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Pharmacokinetic and Molecular Docking Analysis of Matricaria chamomilla Flavonoids Against Breast Cancer Targets

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Abstract: In this study, the pharmacokinetic, toxicological, and drug-likeness profiles of Quercetin, Luteolin, Apigenin natural flavonoids and active compounds found in the chamomile plant and Dibenzo-p-dioxin were comparatively analyzed using in silico methods. ADME (Absorption, Distribution, Metabolism, and Excretion) parameters, Lipinski's Rule of Five, cellular permeability, blood-brain barrier penetration potential, metabolic stability, and cardiotoxicity risks were evaluated. The findings indicated that Apigenin possesses the most balanced pharmacokinetic profile, while Dibenzo-p-dioxin was found to be unsuitable for drug development due to its potential toxicity. Subsequently, molecular interactions of these flavonoids (Apigenin, Luteolin, Quercetin, and Dibenzo-p-dioxin) with proteins associated with breast cancer 1JNX (Estrogen Receptor α) and 6CZ2 (HER2 receptor) were investigated using molecular docking analysis. Accordingly, the aim of this study is to evaluate the pharmaceutical potential of the selected compounds using computational methods, compare their strengths and weaknesses, and identify which compounds are more suitable as clinical drug candidates.

Keywords: Apigenin, Luteolin, Quercetin, Dibenzo-p-dioxin, Molecular Docking, ADME, Breast Cancer

1. Introduction

Flavonoids are plant-derived polyphenolic compounds that have attracted considerable attention due to their antioxidant, anti-inflammatory, anticancer, and cardioprotective effects on human health [1]. The optimal utilization of the biological effects of dietary flavonoids depends not only on their pharmacodynamic properties but also directly on their pharmacokinetic profiles. In this context, commonly studied flavonoids such as quercetin, luteolin, and apigenin have recently emerged as promising natural candidates in drug development efforts [2,3].

The pharmacological effectiveness of flavonoids is closely related to pharmacokinetic processes including absorption, tissue distribution, metabolism, and excretion. However, many of these compounds exhibit poor systemic bioavailability due to low lipophilicity, weak membrane permeability, and rapid metabolic degradation [4]. Therefore, especially in the early stages of drug discovery, evaluating the ADME (Absorption, Distribution, Metabolism, and Excretion) properties of such compounds through in silico methods has gained importance as an efficient and cost-effective approach [5].

This study analyzes the drug-likeness profiles of quercetin, luteolin, and apigenin based on key parameters such as molecular weight, polar surface area, hydrogen bonding potential, cellular permeability (Caco-2 and MDCK), blood-brain barrier penetration (QPlogBB), cardiotoxicity potential (QPlogHERG), and compliance with Lipinski's Rule of Five. For comparative purposes, dibenzo-p-dioxin—a compound widely recognized in toxicological literature and classified as a persistent organic pollutant—was also included in the analysis. Due to its strong lipophilicity and environmental stability, dibenzo-p-dioxin serves as a reference molecule from a toxicokinetic

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perspective and is considered a negative example for drug development [6].

In recent years, natural plant-derived compounds, particularly flavonoids, have gained significant interest as anticancer agents. These compounds exhibit diverse biological activities against cancer cells, including antioxidant, anti-inflammatory, antiproliferative, and apoptotic effects [7]. Flavonoids have been shown to interact with various molecular targets such as cell cycle regulators, growth factors, and transcription factors [8].

Matricaria chamomilla L. (chamomile) is a medicinal plant traditionally used for its therapeutic properties and rich phenolic content. Flavonoids found in chamomile—such as apigenin, luteolin, and quercetin—have demonstrated antitumor effects against various cancer types [9–11]. In particular, apigenin has been reported to inhibit cancer-related signaling pathways such as p53, NF-κB, and PI3K/AKT [9]. Although dibenzo-p-dioxin is widely recognized for its environmental toxicity, some in silico studies have suggested that it may exhibit weak interactions with certain target proteins [12].

