features highlight both the potential and limitations of luteolin, particularly the need for formulation strategies such as nanoparticle delivery or derivatization to overcome solubility and metabolic barriers.

In modern drug development, in silico approaches like molecular docking are used to evaluate the interaction of luteolin with specific protein targets such as ER-α. This technique allows for the prediction of binding affinity, complex stability, and binding specificity [14]. Software like AutoDock Vina has been widely utilized for this analysis [15], with studies showing that luteolin has potential as an ER-α inhibitor based on docking results that indicate high binding affinity and good complex stability [16].

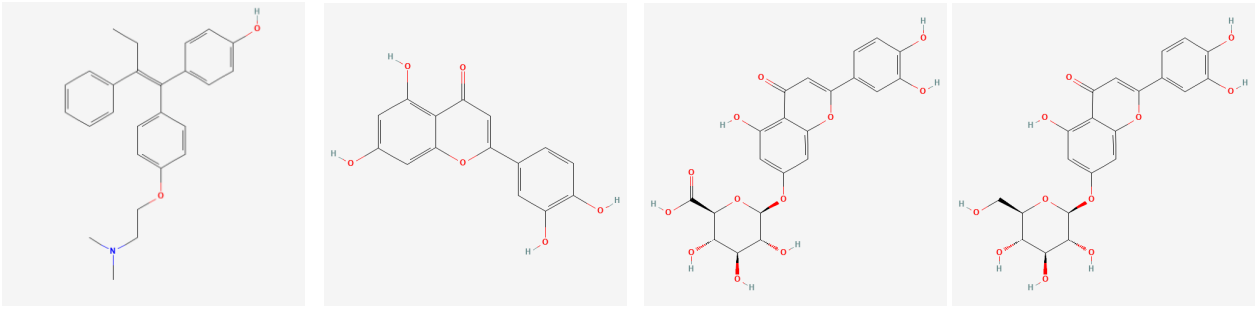
Besides docking, pharmacophore identification is an important strategy in virtual screening and drug design. A pharmacophore describes the essential chemical and spatial features of a ligand that enable optimal interaction with a biological target [17]. This approach has advanced with the application of deep learning, such as the Pharmacophore-Guided deep learning approach for bioactive Molecule Generation (PGMG), which facilitates the design of new molecules based on specific pharmacophores [18].

Previous research has shown that luteolin can inhibit triple-negative breast cancer (TNBC) by inducing apoptosis and autophagy in the SGK1-FOXO3a-BNIP3 pathway [19], and interacts with various molecular targets in other diseases like COVID-19 [14], which indicates its multifunctional potential. Thus, the exploration of luteolin's pharmacophore through a molecular docking approach is expected to strengthen the scientific basis for developing a more selective, effective, and minimally toxic flavonoid-based anticancer agent.

Experimental Section

Materials and Apparatus

This study used the estrogen receptor alpha (ER-α) protein target structure obtained from the Protein Data Bank (PDB) with PDB code 7UJ8. The ligand structures, including luteolin and its derivatives, were retrieved from the PubChem and ZINC databases in SDF or MOL2 format. The software used in this research included PyRx 0.8 for the molecular docking process, PyMOL Ver. 3.1.6.1 for the visualization and preparation of protein and ligand structures, and Discovery Studio 2025 for the analysis and visualization of molecular docking results. This research was conducted in silico using a laptop with the following hardware specifications: Windows 11 64-bit, AMD Ryzen 3 4300U 2.70 GHz, and 8 GB of RAM.



(A) (B) (C) (D)

Figure 1. 2D Structures of Test Ligands (A) 4-Hydroxytamoxifen (B) Luteolin (C) Luteolin 7-glucuronide (D) Luteolin 7-O-glucoside

Target Protein Preparation

The three-dimensional structure of the ER-α target protein (PDB code: 7UJ8) was downloaded from the Protein Data Bank (PDB). The selection criteria for the protein were a resolution of ≤ 2.5 Å and originating from the Homo sapiens organism [20]. The protein was then prepared using PyMOL by removing water molecules, co-crystallized ligands, and unnecessary ions. The structure optimization process was performed to obtain a stable protein conformation before the docking procedure was executed [16].

In the docking study of luteolin and its derivatives against ER-α, the presence of structured water molecules within the binding pocket often acts as a "bridge" forming water-mediated hydrogen bonds, thereby stabilizing the complex and improving ligand orientation [21,22]. Thermodynamically, this water network can lower the free energy through new enthalpic contributions (water-mediated hydrogen bonds) or entropic gains when structured water is displaced, thus modulating the calculated or validated binding ΔG using advanced computational methods [23]. Relevant to the rationale for analyzing both ER-α subunits separately, ER-α is a homodimer that exhibits asymmetric allostery the same ligand may stabilize different conformations in each monomer, resulting in variations in binding strength, water networks, and functional

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responses; these differences have biological implications for dimer stability, DNA binding, and co-regulator/transcriptional recruitment [24]. Full-domain studies also reveal the asymmetric architecture of ER-α and the allosteric communication pathway between the ligand-binding domain and the DNA-binding domain, reinforcing the justification that results for each subunit may differ and hold biological significance for inhibitor effectiveness[25,26].

Docking Method Validation

The docking method was validated by re-docking the co-crystallized ligand to the target protein to ensure that the method used was accurate. The validation was considered successful if the Root Mean Square Deviation (RMSD) value of the docking result was within a range of ≤ 2 Å. This indicates a good match between the docked ligand and the original ligand's position in the crystal structure [15,27].

Test Compound Preparation

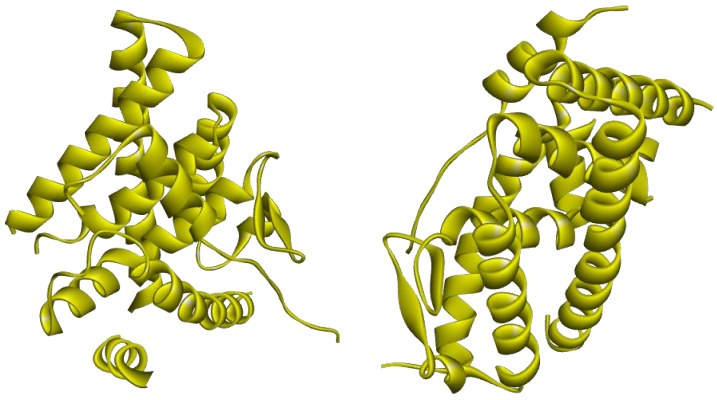
Luteolin and its derivatives were obtained from the PubChem and ZINC databases. The structures were converted from SDF or MOL2 format to PDB format using PyMOL. Subsequently, structure optimization and energy minimization were performed to obtain the most stable ligand conformation before the docking process. This preparation step ensures that the ligands are in an optimal state to interact with the target protein [6,8].

