Computational Exploration of Xanthohumol as a Safer Natural Substitute for Tamoxifen in Estrogen Receptor-Positive Breast Cancer

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Abstract

Background: Breast cancer remains a major health burden, with estrogen receptor-positive (ER^+) subtypes constituting most cases. Tamoxifen, a selective estrogen receptor modulator (SERM), has been a frontline therapy for decades, yet its long-term use often leads to toxicity, resistance, and pharmacokinetic limitations. This study employed in-silico approaches to assess xanthohumol , a prenylated chalcone derived from Humulus lupulus, as a potential natural substitute for tamoxifen. **Method:** Using AutoDock Vina (PDB: 3ERT), both ligands were docked to the ERα ligand-binding domain. **Results:** *Xanthohumol* displayed a slightly superior binding affinity (–8.0 kcal/mol) compared to tamoxifen (–7.5 kcal/mol) and formed a stabilizing hydrogen bond with MET522, along with π–π interactions with TRP383, unlike tamoxifen's purely hydrophobic contacts. SwissADME analysis revealed *xanthohumol* to possess better solubility, high gastrointestinal absorption, and no Lipinski violations, indicating strong drug-likeness. ProTox-II toxicity predictions demonstrated a higher LD50 (3800 mg/kg) and fewer toxic liabilities for *xanthohumol*, while tamoxifen showed elevated neurotoxicity and CYP3A4 interaction risks. The BOILED-Egg model further indicated that xanthohumol has high intestinal absorption but limited blood–brain barrier permeability, suggesting reduced neurotoxic potential. **Conclusion:** Overall, these computational findings support *xanthohumol* as a pharmacologically favorable and safer natural alternative to tamoxifen. Further in-vitro and in-vivo validation is warranted to substantiate its therapeutic viability in hormone-dependent breast cancer.

Keywords: *Xanthohumol*; Tamoxifen; Estrogen Receptor Alpha (ERα); Molecular Docking; ADMET Analysis

Significance | This study identifies *xanthohumol* as a safer, effective natural alternative to tamoxifen through comprehensive in-silico docking and toxicity profiling.

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1. Introduction

Breast cancer remains one of the leading causes of cancer-related mortality among women worldwide, accounting for a significant proportion of new cancer diagnoses each year. Among its subtypes, hormone receptor-positive (HR^+) breast cancer, characterized by the overexpression of estrogen receptor alpha (ERα), constitutes nearly 70% of all breast cancer cases. Estrogen receptor signaling plays a pivotal role in the proliferation, survival, and progression of breast tumor cells, and therefore, targeting ERα has long been a cornerstone in breast cancer therapy (Testa et al., 2020; Thanopoulou et al., 2020).

Since its clinical introduction, tamoxifen, a selective estrogen receptor modulator (SERM), has remained a cornerstone in the treatment of estrogen receptor-positive (ER^+) breast cancer. It exerts its therapeutic effect by competitively binding to the ligand-binding domain (LBD) of the estrogen receptor, thereby blocking endogenous estrogen from activating downstream transcriptional

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pathways responsible for tumor proliferation (Jameera Begam et al., 2017). Over the past decades, tamoxifen has saved countless lives, substantially improving survival Outcomes in both early-stage and metastatic breast cancer patients, and continues to serve as a benchmark therapy in hormone-dependent cancer management (Bodai & Nakata, 2020).

However, despite its clinical success, tamoxifen is far from a perfect therapeutic agent. Long-term administration often results in the emergence of drug resistance, both de novo and acquired, limiting its efficacy over time (Yao et al., 2020). Moreover, its adverse effects-including endometrial cancer, thromboembolic complications, hepatic toxicity, and neurotoxic manifestations-pose substantial challenges to sustained treatment. At the molecular level, tamoxifen's high lipophilicity, low aqueous solubility, and poor oral bioavailability further complicate its pharmacokinetic performance (GAO et al., 2016). These limitations collectively underscore the urgent need for safer, more effective alternatives capable of modulating ERα signaling without eliciting severe systemic toxicity.