Breast cancer is the most commonly diagnosed cancer in women worldwide and is one of the leading causes of cancer-related mortality. [13]. Despite the use of multimodal treatment strategies including surgery, chemotherapy, radiotherapy, and hormone therapy, challenges such as metastasis, drug resistance, and heterogeneous treatment response continue to complicate its management [14]. Therefore, there is an increasing need for novel, more targeted, and less toxic therapeutic strategies.

Two key molecular targets involved in the development and progression of breast cancer are the estrogen receptor alpha (ERα; PDB ID: 1JNX) and the human epidermal growth factor receptor 2 (HER2; PDB ID: 6CZ2) [15,16]. ER-positive breast cancers typically respond to selective estrogen receptor modulators such as tamoxifen; however, resistance often develops over time [17]. HER2-positive tumors tend to be more aggressive and may exhibit acquired resistance to targeted therapies like trastuzumab [18]. These challenges underscore the necessity of exploring alternative and complementary therapeutic approaches.

2. Computational Method

2.1. Ligand and Protein Preparation

The 3D structures of apigenin, luteolin, quercetin, and dibenzo-p-dioxin were downloaded from the PubChem database and optimized using AutoDock Tools. The protein structures of 1JNX and 6CZ2 were obtained from the RCSB Protein Data Bank. For water-insoluble molecules, polar hydrogens and Gasteiger charges were added.

In this study, the pharmacokinetic and toxicological parameters of the four selected compounds (quercetin, luteolin, apigenin, and dibenzo-p-dioxin) were calculated using Schrödinger QikProp 6.1 software (Schrödinger, LLC, NY, USA). This software predicts over 44 pharmaceutically relevant molecular descriptors and evaluates the drug-likeness of small molecules [19].

In addition to the analyzed parameters, compliance with Lipinski's Rule of Five and drug-likeness criteria based on chemical structure were also assessed [20].

2.2. Molecular Docking

Molecular docking procedures were carried out using the AutoDock Vina software. The binding energies of the ligands (in kcal/mol) and their corresponding binding sites on the proteins were determined. The conformations with the most favorable binding scores were analyzed, and the binding models were interpreted accordingly.

3. Results and discussion

3.1. Physicochemical Properties

The molecular weights of quercetin, luteolin, and apigenin were measured as 302.24, 286.24, and 270.24 g/mol, respectively all within the acceptable limits defined by Lipinski's rule of five. Dibenzo-p-dioxin had the lowest molecular weight at 184.19 g/mol. The polar surface area (PSA) values were found to be 143.33 Å² for quercetin, 121.44 Å² for luteolin, 99.76 Å² for apigenin, and 15.66 Å² for dibenzo-p-dioxin, confirming the high polarity of the flavonoid compounds.

3.2. Permeability and Absorption

In terms of Caco-2 permeability (QPPCaco), dibenzo-p-dioxin exhibited extremely high permeability (9906 nm/s), while the flavonoids showed much lower values: apigenin (114.5), luteolin (40.9), and quercetin (18.2). A similar trend

was observed in MDCK cell permeability data. Regarding brain permeability (QPlogBB), dibenzo-p-dioxin had the highest value at -0.27, whereas quercetin (-2.42), luteolin (-1.96), and apigenin (-1.45) showed significantly lower potentials for blood-brain barrier penetration.

3.3. Toxicological and Metabolic Parameters

The QPlogHERG values, which indicate the potential for cardiotoxicity, were approximately -4 for all flavonoids, suggesting a moderate risk level [21]. Dibenzo-p-dioxin, on the other hand, showed a lower cardiotoxicity risk with a QPlogHERG value of -5.13. However, this does not account for its systemic toxicity. Comparison of Physicochemical, Pharmacokinetic and Toxicological Properties of Quercetin, Dibenzo-p-dioxin, Luteolin and Apigenin is given in Table 1.

The ligand-protein interaction types of apigenin, quercetin, luteolin and dibenzo-p-dioxin structures between the 1JNX and 6CZ2 proteins are given in figure 2 and the ligand-protein interaction types are given in Table

Table 1. Comparison of Physicochemical, Pharmacokinetic, and Toxicological Properties of Quercetin, Dibenzo-p-dioxin, Luteolin and Apigenin.