Molecular Docking of Test Ligands to the Protein

Molecular docking was performed using the PyRx software. Docking parameters, such as the grid box, were determined based on the known location of the active site on the target protein. If the active site was unknown, blind docking was performed to identify potential ligand binding sites [17]. The docking process was carried out with a customized algorithm, along with specific settings for iterations and population to obtain optimal results. The docking results were compared with a standard ligand, such as 4-Hydroxytamoxifen, which is a known ER-α inhibitor, serving as a positive control [16,28].

Analysis and Visualization of Molecular Docking Results

Molecular docking results were analyzed based on the binding affinity (binding energy) values, expressed in kcal/mol. A more negative binding energy value indicates a stronger affinity of the ligand for the target protein. Additionally, molecular interactions such as hydrogen bonds, hydrophobic interactions, and electrostatic interactions were analyzed using Discovery Studio 2025 to evaluate the stability and strength of the formed complex [14].



(A) (B)

Figure 2. 3D Macromolecular Structures (A) ER-α A (B) ER-α B

Results and Discussion

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Target Protein Preparation

The protein structure to be used was downloaded from the PDB Bank (http://www.rscb.org/). The receptor was selected based on a resolution criterion of ≤2.5 Å. In the original downloaded file, there were still bonds between the original ligand complex and water molecules. Ligand preparation was carried out in two scenarios: one set of ligands was prepared by removing the water molecules, and the other set was prepared without removing them. The purpose of this was to observe the differences in docking results from both conditions.

Table 1. 4-Hydroxytamoxifen Ligand Docking Validation Results

Grid Box							RMSD (Å)
Macromolecule	**Center**			**Dimension**			
Koordinat	**x**	**y**	**z**	**x**	**y**	**z**	
ER-α A without water molecules	20.5709	-29.1595	10.7363	9.6662	13.4918	7.7463	0.284
ER-α B without water molecules	-6.6585	-17.0574	15.0253	6.0439	10.2173	13.6664	0.733
ER-α A with water molecules	21.7021	-28.3180	12.0886	10.7111	11.6303	10.5007	1.879
ER-α B with water molecules	-6.8617	-16.6406	14.8926	6.818	11.2319	13.8627	0.694

Estrogen receptor alpha (ERα) belongs to the nuclear hormone receptor superfamily, which functions as a ligand-dependent transcription factor. Upon binding with a ligand, ERα regulates the transcription of various genes involved in cell proliferation, differentiation, and tumorigenesis in breast tissue [29]. Based on its classification, ERα is not a receptor tyrosine kinase (RTK) but rather a nuclear hormone receptor (NHR) that works by modulating the transcription of target genes through protein conformational changes after ligand binding.

The ERα structure consists of two homologous isoforms, ERα subtype A and ERα subtype B, which were used in this study based on the PDB ID 7UJ8 crystal structure. Both isoforms have high structural homology, particularly in the ligand-binding domain (LBD) and the DNA-binding domain (DBD). However, there are structural differences in the activation function areas (AF-1 and AF-2), which cause variations in tissue expression patterns and biological responses [30].

Mechanistically, ERα can form homodimers or heterodimers (with ERβ), facilitating conformational changes after ligand binding that then enable the recruitment of co-activator proteins in the process of regulating target gene transcription [31]. In the context of structure and evolution, homologues are defined as proteins that have similar sequences and structures due to an evolutionary relationship. In this case, ERα and ERβ are two homologous receptors within the estrogen receptor family, despite having key differences in their activation domains and tissue expression patterns [30].

Unlike ERα, receptor tyrosine kinases (RTKs) such as HER2 have intrinsic enzymatic activity, which is the ability to phosphorylate target proteins after being activated by a ligand. This RTK activation then triggers downstream signaling pathways like MAPK or PI3K/AKT, which play a crucial role in cell proliferation and cancer development [32]. Therefore, the mechanism of RTKs is very different from that of ERα, which functions as a nuclear transcription receptor without involving catalytic activity, instead relying on structural conformational changes to regulate gene expression.

Docking Method Validation

The docking method was validated by establishing the Root Mean Square Deviation (RMSD) value as the reference parameter. In this study, the success criterion for validation was an RMSD value of ≤2.0 Å, in accordance with a reference from Trijuliamos Manalu (2021). Validating this method is essential to ensure the suitability of the method used in the compound testing [33].

The validation process also included determining the grid box using the PyMOL application. The purpose of determining the grid box is to identify the coordinates of the protein's binding site, which is crucial for molecular docking.

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In molecular docking, a grid box is a three-dimensional spatial parameter that defines the search area for ligand binding within the target protein structure. This area must encompass the active site or a potential binding pocket to ensure the docking process is efficient [34]. The grid box is determined based on the coordinates of the active site from crystallography data or previous analysis. In this study, the grid box was determined based on the location of the active pocket on ERα using the PDB 7UJ8 structure data.

The docking validation results are presented in Table 1. The RMSD values for the ERα A receptor, both without and with water molecules, were 0.284 Å and 1.879 Å, respectively. Meanwhile, the RMSD values for the ERα B receptor, without and with water molecules, were 0.733 Å and 0.694 Å, respectively. Referring to the validation criterion of RMSD ≤2.0 Å, all the obtained values were within the required limits. Therefore, it can be concluded that these docking validation results meet the validity requirements.

Test Compound Preparation

In this study, the compounds analyzed included Luteolin and two of its derivatives: Luteolin 7-glucuronide and Luteolin 7-O-glucoside. As a positive control, 4-Hydroxytamoxifen, a therapeutic agent commonly used in breast cancer treatment, was used. The three-dimensional structures of all compounds were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov) in SDF (Structure Data File) format, which is suitable for molecular docking purposes.