In recent years, attention has increasingly turned toward naturally derived bioactive compounds as viable sources for anticancer drug discovery. Natural products, particularly polyphenols and flavonoids, have demonstrated diverse mechanisms of anticancer activity, including antioxidant, anti-inflammatory, and hormone-modulatory effects. Among them, *xanthohumol,* a prenylated chalcone derived from the hop plant *(Humulus lupulus)*, has emerged as a particularly interesting candidate (Kłósek et al., 2016; Saito et al., 2018).

Xanthohumol has shown broad-spectrum biological activities, including anti-proliferative, anti-angiogenic, and pro-apoptotic effects against several cancer types. Structurally, it possesses functional groups that facilitate both hydrophobic and polar interactions with target proteins-attributes desirable for receptor-binding modulation. Importantly, *xanthohumol* has been reported to exert phytoestrogenic activity, suggesting potential affinity for estrogen receptor targets, particularly ERα, while maintaining a comparatively safer toxicity profile (Liu et al., 2015; Miller et al., 2017).

Modern computational methods, particularly molecular docking and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) prediction, provide powerful tools to assess and compare potential drug candidates at the molecular level. Molecular docking simulates the interaction between a ligand and a receptor, predicting the optimal binding conformation and affinity within the active site. This technique enables researchers to evaluate how effectively a compound can mimic or inhibit natural ligand behavior-here, the interaction of estrogen or tamoxifen with ERα (Kar & Leszczynski, 2018).

The ADMET and toxicity profiling complement docking studies by predicting pharmacokinetic and safety parameters that influence a compound's drug-likeness and clinical viability. In-silico models such as SwissADME, ProTox-II, and BOILED-Egg analysis can efficiently estimate a compound's solubility, permeability, bioavailability, and potential toxicity, substantially reducing the need for initial experimental screening. These computational frameworks, though predictive, serve as a valuable foundation for identifying promising therapeutic leads for subsequent experimental validation (Chandrasekaran et al., 2018).

Tamoxifen's clinical relevance as a benchmark ERα antagonist provides an ideal reference for assessing new compounds. Comparing the binding affinity, molecular interactions, and pharmacokinetic behavior of *xanthohumol* with tamoxifen offers crucial insights into whether a natural ligand can achieve comparable or improved therapeutic performance. Previous studies have suggested that *xanthohumol* exhibits strong binding to ERα, forming both π–π stacking and hydrogen bond interactions, and demonstrating stability comparable to tamoxifen's complex (Miranda et al., 2018). However, its higher topological polar surface area (TPSA) and moderate lipophilicity imply better solubility and gastrointestinal absorption-properties favorable for oral drug development.

Furthermore, toxicity prediction models indicate that *xanthohumol* is associated with a higher LD_{50} value and fewer organ-level toxicities compared to tamoxifen. Its limited blood-brain barrier (BBB) permeability also reduces the likelihood of central nervous system side effects-a significant advantage over tamoxifen's neurotoxic tendencies. Collectively, these properties position *xanthohumol* as a promising candidate for future therapeutic development (Wang et al., 2020) t.

While numerous studies have explored the anticancer potential of *xanthohumol*, few have directly compared its ERα binding characteristics, ADMET profile, and toxicity patterns against tamoxifen within a unified computational framework. Understanding these comparative features is critical for establishing the mechanistic basis of *xanthohumol* 's receptor modulation and predicting its suitability as a drug-like molecule (Liu et al., 2015).

Moreover, most existing data are derived from experimental models focusing on *xanthohumol* 's biological effects rather than its molecular pharmacology. Therefore, an integrated in-silico assessment that combines molecular docking, ADMET prediction, and toxicological evaluation can bridge this gap-offering an evidence-based rationale for further preclinical exploration (Orhan et al., 2018).

This study contributes to the ongoing effort to identify natural, effective, and safer alternatives to synthetic endocrine therapies. By employing a comprehensive computational approach, it provides a mechanistic insight into the interaction of *xanthohumol* with estrogen receptor alpha, highlighting its potential as a phytoestrogen-based SERM candidate (Logan et al., 2019). If

validated experimentally, *xanthohumol* could serve as a foundation for developing the next generation of ERα-targeted therapies with improved safety, efficacy, and patient compliance.