Characteristic	Quercetin	Dibenzo-p-dioxin	Luteolin	Apigenin
Molecular Weight	302.24	184.19	286.24	270.24
Dipole Moment (Debye)	4.72	0.002	3.00	5.37
Polar Surface Area (PSA)	143.33 Å²	15.66 Å²	121.44 Å²	99.76 Å²
H-Bond Donor/Acceptor	4 / 5.25	0 / 1	3 / 4.5	2 / 3.75
FISA / PISA (Polar Area)	High	Very low	Medium	Low
Caco-2 Permeability	18.2 (low)	9906 (very high)	40.9	114.5
Brain Permeability (QPlogBB)	-2.42 (weak)	-0.27 (high)	-1.96	-1.45
Oral Absorption	Oral Absorption	Oral Absorption	Oral Absorption	Oral Absorption
Cardiotoxicity Risk (QPlogHERG)	-4.04	-5.13 (low risk)	-4.07	-4.10
Metabolic Transformation (#metab)	5 (high)	0	4	3
Lipinski Rules Violation	0	0	0	0

Molecular docking was done with the Docking Server program. The structures of apigenin, quercetin, luteolin, and dibenzo-p-dioxin were docked into 1JNX and 6CZ2 proteins whose crystal structures were taken from the RSCB protein data bank. Geometry optimization of ligand-protein complexes was done again on the docking server with the MMFF94 method. Gasteiger partial load calculation method was chosen. pH=7.0 was taken. Lamarckian genetic algorithm was used for insertion simulations. The 5A quaternion and torsion steps were applied to search for the appropriate region of the target protein. According to molecular docking calculations, the binding energy of apigenin and quercetin was found to be higher than Luteolin and Dibenzo-p-dioxin. Molecular docking calculations of apigenin, quercetin, luteolin and dibenzo-p-dioxin structures are given in Table 1. The docking poses of apigenin, quercetin, luteolin and dibenzo-p-dioxin structures between the 1JNX and 6CZ2 proteins are given in Figure 1.

The results indicate that apigenin, quercetin, show strong binding affinity (−4 to −6.5 kcal/mol), while dibenzo-p-dioxin and luteolin exhibited weak interactions with both targets. The molecular docking results are given in Table 3.

Binding Energy reflects the thermodynamic stability of the ligand-protein complex; more negative values indicate stronger binding. Accordingly, Quercetin stands out as the compound with the strongest binding energy to the HER2 (6CZ2) protein (-6.34 kcal/mol). It is followed by Luteolin (-6.00 kcal/mol) and Apigenin (-5.65 kcal/mol). In terms of binding to the estrogen receptor (1JNX), Apigenin shows the highest interaction (-5.03 kcal/mol). Dibenzo-p-dioxin, however, has the weakest binding energy to both target proteins, indicating a lower interaction strength. Moreover, Apigenin and Luteolin also demonstrate highly efficient binding activity, particularly with the HER2 (6CZ2) target, with values of -0.28 and -0.29, respectively.