Molecular Docking of Test Ligands to the Protein

The molecular docking process in this study produced parameters in the form of binding affinity scores and Root Mean Square Deviation (RMSD). According to Shofi (2022), the smaller the binding affinity value, the stronger the affinity between the ligand and the receptor [35]. Conversely, a larger binding affinity value indicates a weaker interaction between the ligand and the receptor.

The molecular docking results showed that Luteolin, Luteolin 7-glucuronide, and Luteolin 7-O-glucoside have varying binding affinities for the estrogen alpha receptor (ER-α). In the condition without water molecules, Luteolin showed a binding affinity score of -7.5 kcal/mol at the ER-α A site and -8.0 kcal/mol at the ER-α B site. These values were better than those of its two derivatives, Luteolin 7-glucuronide and Luteolin 7-O-glucoside, which showed binding affinities of -4.9 and -5.9 kcal/mol at ER-α A, and -6.2 and -6.6 kcal/mol at ER-α B, respectively. For comparison, 4-Hydroxytamoxifen produced a higher binding affinity score, specifically -9.0 kcal/mol at ER-α A and -9.4 kcal/mol at ER-α B.

In the condition with water molecules present, Luteolin's binding affinity values were relatively stable, with scores of -7.6 kcal/mol at ER-α A and -7.2 kcal/mol at ER-α B. Meanwhile, Luteolin 7-glucuronide and Luteolin 7-O-glucoside showed a significant decrease in affinity, with binding affinity scores of -2.6 and -3.8 kcal/mol at ER-α A, and -6.2 and -5.9 kcal/mol at ER-α B, respectively. In this condition, the comparator ligand 4-Hydroxytamoxifen continued to show the highest binding affinity value, with scores of -8.9 kcal/mol at ER-α A and -9.0 kcal/mol at ER-α B.

Table 2. Binding Affinity Results of Ligand Docking with the Target Protein

Protein Target	Binding Affinity (Kkal/mol)			
	Luteolin	Luteolin 7-glucuronide	Luteolin 7-O-glucoside	4-Hydroxytamoxifen
ER-α A without water molecules	-7.5	-4.9	-5.9	-9.0
ER-α B without water molecules	-8.0	-6.2	-6.6	-9.4
ER-α A with water molecules	-7.6	-2.6	-3.8	-8.9
ER-α B with water molecules	-7.2	-6.2	-5.9	-9.0

Overall, the results of this study indicate that luteolin has a better binding affinity compared to its two derivatives, both in conditions with and without water molecules. However, luteolin was still unable to surpass the binding affinity potential of 4-Hydroxytamoxifen, which consistently yielded the highest binding affinity scores at both ER-α binding sites.

Binding affinity is a quantitative measure of the strength of the interaction between a ligand and a target protein, expressed in kcal/mol. A more negative binding energy value indicates a stronger and more stable interaction [36]. Luteolin's superior affinity compared to its derivatives is likely due to the absence of large polar substituents like glucuronide and glucoside groups. In the derivatives, these groups cause steric

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hindrance and a decrease in hydrophobic interactions within the ER-α active pocket, resulting in a lower binding affinity. Therefore, luteolin shows potential as a better ER-α ligand candidate than its derivatives, though it remains inferior to the comparator ligand, 4-Hydroxytamoxifen.

Furthermore, an evaluation of the Root Mean Square Deviation (RMSD) values from the molecular docking results showed that all test compounds had a valid level of conformational fit, as indicated by all RMSD values being within the range of ≤ 2 Å. An RMSD value below this threshold is widely recognized as evidence of a reliable reproduction of the crystallographic ligand conformation in the binding site. This demonstrates that the docking method employed is accurate and reliable, thereby providing confidence in the subsequent predictions of ligand–receptor interactions and binding affinities.

In the condition without water molecules, Luteolin, Luteolin 7-glucuronide, and Luteolin 7-O-glucoside showed RMSD values of 0.743 Å, 0.828 Å, and 0.843 Å, respectively, at the ER-α A site, and 0.682 Å, 1.036 Å, and 1.227 Å at the ER-α B site. Meanwhile, the comparator ligand, 4-Hydroxytamoxifen, showed lower RMSD values of 0.284 Å at ER-α A and 0.733 Å at ER-α B, indicating very good interaction stability compared to the test ligands.

In the condition with water molecules present, the RMSD values for Luteolin, Luteolin 7-glucuronide, and Luteolin 7-O-glucoside were recorded as 0.601 Å, 1.498 Å, and 0.843 Å at ER-α A, and 1.366 Å, 0.861 Å, and 0.296 Å at ER-α B, respectively. 4-Hydroxytamoxifen yielded RMSD values of 1.879 Å at ER-α A and 0.694 Å at ER-α B.

Overall, the RMSD values for all compounds were below the maximum limit of 2 Å, indicating that the docking method used in this study produced a valid and reliable spatial fit for further ligand-receptor interaction analysis.

RMSD value of ≤ 2 Å generally indicates that the ligand's position within the active pocket is relatively stable and consistent throughout the docking process [37]. In this study, Luteolin and 4-Hydroxytamoxifen showed good complex stability, with RMSD values ranging from 0.68 to 1.8 Å. On the other hand, the two luteolin derivatives showed RMSD values that tended to approach the 2 Å threshold in some conditions. This indicates a tendency towards conformational instability, which is presumed to be due to the greater flexibility and size of the polar side groups in their derivative structures. Thus, this RMSD evaluation further reinforces that Luteolin, while more stable than its derivatives, still shows slightly lower stability compared to the comparator ligand 4-Hydroxytamoxifen, which demonstrated the best conformational consistency among all the test compounds.

Table 3. RMSD Values from Ligand Docking with the Target Protein

Target Protein	RMSD (Å)			
	Luteolin	Luteolin 7-glucuronide	Luteolin 7-O-glucoside	4-Hydroxytamoxifen
ER-α A without water molecules	0.743	0.828	0.843	0.284
ER-α B without water molecules	0.682	1.036	1.227	0.733
ER-α A with water molecules	0.601	1.498	0.843	1.879
ER-α B with water molecules	1.366	0.861	0.296	0.694

Analysis and Visualization of Molecular Docking Results

The analysis of ligand and receptor interactions in this study was performed through two-dimensional visualization using Discovery Studio 2025 software. This visualization aims to illustrate the specific interactions formed between the ligand and the receptor, especially hydrophobic bonds and hydrogen bonds, which are identified based on the amino acid residues involved in the binding process [38].