2. Materials and Methods

2.1 Study design

This in-silico study compared tamoxifen (reference ligand) and *xanthohumol* (literature-derived natural lead) at the ligand-binding domain of human ERα using a co-crystal-derived PDB structure. After preparing the protein and generating energy-minimized 3D conformers of both ligands, molecular docking was performed in PyRx (AutoDock Vina) against an identical binding-site grid. Top-ranked poses were evaluated for binding scores, pose stability/consistency, and interaction fingerprints with key residues to determine the extent to which *xanthohumol* reproduces a tamoxifen-like interaction motif. In parallel, drug-likeness and ADME properties were profiled with SwissADME, and preliminary toxicity liabilities were predicted with ProTox-II. As a purely computational analysis, the findings are hypothesis-generating and require subsequent experimental validation.

2.2 Protein preparation

Protein preparation was performed in BIOVIA Discovery Studio Visualizer 2021 (v21.1) using the human ERα ligand-binding domain co-crystal structure PDB: 3ERT (4-hydroxytamoxifen-bound). Nonessential heteroatoms and bulk waters were removed, retaining only conserved binding-site waters when present (residue IDs recorded). Alternate locations were resolved by keeping the highest-occupancy conformers. Protonation states and hydrogens were assigned with Protonate 3D at pH 7.4, optimizing the hydrogen-bond network and manually inspecting His tautomers (HID/HIE/HIP) near the pocket. Minor geometric issues were corrected with Clean Geometry followed by a backbone-restrained local energy minimization (short steepest-descent) to relieve clashes. The docking site was defined by a grid centered on the co-ligand centroid and sized to enclose key residues (e.g., E353, D351, H524); the grid center (x,y,z) and box dimensions (Å) were recorded for reuse in PyRx/Vina. The cleaned receptor was saved as pdb and subsequently converted to PDBQT for docking.

2.3 Ligands preparation

Structures of tamoxifen and *xanthohumol* were obtained from PubChem (accessed 2022). SMILES/SDF records were imported into PyRx and converted to 3D with Open Babel v3.1.1; stereochemistry was verified and probable protonation/tautomeric states were set for pH 7.4. Geometries were energy-minimized (MMFF94), Gasteiger charges assigned, and rotatable bonds defined. The ligands were exported as PDBQT and used for docking in PyRx (AutoDock Vina v1.1.2); all conversion parameters and filenames were retained for reproducibility.

2.4 Molecular docking protocol

Molecular docking analysis was performed using PyRx to investigate ligand–receptor interactions in the context of ER-positive breast cancer therapy. The prepared ERα ligand-binding domain (PDB: 3ERT) and the ligands tamoxifen (reference) and *xanthohumol* (literature-derived natural lead) were docked using the AutoDock Vina module. During docking, the binding-site grid box was defined around the co-crystallized antagonist pocket, and the torsional flexibility of the ligands was maintained. Multiple binding poses were generated in each run, and the pose with the highest binding affinity (lowest Vina score) was selected. Docking results were visualized in BIOVIA Discovery Studio Visualizer to analyze hydrogen bonding, hydrophobic interactions, π-stacking/π-cation contacts, and interactions with key residues (e.g., E353, D351, H524). This analysis provided valuable insights into the molecular basis of binding for tamoxifen and *xanthohumol* at ERα, enabling a comparative assessment of their potential ERα-targeted antagonism.

2.5 ADMET Profiling

In this study, SwissADME (accessed 2022) was used to evaluate the ADME/drug-likeness profiles of tamoxifen and *xanthohumol*. Using PubChem (2022) SMILES/SDF inputs, we computed Lipinski/Veber compliance, consensus LogP, TPSA, HBD/HBA, rotatable bonds, water solubility (ESOL), BOILED-Egg-based predictions of GI absorption and BBB permeability, P-gp substrate status, and CYP450 inhibition (1A2, 2C9, 2C19, 2D6, 3A4); bioavailability score and PAINS/structural alerts were also recorded. For preliminary safety signals, ProTox-II (accessed 2022) was employed to predict LD50 ($mg \cdot kg^{-1}$) and toxicity class, as well as risks for hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity. All metrics obtained from SwissADME and ProTox-II were systematically documented; these web-tool predictions are treated as hypothesis-generating and earmarked for subsequent experimental validation.