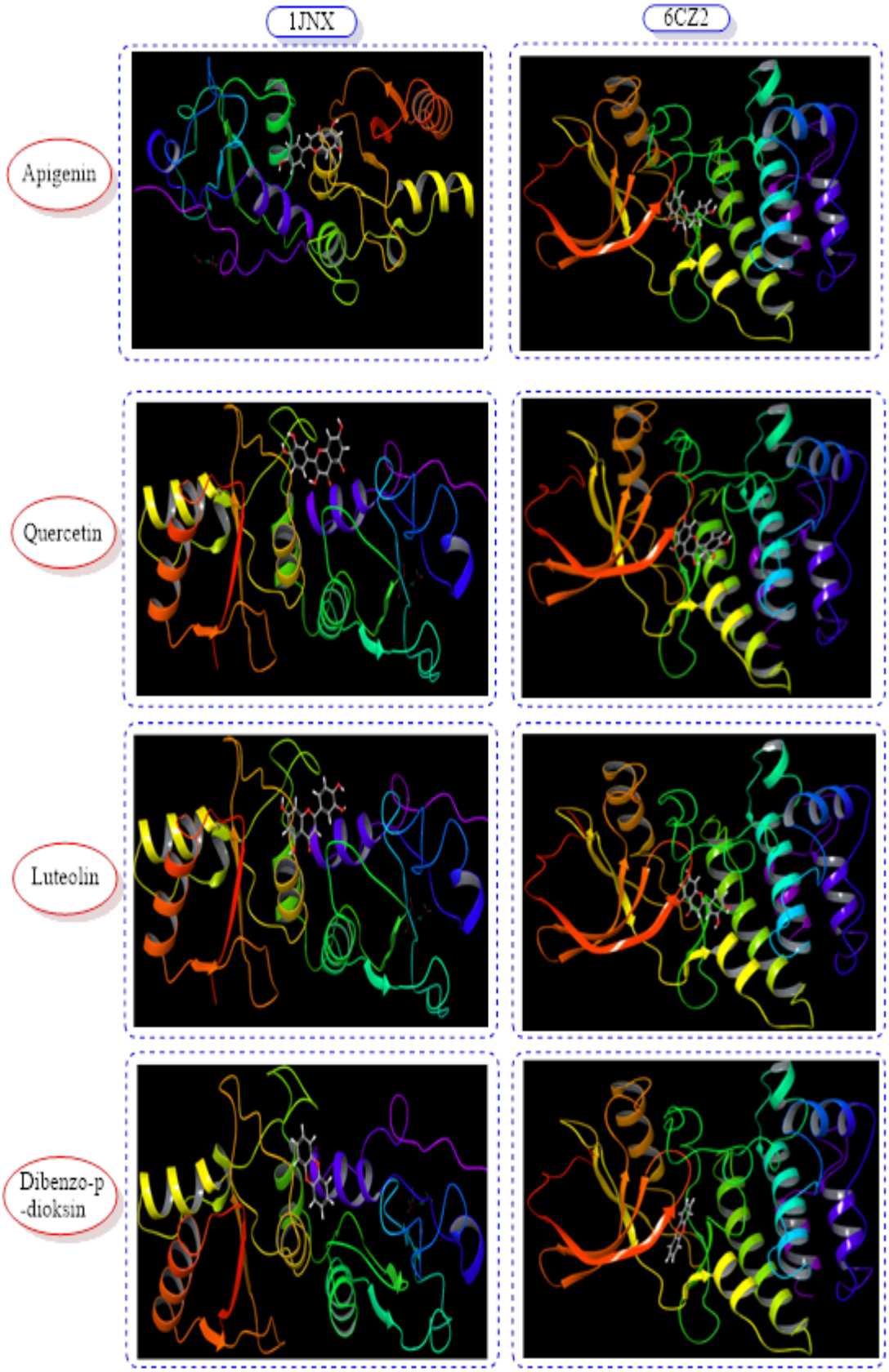

Figure 1. Docking poses between Apigenin, Quercetin, Luteolin and Dibenzo-p-dioxin structures with 1JNX and 6CZ2 proteins.