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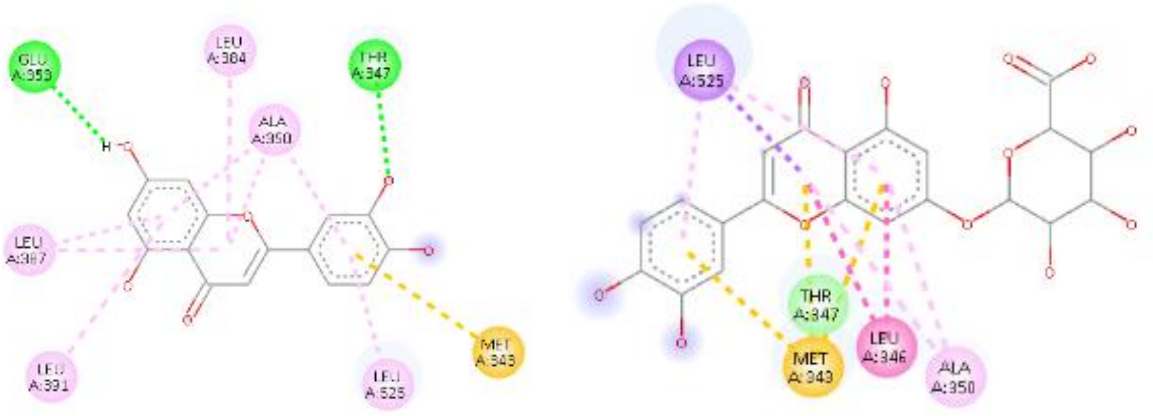
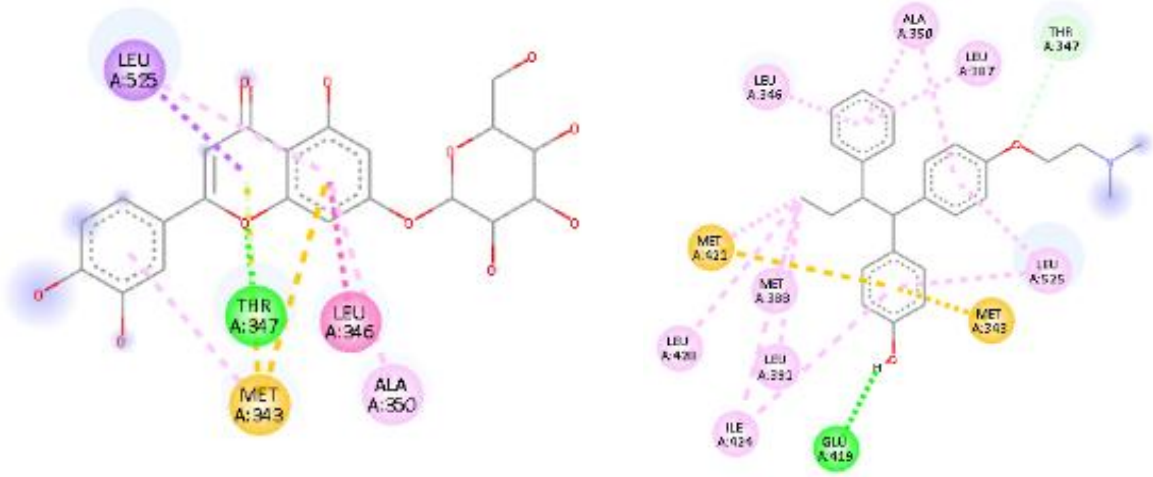


(A) (B)

Figure 3. Visualization of target protein ER-α A without water molecules: Luteolin (A) Luteolin 7-glucuronide (B)



(C) (D)

Figure 4. Visualization of target protein ER-α A without water molecules: Luteolin 7-O-glucoside (C) 4-Hydroxytamoxifen (D)

Based on the visualization results in Table 4 for ER-α A without water molecules, the four compounds displayed distinct binding interaction profiles that highlight both similarities and differences in their stabilization within the receptor's binding pocket.

The Luteolin compound exhibited two hydrogen bonds with GLU A:353 and THR A:347, which contribute to its anchoring in the active site. In addition, it showed multiple hydrophobic interactions, including π-alkyl contacts with LEU A:384, ALA A:350, LEU A:525, LEU A:391, and LEU A:387, as well as a π-sulfur interaction with MET A:343. These combined interactions suggest that Luteolin achieves a relatively balanced stabilization between polar and nonpolar contacts, although no ionic or halogen bonds were detected.

In contrast, Luteolin 7-glucuronide did not form hydrogen bonds, indicating reduced polar anchoring within the binding site. Its stability was maintained primarily by hydrophobic interactions, such as π-sigma with LEU A:525, π-alkyl with ALA A:350, and amide-π stacked with LEU A:346, in addition to a π-sulfur contact with MET A:343. Furthermore, a van der Waals interaction with THR A:347 was observed, providing additional but weaker stabilization. The absence of hydrogen bonding may explain its lower binding strength compared to Luteolin.

Similarly, Luteolin 7-O-glucoside showed both conventional and π-donor hydrogen bonds with THR A:347, which enhance its stability in the receptor. The compound also engaged in multiple hydrophobic contacts, including π-sigma with LEU A:525, π-alkyl with ALA A:350, amide-π stacked with LEU A:346, and π-sulfur with MET A:343. These interactions indicate that, compared with Luteolin 7-glucuronide, the 7-O-glucoside derivative has improved polar anchoring while maintaining strong hydrophobic stabilization.