2.6 Data Analysis

Analyses were performed with PyRx v0.9.9 (engine: AutoDock Vina v1.1.2) for docking; BIOVIA Discovery Studio Visualizer 2021 (v21.1) for pose inspection, 2D interaction diagrams. Ligand records were retrieved from PubChem (accessed 2022). ADME/drug-likeness metrics were obtained from SwissADME (accessed 2022), and toxicity predictions (LD50/class and organ-level risks) from ProTox-II (accessed 2022). All software versions, grid parameters, and web-tool access dates were logged to ensure reproducibility.

3. Results

3.1 Molecular Docking by Targeted Protein with Ligands

In Figure 1 (A and C), the tamoxifen pose occupies the hydrophobic cavity of the ERα LBD in a tightly packed configuration and is stabilized predominantly by a network of π-alkyl/alkyl contacts-

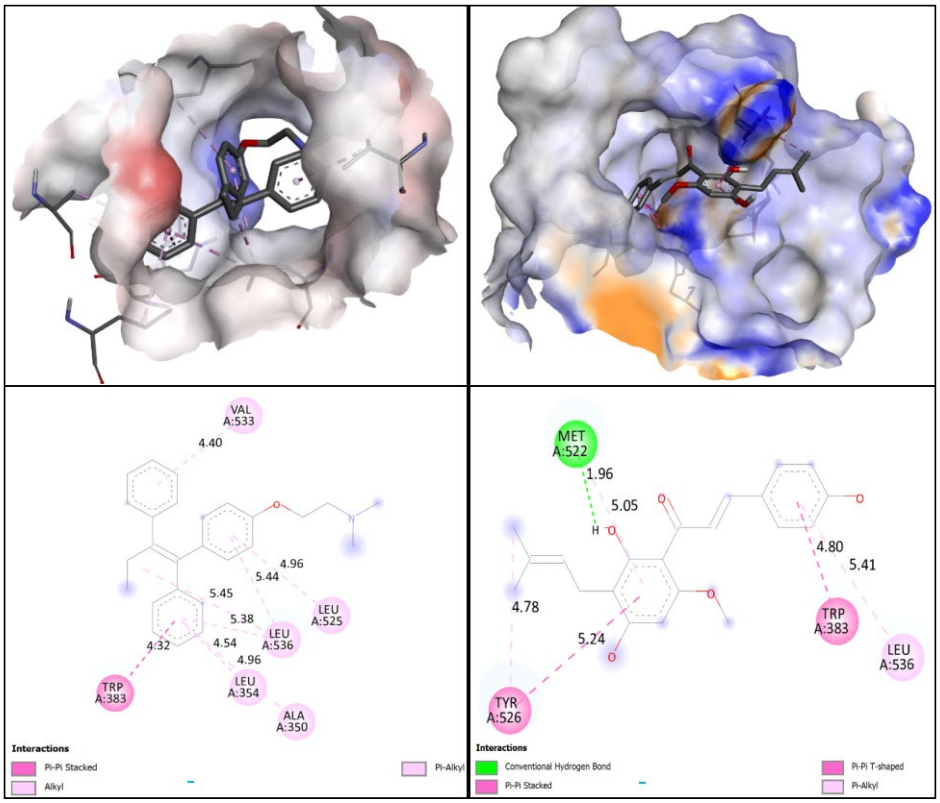

Figure 1. Docking poses of tamoxifen and xanthohumol in the ERα ligand-binding domain (LBD). (A) Tamoxifen 3D surface view and (B) xanthohumol 3D surface view; (C) tamoxifen 2D interaction map (tight hydrophobic packing; no conventional H-bond; Vina ≈ -7.5 kcal·mol-1) and (D) xanthohumol 2D interaction map (retains hydrophobic packing plus a MET522 H-bond and π-π at TRP383; Vina ≈ -8.0 kcal·mol-1).