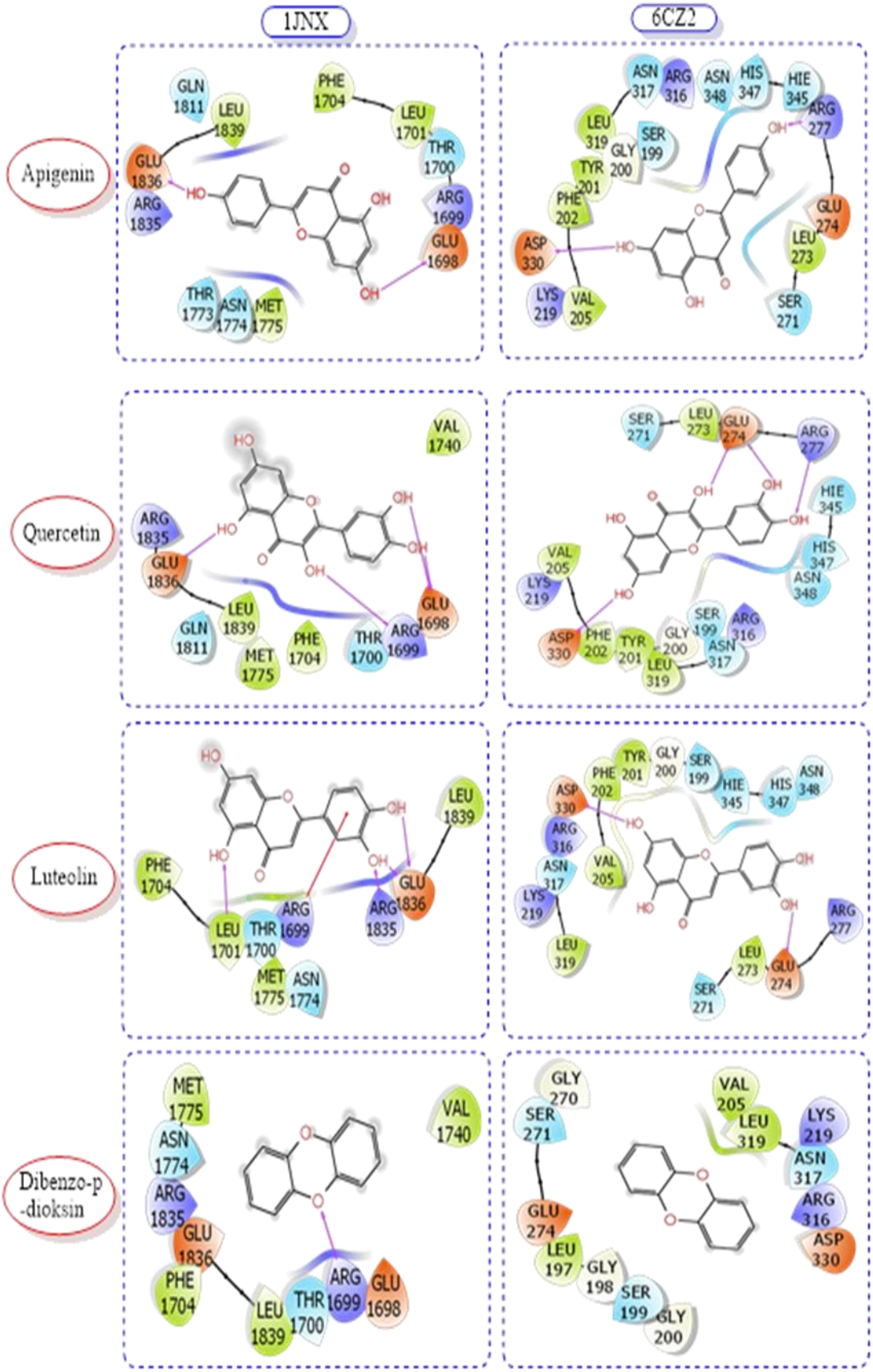

Figure 2. The ligand-protein interaction types of between Apigenin, Quercetin, Luteolin and Dibenzo-p-dioxin structures with 1JNX and 6CZ2 proteins.

Table 2. Types of interactions between Apigenin, Quercetin, Luteolin and Dibenzo-p-dioxin with 1JNX and 6CZ2 proteins

	1JNX			6CZ2		
	H- bonds	Polar	Hydrophobic	H- bonds	Polar	Hydrophobic
Apigenin	GLU1836 GLU1698	GLN1811 THR1773 ASN1774 THR1700	LEU1839 PHE1704 LEU1701 MET1775	ASP330 GLU274	ASN317 SER199 ASN348 HIS347 HIE345 SER271	VAL205 PHE202 TYR201 LEU319 LEU273
Quercetin	GLU1698 GLU1836	GLN1811 THR1700	LEU1839 MET1775 PHE1704 VAL1740	ASP330 GLU274 AGR277	SER271 HIE345 HIS347 ASN348 SER199 ASN317	VAL205 PHE202 TYR201 LEU319 LEU273
Luteolin	GLU1836	THR1700 ASN1774	PHE1704 LEU1701 MET1775 LEU1839	ASP330 GLU274	ASN317 SER199 HIE345 HIS347 ASN348 SER271	LEU319 VAL205 PHE202 TYR201 LEU273
Dibenzo-p-dioxin	GLU1836 GLU1698	THR1700 ASN1774	MET1775 VAL1740 PHE1704 LEU1839	GLU274 ASP330	SER271 SER199 ASN317	LEU197 VAL205 LEU319