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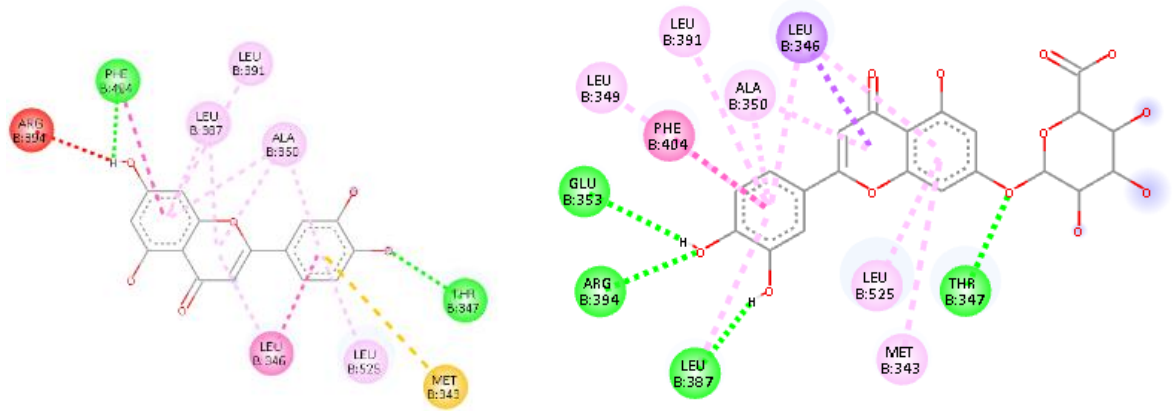
Table 4. Visualization Results of Target Protein ER-α A without Water Molecules

Compound Name	Hydrogen Bonds	Hydrophobic Bonds	Ionic Bond
Luteolin	GLU A:353, THR A:347	π-Alkyl: LEU A:384, ALA A:350, LEU A:525, LEU A:391, LEU A:387 π-Sulfur: MET A:343	-
Luteolin 7-glucuronide	-	π-Sigma: LEU525 π-Alkyl: ALA350 Amide-π Stacked: LEU346 π-Sulfur: MET343 Van der walls: THR A:347	-
Luteolin 7-O-glucoside	Conventional & π-donor Hydrogen bond: THR347	π-Sigma: LEU525 π-Alkyl: ALA350 Amide-π Stacked: LEU346 π-Sulfur: MET343	-
4-Hydroxytamoxifen	Conventional Hydrogen Bond: GLU419 Carbon Hydrogen Bond: THR347	π-Sulfur: MET343, MET388, MET421 Alkyl: LEU346, LEU387, ALA350, LEU391, LEU428, ILE424 π-Alkyl: LEU525	-

Meanwhile, 4-Hydroxytamoxifen, the reference drug, demonstrated a stronger and more complex interaction profile. It formed one conventional hydrogen bond with GLU A:419 and one carbon hydrogen bond with THR A:347, alongside multiple hydrophobic interactions. These included π-sulfur with MET A:343, MET A:388, and MET A:421, alkyl interactions with LEU A:346, LEU A:387, ALA A:350, LEU A:391, LEU A:428, and ILE A:424, and a π-alkyl interaction with LEU A:525. This extensive network of hydrogen and hydrophobic interactions suggests that 4-Hydroxytamoxifen achieves stronger binding stability within ER-α compared to the luteolin derivatives, consistent with its established role as a selective estrogen receptor modulator.



(A) (B)

Figure 5. Visualization of target protein ER-α B without water molecules: Luteolin (A) Luteolin 7-glucuronide (B)

In Table 5, for ER-α B without water molecules, Luteolin interacted through two conventional hydrogen bonds with PHE B:404 and THR B:347, along with one unfavorable donor–donor interaction involving ARG B:394. Hydrophobic stabilization was provided by a π-sulfur interaction with MET B:343, π-alkyl contacts with LEU B:346 and LEU B:525, an amide-π stacked interaction with ALA B:350, and π–π T-shaped interactions with LEU B:391 and LEU B:387.

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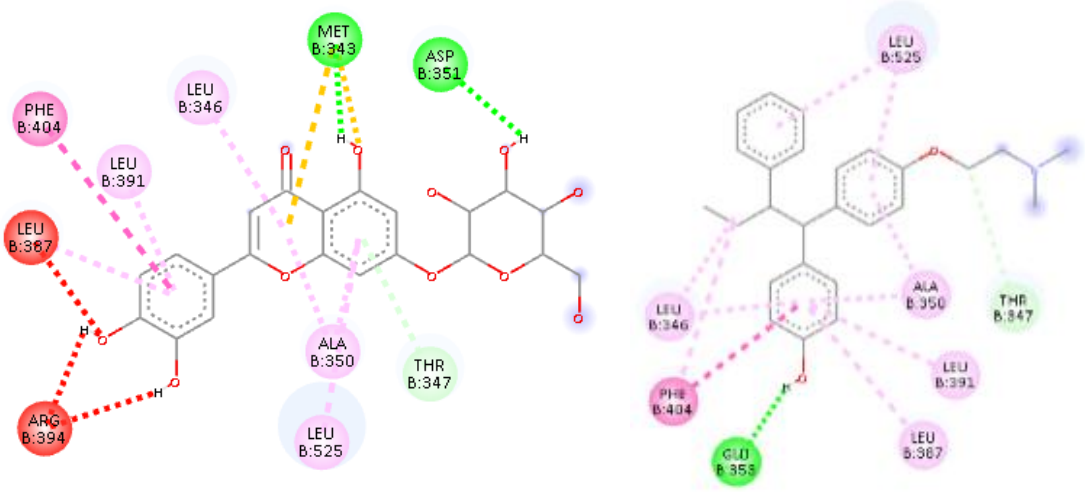

(C) (D)

Figure 6. Visualization of target protein ER-α B without water molecules: (C) 4-Hydroxytamoxifen (D)

Table 5. Visualization Results of Target Protein ER-α B without Water Molecules

Compound Name	Hydrogen Bonds	Hydrophobic Bonds	Ionic Bond
Luteolin	Conventional: PHE B:404, THR B:347 Unfavorable donor–donor: ARG B:394	π-Sulfur: MET B:343 π-Alkyl: LEU B:346, LEU B:525 Amide-π stacked: ALA B:350 π–π T-shaped: LEU B:391, LEU B:387	-
Luteolin 7-glucuronide	Conventional: GLU B:353, ARG B:394, THR B:347, PHE B:404	π-Sigma: LEU B:349 π-Alkyl: LEU B:525, LEU B:346 π–π T-shaped: LEU B:391, ALA B:350, LEU B:387	-
Luteolin 7-O-glucoside	Conventional: ASP B:351, THR B:347 π-Donor Hydrogen Bond: ASP B:351 Unfavorable donor–donor: ARG B:394, LEU B:387 Unfavorable acceptor–acceptor: ARG B:394	π-Sulfur: MET B:343 π–π T-shaped: PHE B:404 π-Alkyl: LEU B:525, LEU B:346 Amide-π stacked: LEU B:391	-
4-Hydroxytamoxifen	Conventional: GLU B:353 Carbon Hydrogen Bond: THR B:347	π–π T-shaped: PHE B:404 π-Alkyl: LEU B:387, LEU B:391, LEU B:346 Alkyl: ALA B:350, LEU B:525	-

Luteolin 7-glucuronide formed four conventional hydrogen bonds with GLU B:353, ARG B:394, THR B:347, and PHE B:404. Additional hydrophobic interactions included a π-sigma contact with LEU B:349, π-alkyl contacts with LEU B:525 and LEU B:346, and π–π T-shaped interactions with LEU B:391, ALA B:350, and LEU B:387.