notably with LEU354, ALA350, LEU525, LEU536, and VAL533-together with a π interaction near TRP383 (≈ 4.3-5.5 Å). No conventional hydrogen bond is observed in Table 1, which is consistent with tamoxifen's very low TPSA and high lipophilicity. This hydrophobically driven fit yields a Vina binding score of -7.5 kcal·mol^{-1}, which is in line with the interaction pattern. By contrast, Figure B/D shows *xanthohumol* maintaining a tamoxifen-like hydrophobic fit while introducing an additional polar anchor: a conventional H-bond to MET522 (~1.96 Å), alongside π-π (T-shaped/stacked) contacts with TRP383 and π-alkyl/alkyl interactions with LEU536 and TYR526 (≈ 4.8-5.4 Å). The surface view (B) indicates that the ligand extends toward a more polar patch of the pocket to engage MET522 while preserving surrounding hydrophobic contacts. This "polar anchor plus hydrophobic shielding" architecture-chemically consistent with xanthohumol 's moderate lipophilicity and higher TPSA-plausibly accounts for its slightly more favorable docking score (- 8.0 kcal·mol^{-1}).

3.2 The ADMET Study of the Compounds

SwissADME profiling showed in Table 2, tamoxifen to be highly lipophilic (XlogP3 = 8.71; WLogP = 6.93) and consistently poorly water-soluble-ESOL LogS = - 7.16 (Class: Poorly soluble), with corroborating Ali - 8.85 (PS) and Silicos-IT - 5.44 (MS)-aligning with a prediction of Low GI absorption and No BBB permeability. Despite a low TPSA (12.47 Å^2), HBA/HBD = 2/0, and RotB = 9, the extreme lipophilicity and poor solubility indicate oral absorption liabilities; Lipinski's violations: 1, with a bioavailability score of 0.55. In contrast, *xanthohumol* exhibited moderate lipophilicity (XlogP3 = 2.67; WLogP = 3.53) and more favorable aqueous solubility-ESOL LogS = - 3.28 (Class: Soluble), Ali - 4.15 (MS), Silicos-IT - 2.77 (S)-yielding High GI absorption, No BBB permeability, no Lipinski violations (0), and the same bioavailability score (0.55), with TPSA 86.99 Å^2, HBA/HBD = 5/3, and RotB = 8. Collectively, these in-silico outputs support a more favorable developability profile for *xanthohumol* versus tamoxifen, particularly with respect to solubility and predicted GI uptake; nevertheless, the predictions are hypothesis-generating and warrant confirmation via pharmaceutical formulation studies and experimental ADME/permeability assays.

3.3 Toxicological Prediction

In ProTox-II, *xanthohumol* shows a higher predicted LD_{50} than tamoxifen (3800 vs 1190 mg.kg^{-1}), indicating comparatively lower dose-dependent acute toxicity for *xanthohumol* Among toxicity

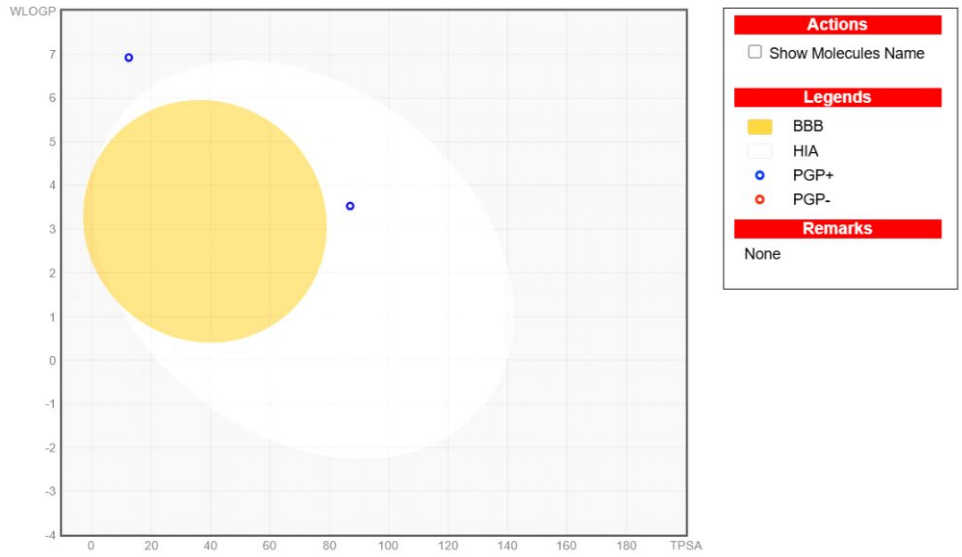

Figure 2. Molecules are positioned in WLOGP (y-axis) versus TPSA (x-axis) space; the yellow region denotes predicted BBB permeability, and the white region denotes high intestinal absorption (HIA) without BBB entry. Tamoxifen lies within the BBB region, whereas xanthohumol lies in the HIA region outside the BBB zone. (WLOGP, Wildman-Crippen logP; TPSA, topological polar surface area).