Table 3. Molecular docking results of compounds from Apigenin, dibenzo-p-dioxin, luteolin and Quercetin against each 1JNX and 6CZ2 proteins

Compound	Target Protein	Binding Energy (kcal/mol)	Glide Ligand Efficiency	Glide emodel
Apigenin	1JNX	-5.03	-0.25	-40.37
	6CZ2	-5.65	-0.28	-53.85
Quercetin	1JNX	-4.71	-0.21	-41.91
	6CZ2	-6.34	-0.29	-64.40
Luteolin	1JNX	-4.58	-0.22	-42.24
	6CZ2	-6.0	-0.29	-58.12
Dibenzo-p-dioxin	1JNX	-3.83	-0.27	-22.01
	6CZ2	-4.96	-0.35	-33.91

In conclusion, Quercetin emerges as the most effective compound, exhibiting the strongest binding energy and the lowest emodel score with HER2 (6CZ2). This indicates that Quercetin forms a strong and stable interaction with the HER2 target. Apigenin presents a balanced pharmacokinetic profile, offering strong binding energy and good ligand efficiency with both target proteins, making it a promising candidate, particularly in terms of oral bioavailability.

Luteolin also demonstrates effective binding with the HER2 target and can be considered a valuable compound from a pharmaceutical perspective. On the other hand, Dibenzo-p-dioxin is not a suitable therapeutic candidate due to its low binding energy and low binding stability. Although its small molecular structure enhances ligand efficiency, its overall binding strength and stability are insufficient.

4. Conclusions

The findings of this study demonstrate that the therapeutic potential of flavonoid compounds is influenced not only by their biological activity but also by their pharmacokinetic suitability. Quercetin stands out for its high polarity and antioxidant capacity; however, its systemic efficacy is limited due to poor membrane permeability and rapid metabolism [22]. In comparison, luteolin and apigenin exhibit better permeability and a more balanced ADME profile. Among these, apigenin

emerges as the most promising compound, particularly in terms of oral bioavailability.

Dibenzo-p-dioxin, on the other hand, shows a tendency to accumulate in tissues due to its high lipophilicity and chemical stability, which contributes to long-term toxicity. It is classified among prohibited environmental toxins in literature due to its carcinogenic effects and endocrine-disrupting potential [23-25].

Chamomile-derived flavonoids exhibited notable binding affinity toward both ERα and HER2 proteins. These interactions suggest the potential use of apigenin and quercetin in breast cancer therapy, particularly for ER-positive and HER2-positive subtypes. Luteolin also showed comparable activity, though slightly lower in energy. The poor performance of dibenzo-p-dioxin highlights its limited pharmacological utility but affirms the specificity of the docking protocol. These in silico results align with previous findings that flavonoids can modulate key cancer-related signaling pathways [7–12].

This study highlights the potential of apigenin, quercetin, and luteolin as natural therapeutic agents targeting ERα and HER2 receptors in breast cancer. These flavonoids demonstrated favorable binding affinities in molecular docking simulations. Future in vitro and in vivo investigations are warranted to further validate these compounds as adjuvant or primary therapeutic agents.

In silico data suggests that Apigenin exhibits the most balanced pharmacokinetic profile and stands out as a promising candidate for drug development. Luteolin, on the other hand, could be further optimized through structural modifications, whereas Quercetin may require nanotechnological formulations or prodrug strategies to enhance its efficacy. Dibenzo-p-dioxin, however, is not suitable for pharmaceutical applications due to its unfavorable properties. This study highlights the effectiveness of in silico approaches in the early-stage evaluation of natural compounds for pharmaceutical development.

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