Luteolin 7-O-glucoside established two conventional hydrogen bonds with ASP B:351 and THR B:347, as well as one π-donor hydrogen bond with ASP B:351. Unfavorable donor–donor interactions were observed with ARG B:394 and LEU B:387, along with an unfavorable acceptor–acceptor interaction at ARG B:394. Its hydrophobic profile was defined by a π-sulfur contact with MET B:343, a π–π T-shaped interaction with PHE B:404, π-alkyl contacts with LEU B:525 and LEU B:346, and an amide-π stacked interaction with LEU B:391.

Meanwhile, 4-Hydroxytamoxifen exhibited one conventional hydrogen bond with GLU B:353 and one carbon hydrogen bond with THR B:347. Hydrophobic interactions included a π–π T-shaped interaction with

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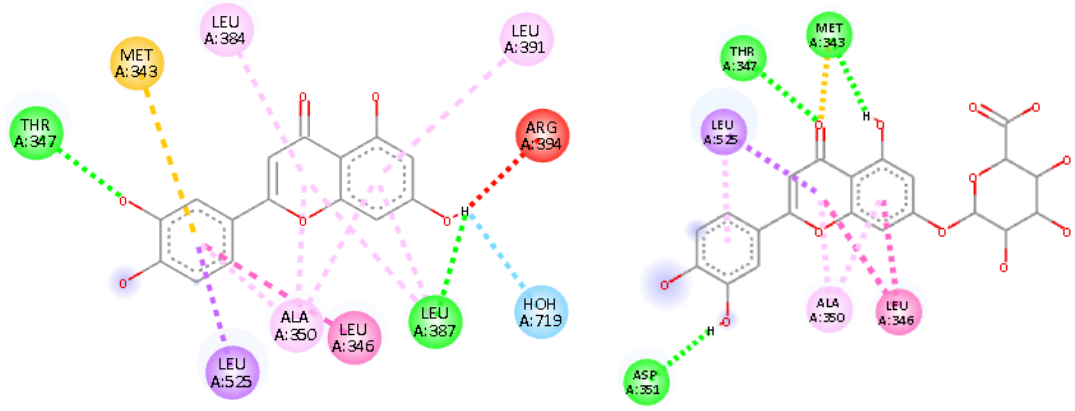
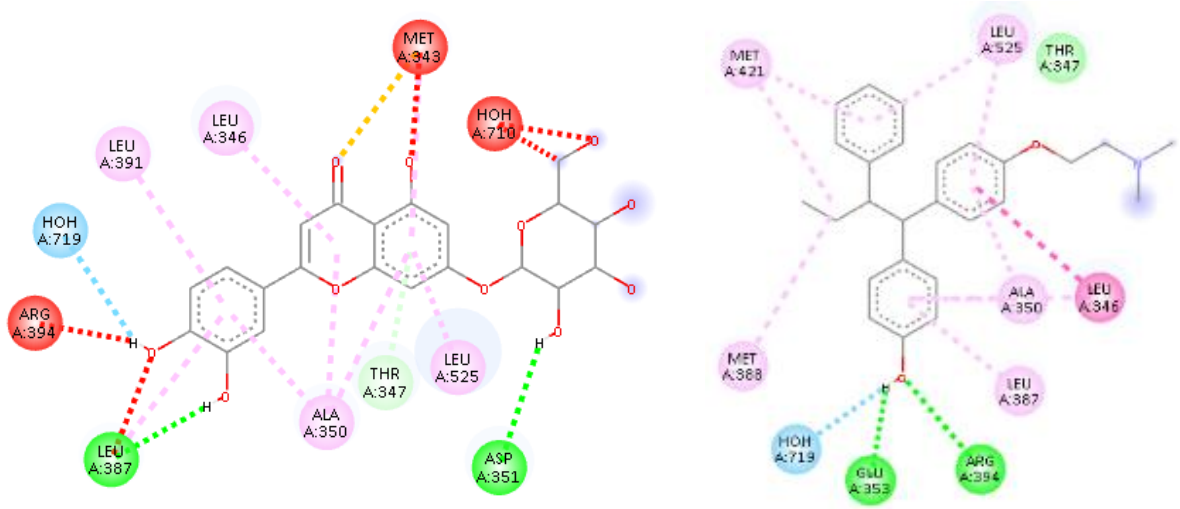
PHE B:404, π-alkyl contacts with LEU B:387, LEU B:391, and LEU B:346, as well as alkyl interactions with ALA B:350 and LEU B:525.



(A) (B)

Figure 7. Visualization of target protein Erα-A with water molecules: Luteolin (A) Luteolin 7-glucuronide (B)



(C) (D)

Figure 8. Visualization of target protein Erα-A with water molecules: Luteolin 7-O-glucoside (C) 4-Hydroxytamoxifen (D)

In the presence of water molecules, the visualization for ER-α A in Table 6 shows that Luteolin formed one conventional hydrogen bond with THR A:347 and an additional water-mediated hydrogen bond with HOH A:719. Its hydrophobic stabilization involved a π-sulfur interaction with MET A:343, π-alkyl contacts with LEU A:346, LEU A:384, and LEU A:391, and a π-sigma interaction with ALA A:350.

Luteolin 7-glucuronide established two conventional hydrogen bonds with THR A:347 and ASP A:351. Hydrophobic interactions included a sulfur–X contact with MET A:343, a π-alkyl interaction with LEU A:346, a π-sigma interaction with LEU A:525, and an amide-π stacked interaction with ALA A:350.