endpoints, tamoxifen exhibits high probabilities for neurotoxicity (0.87), CYP3A4 interaction (0.98), respiratory toxicity (0.98), and ecotoxicity (0.73), delineating a broad predicted toxicological risk pattern. By contrast, *xanthohumol* presents a moderate CYP3A4 probability (0.52), with no values reported for respiratory or ecotoxic endpoints in this dataset (Table 3). Immunotoxicity probabilities are high for both ligands-0.96 for tamoxifen and 0.99 for *xanthohumol* Overall, the results differentiate the compounds by a higher LD_{50} and a narrower set of flagged endpoints for *xanthohumol,* versus multiple high-probability liabilities for tamoxifen, with immunotoxicity emerging as a shared predominant signal. Across both ligands, immunotoxicity emerges as the dominant common signal, with probabilities of 0.96 for tamoxifen and 0.99 for *xanthohumol,* respectively. Taken together, the pattern characterizes *xanthohumol* by a higher LD_{50} and a narrower panel of flagged endpoints relative to tamoxifen, whereas tamoxifen is associated with multiple high-probability toxicological liabilities within the model outputs.

3.4 BOILED-EGG Model for Interpret Gut-Brain Interaction

BOILED-Egg analysis indicates in Figure 2 that tamoxifen (WLOGP ≈ 6.9-7.0; TPSA ≈ 12.5 $Å^2$) lies squarely within the BBB-permeant (yellow) region, consistent with its very high lipophilicity and low polar surface area, and predicting both brain penetration and high intestinal absorption (HIA). In contrast, *xanthohumol* (WLOGP ≈ 3.5; TPSA ≈ 87-90 $Å^2$) falls in the HIA (white) region but outside the BBB zone-i.e., high GI absorption is predicted while BBB permeability is limited. This positional divergence reflects their physicochemical profiles: tamoxifen's extreme lipophilicity and minimal TPSA favor potential CNS exposure, whereas *xanthohumol* 's moderate lipophilicity and higher TPSA support oral absorption but are less conducive to CNS penetration.

4. Discussion

Although tamoxifen has long been used in the treatment of hormone-dependent breast cancer, its side effects and the emergence of genetic resistance have prompted a critical re-evaluation of its continued use. Despite its therapeutic efficacy, tamoxifen has been linked to various toxicities, particularly neurotoxicity and complex drug interactions (Hale et al., 2020). In this context, the search for safer alternatives from natural sources has become a major focus in current research. In this study, *xanthohumol,* a chalcone-class compound derived from hops, was evaluated as a potential alternative to tamoxifen through in-silico analysis, comparing their structural, pharmacokinetic, and toxicological properties (Liu et al., 2015).

Both tamoxifen and *xanthohumol* exhibit strong interactions with the ligand-binding domain (LBD) of estrogen receptor alpha (ERα); however, the results of this in-silico study clearly indicate that *xanthohumol* presents a more optimized binding architecture-featuring not only hydrophobic interactions but also an additional polar hydrogen bond with MET522. In the case of tamoxifen, only π-alkyl and alkyl interactions are observed (notably with LEU354, ALA350, LEU525, LEU536, and VAL533), but no conventional hydrogen bond is formed, which is consistent with tamoxifen's low topological polar surface area (TPSA) and high lipophilicity.

Table 1. Docking summary in Estrogen Receptor alpha (ERα): protein (PDB: 3ERT), ligands (Tamoxifen: CID 2733526 and Xanthohumol: CID 639665), binding energy, interaction types (Å), and core binding-site residues.