Luteolin 7-O-glucoside displayed two conventional hydrogen bonds with THR A:347 and ASP A:351, as well as a water hydrogen bond with HOH A:719. The compound also formed a π-donor hydrogen bond with LEU A:525, along with hydrophobic interactions consisting of π-alkyl contacts with LEU A:346 and LEU A:391 and a sulfur–X interaction with MET A:343.

Meanwhile, 4-Hydroxytamoxifen showed two conventional hydrogen bonds with GLU A:353 and ARG A:394, as well as one water-mediated hydrogen bond with HOH A:719. Hydrophobic stabilization was observed through π-alkyl interactions with LEU A:346, LEU A:387, MET A:388, and MET A:421, an amide-π stacked interaction with ALA A:350, and one alkyl contact with LEU A:525.

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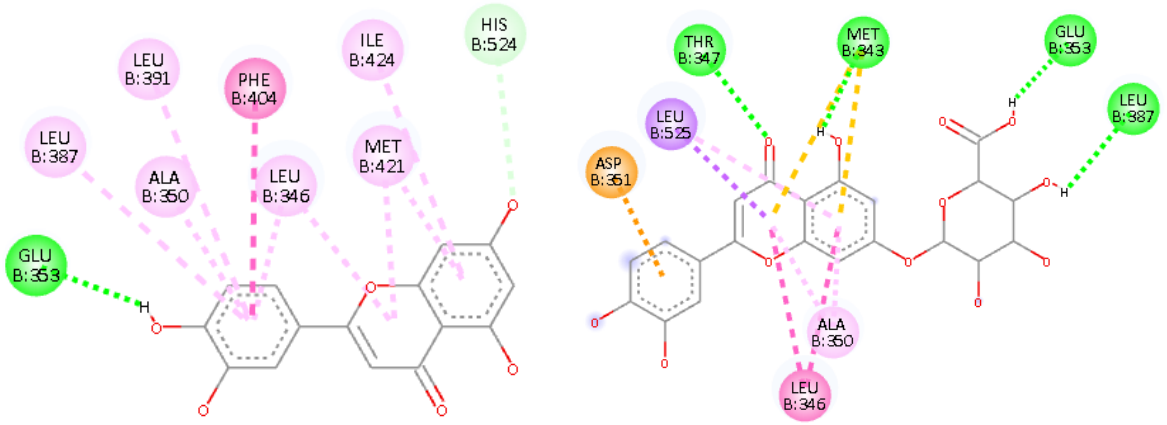
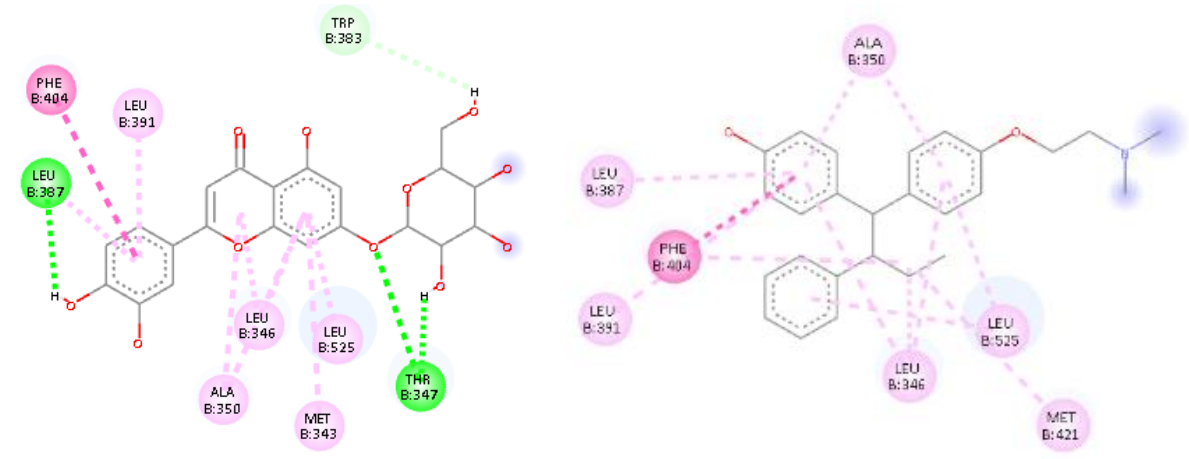
Table 6. Visualization Results of Target Protein ER-α A with Water Molecules

Compound Name	Hydrogen Bonds	Hydrophobic Bonds	Ionic Bond
Luteolin	Conventional Hydrogen Bond: THR A:347 Water Hydrogen Bond: HOH A:719	π -Sulfur: MET A:343 π -Alkyl: LEU A:346, LEU A:384, LEU A:391 π -Sigma: ALA A:350	-
Luteolin 7-glucuronide	Conventional Hydrogen Bond: THR A:347, ASP A:351	Sulfur-X: MET A:343 π -Alkyl: LEU A:346 π -Sigma: LEU A:525 Amide- π Stacked: ALA A:350	-
Luteolin 7-O-glucoside	Conventional Hydrogen Bond: THR A:347, ASP A:351 Water Hydrogen Bond: HOH A:719	π -Alkyl: LEU A:346, LEU A:391 π -Donor Hydrogen Bond: LEU A:525 Sulfur-X: MET A:343	-
4-Hydroxytamoxifen	Conventional Hydrogen Bond: GLU A:353, ARG A:394 Water Hydrogen Bond: HOH A:719	π -Alkyl: LEU A:346, LEU A:387, MET A:388, MET A:421 Amide- π Stacked: ALA A:350 Alkyl: LEU A:525	-



(A) (B)

Figure 9. Visualization of target protein Erα-B with water molecules: Luteolin (A) Luteolin 7-glucuronide (B)



(C) (D)

Figure 10. Visualization of target protein Erα-B with water molecules: Luteolin 7-O-glucoside (C) 4-Hydroxytamoxifen (D)

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Meanwhile, in Table 7, for ER-α B with water molecules, Luteolin formed two hydrogen bonds, including one conventional hydrogen bond with GLU B:353 and one carbon hydrogen bond with HIS B:524. Hydrophobic interactions were dominated by a π–π T-shaped interaction with PHE B:404, together with π-alkyl contacts involving LEU B:346, LEU B:387, LEU B:391, MET B:421, ILE B:424, and ALA B:350. No ionic bonds were detected.