Protein from PDB	Ligand from PubChem	Chemical Bond Interaction (Å)					Core Amino Acid on Binding Site
		Binding Energy (kcal/mol)	H-bonds with Bond Distances (Å) ● Conventional H-Bond ● Carbon H-Bond	Charge ● π-Anion/π-Cation ● Halogen (F)	Hydrophobic Interactions ● Alkyl ●π-Sigma ● π-alkyl ● π-π T-shaped ● π-π Stacked	Another interaction ●Van-der Waals ●Unfavorable Donor-Donor ●Unfavorable Acceptor-Acceptor	
Estrogen Receptor alpha (ERα) PDB: 3ERT	Tamoxifen (CID 2733526)	- 7.5			● VAL533 (4.40), LEU525(4.96), LEU354(4.54), ALA350(4.96) ● LEU536(5.44), LEU536(5.45), LEU536(5.38) ● TRP383(4.32)		LEU536
	Xanthohumol (CID 639665)	- 8.0	● MET522 (1.96)		● MET522 (5.05), LEU536 (5.41) ● TYR526(5.24), TYR526 (4.78), TRP383 (4.80)		MET522, TYR526

This observation aligns with the findings of Landeros-Martínez et al. (2018), who demonstrated that *xanthohumol* not only targets the PI3K/AKT pathway but also exhibits effective docking at ERα, with binding stability often superior to that of tamoxifen (Landeros-Martínez et al., 2018). More notably, Orhan et al. (2018) highlighted in their review that the chalcone structure of *xanthohumol* is particularly suited for unique binding within the ERα ligand-binding domain (LBD)-especially through π-π stacking interactions-which modulate receptor binding in a manner distinct from tamoxifen (Orhan et al., 2018).

Furthermore, Trifunović et al. (2017) demonstrated that natural compounds possessing relatively higher TPSA and moderate lipophilicity can bind effectively to ERα, exhibiting performance comparable to tamoxifen-and in some cases, even showing enhanced efficacy (Trifunović et al., 2017).

The high lipophilicity and limited aqueous solubility of tamoxifen indicate certain structural constraints that may affect its oral absorption and bioavailability, thereby influencing its therapeutic efficacy. In contrast, *xanthohumol* exhibits a more balanced pharmacokinetic profile, characterized by improved solubility, better bioavailability, and compliance with Lipinski's rule of five, making it a promising drug candidate.

This distinction is also reflected in the studies of Williamson et al. (2018) and Brglez et al. (2016), which reported that natural flavonoid-class compounds generally possess favorable absorption capacity and improved safety profiles (Brglez Mojzer et al., 2016; Williamson et al., 2018). In particular, such compounds show strong potential in pharmaceutical research due to their enhanced gastrointestinal absorption and lower toxicity.

Toxicity prediction based on ProTox-II revealed a clear distinction between tamoxifen and *xanthohumol*. Tamoxifen exhibited high probabilities across multiple toxicity parameters, particularly for neurotoxicity, respiratory toxicity, and potential interactions with the cytochrome P450 system (notably CYP3A4). As a result, tamoxifen demonstrates a broad and multifaceted toxicological profile, which may elevate clinical risks during long-term therapy. These findings are consistent with those of Tarnow et al. (2019), who reported the involvement of tamoxifen in complex CYP enzyme pathway interactions and organ-specific (Tarnow et al., 2019). Additionally, environmental toxicity has been highlighted as a critical issue for tamoxifen, with previous studies indicating potential adverse effects on aquatic biodiversity (Orias et al., 2015). According to BOILED-Egg analysis, tamoxifen and *xanthohumol* also differ markedly in absorption and brain permeability, reflecting their distinct structural features and pharmacokinetic

Table 2. Comprehensive SwissADME-derived ADME and drug-likeness profiles of Tamoxifen and Xanthohumol (physicochemical descriptors, lipophilicity, aqueous solubility models, pharmacokinetic predictions, and rule-based drug-likeness).

Properties		Tamoxifen	Xanthohumol
Physicochemical Properties	Molecular wt. (g/mol)	371.5	368.51
	Rotatable Bond	9	8
	H-Bond Acceptors	2	5
	H-Bond Donors	0	3
	TPSA (Å2)	12.47	86.99
Lipophilicity	XlogP3	8.71	2.67
	WLogP	6.93	3.53
Water Solubility	ESOL LogS	-7.16	-3.28
	ESOL Class	PS	S
	Ali LogS	-8.85	-4.15
	Ali Class	PS	MS
	Silicos-IT LogS	-5.44	-2.77
	Silicos-IT Class	MS	S
Pharmacokinetics	GI Absorption	L	H
	Blood Brain Barrier	NO	NO
Druglikeness	Lipinski's Violation	Y, 1	Y, 0
	Bioavailability Score	0.55	0.55

Note: PS (Poorly Soluble), L (Low), MS (Moderately Soluble), Y (Yes), S (Soluble), H (High).

behaviors. Tamoxifen occupies the "yellow zone" in the BOILED-Egg model, corresponding to its potential to cross the blood-brain barrier (BBB). This property can be attributed to its high lipophilicity and very low polar surface area. Such characteristics increase the likelihood of neurological side effects, a phenomenon also noted in previous studies, which reported that long-term use of tamoxifen may be associated with certain neurotoxic effects (Cox-York et al., 2019).

In contrast, *xanthohumol* is positioned in the "white zone" of the BOILED-Egg model, which indicates high gastrointestinal absorption (HIA) but comparatively low potential to cross the blood–brain barrier (BBB). Its moderate lipophilicity and higher topological polar surface area (TPSA) make it both orally bioavailable and pharmacologically safe, while reducing the likelihood of central nervous system (CNS) exposure. This characteristic is often desirable, particularly when minimizing CNS-related side effects is a therapeutic goal. According to Mi et al. (2020) and Chedik et al., 2017, phytoestrogens with limited BBB permeability can achieve strong peripheral efficacy without inducing neurological complications, thereby supporting their potential as safer therapeutic alternatives (Chedik et al., 2017; Mi et al., 2020).

Table 3. ProTox-II-predicted toxicity profile of Tamoxifen and Xanthohumol: acute-toxicity estimates and multi-endpoint risk scores.

Ligand	LD_{50} (mg/kg)	Neuro	CYP3A4	Respirato	Ecotoxicity	Immuno
Tamoxifen	1190	0.87	0.98	0.98	0.73	0.96
Xanthohumol	3800	-	0.52	-	-	0.99

Neurotoxicity (Neuro), Cytochrome (CYP3A4), Respiratory toxicity (Respirato), Immunotoxicity (Immuno).

In this study, the structural and pharmacological characteristics of tamoxifen and *xanthohumol* were comparatively analyzed using in-silico approaches. The results indicate that *xanthohumol* is not only an effective ligand but also a safer and more acceptable drug candidate capable of serving as a potential replacement for tamoxifen (Liu et al., 2015; Saito et al., 2018; Wang et al., 2020). Its superior docking score, enhanced ADMET profile, lower predicted toxicity, and favorable BOILED-Egg positioning collectively strengthen the evidence supporting *xanthohumol* as a promising natural alternative to tamoxifen.

However, the in-silico results are not conclusive-they are hypothesis-generating in nature. To substantiate these preliminary findings, further in-vitro and in-vivo validations are required, particularly focusing on binding kinetics, cellular uptake, toxicity assays, and the overall pharmacodynamic impact.

5. Conclusion

This in-silico study suggests that *xanthohumol* may serve as a safer and pharmacokinetically superior natural alternative to tamoxifen, specifically targeting estrogen receptor alpha (ERα). While tamoxifen exhibited strong hydrophobic interactions, it was also associated with poor solubility, limited drug-likeness, and multiple predicted toxic liabilities-particularly CNS penetration. In contrast, *xanthohumol* demonstrated a balanced hydrophobic-plus-polar binding mode, along with improved ADMET properties, higher gastrointestinal absorption, and a comparatively safer toxicity profile. Overall, these findings position *xanthohumol* as a promising lead compound that could play a significant role in the development of next-generation ERα-targeted therapies.

Author contributions

A.K.M. conceived and designed the study. M.F.A. and M.R.I. performed data collection and computational analyses. T. contributed to data interpretation and visualization. M.A.B.S. supervised the research and reviewed the manuscript. All authors discussed the results, contributed to the writing, and approved the final version of the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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