Table 7. Visualization Results of Target Protein ER-α B with Water Molecules

Compound Name	Hydrogen Bonds	Hydrophobic Bonds	Ionic Bond
Luteolin	Conventional Hydrogen Bond: GLU B:353, Carbon Hydrogen Bond: HIS B:524	π - π T-shaped: PHE B:404 π -Alkyl: LEU B:346, LEU B:387, LEU B:391, MET B:421, ILE B:424, ALA B:350	-
Luteolin 7-glucuronide	Conventional Hydrogen Bond: THR B:347, GLU B:353	π -Alkyl: LEU B:346 π -Sulfur: MET B:343 Amide- π Stacked: ALA B:350 π -Sigma: LEU B:525	π-Anion: ASP B:351
Luteolin 7-O-glucoside	Conventional Hydrogen Bond: LEU B:387, THR B:347 Pi-Donor Hydrogen Bond: TRP B:383	π - π T-shaped: PHE B:404 π -Alkyl: LEU B:346, LEU B:391, MET B:343, LEU B:525, ALA B:350	-
4-Hydroxytamoxifen	-	π - π T-shaped: PHE B:404 π -Alkyl: LEU B:346, LEU B:387, LEU B:391, LEU B:525, MET B:421, ALA B:350 Alkyl: MET B:421	-

Luteolin 7-glucuronide established two conventional hydrogen bonds with THR B:347 and GLU B:353. Its hydrophobic interactions consisted of π-alkyl contact with LEU B:346, a π-sulfur interaction with MET B:343, an amide-π stacked interaction with ALA B:350, and a π-sigma interaction with LEU B:525. Additionally, one π-anion interaction was observed with ASP B:351, indicating ionic stabilization.

Luteolin 7-O-glucoside displayed two hydrogen bonds, namely conventional hydrogen bonds with LEU B:387 and THR B:347, as well as one π-donor hydrogen bond with TRP B:383. Hydrophobic stabilization was mediated by a π–π T-shaped interaction with PHE B:404, along with π-alkyl contacts with LEU B:346, LEU B:391, MET B:343, LEU B:525, and ALA B:350. No ionic bonds were present.

In contrast, 4-Hydroxytamoxifen did not form any hydrogen bonds but showed strong hydrophobic stabilization through a π–π T-shaped interaction with PHE B:404, π-alkyl contacts with LEU B:346, LEU B:387, LEU B:391, LEU B:525, MET B:421, and ALA B:350, as well as an alkyl interaction with MET B:421. No ionic bonds were identified.

Overall, the molecular interaction visualization results show that the majority of interactions formed between the ligand and the receptor in all conditions were dominated by hydrophobic bonds, while the presence of hydrogen bonds was more limited. This finding indicates that the binding affinity of ligands to ER-α is generally influenced by the strength of the hydrophobic interactions occurring within the receptor's active pocket.

Further analysis shows that Luteolin forms a large number of hydrophobic interactions with key residues in the ER-α active site, such as LEU A:525, ALA A:350, MET A:343, and PHE B:404. Additionally, π-π stacking interactions occurred between the aromatic ring of luteolin and aromatic residues in the active pocket, which also contributed to the stability of the ligand-receptor complex. These interactions support Luteolin's relatively strong binding affinity value.

Conversely, the comparator ligand 4-Hydroxytamoxifen formed a combination of important hydrophobic interactions and hydrogen bonds, especially with residues GLU A:353 and ARG A:394. This combination of interactions allows 4-Hydroxytamoxifen to form a more stable complex, which is consistent with its higher binding affinity value compared to luteolin and its derivatives [39].

Based on the visualization results, luteolin was able to occupy the ER-α active pocket more optimally than its two derivatives. This is due to luteolin's simpler structure and lack of large polar substituents. In

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contrast, in Luteolin 7-glucuronide and Luteolin 7-O-glucoside, the presence of glucuronide and glucoside groups increases molecular size and polarity, thereby inhibiting the formation of π-π stacking interactions and reducing the hydrophobic contact area within the active pocket [40]. This condition caused both derivatives to show a lower binding affinity than luteolin.

Meanwhile, 4-Hydroxytamoxifen showed an optimal ability to fill the ER-α active pocket. This molecule was able to form an effective combination of hydrophobic and hydrogen bonds, which explains why this compound produced the highest binding affinity among all the tested ligands.

In the context of estrogen receptor alpha (ER-α), certain amino acid residues play a crucial role in determining whether a ligand acts as an agonist or antagonist. For example, GLU353 and ARG394 form critical hydrogen bonds with the hydroxyl group of estradiol, stabilizing the receptor in its active conformation and facilitating the recruitment of co-activators [39,41]. HIS524 is also essential in maintaining the hydrogen bond network that contributes to the agonistic effect of estradiol [39,42]. In contrast, antagonists such as 4-hydroxytamoxifen (4-OHT) retain interactions with GLU353 and ARG394 but, due to their bulky side chains, displace helix-12 of the receptor. This conformational shift prevents co-activator binding and promotes co-repressor recruitment, thereby inhibiting transcriptional activation [43,44]. Compared to estradiol and 4-OHT, luteolin demonstrates a binding profile that emphasizes hydrophobic and π–π stacking interactions with residues such as LEU525, MET343, and PHE404 [41,42,44], with fewer stable hydrogen bonds at GLU353 and ARG394. This suggests that luteolin may not fully mimic the agonistic hydrogen bond pattern of estradiol, but rather adopts an intermediate binding mode closer to a partial antagonist. Such differences in binding patterns imply that luteolin may exert modulatory effects on ER-α signaling, potentially contributing to its reported anticancer activity through mechanisms distinct from classical SERMs [41,42].

Conclusions

This study demonstrates that luteolin exhibits stronger binding affinity to ER-α compared to its glycosylated derivatives, luteolin 7-glucuronide and luteolin 7-O-glucoside, but remains significantly weaker than the reference drug 4-hydroxytamoxifen. The superiority of luteolin is primarily attributed to its ability to maintain optimal hydrophobic interactions within the ER-α binding pocket, whereas the addition of bulky and polar glycoside groups hinders these interactions and reduces binding affinity. Thus, the main strength of this work lies in its structural explanation showing that glycosylation of luteolin is detrimental to binding activity, highlighting that future development strategies should focus on improving luteolin's bioavailability without compromising its critical hydrophobic contacts.

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